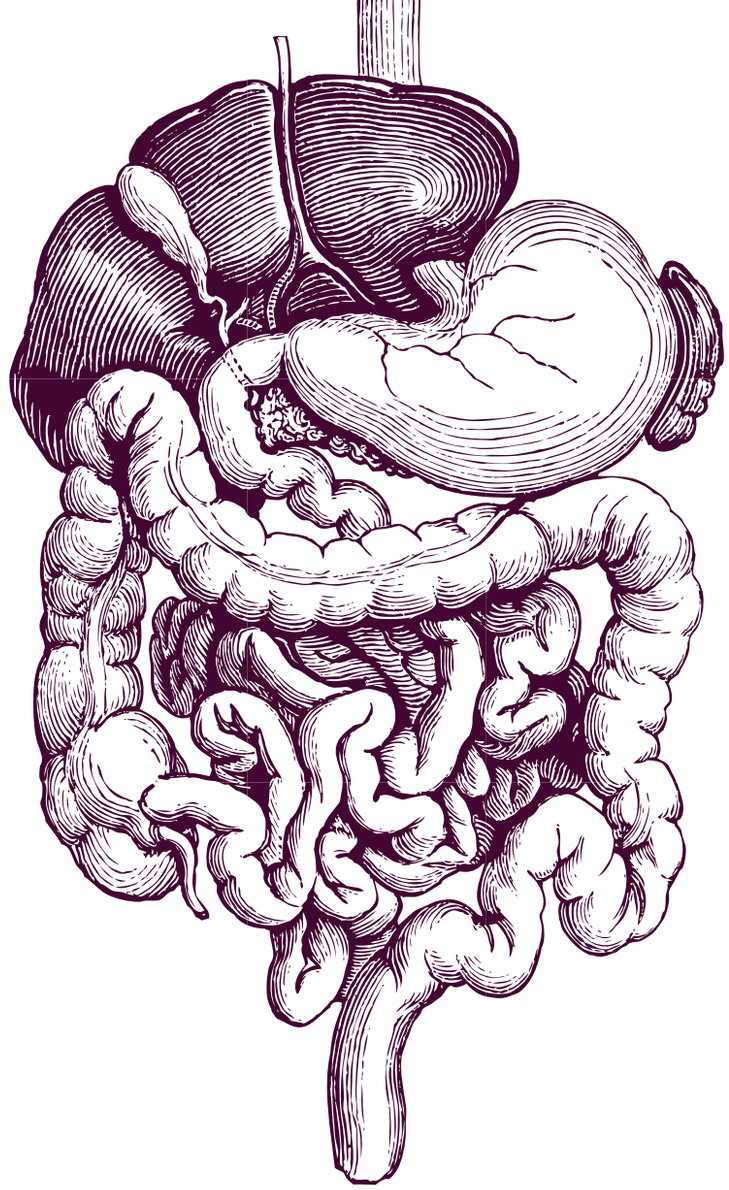
Surgery for inflammatory bowel disease, crossing borders

Gardenbroek, T.J.

Publication date
2014
Document Version
Final published version

SURGERY FOR INFLAMMATORY BOWEL DISEASE, CROSSING BORDERS

TJIBBE GARDENBROEK



SURGERY FOR INFLAMMATORY BOWEL DISEASE, CROSSING BORDERS

TJIBBE GARDENBROEK

Surgery for inflammatory bowel disease, crossing borders

Tjibbe Gardenbroek

Surgery for inflammatory bowel disease, crossing borders

IBSN: 978-94-6169-565-9
Cover design: Condept, Utrecht, The Netherlands
Lay-out: Optima Grafische Communicatie, Rotterdam, The Netherlands
Printed by: Optima Grafische Communicatie, Rotterdam, The Netherlands

Surgery for inflammatory bowel disease, crossing borders

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 16 oktober 2014, te 12:00 uur

door

Tjibbe Jorrit Gardenbroek
geboren te Gouda

PROMOTIECOMMISSIE

Promotores

Prof. dr. W.A. Bemelman
Prof. dr. G.R.A.M. D'Haens

Copromotores

Dr. C.Y. Ponsioen
Dr. C.J. Buskens

Overige leden

Prof. dr. D.J. Gouma
Prof. dr. G.R. van den Brink
Prof. dr. L.P.S. Stassen
Prof. dr. M.A. Cuesta
Dr. M. Löwenberg

Faculteit der Geneeskunde

TABLE OF CONTENTS

General introduction and outline of the thesis

GENERAL INTRODUCTION

Inflammatory bowel disease (IBD)

IBD is a chronic, idiopathic inflammatory disease of the gastrointestinal tract. Patients with IBD are diagnosed with either Crohn's disease (CD) or ulcerative colitis (UC). A small portion of patients is classified as having unspecified disease (IBD-U). Incidence of IBD in the Western countries has risen in the past decades to 6-15 per 100,000 individuals for CD and 8-14 per 100,000 individuals for UC [1]. In the Netherlands, yearly approximately 1000 patients with CD and 1500 patients with UC are newly diagnosed with an estimated prevalence of 20,000 and 30,000 patients respectively [2]. In CD, the peak age of onset is in the 2nd or 3rd decade, while UC is most frequently diagnosed in patients between 15 - 40 years and the middle aged [1]. Both CD and UC are characterized by episodes of relapse and remission.

Crohn's disease

CD can occur throughout the entire gastrointestinal tract. It is characterized by transmural inflammation and a skip lesion pattern, and can present with structuring and penetrating complications [1]. Patients with CD often present with a history of abdominal cramping, persistent diarrhoea, fever with or without anorexia and possibly nausea and vomiting as signs of obstructive intestinal disease [3]. Smoking increases the risk for CD [1].

Patients with CD are commonly treated according to the step-up approach [4]. Patients are initially treated with the least toxic, but also least potent drug. Treatment is intensified by using stronger medication (e.g. anti-tnf; anti-tumour necrosis factor) if necessary. Indications for surgery are obstructive disease, medical refractory disease, fistulas or complications such as abscesses, perforations or bleeding. Despite the current variety of available medications, more than two thirds of patients will require surgery during their lifetime, and nearly half of these patients will undergo repeat surgical interventions [5].

Ileocolic resection

In approximately 30-35% of all CD patients, the disease activity is confined to the terminal ileum [6]. The ileocolic resection is the most performed resection in IBD. Many studies have established short and long term advantages of the laparoscopic ileocolic resection [7].

Ulcerative colitis

In UC, disease activity is confined to the colon, and typically involves the rectum [1]. The disease diffusely affects the superficial mucosa of the colon. Patients with UC often present with a history of abdominal cramping, bloody diarrhoea, fatigue and weight loss [3]. Smoking lowers the risk for UC [1].

Treatment of UC is primarily medical, according to the step-up approach [8]. Colitis refractory to medical treatment requires surgery. Basically there are two procedures commonly applied, the emergency colectomy and (completion) proctocolectomy with ileoanal pouch reconstruction. Reported operation rates vary in the literature, but are between 20-30% after25 years of UC [1;9;10].

Subtotal colectomy

In case of severe colitis refractory to medical therapy a subtotal colectomy is performed. In a laparoscopic or open procedure the colon is removed and an end-ileostomy is created. Then, in an elective setting, a completion proctectomy and ileal pouch anal anastomosis (IPAA) is performed [11].

Restorative (completion) proctocolectomy and pouch procedure

In an elective procedure, a restorative proctocolectomy (RPC) is performed. During this procedure the (remaining) colon is removed, followed by a proctectomy and IPAA. For creation of the IPAA, the J-pouch configuration is most commonly used. The J-pouch is created by stapling a folded loop of the terminal ileum. The pouch is subsequently stapled or sewn to the anal canal. In patients with an increased risk of anastomotic complications, such as preoperative high doses of steroids or technical difficulties during the procedure, a defunctioning loop ileostomy is created. An RPC can be performed as an open or laparoscopic procedure, in which the laparoscopic procedure has different advantages over the open approach [12-15]. The quality of life increases after creation of a pouch, even to a level comparable to that of the general healthy Dutch population [16;17].

A restorative proctocolectomy is also performed in patients with familial adenomatous polyposis (FAP). In these patients hundreds of adenomas develop in the colon and rectum during childhood and adolescence. Without treatment, the colorectal cancer rate is 100% around age 40 to 50. Incidence of FAP is estimated 1 per 100,000 individuals. Indication for surgery is the presence of large numbers of adenoma's over 5mm in size, including adenomas showing high grade dysplasia. This criterion is often reached between the age of 15 and 25 years [18]

Appendectomy

Although the trigger for the development of UC is still unknown, T-helper type II cells and their cytokines are suggested to enhance the development of UC [19]. Over the past 20 years evidence has accumulated suggesting a role of the appendix in the development and disease course of UC [20-25]. Cytokine production in the appendix has been proposed to trigger an immunological cascade in the colorectum. The appendix is suggested to be a potential priming site in the development of UC. Several studies show a beneficial effect

of appendectomy on the disease course of UC [26-29]. Therefore, the role of the appendix in UC is further evaluated.

Laparoscopic surgery

Laparoscopic techniques have transformed colorectal surgery in the last decades, and meanwhile numerous studies have shown the safety and advantages of laparoscopic surgery in Crohn's disease and colitis [30-36].

Especially young patients and patients undergoing repeat surgery may benefit from bowel-sparing techniques and minimally invasive surgery with reduced adhesion formation. These minimally invasive procedures have further developed into even more minimal invasive techniques, e.g.single-incision laparoscopic surgery, natural orifice specimen extraction, close rectal dissection techniques and transperineal resectional surgery.

Complications after surgery

Surgery is inevitable associated with complications. The Achilles' heel of ileoanal pouch surgery is anastomotic leakage. Leakage might result in a chronic presacral sinus precluding stoma closure or jeopardizing pouch function if the stoma can be closed. It is for debate whether creating a primary defunctioning ileostomy after IPAA benefits the patient. The same applies to the influence of the type of proctectomy performed in ileoanal pouch surgery, e.g. total mesorectal excision or close rectal dissection, on the clinical significant anastomotic leaks. When an anastomotic leak after pouch surgery has developed there are only a few options other than a defunctioning ileostomy to solve the problem. A relatively new technique to take care of the leaking low anastomosis is applying the Endo-sponge technique. Weidenhagen et al. described a technique to treat the presacral sinus with vacuum assisted drainage [37]. A modification of this technique is currently used in which the Endo-sponge is used to clean the cavity during two or three Endo-sponge® placements. When the cavity is clean and is surrounded by healthy granulation tissue, the anastomotic defect is closed surgically. With the use of this novel technique a higher percentage of secondary healed anastomosis and a better long term pouch function is expected.

AIM OF THE THESIS

The aim of this thesis was to present recent developments in the surgical treatment of patients with CD, UC and FAP. Part I of the thesis presents the results of studies on the developments in surgical treatment and surgical techniques. Part II focuses on the appendix as a new and promising aspect in the (surgical) treatment of UC.

OUTLINE OF THE THESIS

The first part of this thesis focusses on the developments in the surgical treatment of patients with inflammatory bowel disease and familial adenomatous polyposis and it concentrates on new developments in surgical techniques. In **Chapter 1** we perform a systematic review with meta-analysis to compare short-term outcomes after laparoscopic and open emergency colectomy for acute medically refractory colitis. In **Chapter 2** the results of a series of patients who underwent emergency colectomy at the Academic Medical Centre are presented. In this chapter we have aimed to determine possible risk factors for postoperative complications. **Chapter 3** describes different extraction techniques to remove the specimen from the abdominal cavity after emergency colectomy, such as the rectum or stoma site. The short term results of two surgical dissection techniques in the creation of an ileal pouch-anal anastomosis (IPAA) are compared in a randomized controlled trial presented in **Chapter 4**. Aim of the latter study is to compare morbidity and quality of life in patients having total mesorectal excision or close rectal dissection during proctectomy followed by IPAA for benign disease. In **Chapter 5** we compared the results of 2 cohorts of patients undergoing IPAA surgery with or without primary defunctioning ileostomy. Both surgical outcomes, functional results and quality of life of these patients are analysed. A novel solution for the treatment of anastomotic leakage after IPAA is presented in **Chapter 6** and compared to the conventional treatment of this challenging complication by investigating the effectiveness and direct medical costs of both treatment modalities. **Chapter 7** discusses the most recent developments in the surgical techniques in the treatment of patients with CD. One of these developments, the single-port laparoscopic ileocolic resection, is explored in **Chapter 8** by comparing short term surgical outcomes in two cohorts of patients undergoing either single-port or multi-port laparoscopic ileocolic resection for CD.

The second part of this thesis focuses on the appendix and its role in UC. There is evidence that appendectomy protects against development of UC and may influence the disease course of UC. Furthermore, the appendix is suggested to be a potential priming site in the development of UC. In **Chapter 9**, a systematic review of studies investigating the effect of appendectomy on the disease course of patients with UC is presented. **Chapter 10** describes the study protocol of the ACCURE trial, an international multicentre randomised trial in patients with UC that will provide evidence on the role of appendectomy in the treatment of UC and the effects of appendectomy on the disease course. In depth analysis of the appendix is performed in **Chapter 11**. In this study T cell infiltration in the appendices of UC patients is analysed and compared to the appendices of patients with CD, acute appendicitis and non-inflammatory controls.

REFERENCES

1 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. **Epidemiology and natural history of inflammatory bowel diseases.** Gastroenterology 2011; 140(6):1785-1794.

2 www.crohn-colitis.nl. 2014.

3 Baumgart DC, Sandborn WJ. **Inflammatory bowel disease: clinical aspects and established and evolving therapies.** Lancet 2007; 369(9573):1641-1657.

4 Dignass A, Van AG, Lindsay JO, Lemann M, Soderholm J, Colombel JF et al. **The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management.** J Crohns Colitis 2010; 4(1):28-62.

5 Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. **Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery.** Gut 2005; 54(2):237-241.

6 Hanauer SB. **Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities.** Inflamm Bowel Dis 2006; 12 Suppl 1:S3-S9.

7 Polle SW, Wind J, Ubbink DT, Hommes DW, Gouma DJ, Bemelman WA. **Short-term outcomes after laparoscopic ileocolic resection for Crohn's disease. A systematic review.** Dig Surg 2006; 23(5-6):346-357.

8 Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M et al. **Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management.** J Crohns Colitis 2012; 6(10):991-1030.

9 Henriksen M, Jahnsen J, Lygren I, Sauar J, Kjellevold O, Schulz T et al. **Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study).** Inflamm Bowel Dis 2006; 12(7):543-550.

10 Langholz E, Munkholm P, Davidsen M, Binder V. **Course of ulcerative colitis: analysis of changes in disease activity over years.** Gastroenterology 1994; 107(1):3-11.

11 Parks AG, Nicholls RJ. **Proctocolectomy without ileostomy for ulcerative colitis.** Br Med J 1978; 2(6130):85-88.

12 Ahmed AU, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG et al. **Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis.** Cochrane Database Syst Rev 2009;(1):CD006267.

13 Bartels SA, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. **Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study.** Ann Surg 2012; 256(6):1045-1048.

14 Dunker MS, Bemelman WA, Slors JF, van DP, 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.

15 Polle SW, Dunker MS, Slors JF, Sprangers MA, Cuesta MA, Gouma DJ et al. **Body image, cosmesis, quality of life, and functional outcome of hand-assisted laparoscopic versus open restorative proctocolectomy: long-term results of a randomized trial.** Surg Endosc 2007; 21(8):1301-1307.

16 Heikens JT, Gooszen HG, Teepen JL, Hueting WE, Oostvogel HJ, van Vroonhoven TJ et al. **The ileo neo rectal anastomosis: long-term results of surgical innovation in patients after ulcerative colitis and familial adeno-**

matous polyposis. Int J Colorectal Dis 2013; 28(1):111-118.

17 Heikens JT, Gooszen HG, Rovers MM, van Laarhoven CJ. **Stages and evaluation of surgical innovation: a clinical example of the ileo neorectal anastomosis after ulcerative colitis and familial adenomatous polyposis.** Surg Innov 2013; 20(5):459-465.

18 Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L et al. **Guidelines for the clinical management of familial adenomatous polyposis (FAP).** Gut 2008; 57(5):704-713.

19 Rachmilewitz D, Karmeli F, Takabayashi K, Hayashi T, Leider-Trejo L, Lee J et al. **Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis.** Gastroenterology 2002; 122(5):1428-1441.

20 D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. **Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study.** Am J Gastroenterol 1997; 92(8):1275-1279.

21 Gilat T, Hacohen D, Lilos P, Langman MJ. **Childhood factors in ulcerative colitis and Crohn's disease.** An international cooperative study. Scand J Gastroenterol 1987; 22(8):1009-1024.

22 Groisman GM, George J, Harpaz N. **Ulcerative appendicitis in universal and nonuniversal ulcerative colitis.** Mod Pathol 1994; 7(3):322-325.

23 Panaccione R, Sandborn WJ. **The appendix in ulcerative colitis: a not so innocent bystander.** Gastroenterology 1999; 117(1):272-273.

24 Perry WB, Opelka FG, Smith D, Hicks TC, Timmcke AE, Gathright JB, Jr. et al. **Discontinuous appendiceal involvement in ulcerative colitis: pathology and clinical correlation.** J Gastrointest Surg 1999; 3(2):141-144.

25 Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. **Appendectomy protects against ulcerative colitis.** Gastroenterology 1994; 106(5):1251-1253.

26 Bolin TD, Wong S, Crouch R, Engelman JL, Riordan SM. **Appendicectomy as a therapy for ulcerative proctitis.** Am J Gastroenterol 2009; 104(10):2476-2482.

27 Florin TH, Pandeya N, Radford-Smith GL. **Epidemiology of appendicectomy in primary sclerosing cholangitis and ulcerative colitis: its influence on the clinical behaviour of these diseases.** Gut 2004; 53(7):973-979.

28 Naganuma M, Iizuka B, Torii A, Ogihara T, Kawamura Y, Ichinose M et al. **Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: results of a multicenter case-controlled study in Japan.** Am J Gastroenterol 2001; 96(4):1123-1126.

29 Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG et al. **Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease.** Gut 2002; 51(6):808-813.

30 Hull TL, Joyce MR, Geisler DP, Coffey JC. **Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis.** Br J Surg 2012; 99(2):270-275.

31 Bartels SA, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. **Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study.** Ann Surg 2012; 256(6):1045-1048.

32 Bartels SA, Vlug MS, Henneman D, Ponsioen CY, Tanis PJ, Bemelman WA. **Less adhesiolysis and hernia repair during completion proctocolectomy after laparoscopic emergency colectomy for ulcerative colitis.** Surg Endosc 2012; 26(2):368-373.

33 Bartels SA, Vlug MS, Hollmann MW, Dijkgraaf MG, Ubbink DT, Cense HA et al. **Small bowel obstruction, incisional hernia and survival after laparoscopic and open colonic resection (LAFA study).** Br J Surg 2014; 101(9):1153-1159.

34 Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA et al. **Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease.** Br J Surg 2010; 97(4):563-568.

35 Kolfschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J et al. **Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals.** Ann Surg 2013; 257(5):916-921.

36 Schwenk W, Haase O, Neudecker J, Muller JM. **Short term benefits for laparoscopic colorectal resection**. Cochrane Database Syst Rev 2005;(3):CD003145.

37 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(8):1818-1825.

I

DEVELOPMENTS IN SURGERY FOR INFLAMMATORY BOWEL DISEASE

1

A systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis

Tjibbe J. Gardenbroek[1], Sanne A. L. Bartels[1], Dirk T. Ubbink[1,2], Christianne J. Buskens[1], Pieter J. Tanis[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Quality Assurance and Process Innovation, Academic Medical Centre, Amsterdam, The Netherlands

British Journal of Surgery 2013

ABSTRACT

Background

This review compared short-term outcomes after laparoscopic versus open subtotal colectomy for acute medically refractory colitis.

Methods

A systematic review of the literature was carried out using MEDLINE, Embase and the Cochrane databases. Overall study quality was assessed by the modified Methodological Index for Non-Randomized Studies (MINORS). Meta-analysis was performed for conversion, reoperation, wound infection, ileus, gastrointestinal bleeding, intra-abdominal abscess, postoperative length of stay and mortality.

Results

The search identified nine non-randomized studies: six cohort studies and three case-matched series, comprising 966 patients in total. The pooled conversion rate was 5.5 (95 per cent confidence interval (c.i.) 3.6 to 8.4) per cent in the laparoscopic group. The pooled risk ratio of wound infection was 0.60 (95 per cent c.i. 0.38 to 0.95; P = 0.03) and that of intra-abdominal abscess was 0.27 (0.08 to 0.91; P = 0.04), both in favour of laparoscopic surgery. Pooled risk ratios for other complications showed no significant differences. Length of stay was significantly shorter after laparoscopic subtotal colectomy, with a pooled mean difference of 3.17 (95 per cent c.i. 2.37 to 3.98) days ($P < 0.001$).

Conclusion

Where the procedure can be completed laparoscopically, there may be short-term benefits over open colectomy for colitis. These results cannot be generalized to critically ill patients in need of an emergency subtotal colectomy.

INTRODUCTION

Ulcerative colitis or Crohn's disease may present with medically refractory acute severe colitis requiring urgent subtotal colectomy as either an open or laparoscopic procedure. Laparoscopic surgery has better short-term outcomes than open surgery, with reduced morbidity, pain, hospital stay and time to resumption of normal daily activities[1,2]. Possible long-term advantages of laparoscopic colorectal surgery include less adhesion formation, lower risk of small bowel obstruction, fewer incisional hernias and better preservation of fertility[3–9]. The aim of this systematic review was to compare short-term outcomes after laparoscopic and open subtotal colectomy with end ileostomy for inflammatory bowel disease (IBD).

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[10]. Inclusion criteria for article selection were: randomized clinical trials, cohort studies (both prospective and retrospective) and case-matched studies comparing open and laparoscopic subtotal colectomy in adult patients with IBD. A subtotal colectomy was defined as a total or subtotal colectomy with end ileostomy, being performed in an acute or subacute setting because of medically refractory disease. The reported intervention and control groups had to contain at least ten patients each. For the purpose of this review, hand-assisted laparoscopic surgery data were analysed as 'laparoscopic'.

Search strategy

MEDLINE (PubMed), Embase (Ovid) and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (Wiley) were searched by a clinical librarian. No restrictions regarding language or publication date were applied and no methodological filter was used. The final search was carried out on 21 June 2012. The keywords and medical subject heading (MeSH) terms used for MEDLINE were: (('Colitis'[Mesh] OR 'Crohn Disease'[Mesh] OR 'Inflammatory Bowel Diseases'[Mesh] OR ibd[tiab] OR crohn* disease[tiab] OR colon inflamm*[tiab] OR inflammatory bowel disease*[tiab] OR ulcerative colitis[tiab] OR colitis ulcerosa[tiab]) AND ('Colectomy'[Mesh] OR colectom*[tiab] OR 'Proctocolectomy, Restorative'[Mesh] OR proctocolectom*[tiab] OR coloproctectom*[tiab])) AND ('Laparoscopy'[Mesh] OR laparoscop*[tiab] OR single port[tiab] OR natural orifice specimen extraction[tiab] OR hand-assisted colectom*[tiab]). For Embase the combination of Emtree terms used was: [ulcerative colitis OR Crohn disease OR enteritis OR (ibd or inflammatory bowel diseas* or colon inflamm* or inflammatory bowel disease* or

ulcerative colitis or colitis ulcerosa).ti,ab OR crohn* disease.ti,ab] AND [colon resection OR intestine resection OR proctocolectomy OR (colectom* or proctocolectom* or coloproctectom*).ti,ab.] AND [exp laparoscopy or endoscopic surgery or (laparoscop* or single port or natural orifice specimen extraction or hand-assisted colectom*).ti,ab.]. The keywords used for searching the Cochrane database were 'colectomy' and 'laparoscopy'. Two reviewers independently selected relevant studies based on their titles and abstracts. Full-text articles were read by both reviewers. Additionally, the references of relevant studies were hand-searched. Authors of relevant conference abstracts were contacted to provide more details. Discrepancies were solved by consensus discussion.

Outcome measures

Outcomes considered for this review were conversion rate of laparoscopy, duration of operation, reoperation rate, wound infection, ileus, gastrointestinal bleeding, intra-abdominal abscess, length of stay and mortality. These outcomes were selected based on their clinical relevance.

Data extraction and analysis

Data were extracted independently by two reviewers on to a predefined data sheet that contained the following items: year of publication, country, study design, inclusion period, type of procedure, definition of intervention, characteristics of included patients, exclusion criteria, number of patients and predefined outcome measures. Discrepancies were resolved by consensus. If original continuous data were not displayed as mean(s.d.), or could not be transformed into a mean with s.d., the authors were contacted and requested to provide these data for the purpose of meta-analysis. The methodological quality of the included studies was assessed independently by two reviewers using the modified Methodological Index for Non-Randomized Studies (MINORS)[11,12].

Statistical analysis

To determine whether meta-analysis of the data was appropriate, clinical heterogeneity was assessed by comparing inclusion and exclusion criteria for each study, the outcome parameters studied, the types of laparoscopic surgery, and baseline characteristics of the included patients. Methodological heterogeneity was assessed using the MINORS tool[11,12]. Heterogeneity was examined using the χ^2 test and quantified by means of I^2 (the proportion of total variance explained by heterogeneity). An I^2 value of at least 50 per cent was considered to suggest a marked inconsistency in effect between studies, and no meta-analysis was done. If I^2 was less than 50 per cent, effect estimates were pooled using conservative random-effects models to account for possible between-study variance and any clinical heterogeneity.

For dichotomous data, a risk ratio (RR) was calculated with 95 per cent confidence interval (c.i.). To appreciate clinical relevance, absolute risk differences and number needed to treat (NNT) were added if RRs were significantly different from zero. For continuous data, a mean difference with 95 per cent c.i. was calculated based on the inverse variance method. $P < 0.050$ was considered statistically significant. Statistical analysis was done using Review Manager version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2.2.064 (Biostat, Englewood, New Jersey, USA).

RESULTS

Details of the literature search are shown in *Figure 1*. The nine included studies were non-randomized cohort studies or case-matched series[4,13–20]. Characteristics of the studies are shown in *Table 1*. A total of 966 patients were included in the nine studies, 421 in the laparoscopic group and 545 in the open group. All but two studies[4,16] comprised consecutive series of patients. The case-matched series were all matched by disease type, sex, body mass index (BMI) and age.

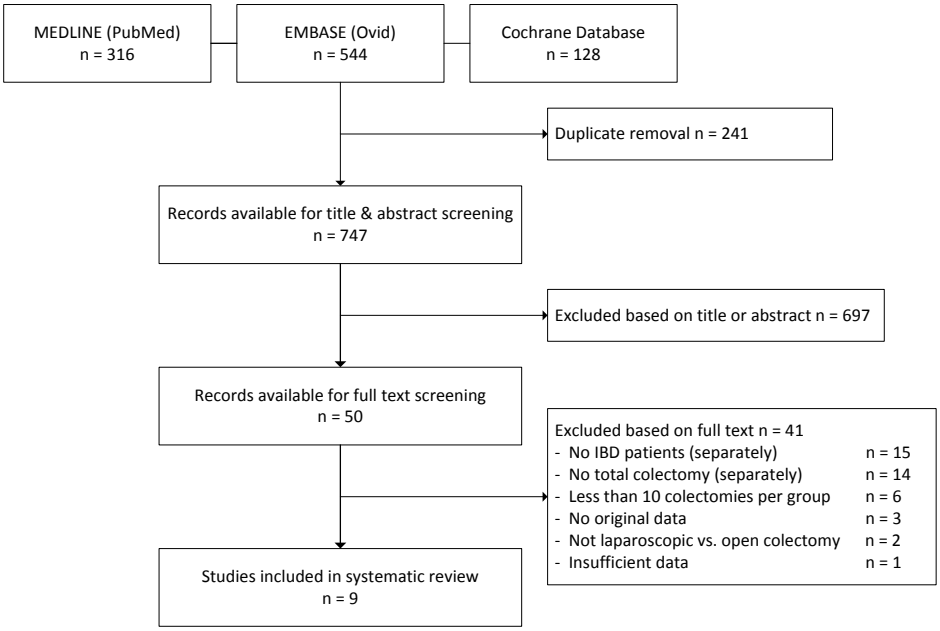


Figure 1 Flow chart showing selection of articles for review. IBD, inflammatory bowel disease.

Table 1 Characteristics of included studies

Reference	Year	Country	Study design	Inclusion period	Procedure	Intervention
Gu *et al.*[13]	2012	USA	Cohort	2006–2010	Total colectomy	Straight laparoscopy (151), HALS (26), single-incision laparoscopic surgery (20)
Bartels *et al* [4]	2012	The Netherlands	Cohort	1999–2010	Two- or three-stage restorative proctocolectomy	HALS via Pfannenstiel incision (32), straight laparoscopy (4), extraction via stoma site or transrectally
Telem *et al.*[14]	2010	USA	Cohort	2002–2007	(Sub)total colectomy, end ileostomy	Straight laparoscopy, extraction via stoma site or Pfannenstiel incision
Watanabe *et al.*[15]	2009	Japan	Cohort	2000–2004	(Sub)total colectomy, end ileostomy and mucous fistula	HALS, extraction via 7-cm paramedian incision
Chung *et al.*[16]	2009	USA	Cohort	2002–2008	Three-stage restorative proctocolectomy	HALS and straight laparoscopy, extraction via hand port, suprapubic or left lower quadrant incision or stoma site
Ouaïssi *et al.*[17]	2008	France	Case-matched	2000–2006	(Sub)total colectomy, end ileostomy and sigmoidostomy	Straight laparoscopy, extraction via 5-cm incision in right iliac fossa
Marceau *et al.*[18]	2007	France	Case-matched	Open: before 1999 Laparoscopy: 1999 onwards	(Sub)total colectomy, end ileostomy	Straight laparoscopy, extraction via incision in right iliac fossa
Marcello *et al.*[19]	2001	USA	Case-matched	1997–1999	Total colectomy, end ileostomy and mucous fistula	Straight laparoscopy, extraction via incision in right lower quadrant
Dunker *et al.*[20]	2000	The Netherlands	Cohort	1996–1999	(Sub)total colectomy, end ileostomy	HALS (2) or straight laparoscopy (8), extraction via Pfannenstiel incision

HALS, hand-assisted laparoscopic surgery.

Patient characteristics and outcomes reported are shown in *Table 2*. The mean age was comparable between the two groups in six studies, but three reported a significantly different age at baseline[4,13,15]. Other baseline data were relatively homogenous; sex did not differ between the groups in any of the nine studies, and a baseline difference in BMI was reported in only one[13] of the seven that detailed it[4,13,15–18,20]. Duration of (short-term) follow-up was 30 days in three studies[4,13,14] , and was not defined in the remaining studies. Two studies included only patients who also had a completion proctectomy in a second stage[4,16]. Data were collected retrospectively in seven studies[4,13-16,18,19]. Assessment of the endpoints was not unbiased (unblinded) in any of the studies.

Table 2 Patient and study characteristics

			No. of patients		Mean age (years)		Relevant
Reference	Diagnosis	Exclusion criteria	Laparoscopic	Open	Laparoscopic	Open	endpoints
Gu *et al.*[13]	UC	Megacolon, perforation, massive haemorrhage	197	215	39	44‡	C, OT, M, R, WI, I, LOS
Bartels *et al.*[4]	UC	No subsequent IPAA	36	64	33	39‡	C, M, R
Telem *et al.*[14]	UC	Toxic megacolon, dysplasia, neoplasm	29	61	40	43	C, OT, M, R, WI, I, GIB, LOS
Watanabe *et al.*[15]	UC	Toxic megacolon, perforation, shock	30	30	32	42‡	C, OT, M, R, WI, I, GIB, A, LOS
Chung *et al.*[16]	UC	No subsequent IPAA, perforation	37	44	38	38	C, OT, M, R, WI, I, GIB, A, LOS†
Ouaïssi *et al.*[17]	UC, CD	Toxic dilatation, perforation, peritonitis, haemorrhage	23	22	41	44	C, OT, M, R, WI, I, A, LOS
Marceau *et al.*[18]	UC, CD, IBD	Toxic megacolon, perforation, peritonitis	40	48	41	37	C, OT, M, R, WI, I, GIB, LOS
Marcello *et al.*[19]	UC, CD	At least one sign of toxicity (heart rate, temperature, peritonitis, etc.)	19	29	32*	33*	C, OT, WI, I, GIB, LOS
Dunker *et al.*[20]	UC, CD	Not defined	10	32	33	37	C, OT, M, R, LOS

*Values are median. †Only the complication with the highest Clavien–Dindo grade was reported for each patient. UC, ulcerative colitis; C, conversion; OT, operating time; M, mortality; R, reoperation; WI, wound infection; I, ileus; LOS, length of stay; IPAA, ileal pouch–anal anastomosis; GIB, gastrointestinal bleed; A, abscess; CD, Crohn's disease; IBD, inflammatory bowel disease (unclassified). ‡Significantly different *versus* laparoscopy group.

Definitions of outcome measures

Conversion was defined as an unplanned laparotomy or extension of the initial extraction site[4,13,16], any unplanned incision or a planned incision longer than 6 cm for specimen extraction[17], a midline incision[18], or no definition was given[14,15,19,20]. Duration of operation was defined as operating room time[16,19], time from skin incision to wound closure[13], or no definition was provided[14,15,17,18,20]. Reoperation was defined as a further operation within 30 days after the index operation[4,13,14] or no definition was given[15–18,20]. A definition of wound infection was provided only by Gu and colleagues[13]: signs of infection or purulent drainage, requiring deliberate opening of the wound or antibiotic treatment, and a positive culture. They defined ileus as absence of adequate bowel function on day 5 after surgery, or the need to insert a nasogastric tube because of abdominal distension, nausea or emesis after starting a liquid diet, in the absence of mechanical obstruction (imaging studies or operation)[13]. No clear definition was given in the other included studies reporting on ileus[14–19]. Gastrointestinal bleeding and intra-abdominal abscess were not defined in any of the studies that reported on these outcomes[14–19]. Length of stay was defined as total postoperative stay[13,15,16] , hospital stay including readmission for complications[17], overall length of stay[19], or no definition was given[14,18,20]. Mortality was defined as death within 30 days after the index operation[4,13,14], and/ or death occurring in hospital[17,18], or no definition was given[15,16,20].

Outcomes and meta-analysis

The authors of six studies were contacted for original continuous data reported as mean(s.d.) for the purpose of meta-analysis[13–15,19–21]. However, only data for two studies were provided by the authors[13,15].

All nine studies reported a conversion rate and were included in the meta-analysis. The pooled conversion rate was 5.5 (95 per cent c.i. 3.6 to 8.4) per cent for the laparoscopic group comprising 421 patients. No meta-analysis was done for operating time; the definitions differed or were unclear in most of the included studies and there was considerable statistical heterogeneity (I^2 = 71 per cent). The reoperation rate was reported in eight studies comprising 918 patients; only the study by Marcello and co-workers[19] did not report on reoperations. The pooled RR for reoperation was 0.83 (95 per cent c.i. 0.51 to 1.34; P = 0.44, I^2 = 0 per cent) in favour of laparoscopic resection.

Seven studies comprising 824 patients were included in the meta-analysis of wound infection and ileus; only the studies by Bartels and colleagues[4] and Dunker *et al.*[20] did not report on either complication. *Figure 2* shows the results of meta-analysis for wound infection. The pooled RR for wound infection was 0.60 (0.38 to 0.95; P = 0.03, I^2 = 0 per cent), indicating a significant difference in favour of the laparoscopic group. This was equal to a risk difference of 6 (95 per cent c.i. 2 to 9) per cent, and a NNT of 19 (95 per cent c.i. 11 to 70). The pooled RR for ileus was 0.83 (0.43 to 1.61; P = 0.58, I^2 = 40 per cent). Postoperative

gastrointestinal bleeding was mentioned in five studies comprising 367 patients[14-16,18,19]. The pooled RR for a postoperative gastrointestinal bleed was 1.03 (0.25 to 4.24; P = 0.97, I^2 = 1 per cent).

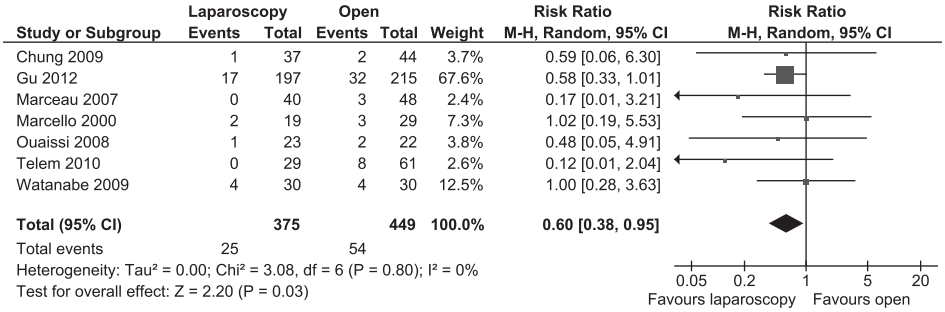


Figure 2 Forest plot showing wound infection rate after laparoscopic versus open surgery. A Mantel–Haensel random-effects model was used for meta-analysis. Risk differences are shown with 95 per cent confidence intervals

Figure 3 shows the results of meta-analysis for intra-abdominal abscess. Three studies, comprising 186 patients, reported on intra-abdominal abscess[15–17]. The pooled RR for developing an intra-abdominal abscess was 0.27 (0.08 to 0.91; P = 0.04, I^2 = 0 per cent), a significant difference in favour of laparoscopic resection. This was equal to a risk difference of 9.1 (1.6 to 16.8) per cent and a NNT of 11 (6 to 63).

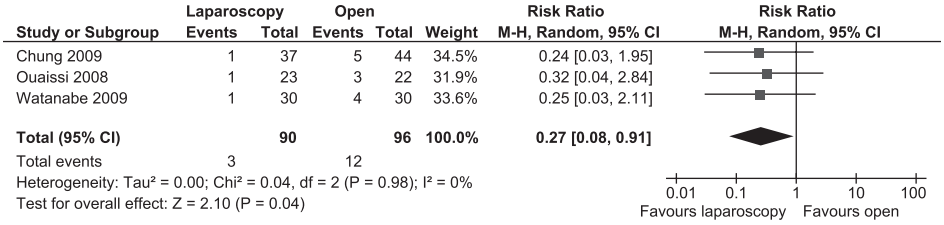


Figure 3 Forest plot showing rate of intra-abdominal abcess after laparoscopic versus open surgery. A Mantel–Haensel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals

Eight studies reported on the length of stay after colectomy, but data from only six of these, comprising 758 patients, were available for meta-analysis[13,14,16–18,20]. Marcello *et al*.[19] did not provide mean(s.d.) values; the data of Watanabe and colleagues[15] were excluded as a very extended hospital stay was reported, probably due to the organization of the healthcare system in Japan. *Figure 4* shows the results of meta-analysis for length of stay. The pooled mean difference was 3.17 (95 per cent c.i. 2.37 to 3.98) days (P < 0.001, I^2 = 0 per cent), significantly favouring laparoscopic surgery.

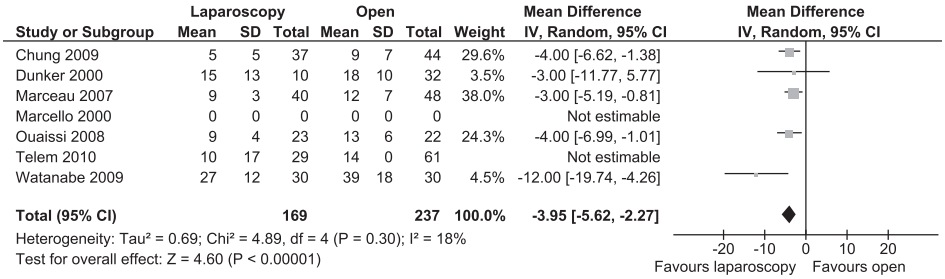


Figure 4 Forest plot showing length of hospital stay after laparoscopic versus open surgery. An inverse variance random-effects model was used for meta-analysis. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals

Eight studies, comprising 918 patients, reported on mortality; a total of one of 402 patients in the laparoscopic group died and three of 516 patients in the open group. Marcello and colleagues[19] did not report clearly on mortality and their results were therefore not included in the meta-analysis. Watanabe and co-workers[15] reported on one patient who died from intracranial thrombosis and cerebral bleeding 4 days after surgery. The other three postoperative deaths occurred in the largest study, but no details were given[13]. The pooled RR for death was 0.46 (0.07 to 3.07; P = 0.42, I^2 = 0 per cent).

DISCUSSION

A favourable effect of laparoscopy was observed in terms of the risk of superficial and deep surgical-site infection as well as a shorter hospital stay. There were no significant differences in rates of reoperation, ileus, gastrointestinal bleeding or mortality.

The findings of this systematic review are consistent with those of the Cochrane systematic review of outcomes in colorectal cancer[1], except the latter did not show a difference in intra-abdominal abscess and ileus was less likely after laparoscopic resection. Elective colorectal cancer surgery differs from (sub)acute surgery for colitis with regard to the presence of an anastomosis, pre-existing inflammation and physical condition of the patient. The defence mechanisms against abscess formation may be further deteriorated by open surgery in an already compromised patient with IBD.

Laparoscopic subtotal colectomy can be technically more difficult than the open procedure. The included studies report on data collected between 1996 and 2010; in this interval, laparoscopic techniques were already used intensively in different colorectal procedures, and many surgeons already performed laparoscopic surgery for colorectal cancer[21–24]. To what extent a learning curve for the laparoscopic procedure has influenced the outcomes of the included studies is difficult to determine.

One of the potential pitfalls in the present study is the degree of patient and procedure heterogeneity. Even though Crohn's disease and ulcerative colitis have a distinctly different aetiology, both can cause severe colitis[25]. Potential differences in postoperative outcomes for patients with Crohn's disease and ulcerative colitis are to be anticipated in the long term. Differences in short-term postoperative outcomes are not expected, and so both groups were analysed together in this systematic review, as in other studies[26,27].

A recent meta-analysis showed no difference in complications or duration of operation between hand-assisted and straight laparoscopic surgery; only an obviously lower conversion rate was observed in hand-assisted procedures[28]. As done previously in large reviews of laparoscopic colorectal cancer surgery[1], hand-assisted laparoscopy was analysed together with straight laparoscopic surgery.

The most important limitation of this systematic review is that no randomized trials have been carried out at present; therefore, the results are prone to selection bias. Patients undergoing laparoscopic colectomy are most likely to be operated on by an experienced laparoscopic surgeon, in contrast to those having an open procedure, which can be performed by any qualified surgeon. Almost all included studies had strict criteria to exclude severely ill patients, thereby limiting the external validity of this review; the present results cannot be generalized to critically ill patients in need of an emergency subtotal colectomy.

The methodological quality of the studies was average. Not all studies clearly defined their outcome measures, thereby increasing heterogeneity, and none included a blinded assessment of the endpoints, which could have led to expectation bias.

Despite these limitations, meta-analysis was found to be appropriate for the outcomes conversion rate, reoperation rate, wound infection, ileus, gastrointestinal bleeding, intra-abdominal abscess, length of stay and mortality. With the expected long-term benefits of the approach, such as fewer incisional hernias and adhesions[3,5,7], laparoscopic (sub)acute colectomy can be regarded as ideal in centres with experienced surgeons.

REFERENCES

1 Schwenk W, Haase O, Neudecker J, Müller JM. **Short term benefits for laparoscopic colorectal resection**. Cochrane Database Syst Rev 2005; (3)CD003145.

2 Kolfschoten NE, van Leersum NJ, Gooiker GA, van de Mheen PJ, Eddes EH, Kievit J et al. **Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals.** Ann Surg 2012;[Epub ahead of print].

3 Taylor GW, Jayne DG, Brown SR, Thorpe H, Brown JM, Dewberry SC et al. **Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial.** Br J Surg 2010; 97: 70–78.

4 Bartels SA, Vlug MS, Henneman D, Ponsioen CY, Tanis PJ, Bemelman WA. **Less adhesiolysis and hernia repair during completion proctocolectomy after laparoscopic emergency colectomy for ulcerative colitis.** Surg Endosc 2012; 26: 368–373.

5 Laurent C, Leblanc F, Bretagnol F, Capdepont M, Rullier E. **Long-term wound advantages of the laparoscopic approach in rectal cancer.** Br J Surg 2008; 95: 903–908.

6 Hull TL, Joyce MR, Geisler DP, Coffey JC. **Adhesions after laparoscopic and open ileal pouch–anal anastomosis surgery for ulcerative colitis.** Br J Surg 2012; 99: 270–275.

7 Bartels SA, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. **Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study.** Ann Surg 2012; 256: 1045–1048.

8 Burns EM, Currie A, Bottle A, Aylin P, Darzi A, Faiz O. **Minimal-access colorectal surgery is associated with fewer adhesion-related admissions than open surgery.** Br J Surg 2013; 100: 152–159.

9 Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA et al. **Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease.** Br J Surg 2010; 97: 563–568.

10 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** J Clin Epidemiol 2009; 62: 1006–1012.

11 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. **Methodological index for non-randomized studies (minors): development and validation of a new instrument.** ANZ J Surg 2003; 73: 712–716.

12 Ahmed AU, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG et al. **Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis.** Cochrane Database Syst Rev 2009; (1)CD006267.

13 Gu J, Stocchi L, Remzi F, Kiran RP. **Total abdominal colectomy for severe ulcerative colitis: does the laparoscopic approach really have benefit?** Dis Colon Rectum 2012; 55: e176.

14 Telem DA, Vine AJ, Swain G, Divino CM, Salky B, Greenstein AJ et al. **Laparoscopic subtotal colectomy for medically refractory ulcerative colitis: the time has come.** Surg Endosc 2010; 24: 1616–1620.

15 Watanabe K, Funayama Y, Fukushima K, Shibata C, Takahashi K, Sasaki I. **Hand-assisted laparoscopic vs. open subtotal colectomy for severe ulcerative colitis.** Dis Colon Rectum 2009; 52: 640–645.

16 Chung TP, Fleshman JW, Birnbaum EH, Hunt SR, Dietz DW, Read TE et al. **Laparoscopic vs. open total abdominal colectomy for severe colitis: impact on recovery and subsequent**

completion restorative proctectomy. Dis Colon Rectum 2009; 52: 4–10.

17 Ouaïssi M, Lefevre JH, Bretagnol F, Alves A, Valleur P, Panis Y. **Laparoscopic 3-step restorative proctocolectomy: comparative study with open approach in 45 patients.** Surg Laparosc Endosc Percutan Tech 2008; 18: 357–362.

18 Marceau C, Alves A, Ouaissi M, Bouhnik Y, Valleur P, Panis Y. **Laparoscopic subtotal colectomy for acute or severe colitis complicating inflammatory bowel disease: a case-matched study in 88 patients.** Surgery 2007; 141: 640–644.

19 Marcello PW, Milsom JW, Wong SK, Brady K, Goormastic M, Fazio VW. **Laparoscopic total colectomy for acute colitis: a case–control study.** Dis Colon Rectum 2001; 44: 1441–1445.

20 Dunker MS, Bemelman WA, Slors JF, van Hogezand RA, Ringers J, Gouma DJ. **Laparoscopic-assisted vs open colectomy for severe acute colitis in patients with inflammatory bowel disease (IBD): a retrospective study in 42 patients.** Surg Endosc 2000; 14: 911–914.

21 Li JC, Hon SS, Ng SS, Lee JF, Yiu RY, Leung KL. **The learning curve for laparoscopic colectomy: experience of a surgical fellow in an university colorectal unit.** Surg Endosc 2009; 23: 1603–1608.

22 Reichenbach DJ, Tackett AD, Harris J, Camacho D, Graviss EA, Dewan B et al. **Laparoscopic colon resection early in the learning curve: what is the appropriate setting?** Ann Surg 2006; 243: 730–735.

23 Tekkis PP, Senagore AJ, Delaney CP, Fazio VW. **Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections.** Ann Surg 2005; 242: 83–91.

24 Son GM, Kim JG, Lee JC, Suh YJ, Cho HM, Lee YS et al. **Multidimensional analysis of the learning curve for laparoscopic rectal cancer surgery.** J Laparoendosc Adv Surg Tech A 2010; 20: 609–617.

25 Abraham C, Cho JH. **Inflammatory bowel disease.** N Engl J Med 2009; 361: 2066–2078.

26 Alves A, Panis Y, Bouhnik Y, Maylin V, Lavergne-Slove A, Valleur P. **Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy.** J Am Coll Surg 2003; 197: 379–385.

27 Hyman NH, Cataldo P, Osler T. **Urgent subtotal colectomy for severe inflammatory bowel disease.** Dis Colon Rectum 2005; 48: 70–73.

28 Moloo H, Haggar F, Coyle D, Hutton B, Duhaime S, Mamazza J et al. **Hand assisted laparoscopic surgery versus conventional laparoscopy for colorectal surgery.** Cochrane Database Syst Rev 2010; (10) CD006585.

2

Prolonged preoperative hospital stay is a risk factor for complications after emergency colectomy for severe colitis

Sanne A. L. Bartels[1], Tjibbe J. Gardenbroek[1], Leon Bos[1], Cyriel Y. Ponsioen[2], Geert R.A.M. D'Haens[2], Pieter J. Tanis[1], Christianne J. Buskens[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Colorectal Disease 2013

ABSTRACT

Background

Risk factors for postoperative complications in patients undergoing emergency colectomy for severe colitis in inflammatory bowel disease have hardly been studied. Therefore, this study aimed to define predictors of a complicated postoperative course in these patients.

Methods

A retrospective review was performed of 71 consecutive patients who underwent emergency colectomy for severe colitis between 1999 and 2012 at a tertiary referral centre. Complications were graded according to the Clavien-Dindo classification. Patients with a complication Grade II or higher were compared to those with no complications or a Grade I complication.

Results

Nineteen patients (26.7%) had at least one postoperative complication classified as Clavien-Dindo Grade II or higher. In the group with postoperative complications, patients had a higher age (mean 45 *vs.* 35 years, P = 0.020) and a higher body mass index (BMI) (mean 25.9 vs. 21.0, P = 0.006). Length of preoperative hospital stay (median 15 *vs.* 6 days, P = 0.032) was longer in the group with postoperative complications. During the study period, the preoperative hospital stay decreased by 0.8 day per study year (95% confidence interval 0.2 - 1.5 days, P < 0.001). However, this did not influence the complication rate over time.

Conclusion

Factors increasing the risk of complications after emergency colectomy for severe colitis were a higher age, a higher BMI, and a longer preoperative hospital stay.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBDs) affecting the colon, with increased incidence and prevalence in the past decades[1]. Although patients can often be successfully treated medically, surgery remains an important therapeutic consideration in the treatment of IBD. Around 15% of patients[2;3] with UC and up to 80% of patients with CD will need surgery to control their disease at some point in their disease history[2;4-6]. Surgery for IBD is performed in either an acute or elective setting depending on clinical symptoms. Between 10 and 25% of patients admitted with a severe colitis fail to respond to medical therapy or develop severe complications (e.g., toxic megacolon, excessive bleeding) and require an emergency colectomy[2;7]. Subtotal colectomy with end-ileostomy is then performed, leaving the rectal stump in situ. Complications following colectomy are not uncommon, especially in the emergency setting[8], and often result in a prolonged hospital stay. It is therefore useful to identify possible risk factors for postoperative complications following subtotal colectomy.

At present, most studies on complications after surgery for medical refractory colitis describe patients operated in an elective setting and often combined with ileal pouch-anal anastomosis (IPAA) procedures[9;10]. Risk factors for postoperative complications in patients undergoing emergency colectomy for severe colitis in IBD have hardly been studied. Therefore, this study aimed to define predictors of a complicated postoperative course in these patients.

METHODS

All patients who underwent colectomy for IBD from January 1999 to February 2012 were identified from a prospective surgical database of the Academic Medical Centre, Amsterdam, the Netherlands. Subsequently, patients who underwent emergency colectomy were selected. Emergency colectomy was defined as an expedited colectomy performed in patients admitted with a severe acute colitis that failed to respond to in-hospital rescue therapy or in which severe complications of IBD developed during admittance (e.g. toxic colitis, persistent blood loss per anum). Rescue therapy was defined as intravenous steroid therapy of 40mg/day for a minimum of 3 days. If clinical improvement lagged, either cyclosporine or anti-tumour necrosis factor (anti-TNF) therapy was started. Patient data on disease, surgery and outcomes were retrospectively extracted from patient charts. The Institutional Review Board (IRB) of the Academic Medical Centre in Amsterdam, The Netherlands, has granted this study exemption from IRB approval.

Outcomes

Postoperative complications were defined as any deviation from the normal postoperative course within 30 days after emergency colectomy. Complications were graded according to the Clavien-Dindo Classification of Surgical Complications[11]. This scale grades complications based on their management. If a patient had more than one complication, only the most severe complication was graded. Details on all complications that occurred were also recorded. Leakage of the rectal stump was defined as leakage demonstrated by CT scan or during endoscopic or surgical intervention. An abscess was defined as an abscess demonstrated by CT scan or during (radiological) re-intervention. The definition of postoperative ileus was persistent nausea, vomiting and intolerance of solid food in the absence of passage of flatus or stool requiring nasogastric tube placement. Wound infection was defined as signs of infection or purulent discharge, requiring deliberate opening of the wound or antibiotic treatment.

For the purpose of identifying possible risk factors for postoperative complications, a large set of variables was collected, including patient characteristics, characteristics of the disease and medical treatment, and details of the surgery. For the outcome measures, data on the postoperative course were collected. All reported laboratory values were the last measurements available at the time of surgery, with a maximum of 30 days preoperatively. Peri-operative steroid use was defined as such if it was administered during hospital admission. The presented dose is that of the last day before surgery. Preoperative use of anti-TNF or cyclosporine as rescue therapy was defined as such if it was administered a maximum of 10 days before surgery. Peri-operative blood transfusion was defined as such from 2 days before surgery through 1 day postoperatively.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR) according to distribution. Categorical data are presented as frequencies and percentages. The independent t-test was used to compare means, and the Mann-Whitney-U test was used for continuous, non-normally distributed data. For dichotomous outcomes, groups were compared by means of the χ^2-test. Univariable logistic regression was performed to determine an odds ratio (OR) with 95% confidence interval (CI) on complications Grade II or higher for length of preoperative hospital stay (i.e. 0-7 days versus >7 days). To analyse if preoperative hospital stay changed throughout the years a univariable linear regression was done. A *P*-value <0.05 was considered to be statistically significant. Multivariate analysis was not possible due to the restricted number of events. Statistical analysis was done with IBM SPSS Statistics for Windows®, Version 19.0 (IBM Corp., Armonk, NY, United States).

RESULTS

A total number of 392 patients underwent total colectomy for IBD in the study period. Of these patients 71 (18.1%) had an emergency colectomy for severe colitis and were included in the study. Nineteen patients (26.7%) had at least one postoperative complication classified as Clavien-Dindo Grade II or higher. *Table 1* shows the characteristics of all patients, as well as the same characteristics compared for the groups with (n = 19) and without (n = 52) postoperative complications classified as Grade II or higher. In the group with postoperative complications, patients had a higher age (mean 45 *vs.* 35 years, P = 0.020) and a higher BMI (mean 25.9 *vs.* 21.0, P = 0.006). Moreover, the preoperative length of hospital stay (median 15 *vs.* 6 days, P = 0.032) was longer in the group with postoperative complications. Preoperative laboratory values were similar in both groups; however C-reactive protein seemed to be higher in the patients with postoperative complications, although the difference did not reach statistical significance. No difference was observed in peri-operative use of steroids, cyclosporine or anti-TNF. Anti-TNF was used since November 2001; when comparing only the 52 patients who had an emergency colectomy after that period, there still was no difference in complication rate (14.3% anti-TNF use in the group with complications vs. 15.8% in the group without complications, P = 1.000).

Table 2 shows the number of patients who experienced a postoperative complication with corresponding grading of the complications. Of the 71 patients, two patients were admitted to the intensive care unit (Clavien-Dindo Grade IV). The first patient was postoperatively admitted for life-threatening complications including severe hypokalaemia with non-sustained ventricular tachycardia, pneumonia and an ileus. The second patient was already admitted to the ICU with an abdominal sepsis before surgery, which improved after colectomy. A tracheostomy was performed because of difficulties with weaning from ventilation. Moreover, she had a recurring pneumothorax requiring several chest tubes. Four patients had a Grade IIIb complication requiring re-operation for the following reasons: perforation in the mid-ileum with an intra-abdominal abscess, fascial dehiscence, leakage of a mucous fistula, and drainage of an ischiorectal abscess under general anaesthesia. All complications are specified in *Table 3*. Overall, 31 complications (Grades I - IV) were observed in 22 patients. Abscess formation (n = 6) was the most frequent occurring complication. One patient had leakage of the rectal stump.

Figure 1 shows the interval between hospital admission and colectomy in days (x-axis) in relation to the number of patients with or without a complication ffl Grade II (y-axis). As was shown in *Table 1*, preoperative hospital stay was significantly longer in the group with complications. Of the patients who were admitted 0-7 days before surgery 4 of 35 (11%) had postoperative complications. Of the patients who were admitted for 7 days or longer 15 of 36 (42%) had a complication after surgery. The odds ratio of a complication ffl Grade II after a preoperative hospital stay of 7 days or longer was 5.5 (95% CI 1.6 – 19.0, P =

Table 1 Patient and clinical characteristics

	Total cohort (n = 71)	Patients with ≥ grade 2 complication (n = 19)	Patients with no or grade 1 complication (n = 52)	P value
Male	43 (60.6)	9 (47.4)	34 (65.4)	0.169[a]
Female	28 (39.4)	10 (52.6)	18 (34.6)	
Age at colectomy (years)	37.5 ± 14.8	44.8 ± 15.5	34.9 ± 13.8	0.020[b]
Body Mass Index (kg/m^2)	22.1 ± 4.5	25.9 ± 5.0	21.0 ± 3.7	0.006[b]
Current smoker	10 (13.9)	2 (13.3)	8 (18.2)	1.000[d]
Previous abdominal surgery	9 (12.7)	3 (15.8)	6 (11.5)	0.693[d]
Diabetes	3 (4.2)	1 (5.3)	2 (3.8)	1.000[d]
Diagnosis				1.000[d]
Ulcerative colitis	57 (80.3)	16 (84.2)	41 (78.8)	
IBD-undetermined	6 (8.5)	1 (5.3)	5 (9.6)	
Crohn's colitis	8 (11.3)	2 (10.5)	6 (11.5)	
Interval diagnosis and surgery (months)	36 [5 - 86]	64 [13 - 102]	33 [4 - 68]	0.061[c]
White blood cell count (x10^9/l)	9.0 [5.2 - 11.6]	10.2 [4.6 - 11.2]	8.1 [5.2 - 12.2]	0.793c
Haemoglobin level (mmol/l)	6.1 ± 0.9	6.4 ± 0.7	6.0 ± 1.0	0.322[b]
Albumin level (g/l)	26.0 [20.8 - 30.0]	26.3 ± 5.0	26.5 ± 7.2	0.924[b]
C-Reactive Protein level (mg/l)	76.1 [31.4 - 141.3]	87.0 [57.0 - 153.5]	71.0 [28.3 - 135.0]	0.232[c]
Extent of disease				1.000[d]
Pancolitis	63 (88.7)	17 (89.5)	46 (88.5)	
Left-sided colitis	8 (11.3)	2 (10.5)	6 (11.5)	
ASA-score				0.237[d]
1	2 (2.8)	1 (5.3)	1 (1.9)	
2	49 (69.0)	11 (57.9)	38 (73.1)	
3/ 4	14 (19.7)	5 (26.3)	9 (17.3)	
Perioperative steroid therapy	65 (91.5)	18 (94.7)	47 (90.4)	1.000[a]
Prednisolone equivalent dose (mg/day)	40 [30 - 50]	40 [40 - 40]	40 [25 - 50]	0.537[c]
Cyclosporine rescue therapy	27 (39.7)	8 (44.4)	19 (38.0)	0.632[a]
Anti-TNF rescue therapy	8 (11.3)	2 (10.5)	6 (11.5)	1.000[d]
Length of preoperative hospital stay	8 [1 - 18]	15 [10 - 22]	6 [1 - 17]	0.032[c]
Operating time (min)	187 ± 59	170 ± 43	194 ± 63	0.077[b]
Year of surgery *	7.0 [4.0 - 12.0]	6.0 [4.0 - 12.0]	7.0 [3.3 - 12.0]	0.901[c]
Laparoscopic approach	36 (49.3)	9 (47.4)	26 (50.0)	0.844[a]
Specialization of surgeon				0.607[a]
Colorectal surgery	49 (69.0)	14 (73.7)	35 (67.3)	
General (or other) surgery	22 (31.0)	5 (26.3)	17 (32.7)	
Resident as primary surgeon	22 (31)	6 (31.6)	16 (30.8)	0.948[a]
Rectal stump				1.000[d]
Mucous fistula	13 (18.3)	3 (15.8)	10 (19.2)	
Closure of stump	58 (81.7)	16 (84.2)	42 (80.8)	
Perioperative blood transfusion	31 (43.7)	8 (42.1)	23 (44.2)	0.873

Data are presented as n (%); mean ± SD or median [IQR]; IBD, inflammatory bowel disease; TNF, tumour necrosis factor. Variables containing missing data: Current smoker: 12 (16.9), haemoglobin level: 2 (2.8), albumin-level: 9 (12.7), CRP-level: 20 (28.2), ASA-score 6 (8.4), cyclosporine-use: 3 (4.2).* Year of surgery: 1 = 1998, 2 = 1999, etc. a: χ^2 test, b: independent t test, c: Mann-Whitney U test, d: Fisher's exact test.

Table 2 Complications graded according to Clavien-Dindo classification

Clavien-Dindo classification	Number of patients
Grade I	3
Grade II	6
Grade IIIa	7
Grade IIIb	4
Grade IV	2
Grade V	0

Grade I: Any deviation from the normal postoperative course without the need for treatment. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Included are blood-transfusion and total parenteral nutrition
Grade IIIa: Requiring surgical, endoscopic or radiological intervention without general anaesthesia
Grade IIIb: Requiring surgical, endoscopic or radiological intervention with general anaesthesia
Grade IV: Life-threatening complication requiring IC/ICU management
Grade V: Death of a patient

Table 3 Specification of complications Grade I - V (31 complications in 22 patients)

Complication	Frequency (n = 31)
Abscess	6 (20.0)
Wound-infection	3 (10.0)
Infections (other than pneumonia)	3 (10.0)
Leakage of rectal stump	1 (3.2)
Dehiscence of mucous fistula with leakage	1 (3.2)
Pneumonia	2 (6.7)
Wound dehiscence	2 (6.7)
Ileus	2 (6.7)
Hypokalaemia	2 (6.7)
Perforation (iatrogenic)	1 (3.3)
Pneumothorax	2 (6.7)
Atelectasis	1 (3.3)
Fistula	1 (3.3)
Pulmonary embolism	1 (3.3)
Thrombosis	1 (3.3)
Extensive postoperative nausea & vomiting	1 (3.3)
Sinus tachycardia	1 (3.3)

0.007).Furthermore, a linear regression was done of preoperative hospital stay throughout the years; during the study period, the preoperative hospital stay decreased by 0.8 day per study year (95% confidence interval 0.2 - 1.5 days, P < 0.001). Analysing year of surgery as categorical variable did not show any impact of this decrease in preoperative hospital stay on complication rate (*Table 1*).

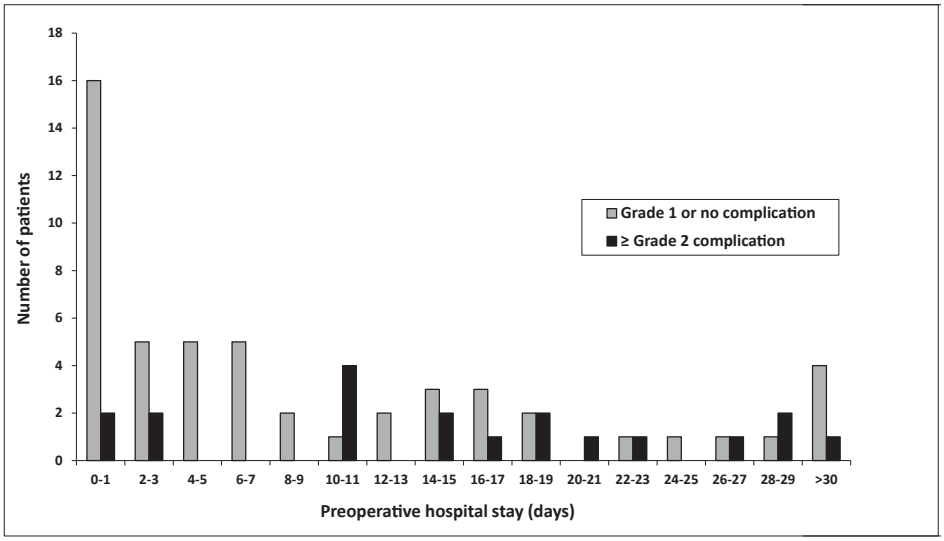


Figure 1 Days of hospital admission before surgery, comparing patients with and without complications (Grade II or higher).

DISCUSSION

This study shows that approximately one-third of patients who underwent emergency colectomy for severe colitis had at least one complication. Age, BMI and preoperative hospital stay were identified as possible risk factors for a complicated postoperative course. During the study period, the preoperative hospital stay decreased. This did not influence the complication rate over time, however. In contrast, complication rates were similar in the groups that had open and laparoscopic surgery. In this relatively small series, steroid, cyclosporine or anti-TNF-usage before surgery neither raised nor lowered the risk for postoperative complications.

A higher age is a known risk factor for postoperative complications in colorectal surgery[12] and a recent study has confirmed that it is a risk factor in ileoanal pouch surgery[9]. It is still a remarkable finding, however, given the relatively young patients in the present study cohort compared with, for example, colorectal cancer patients. This is probably the reason why comorbidities and American Society of Anesthesiologists (ASA) score did

not show any significant association with complication rate in this relatively young and healthy population apart from the primary disease.

Studies on the relation between BMI and postoperative outcomes showed various results; some report a higher complication rate in obese patients[13], while others were not able to detect a higher complication rate in series of patients undergoing colorectal surgery more specifically[14;15]. All of these studies, however, compare obese with non-obese patients; in our study mean BMI in the group with complications was 25.1, which is not nearly obese. Moreover, patients who have been steroid dependent for a longer period are more likely to have gained weight[16]. Previous studies have shown that patients who received systemic corticosteroids have a greater risk of developing postoperative complications[17;18].

An older study showed that the use of cyclosporine was not associated with an increase in perioperative complications[19]. Postoperative complications related to preoperative use of anti-TNF-therapy have been studied widely for the last decade. A meta-analysis showed a positive relation between preoperative infliximab treatment and postoperative complications[20]. In contrast, some individual studies[21;22] and a more recent study did not show a relation between anti-TNF usage and postoperative complications[23]. A possible explanation of these different outcomes can be the growing experience with anti-TNF-usage in the past decade. Either cyclosporine or anti-TNF should be given when steroid treatment fails; sequential therapy only works for some patients and leads to a prolonged hospital stay, which has been proven to result in worse outcomes[24]. A recent randomized clinical trial showed no difference between cyclosporine and anti-TNF-therapy as rescue therapy in steroid refractory UC patients[6].

A higher risk of postoperative morbidity was observed after a longer preoperative hospital stay, and previous studies from the UK, US and Canada confirm this finding in patients with UC[9;25-27]. According to guidelines of the European Crohn's and Colitis Organization, surgery is recommended in the acute phase when patients do not respond to medical therapy, or if a patient has been taking 20 mg or more of prednisolone for more than 6 weeks[28]. Often, surgical options are considered when there is no improvement after 4-7 days of medical rescue therapy. This is in concordance with the results of this current study, in which after 7 days of medical rescue therapy the odds ratio of a complication was 5.5. A potential explanation for the number of complications after a preoperative stay of 0-3 days could be that these represent patients with very severe disease whereas the complications occurring after a preoperative stay of more than 9 days represent patients with complications related to delayed surgery. A multidisciplinary setting can lead to timely surgery and lower postoperative complication rates in severe colitis[29]. In our series, there was no mortality. In a large English cohort of patients who underwent emergency colectomy for severe colitis between 1998 and 2000, 1-month mortality rates were 5.7% (95% CI 4.2 - 7.6) and 2.9% (95% CI 2.0 - 4.1) for UC and CD respectively[30].

Strengths and limitations of the study

Although the absolute sample size is relatively small with 71 true emergency colectomies for UC or CD, this is one of the largest series of emergency colectomies to date, presented by the largest IBD centre in our country. Patients with acute severe colitis are treated according to the latest European guidelines. Previous publications include data on elective colectomies or even proctocolectomies, which are likely to have better complication rates.[8;9] Exclusively analysing emergent cases seems to be clinically relevant, as demonstrated by our finding of a longer preoperative hospital stay being associated with a higher postoperative complication rate.

This study is limited by the retrospective design. It was therefore not possible to adequately and objectively determine the severity of colitis by either Truelove and Witts criteria or a MAYO score[31]. This would have helped in determining if the patients with a preoperative hospital stay of 0-3 days had complications related to disease severity. Blood levels were also determined at different preoperative times. Under-reporting of complications that occurred after discharge is likely. Furthermore, even though this is a relatively large series of strictly emergency colectomies, only a small number of patients experienced a complication. With only 19 events, it was not possible to perform multivariate regression to further explore the influence of the possible risk factors. Also, it is likely that potential existing risk factors are missed because of the small series. Over time, preferences of surgeons change. More laparoscopic surgery is performed nowadays, biological agents were introduced in 2001 and fewer patients have a mucous fistula of the colon. No influence of the surgical approach (open or laparoscopic), use of biologicals or the method of rectal stump closure on postoperative morbidity was found in our study. However, the study was probably underpowered to detect such a difference.

The results of this study underline that an episode of acute severe colitis should be managed by both a gastroenterologist and a colorectal surgeon from the beginning. It is important to evaluate jointly the clinical status of the patient and to evaluate closely clinical progression during the first days of medical therapy[7]. The presence of a multidisciplinary IBD team is essential in order to make a well-considered decision whether to continue medical therapy or to proceed to surgery, and thereby possibly lower postoperative complication rates.

REFERENCES

1 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. **Epidemiology and natural history of inflammatory bowel diseases.** Gastroenterology 2011; 140(6):1785-1794.

2 Filippi J, Allen PB, Hebuterne X, Peyrin-Biroulet L. **Does anti-TNF therapy reduce the requirement for surgery in ulcerative colitis? A systematic review.** Curr Drug Targets 2011; 12(10):1440-1447.

3 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.

4 Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J et al. **Clinical course in Crohn's disease: results of a Norwegian populatio**n-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007; 5(12):1430-1438.

5 Sands BE, Arsenault JE, Rosen MJ, Alsahli M, Bailen L, Banks P et al. **Risk of early surgery for Crohn's disease: implications for early treatment strategies.** Am J Gastroenterol 2003; 98(12):2712-2718.

6 Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J et al. **Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial.** Lancet 2012.

7 Hancock L, Windsor AC, Mortensen NJ. **Inflammatory bowel disease: the view of the surgeon.** Colorectal Dis 2006; 8 Suppl 1:10-14.

8 Soon IS, Wrobel I, deBruyn JC, Sauve R, Sigalet DL, Kaplan BS et al. **Postoperative complications following colectomy for ulcerative colitis in children.** J Pediatr Gastroenterol Nutr 2012; 54(6):763-768.

9 de SS, Ma C, Proulx MC, Crespin M, Kaplan BS, Hubbard J et al. **Postoperative complications and mortality following colectomy for ulcerative colitis.** Clin Gastroenterol Hepatol 2011; 9(11):972-980.

10 Loftus EV, Jr., Delgado DJ, Friedman HS, Sandborn WJ. **Colectomy and the incidence of postsurgical complications among ulcerative colitis patients with private health insurance in the United States.** Am J Gastroenterol 2008; 103(7):1737-1745.

11 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):205-213.

12 Masoomi H, Kang CY, Chen A, Mills S, Dolich MO, Carmichael JC et al. **Predictive factors of in-hospital mortality in colon and rectal surgery.** J Am Coll Surg 2012; 215(2):255-261.

13 Choban PS, Flancbaum L. **The impact of obesity on surgical outcomes: a review.** J Am Coll Surg 1997; 185(6):593-603.

14 Benoist S, Panis Y, Alves A, Valleur P. **Impact of obesity on surgical outcomes after colorectal resection.** Am J Surg 2000; 179(4):275-281.

15 Schwandner O, Farke S, Schiedeck TH, Bruch HP. **Laparoscopic colorectal surgery in obese and nonobese patients: do differences in body mass indices lead to different outcomes?** Surg Endosc 2004; 18(10):1452-1456.

16 Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB et al. **Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data.** Ann Rheum Dis 2006; 65(3):285-293.

17 Heuschen UA, Hinz U, Allemeyer EH, Autschbach F, Stern J, Lucas M et al. **Risk factors for ileoanal J pouch-related septic complications in ulcerative colitis and familial adenomatous polyposis.** Ann Surg 2002; 235(2):207-216.

18 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. **Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients.** Gastroenterology 2003; 125(2):320-327.

19 Hyde GM, Jewell DP, Kettlewell MG, Mortensen NJ. **Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications.** Dis Colon Rectum 2001; 44(10):1436-1440.

20 Yang Z, Wu Q, Wu K, Fan D. **Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis.** Aliment Pharmacol Ther 2010; 31(4):486-492.

21 Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C et al. **Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study.** Gastroenterology 2005; 128(7):1805-1811.

22 Schluender SJ, Ippoliti A, Dubinsky M, Vasiliauskas EA, Papadakis KA, Mei L et al. **Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis?** Dis Colon Rectum 2007; 50(11):1747-1753.

23 Bregnbak D, Mortensen C, Bendtsen F. **Infliximab and complications after colectomy in patients with ulcerative colitis.** J Crohns Colitis 2012; 6(3):281-286.

24 Burger D, Travis S. **Conventional medical management of inflammatory bowel disease.** Gastroenterology 2011; 140(6):1827-1837.

25 Randall J, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. **Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications.** Br J Surg 2010; 97(3):404-409.

26 Coakley BA, Telem D, Nguyen S, Dallas K, Divino CM. **Prolonged preoperative hospitalization correlates with worse outcomes after colectomy for acute fulminant ulcerative colitis.** Surgery 2012.

27 Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. **Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis.** Gastroenterology 2008; 134(3):680-687.

28 Travis SP, Stange EF, Lemann M, Oresland T, Bemelman WA, Chowers Y et al. **European evidence-based Consensus on the management of ulcerative colitis: Current management.** J Crohns Colitis 2008; 2(1):24-62.

29 Ferrante M, D'Hoore A, Vermeire S, Declerck S, Noman M, Van AG et al. **Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis.** Inflamm Bowel Dis 2009; 15(7):1062-1070.

30 Roberts SE, Williams JG, Yeates D, Goldacre MJ. **Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies.** BMJ 2007; 335(7628):1033.

31 Truelove SC, Witts LJ. **Cortisone in ulcerative colitis; final report on a therapeutic trial.** Br Med J 1955; 2(4947):1041-1048.

3

Alternative specimen extraction techniques after laparoscopic emergency colectomy in inflammatory bowel disease

Tjibbe J. Gardenbroek[1,2], Emma J. Eshuis[1,2], Gijs J.D. van Acker[3], Pieter J. Tanis[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands and [3]Department of Surgery, Medical Centre Haaglanden, The Hague, The Netherlands

Surgical Endoscopy 2012

ABSTRACT

Background

Omitting the extraction site incision potentially further decreases the abdominal wall trauma in laparoscopic surgery. The purpose of this study was to report the results of alternative specimen extraction techniques after laparoscopic emergency colectomy in patients with inflammatory bowel disease (IBD).

Methods

Ten consecutive patients with IBD underwent (sub)acute emergency colectomy for refractory disease from October 2009 until December 2010. The specimen was retrieved via the stoma site in three and transrectally in seven patients. Patient data were prospectively collected. In case of later completion proctectomy and pouch procedure, adhesions were systematically scored.

Results

The extraction techniques were all feasible. Median operative time was 219 minutes (interquartile range (IQR) 197-232). The pain scores and morphine requirement in patients decreased quickly after surgery. No infectious complications occurred. In 5 patients a completion proctectomy was done at a median time of 7 months (IQR 3.8-9.3) after colectomy. All patients showed absence of any adhesions in the pelvis. In 2 patients limited adhesions of the cut side of the mesentery was present.

Conclusions

Specimen extraction via the rectum or stoma site is a safe, alternative way to extract the specimen after laparoscopic colectomy. No infectious complications were observed postoperatively and no pelvic adhesions were found during completion proctectomy.

INTRODUCTION

Crohn's disease and (ulcerative) colitis are inflammatory bowel diseases (IBDs) that can affect the entire colon. Up to 75% of patients with Crohn's disease and approximately 10-30% of patients with ulcerative colitis will undergo surgery within the first decade after diagnosis[1-5].

Minimally invasive surgery (MIS) has been used in practically all colorectal procedures for both benign and malignant colorectal diseases[6;7]. Laparoscopic procedures have the advantages of a shorter postoperative stay, early return of bowel function, and decreased complications[6-8]. Still, in laparoscopic colorectal surgery, an abdominal incision is needed to remove the colonic specimen from the peritoneal cavity. This has led to the development of different techniques such as single incision laparoscopic surgery (SILS), natural orifice specimen extraction (NOSE), and natural orifice transluminal endoscopic surgery (NOTES). These techniques are designed to reduce abdominal wall trauma, thereby decreasing postoperative pain, improving cosmesis, and shortening of the recovery period[9-14].

This study was designed to report the feasibility and safety of two specimen extraction techniques without the need for an additional incision after laparoscopic (emergency) subtotal colectomy in patients with IBD refractory to medication and to report the intra-abdominal adhesions during completion proctectomy.

METHODS

All consecutive patients who underwent an acute or subacute laparoscopic subtotal colectomy for IBD colitis with a transrectal or stoma site specimen extraction technique from October 2009 until September 2010 were included. All patients consented before surgery. The insertion of additional ports and/or conversion to laparoscopy-assisted colectomy or laparotomy for reasons of patient safety was assured. Preoperative workup and patient preparation were conform the regular laparoscopic(-assisted) colectomy procedures, and bowel preparation was done in patients who had semi-acute surgery. An experienced laparoscopic surgeon performed all procedures. Patient data were prospectively collected and analysed retrospectively.

Surgical procedures

Laparoscopic subtotal colectomy with transrectal specimen extraction

Surgery was performed under general anaesthesia, and patients received intravenous antibiotic prophylaxis. Patients were placed in the French position, with the legs abducted. A four-trocar approach (subumbilical, 10 mm; right paramedian, 10 or 11 mm; suprapubic, 10 mm; left iliac fossa, 5 mm) and a 30° videoscope were used. A submesenterial window was created on the left side with identification and saving of the superior rectal artery

and ureter. From there, distal to proximal close pericolic dissection of the mesocolic and omental attachments of the colon with identification and transsection of the colic vessels was completed using ultrasonic dissection. The terminal ileum was transsected using a linear endoscopic stapler (EchelonTM 60 ENDOPATH® stapler; Ethicon Endo-Surgery, Cincinnati, Ohio, USA). At the level of the promontorium, the proximal rectum was transsected by using the linear endoscopic stapler.

The rectum was irrigated with Betadine to ensure complete removal of residual stool before opening the stapling line of the rectal stump. To facilitate transrectal specimen extraction, a wound protector (3M™, St. Paul, Minnesota, USA) was inserted through the opened rectum and the colectomy specimen was then extracted in total (*Figure 1*). After complete extraction of the colon, the rectal stump was closed by using another cartridge of the linear stapler. An end ileostomy was created at the right paramedian trocar site. The rectal stump was routinely drained for 5 days using a transanal catheter.

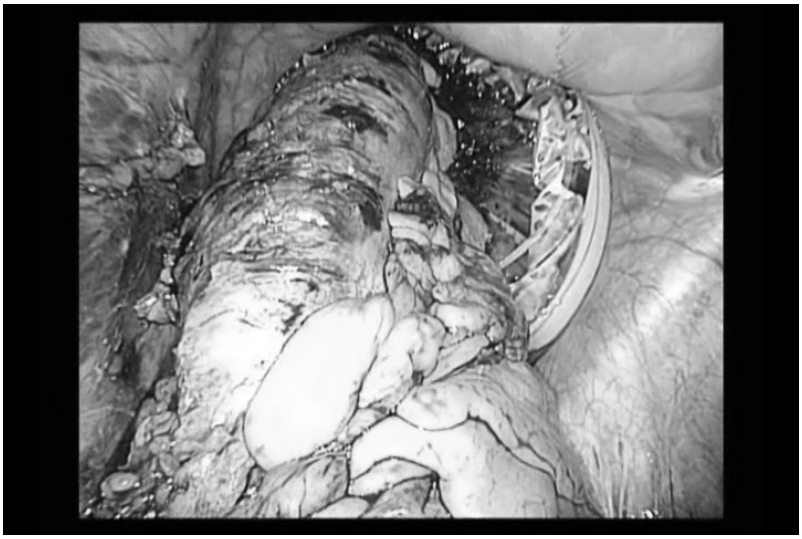


Figure 1 Transrectal extraction of the colectomy specimen through the transrectally inserted wound protector.

Stoma site extraction

The specimen can be extracted through the stoma site in 2 different types of procedures. For patients who require an end ileostomy, the procedure was conducted using the Single Site Laparoscopy Access System (SILS, Ethicon Endo-Surgery, Inc. Cincinnati, Ohio, USA). The port was positioned at the location of the future ileostomy site. The laparoscopic colectomy was conducted as described above. The extraction of the colectomy specimen through the single-port allowed proximal transsection of the terminal ileum to be per-

formed extracorporeally with a linear stapler (Echelon™ 60 ENDOPATH® stapler). After correctly orientating the terminal ileum, an end ileostomy was created (*Figure 2*).

For patients with a previously constructed end ileostomy, the ileostomy was closed using a linear stapler (Echelon™ 60 ENDOPATH® stapler) and was repositioned intra-abdominally. A balloon trocar was inserted in the ileostomy site and three additional trocars (subumbilical, suprapubic and left iliac fossa) were placed to perform the laparoscopic colectomy. After removal of the balloon trocar, a wound protector was placed at the ileostomy site, and the colonic specimen was extracted through the wound protector. The balloon trocar was then reinserted, and a side-to-end ileorectal anastomosis was performed laparoscopically using a double stapling technique.

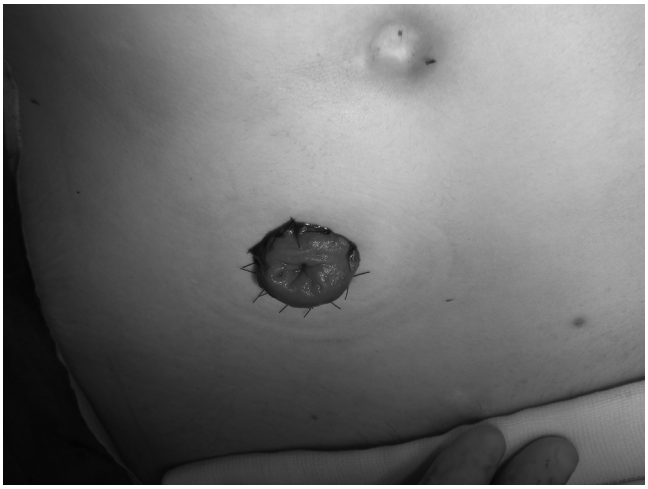


Figure 2 Cosmetic result after Single Port colectomy with an end ileostomy.

Outcome measures

The outcome measures were: feasibility of the specimen extraction techniques, operating time, reoperation rate (within 4 weeks after the operation), postoperative pain scores, morphine requirement, length of hospital stay, and postoperative complications (within 4 weeks after the operation). Postoperative pain was assessed by means of a visual analogue scale (VAS), where 0 represented no pain and 10 the worst pain imaginable. This VAS was measured at days 1 - 3 after the operation. Complications were defined as any deviation from a normal postoperative recovery, and graded according to the Clavien-Dindo Classification of Surgical Complications[15].

Furthermore, adhesions were systematically scored in patients undergoing a completion proctectomy and pouch procedure. They were graded as no adhesions, limited adhesions or numerous adhesions present and their locations were described (e.g. pelvic, cut side of the mesentery).

Statistical analysis

SPSS version 18.0 for Windows® (SPSS Inc, Chicago, Illinois) was used for statistical analysis. Results for continuous data were expressed as median (interquartile range; IQR).

RESULTS

Between October 2009 and December 2010, ten consecutive patients who underwent laparoscopic subtotal colectomy were included. Seven patients underwent transanal specimen extraction, and three patients underwent extraction of the colectomy specimen via the stoma site, of which two patients had the SILS technique. The study included four men and six women with a median age of 21.5 years (IQR 17.8-37). The median body mass index (BMI) was 21.5 kg/m^2 (iqr 18.4-23.1; *Table 1*).

Table 1 Patient characteristics

	n = 10
M:F ratio	2:3
Age (years)*	21.5 (17.8-37)
BMI*	21.5 (18.4-23.1)
Diagnosis	
- Ulcerative colitis	4
- IBD-U (undefined)	3
- Crohn's disease	3
Pre-operative medication	
- Steroids	2
- Biologicals	6
Disease duration (years)*	5.5 (3.1-12.3)

*median (interquartile range; iqr)

Clinical outcomes

Outcomes are summarized in *Table 2*. Previous abdominal surgery was performed in three patients; in two patients this was a laparoscopically created ileostomy, and in one patient a laparoscopic cholecystectomy.

Nine patients were operated in a subacute setting; one patient was operated in an acute setting. All patients had a medical refractory inflammatory bowel disease, two patients were preoperatively treated with high dose steroids, and six patients with biologicals. One patient developed a toxic colitis.

Table 2 Clinical outcomes

	n = 10
Operating time (minutes)*	219 (197-232)
Length of resected bowel (cm) *	93 (75.8-116.5)
Postoperative hospital stay*	7.5 (4-10.5)
Pain scores*†:	
- postoperative day 1	4.5 (2.0 – 6.3)
- postoperative day 2	4.5 (1.8 – 5.3)
- postoperative day 3	3 (1.0 – 4)
No of patients with PCA*	9
- morphine requirement day 1 (mg)	60 (30 – 95)
- morphine requirement day 2 (mg)	49 (0 – 50)
- morphine requirement day 3 (mg)	0 (0 – 0)
Complications Grade 1 or 2‡	2
- Ileostomy dysfunction	
Complications ffl Grade 3‡	0
Readmission within 30 days	0
Completion proctectomy and pouch procedure performed	5
Time between colectomy and completion proctectomy (months)*	7 (3.8-9.3)
Pelvic adhesions present	0

*median (interquartile range)
†derived from nursing records, on a scale from 1 (no pain) – 10 (worst pain)
‡according to the Clavien-Dindo scale

All colectomy specimen extraction techniques were feasible in the selected patients. One patient had a stool loaded colon that restricted transrectal specimen extraction; in this case, the liquid stool and air was drained via an incision of the externalised large bowel. Thereafter, the specimen could be extracted completely.

After surgery, two patients experienced dysfunction of the end ileostomy. This was treated with conservative measures; however it resulted in a prolonged hospital stay of 10 and 15 days, respectively. This complication was graded a Grade 1 complication according to the Clavien-Dindo scale. No infectious complications or reoperations were reported.

Postoperative pain scores and morphine requirement

The median pain score (VAS) was 4.5 on postoperative day 1 and decreased to score 3 on day 3. Correspondingly the morphine requirement decreased from 60 mg on day 1 to 0 mg on day 3 postoperatively.

Adhesions during completion proctectomy and pouch procedure

For 5 patients, a completion proctectomy with an ileo-anal pouch procedure was performed through a transverse suprapubic incision at a median time after colectomy of 7

months (IQR 3.8-9.3). All patients showed absence of any adhesions in the pelvis, around the small bowel or around the rectal stump. In two patients, adhesions of the cut side of the mesentery were present; these were scored as 'limited adhesions present' by the surgeon.

DISCUSSION

This study shows that the presented alternative extraction methods are technically feasible in patients undergoing laparoscopic emergency colectomy and are associated with a low morbidity rate and very limited adhesion formation at completion proctectomy in this small series.

Due to the transrectal specimen removal, the possibility of the development of intra-abdominal infections is present because of the prolonged time the staple-line is opened to facilitate specimen extraction. However, neither postoperative abscesses nor increased adhesion formation at the rectal stump during subsequent completion proctectomy were observed. Nearly all patients were on steroids or biologicals during surgery; however, we did not see any rectal stump related complications in patients undergoing transrectal specimen removal.

Although this study included only ten patients, it shows the feasibility of the extraction methods without peroperative complications. All patients in this series were in compromised clinical condition due to the colitis that failed to respond to medical therapy. For these patients especially, a minimally invasive approach is important in order to minimise surgical trauma and to prevent wound complications.

Many surgeons conduct laparoscopic-assisted colectomy or hand-assisted laparoscopic colectomy procedures (HALS)[16]. For colectomy specimen retrieval, mostly a periumbilical midline or transverse suprapubic (hand-port) incision is used. Wound infection rates of 0-16% and minilaparotomy hernia percentages of 0-6% are reported[16;17]. Thus, this might delay a patient's recovery and influence cosmesis. Different laparoscopic procedures are developed to avoid the minilaparotomy and its associated complications, mainly wound infection[9-14].

There are some limitations to the laparoscopic procedures[18]. It can be difficult to extract a specimen from an obese patient with thickened mesentery or a specimen full of faecal content. It is therefore important to tailor the appropriate procedure to the individual patient. In this study the patients were slim (median BMI 21.5) and had no malignant disease. Close pericolic dissection was therefore justified facilitating specimen removal via the rectum or via the ileostomy site. Apart from close colon resection, preoperative bowel preparation is important to reduce the diameter of the bowel enabling easier

extraction. In the acute setting, the bowel was generally empty or contained only fluid stools because of the colitis.

The single-port techniques require a larger incision than strictly necessary for the ileostomy increasing the likelihood of future parastomal hernia. This technique must be reserved for patients who will have a later completion proctectomy and pouch procedure, where the stoma site is closed eventually. In patients with Crohn's disease and high likelihood of permanent ileostomy, the colon is best removed transanally. Because the presented extraction techniques are still considered experimental, it is important that laparoscopic subtotal colectomy and extraction of the specimen via one of the alternative routes is conducted in an audit setting.

This study suggests that the transrectal and transstomal extraction techniques are feasible and safe for retrieval of the colectomy specimen after laparoscopic subtotal colectomy with low postoperative morbidity and few intra-abdominal adhesions. The foresights for these alternative extraction techniques are promising; however, the techniques still need refinement and are only applicable in selected patients.

REFERENCES

1 Hoie O, Wolters FL, Riis L, Bernklev T, Aamodt G, Clofent J et al. **Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years.** Gastroenterology 2007; 132(2):507-515.

2 Bernell O, Lapidus A, Hellers G. **Risk factors for surgery and postoperative recurrence in Crohn's disease.** Ann Surg 2000; 231(1):38-45.

3 Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. **Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease.** Gut 2001; 49(6):777-782.

4 Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R et al. **Long-term evolution of disease behavior of Crohn's disease.** Inflamm Bowel Dis 2002; 8(4):244-250.

5 Keswani RN, Cohen RD. **Postoperative management of ulcerative colitis and Crohn's disease.** Curr Gastroenterol Rep 2005; 7(6):492-499.

6 Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A et al. **Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis.** Arch Surg 2007; 142(3):298-303.

7 Laurent C, Leblanc F, Wutrich P, Scheffler M, Rullier E. **Laparoscopic versus open surgery for rectal cancer: long-term oncologic results.** Ann Surg 2009; 250(1):54-61.

8 Muhe E. **Long-term follow-up after laparoscopic cholecystectomy.** Endoscopy 1992; 24(9):754-758.

9 Gumbs AA, Fowler D, Milone L, Evanko JC, Ude AO, Stevens P et al. **Transvaginal natural orifice translumenal endoscopic surgery cholecystectomy: early evolution of the technique.** Ann Surg 2009; 249(6):908-912.

10 Rieger NA, Lam FF. **Single-incision laparoscopically assisted colectomy using standard laparoscopic instrumentation.** Surg Endosc 2010; 24(4):888-890.

11 Ostrowitz MB, Eschete D, Zemon H, DeNoto G. **Robotic-assisted single-incision right colectomy: early experience.** Int J Med Robot 2009; 5(4):465-470.

12 Eshuis EJ, Voermans RP, Stokkers PC, van Berge Henegouwen MI, Fockens P, Bemelman WA. **Laparoscopic resection with transcolonic specimen extraction for ileocaecal Crohn's disease.** Br J Surg 2010; 97(4):569-574.

13 Romanelli JR, Earle DB. **Single-port laparoscopic surgery: an overview.** Surg Endosc 2009; 23(7):1419-1427.

14 Palanivelu C, Rangarajan M, Jategaonkar PA, Anand NV. **An innovative technique for colorectal specimen retrieval: a new era of "natural orifice specimen extraction"** (N.O.S.E). Dis Colon Rectum 2008; 51(7):1120-1124.

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):205-213.

16 **Hand-assisted laparoscopic surgery vs standard laparoscopic surgery for colorectal disease: a prospective randomized trial.** HALS Study Group. Surg Endosc 2000; 14(10):896-901.

17 Hackert T, Uhl W, Buchler MW. **Specimen retrieval in laparoscopic colon surgery.** Dig Surg 2002; 19(6):502-506.

18 Tekkis PP, Senagore AJ, Delaney CP, Fazio VW. **Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections.** Ann Surg 2005; 242(1):83-91.

4

Close rectal dissection in ileal pouch-anal anastomosis, preliminary results of a randomized clinical trial

Sanne A. L. Bartels[1], Tjibbe J. Gardenbroek[1], Marielle Aarts[1], Cyriel Y. Ponsioen[2], Pieter J. Tanis[1], Christianne J. Buskens[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Submitted

ABSTRACT

Background

Posterior rectal dissection during IPAA can be performed in the TME plane or close rectal plane. Aim was to compare morbidity and quality of life in patients having total meso-rectal excision (TME) or close rectal dissection (CRD) during proctectomy followed by ileal pouch-anal anastomosis (IPAA) for benign disease.

Methods

In this randomized clinical trial, patients having an IPAA were randomized to TME or CRD. Thirty-day morbidity was classified according to Clavien-Dindo and quality of life (QoL) was assessed by SF-36, GIQLI and COREFO.

Results

Fifty-nine patients were included; 28 in the CRD group and 31 in the TME group. Baseline data were similar, except for more previous laparotomies in the TME group.. Operating time was longer in the CRD group (195 vs. 166 minutes, P = 0.008). More TME patients had a primary defunctioning ileostomy (23% vs. 4%, P = 0.055). In the TME group more severe complications occurred: grade IIIA: 5 vs. 0 patients and grade IIIB: 5 vs. 2 patients (P = 0.027). QoL life was better in the CRD group for several subscales of the questionnaires measured at 1, 3 and 6 months after surgery. At 12 months, QoL was similar in both groups on all subscales.

Conclusion

CRD led to a lower severe complication rate compared to TME.. Short-term QoL was better after CRD for several relevant subscales, but became similar at 12 months.

INTRODUCTION

Restorative proctocolectomy is the procedure of choice in patients with refractory ulcerative colitis and polyposis coli. The procedure can be performed as a one- or two stage procedure and with or without defunctioning of the ileoanal anastomosis. Both the rectal dissection and the pelvic reservoir reconstruction give rise to short and long-term morbidity such as anastomotic leakage, pouch dysfunction, pouchitis as well as retrograde ejaculation and erectile dysfunction due to nerve damage[1;2].

Different techniques can be applied to dissect the rectum. Most surgeons apply the total mesorectal excision (TME) technique, taking advantage of the avascular plane with easy and bloodless dissection. The disadvantage of this technique is the chance of damaging the autonomic nerves which lie immediately anterolateral from the mesorectal fascia. An alternative technique is the close rectal dissection (CRD), in which the rectum is dissected through the non-anatomic perimuscular plane close to the muscularis propria of the rectum. CRD is known to be an elaborate technique due to the non-anatomical dissection[3]. Nowadays, the technique has become less elaborate by the use of vessel sealing devices[4]. In the Academic Medical Centre (AMC) the TME technique is applied in restorative proctocolectomy with the exception that the anterolateral mesorectum is preserved, thereby staying far away from the nerves. Sexual dysfunction in men has therefore been a negligible problem[5].

The primary aim of this randomized clinical trial was to compare pouch compliance between CRD and TME. In this study, preliminary data on short term morbidity and quality of life up to one year is reported.

METHODS

Study Design and Participants

This single-blind randomized clinical trial was performed in a university hospital (Academic Medical Centre, Amsterdam) in the Netherlands. Patients over 18 with ASA classification I or II, being scheduled for single- or multiple stage IPAA in an elective setting were eligible for the study. Patients were included between June 2007 and August 2011. After written informed consent was obtained, patients were randomized in a 1:1 ratio using sealed, opaque, sequentially numbered envelopes using block-randomization with a block size of 6 and 8. All patients were blinded for the type of dissection during the entire study period. Medical staff was not blinded. The study protocol was approved by the IRB of the Academic Medical Centre and the trial and protocol summary were registered at ISRCTN (ISRCTN 35140084). The study protocol includes long-term pouch volume,

distensibility and continence measurements by Barostat. These results will be published at a later stage. Reporting of the data adheres to the CONSORT reporting guidelines.

Total Mesorectal Excision vs. Close Rectal Dissection

All single-stage procedures were done hand-assisted with pouch creation via a Pfannenstiel incision. In two-stage procedures, a midline incision or Pfannenstiel incision was used, depending on the approach (open or laparoscopic) of the emergency colectomy. A 10 cm J pouch was created with a double stapled ileoanal anastomosis. A defunctioning ileostomy was created selectively. All procedures were performed by three experienced colorectal surgeons. Of the 59 procedures, 49 were performed by surgeon A, 8 procedures by surgeon B (who initially trained surgeon A) and 2 procedures by surgeon C. All CRD procedures were performed by surgeon A. Of all procedures (both CRD and TME) 65% were performed by a colorectal fellow under supervision of surgeons A and B.

In both TME and CRD for benign disease, anterior rectal dissection is performed on the outer muscle layer of the distal rectum. The difference is in posterior rectal dissection. After ligation of the superior rectal artery, TME dissection was performed in the areolar avascular plane along the mesorectal fascia down to the pelvic floor. When using the CRD technique, the superior rectal artery was not ligated. The mesorectum was left in place and dissected in the nonanatomical perimuscular plane thereby preserving the mesorectal fat. The dissection was performed close to the muscular tube of the rectum using an ultrasonic device (Ultracision, Johnson and Johnson Medical, Inc., New Brunswick, NJ).

Outcomes

Primary outcome was long-term pouch compliance, determined by Barostat measurements. These results will be published at a later stage. Secondary outcomes were 30-day or in-hospital morbidity, quality of life (QoL) and pouch function in the first year after surgery. Complications were graded according to the Clavien-Dindo Classification of Surgical Complications[6]. If a patient had multiple complications, only the most severe complication was graded. Anastomotic leakage was defined as such if it was diagnosed by means of a CT-scan or during reintervention. QoL was assessed using the Short Form-36 (SF-36) and the gastrointestinal quality of life index (GIQLI) at baseline and at 1, 3, 6 and 12 months[7;8].

Pouch function was assessed using the COloRectal Functional Outcome (COREFO) questionnaire at similar intervals after surgery. The COREFO contains five scales: incontinence, social impact, defecation frequency, stool-related aspects (e.g. pain during bowel movements, blood loss), and use of medication[9]. Missing data is reported and no data imputation was performed. Sexual or urinary dysfunction was not separately enquired after. All

baseline data and data on 30-day or in-hospital morbidity were collected prospectively by the investigators using a case record form.

Statistical analysis

All analyses were carried out according to the intention-to-treat principle. Due to the lack of literature on Barostat measurement data on CRD for restorative proctocolectomy , a sample size calculation could not be made. The sample size of 30 patients in each arm was therefore chosen based upon clinical relevance as well as feasibility of this study within a certain time frame. Categorical data are presented as frequencies and percentages. Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to distribution. To compare dichotomous data the χ^2-test or Fisher's exact test were used. To compare means the independent t-test was used and the Mann-Whitney U test was used to compare skewed data. Morbidity graded by the Clavien-Dindo classification was compared using the χ^2-test for trend. All tests were two-sided and a P-value of <0.05 was deemed significant. Statistical analysis was performed using IBM SPSS Statistics for Windows®, Version 19.0 (IBM Corp., Armonk, NY, United States).

RESULTS

In this study 60 patients were randomly assigned to CRD or TME. A flow chart of patient inclusion and follow-up is shown in *Figure 1*. All patients received the allocated intervention. In one patient a rectal carcinoma was detected during surgery and was excluded from further analysis. Overall, 28 patients were included in the CRD group and 31 patients were included in the TME group. Baseline characteristics of these patients are shown in *Table 1*. *Table 2* shows the characteristics of the surgery. Eight patients had a primary defunctioning ileostomy. Decision on ileostomy in the CRD group was mostly related to poor general condition of the patient, while the indications in the TME group were: severe proctitis (3 patients), prednisone use > 20 mg/day, extensive additional surgery (abdominal wall reconstruction with biological mesh), handsewn anastomosis and an incomplete donut after stapling.

Morbidity and Hospital Stay

The 30-day morbidity and hospital stay are shown in *Table 3*. Significantly more severe (grade III) complications were seen in the TME group (P = 0.027). The overall 30-day anastomotic leakage rates were 2 (7.1%) in the CRD group and 6 (19.4%) in the TME group (P = 0.259). When comparing surgeons to fellows, no statistical difference was observed in anastomotic leakage rate (data not shown). The reasons for creating a secondary defunctioning ileostomy > 30 days after pouch construction in 4 patients were late presentations of anastomotic leakage or a high defecation frequency. Length of stay did not differ between groups.

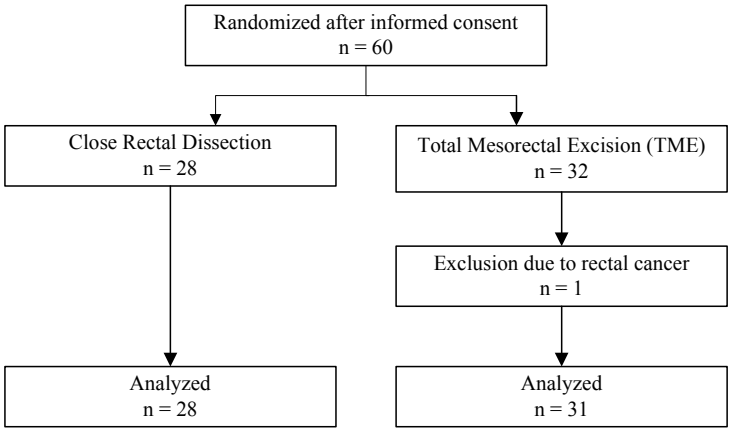


Figure 1 Participant flow chart

Table 1 Baseline characteristics of included patients

	Close Rectal Dissection n = 28	**Total Mesorectal Excision n = 31**
Male	19 (67.9%)	19 (61.3%)
Female	9 (32.1%)	12 (38.7%)
Age (years)	35.3 ± 13.3	34.9 ± 9.0
BMI (kg/ m^2)*	23.9 ± 3.3	24.5 ± 3.8
Smoking (yes)	5 (18%)	7 (23%)
Previous midline laparotomy	6 (21%)	16 (52%)
Indication IPAA		
Familial Adenomatous Polyposis	4 (14%)	2 (7%)
Ulcerative Colitis	23 (82%)	27 (87%)
IBD - U	1 (4%)	2 (7%)
Anti TNF use < 12 weeks before surgery	0	1 (3%)
Perioperative steroid use > 20 mg/day	5 (18%)	1 (3%)

*Data missing for 1 patient

Table 2 Characteristics of the procedure

	Close Rectal Dissection n = 28	Total Mesorectal Excision n = 31	*P*-value
Stages:			
Primary restorative proctocolectomy	13 (46%)	7 (23%)	
Completion proctectomy after IRA	1 (4%)	1 (3%)	
CP after emergency colectomy	14 (50%)	23 (74%)	
Incision type:			
Pfannenstiel	20 (71%)	12 (39%)	
Midline incision	8 (29%)	19 (61%)	
Operating time (minutes):	195 [169 - 292]	166 [146 - 185]	0.008 [A]
Primary RPC	293 [212 - 308]	264 [146 - 301]	0.311 [A]
Completion proctectomy	170 [153 - 199]	162 [147 - 175]	0.155 [A]
Primary defunctioning ileostomy	1 (4%)	7 (23%)	0.055 [B]
Secondary defunctioning ileostomy < 30 days *	1 (4%)	2 (6%)	
Secondary defunctioning ileostomy > 30 days **	1 (4%)	3 (10%)	
Ileostomy reversal at:			
3 months		3	
6 months	1	3	
12 months	1	2	
No ileostomy reversal or > 12 months***	1	4	

CP = completion proctectomy. IPAA = ileal pouch anal anastomosis

* Defunctioning ileostomy at postoperative days 8, 14 and 29.

** Defunctioning ileostomy at postoperative days 140, 155, 193 and 305.

*** In 3 patients ileostomy was not reversed due to persisting high defecation frequency in one patient (CRD group), persisting active proctitis in one patient and anastomotic leakage in one patient (both TME group)

A = Fisher's exact test. B = Chi² test. C = Mann-Whitney U test.

Quality of Life

At baseline the SF-36 and GIQLI response rates were 95% and 97% respectively. At 1, 3, 6 and 12 months after surgery the SF-36/GIQLI/COREFO response rates were 80/80/75%, 78/80/66%, 80/82/75% and 78/80/70%, respectively. Response rates of the COREFO were lower because of exclusion of patients with an ileostomy, in whom this questionnaire is not valid. Baseline measurements for the SF-36 and GIQLI showed no differences between the groups for any of the 8 scales. Details for the SF-36 scores 1 month after surgery are shown in *Figure 2*. At 1 month after surgery there was a significantly higher score on 2 subscales of the SF-36 ('bodily pain' and 'social functioning') in the CRD group. At 3, 6 and 12 months the results were similar in both groups. At 1, 3 and 6 months after surgery patients in the CRD group scored significantly better on several subscales of the GIQLI (*Figure 3*). At 12 months, all results were similar. The COREFO scores at 1 month after surgery were significantly better in the CRD group for the 'incontinence scale', the 'social impact scale',

Table 3 Thirty-day morbidity and hospital stay

	Close Rectal Dissection n = 28	Total Mesorectal Excision n = 31	*P*-value
Clavien Dindo classification:			0.027
No complications	20 (71.4%)	19 (61.3%)	
Grade I	4 (14.3%)	1 (3.2%)	
Grade II	2 (7.1%)	1 (3.2%)	
Grade III A	0 (-)	5 (16.1%)1	
Grade III B	2 (7.1%)2	5 (16.1%)3	
Grade IV / V	-	-	
Anastomotic leakage rate	2 (7.1%)	6 (19.4%)	0.259
Hospital stay:			
Primary hospital stay	8 [7 - 10]	7 [6 - 9]	0.137 [B]
Total hospital stay	9 [7 - 11]	9 [7 - 12]	0.988 [B]
Readmission rate <30 after release	3 (10.7)	12 (39%)	0.018 [C]

A = Chi2 for trend. B = Mann Whitney-U test. C = Fisher's exact test.
1 = Percutaneous drainage of an abscess (n = 4), anastomotic bleed requiring endoscopy of the pouch (n = 1).
2= Presacral abscess with a small anastomotic defect (n = 1) treated by endosponge treatment with early closure of the defect 16 and anastomotic leakage with an abscess (n = 1) for which a defunctioning ileostomy was created. 3 = Anastomotic leakage for which defunctioning ileostomy was created (n = 2), small bowel herniation necessitating laparotomy (n = 1), diagnostic laparoscopy because of a prolonged postoperative ileus (n = 1, no mechanic cause was observed) and suspected anastomotic leakage (n = 1)

the 'medication scale' and the total score (*Figure 4*). At 3 months after surgery the CRD group scored significantly better only on the 'incontinence scale' and at 6 months only on the total score. At 12 months all differences disappeared.

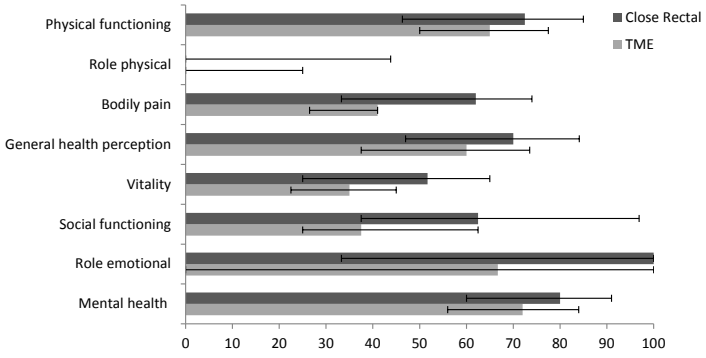


Figure 2 SF-36 results at 1 month after surgery
A higher score indicates a better quality of life.
* Significant difference between groups

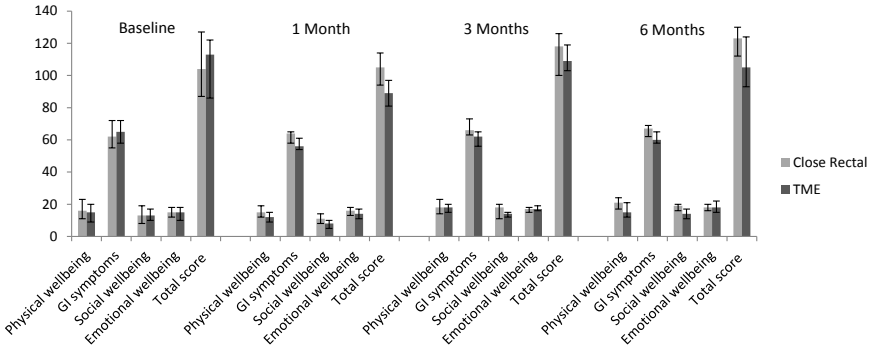


Figure 3 GIQLI scores at baseline and 1, 3 and 6 months after surgery.
A higher score indicates a better wellbeing.
* Significant difference between groups

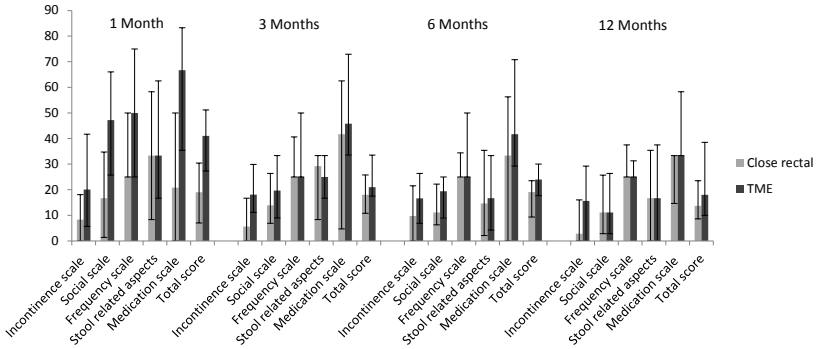


Figure 4 COREFO scores at 1, 3, 6 and 12 months after surgery.
A higher score indicates an increased level of continence disturbance.
* Significant difference between groups

DISCUSSION

The present study showed that CRD as opposed to TME dissection technique in patients having an ileal pouch anal anastomosis was associated with a lower rate of Clavien Dindo grade III complications. With respect to the QoL; SF-36, GIQLI and COREFO showed only short term differences on several subscales in favour of the CRD technique, but QoL became similar at 12 months.

A significant difference in the number of severe complications was found, possibly explained by the higher anastomotic leakage rate in the TME dissection group. This difference is difficult to explain, since more patients in the CRD group used > 20 mg steroids/day in the perioperative setting. It has been suggested that prior use of biologicals might be responsible for an increase in anastomotic leakage[11;12], however only one patient in the TME group used anti-TNF preoperatively. Furthermore, the difference in defunction-

ing ileostomy rate and anastomotic leakage in the TME group could not be explained by preferences or results of individual surgeons or fellows.

In the TME group the rate of primary defunctioning ileostomy was higher than that in the CRD group (23% versus 4%), which would favour a lower leak rate in the defunctioned group. In a meta-analysis Weston et al. showed that a defunctioning ileostomy decreased the leakage rate from 9.3 to 4.3%[13]. The incidence of the 30-day anastomotic leakage rate in the CRD group is in line with these results.

Explanations for the lower leakage rate of the CRD group might be the sealing of a small posterior defect and occlusion of the dead space behind the pouch preventing a presacral abscess, as was suggested by Rink et al as well[14]. By preserving the posterior mesorectum, complications related to a presacral cavity may be reduced. Abscesses formation behind the pouch may result in anastomotic disruption. One might argue that the omentum can be used to fill the cavity. Although that is true, it will often not fill the space immediately behind the anastomosis at the level of the pelvic floor. In case of leakage the pus and debris will push the omentum upward creating a presacral collection anyway. Proponents of the CRD technique argue that sexual and bladder function will be better preserved. A hypothetical argument against preservation of the mesorectum is that the newly constructed pouch needs space to dilate. It can also be speculated that by preserving the mesorectum and its nerves, proprioception might be different as opposed to removing the mesorectum, possibly resulting in a greater awareness of pouch filling.

It is our policy not to perform a routine ileostomy appreciating the added morbidity of the loop ileostomy and its closure. Leaks are aggressively treated with Endosponge therapy enabling a quick closure of the presacral space which possibly avoids the adverse outcome of chronic sepsis on the pouch function10

Operating time appeared different between both groups. However when divided in single or multiple stage procedures this was no longer significant. CRD is challenging, because of the limited exposure as a result of the preserved mesorectal fat, particularly if done via a Pfannenstiel.

A better QoL was observed in the CRD group on several subscales of the SF-36, GIQLI and COREFO at 1, 3 and 6 months after surgery. We hypothesized that the differences were related to the higher number of severe complications in the TME group. The consistent differences of the 'GI symptoms' scale of the GIQLI and the 'incontinence scale' of the COREFO suggest that patients in the TME group had mainly problems with functioning of the pouch. It is hard to find an explanation for this remarkable difference between the TME and CRD groups.

To date, this is the only study that has randomized patients having an IPAA between CRD and TME.

The major limitation of this study is the difference in baseline characteristics, which occurred despite the randomization. However, a study with a small sample size is more susceptible to baseline differences, due to a larger chance of sampling error[15]. It would have been more elegant if we had performed a randomization stratified for primary restorative proctocolectomy or completion proctectomy. Moreover it would have been insightful to have determined an ulcerative colitis disease activity index at the time of surgery. Unfortunately, it is not possible to objectively determine a disease index in retrospect. Surgeon A was the operating or supervising surgeon in the majority of the patients in this study. This might influence the external validation of the results, However, both techniques presented in this study will be performed in tertiary IBD referral centres by a limited amount of experienced surgeons.

One would expect patients having two-stage procedure to be less prone to complications. However, in the TME group, with the highest complication rate, 77% of patients had a completion proctectomy. Furthermore, in the CRD group more patients with polyposis were operated. These patients are generally less susceptible for postoperative complications due to the better preoperative condition compared to IBD patients. However, the small number of patients with polyposis in this study are not likely to influence the results.

Advocates of the CRD technique, as first described by Lee et al. in 1972[16], claim a better preservation of sexual function in men. In a retrospective study, Lindsey et al. found a similar rate of impotence in men having close rectal or mesorectal dissection for inflammatory bowel disease[3]. It would have been interesting to study sexual dysfunction in this series as well. .

In conclusion, CRD in IPAA led to a lower severe complication rate. Short-term QoL was better after CRD for several relevant subscales, but became similar at 12 months. Further and larger studies are needed to confirm these findings and long term results regarding the effect of CRD on pouch volume, distensibility and motility are to be awaited.

Acknowledgements

The authors thank Paul van Koperen and Malaika Vlug for their help with designing the trial and patient inclusion.

REFERENCES

1 Ahmed AU, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG et al. **Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis.** Cochrane Database Syst Rev 2009;(1):CD006267.

2 Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW et al. **Ileal pouch-anal anastomoses complications and function in 1005 patients.** Ann Surg 1995; **222**(2):120-127.

3 Lindsey I, George BD, Kettlewell MG, Mortensen NJ. **Impotence after mesorectal and close rectal dissection for inflammatory bowel disease.** Dis Colon Rectum 2001; **44**(6):831-835.

4 de ZS, Ahmed AU, van der Kolk MB, van Laarhoven KC. **Ileal pouch anal anastomosis with close rectal dissection using automated vessel sealers for ulcerative colitis: a promising alternative.** Dig Surg 2011; **28**(5-6):345-351.

5 van DP, Slors JF, Taat CW, van Lochem LT, Bonsel GJ, de Vries JW et al. **What is the benefit of preoperative sperm preservation for patients who undergo restorative proctocolectomy for benign diseases?** Dis Colon Rectum 2000; **43**(6):838-842.

6 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):205-213.

7 Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. **Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations.** J Clin Epidemiol 1998; **51**(11):1055-1068.

8 Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E et al. **Gastrointestinal Quality of Life Index: development, validation and application of a new instrument.** Br J Surg 1995; **82**(2):216-222.

9 Bakx R, Sprangers MA, Oort FJ, van Tets WF, Bemelman WA, Slors JF et al. **Development and validation of a colorectal functional outcome questionnaire.** Int J Colorectal Dis 2005; **20**(2):126-136.

10 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.

11 Eshuis EJ, Al Saady RL, Stokkers PC, Ponsioen CY, Tanis PJ, Bemelman WA. **Previous infliximab therapy and postoperative complications after proctocolectomy with ileum pouch anal anastomosis.** J Crohns Colitis 2013; **7**(2):142-149.

12 Kopylov U, Ben-Horin S, Zmora O, Eliakim R, Katz LH. **Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis.** Inflamm Bowel Dis 2012; **18**(12):2404-2413.

13 Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJ et al. **Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy.** Arch Surg 2008; **143**(4):406-412.

14 Rink AD, Radinski I, Vestweber KH. **Does mesorectal preservation protect the ileoanal anastomosis after restorative proctocolectomy?** J Gastrointest Surg 2009; **13**(1):120-128.

15 Roberts C, Torgerson DJ. **Understanding controlled trials: baseline imbalance in randomised controlled trials.** BMJ 1999; **319**(7203):185.

16 Lee EC, Dowling BL. **Perimuscular excision of the rectum for Crohn's disease and ulcerative colitis. A conservation technique.** Br J Surg 1972; **59**(1):29-32.

5

Primary defunctioning of the ileoanal pouch results in poorer long-term functional outcome

Tjibbe J. Gardenbroek[1], Christianne J. Buskens[1], Pieter J. Tanis[1], Cyriel Y. Ponsioen[2], Geert R.A.M. D'Haens[2] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Submitted

ABSTRACT

Background

Protecting the ileal pouch–anal anastomosis (IPAA) with a defunctioning ileostomy is done by most surgeons. However, defunctioning of the IPAA may influence pouch function. This study compared postoperative complications, pouch leakage rates, failure rates, functional outcomes and quality of life and in patients who had an IPAA with or without a defunctioning ileostomy.

Methods

All consecutive patients who underwent IPAA for ulcerative colitis or familial adenomatous polyposis between January 1999 and February 2010 were included. Patients with a primary defunctioning ileostomy after IPAA (IPAA-S group) were compared to patients without a primary defunctioning ileostomy (IPAA-NS group). Demographic data, surgical characteristics and the development of pouch leakage and pouch failure were collected from medical charts. Functional outcome and QoL was assessed prospectively by validated questionnaires.

Results

Seventy-one patients were included in the IPAA-S group and 220 patients in the IPAA-NS group. The IPAA leakage rate was comparable (10.5 vs 7%, P = 0.492), no difference in overall postoperative complications or pouch failure was found. The IPAA-S group scored significantly poorer on incontinence and social impact scores (P <0.05). Multivariable logistic regression analysis showed that treatment in the IPAA-S group was a predictive factor for protective pad use (OR 2.7, 95% CI 1.086-6.724). Predictive factors for taking constipating medication were treatment in the IPAA-S group (OR 2.28, 95% CI 1.136-4.606) and the occurrence of pouchitis (OR 2.240, 95% CI 1.191-4.916) .

Conclusion

Primary defunctioning of an IPAA does not result in a lower leakage rate, overall postoperative complications or decreased pouch failure rates. It results in a higher rate of continence disturbances and impaired social functioning scores at long term follow up compared to patients with an IPAA without primary defunctioning ileostomy. Construction of a defunctioning ileostomy after IPAA should be a patient-tailored decision instead of standard practice.

INTRODUCTION

Ileal pouch–anal anastomosis (IPAA) is the procedure of choice in restorative proctocolectomy (RPC) for patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP) [1]. The J-pouch configuration is most commonly used for IPAA. Alternatives are the S-, W-, and K-pouch configurations [2-4]. The systematic review published by Lovegrove *et al.* indicated that the J-pouch is the most optimal configuration [5]. The pouch-anal anastomosis is preferably double stapled to preserve a small rim of rectal mucosa for better continence as opposed to mucosectomy and hand-sewn anastomosis [6].

After construction of an IPAA, the pouch can be defunctioned by the creation of an ileostomy, thereby adding another stage to the procedure. This primary defunctioning is advocated as standard procedure by most surgical groups to diminish postoperative septic complications that could result in long-term compromise of pouch function. Others choose to defunction selectively to avoid excess short- and long-term morbidity of stoma creation and closure [7-11]. A meta-analysis suggested that, while the incidence of anastomotic leak (treated surgically or conservatively) was higher when a stoma was omitted, pouch related sepsis and functional outcomes did not differ between the groups. However, a higher incidence of pouch failure was seen in the stoma group [12]. It can be hypothesised that pouch function might be better if the pouch is in function directly after surgery before presacral fixation of the pouch prevents the pouch to mature. The aim of this study was to evaluate pouch leakage rates, long-term pouch failure rates, functional outcomes and quality of life in patients treated with a primary defunctioned pouch compared to patients without primary defunctioning after IPAA.

METHODS

All consecutive patients that underwent RPC and IPAA for UC or FAP from January 1999 to February 2010 were included. The medical charts of these patients were reviewed and demographic data, surgical characteristics, surgical morbidity and the development of pouch failure were collected. Furthermore, functional outcome and general quality of life was assessed prospectively by questionnaires in all patients with a functional pouch in situ for more than one year. The Ethics Committee of the Amsterdam Medical Centre approved this study.

Outcome measures

Surgical outcomes collected were anastomotic leakages, postoperative complications, reoperations, number of ileostomies created, total number of ileostomies, ileostomies

closed, and pouch failure. Furthermore, functional outcomes and quality of life scores were assessed.

Anastomotic leakages were classified according to their management; Grade A: no change in patients' management, Grade B: leakage requires active therapeutic intervention but is manageable without re-laparotomy/re-laparoscopy, Grade C: leakage requires re-laparotomy/re-laparoscopy [13]. Postoperative complications were defined as any deviation from the normal postoperative course within 30 days after IPAA creation. The number of complications were graded according to the Clavien-Dindo Classification of Surgical Complications [14].This scale grades complications based on their management. If a patient had more than one complication, only the most severe complication was graded. Reoperations were defined as subsequent surgery due to complications after RPC (owing to anastomotic leakage, abdominal sepsis and fistula) and other surgery (including operations for bowel obstruction, incisional and parastomal herniation). Pouch failure was defined as pouch excision or indefinite proximal diversion.

Patients were classified as having pouchitis if the gastroenterologist or surgeon started antibiotic therapy in the presence of clinical findings and/or endoscopic findings compatible with the diagnosis of pouchitis. Patients were classified in three groups: one episode of pouchitis, multiple episodes, or chronic pouchitis.

Functional results and quality of life data after surgery were analysed using the validated Vaizey, COloREctal Functional Outcome (COREFO) and Short Form health survey (SF-36) questionnaires [15-18]. For this purpose, we undertook a postal survey. Patients were sent an invitation to participate in the study, together with information about the study and the questionnaires. Patients who did not respond initially were contacted by telephone to ensure return of the questionnaires.

The Vaizey questionnaire consists of items on type and frequency of incontinence, and on the use of pads or plugs, constipation medication, and the lack of ability to postpone defecation for 15 minutes. The total Vaizey score ranges from 0 (complete continence) to 24 (complete incontinence), with incontinence and social impact subscale scores from 0–12. In the COREFO questionnaire, the functional outcome is assessed in five categories: incontinence, social impact, defecation frequency, stool-related aspects (e.g. pain during bowel movements, blood loss), and use of medication. The five category scores and the total score are transformed to a scale from 0 to 100. A higher score represents an increased level of continence disturbance. The SF-36 includes eight general health dimensions: physical functioning, role limitations due to physical health problems, role limitations due to personal or emotional problems, bodily pain, vitality (energy and fatigue), social functioning, mental health and general health perception. For each dimension, item scores are transformed to a scale from 0 (worst health) to 100 (best health).

Pouch surgery

Colectomy was performed by an open, hand-assisted laparoscopic or total laparoscopic approach. The pouch was created during initial proctocolectomy, or at the time of completion proctectomy in a two- stage procedure. The IPAA was not routinely defunctioned. Creation of a defunctioning ileostomy was at the discretion of the surgeon. An IPAA with defunctioning ileostomy was created in patients regarded to be at risk for anastomotic failure. Important indications were: systemic prednisolone-equivalent corticoid medication of 20 mg/ day, severe proctitis, mucosectomy with a handsewn anastomosis, an incomplete 'doughnut' after stapling or stapling misfire. Patients developing anastomotic leakage postoperatively were defunctioned immediately if not done so primarily, thereby adding one stage to the procedure for closure. The surgical technique of IPAA creation and anastomosis has been described previously [19]. In summary, the rectum was removed according to the total mesorectal or close rectal dissection technique preceded by colectomy. Subsequently, the pouch was created with either a single TLC-75 mm or TLC-100 mm stapler cartridge (Ethicon Endo-Surgery, Inc., Cincinnati, OH). When a TLC-75 was used the efferent loop was reanastomosed with the afferent loop creating a 10 cm B shaped reservoir. The B shaped reservoir was done in the time period that the TLC-100 was not available yet. The ileo-anal anastomosis was performed either using a 29 mm circular stapler or hand-sewn using interrupted sutures in case of anal mucosecomy.

Statistical analysis

Patients with a primary defunctioning ileostomy after IPAA were included in the IPAA-S group, patients without a primary defunctioning ileostomy after IPAA were included in the IPAA-NS group. Outcomes were compared based on an 'intention-to-treat' analysis. Therefore, in patients where an ileostomy was created due to post-operative complications (e.g. in case of anastomotic leakage) were included in the IPAA-NS group. To evaluate the effect of pouch leakage on pouch function, the functional outcomes and quality of life of patients with an anastomotic leak were included in the IPAA-C group for separate analysis.

Descriptive data are reported as median with inter quartile range (iqr). Categorical data were analysed with Fisher's exact test or χ^2 test. Continuous variables were analysed using the Mann-Whitney-Wilcoxon test. Outcomes of the long-term functional outcome and quality of life questionnaires were analysed accordingly or with t-test depending in distribution after linear transformation. Multivariable logistic regression was used to determine possible factors prognostic for pad use. In this regression the indication for surgery, preoperative steroid use, anastomosis type, treatment (IPAA-S or IPAA-NS), pouch leakage, and the occurrence of pouchitis (one/multiple episodes or chronic) were included. Results are shown as odds ratio's (OR) and 95%-confidence intervals (CI). $P < 0.05$

was considered statistically significant. IBM SPSS Statistics for Windows®, version 19.0. (IBM Corp., Armonk, NY, United States) was used for statistical analysis.

RESULTS

A total of 291 patients were identified. *Figure 1* shows the study profile. In 71 patients the IPAA was created with a defunctioning ileostomy (IPAA-S group), in 220 patients the IPAA was created without defunctioning ileostomy (IPAA-NS group). The sex, age and body mass index both patient groups were not significantly different. In the IPAA-S group 91.5% of the patients were diagnosed with UC or IBD-unknown, compared to IPAA-NS group 72.8% (P = 0.003, *Table 1*).

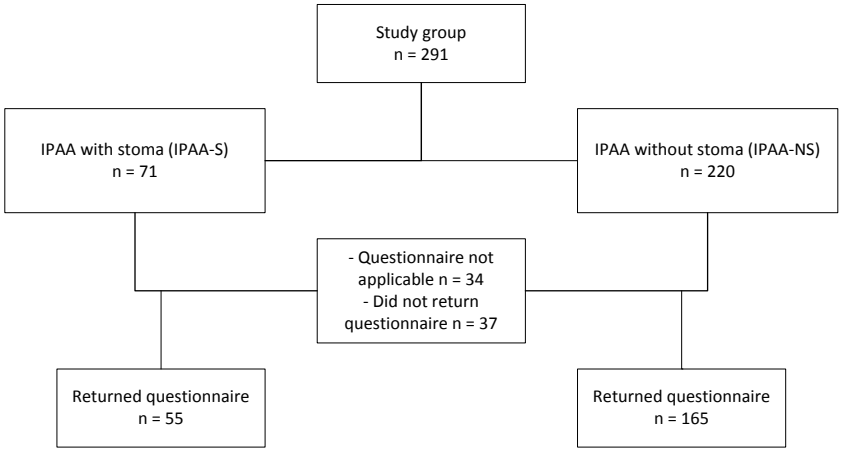


Figure 1 Study profile

Table 1 Patient characteristics

	IPAA-S n = 71	IPAA-NS n = 220	p-value
Sex (M)	43 (60.6)	109 (49.5)	0.133[¶]
Age at surgery (years)	40 ± 12.3	37 ± 12.8	0.053[†]
BMI (kg/m^2)	24.8 ± 4.9	24.1 ± 4	0.481[†]
Diagnosis			0.003[§]
UC	62 (87.3)	148 (67.3)	
FAP	6 (8.5)	60 (27.3)	
IBDU	3 (4.2)	12 (5.5)	
Indication for surgery			<0.000[§]
Refractory UC	62 (87.3)	138 (62.7)	
Dysplasia / carcinoma	6 (8.5)	39 (17.7)	
Preventive	3 (4.2)	43 (19.5)	

Table 1 (Continued)

	IPAA-S n = 71	IPAA-NS n = 220	p-value
Preoperative steroid usage (>20mg/day)*	12 (16.9)	18 (8.2)	0.044[¶]
Colectomy procedure			0.109[§]
Open	45 (63.4)	113 (51.4)	
Total laparoscopic	23 (32.4)	83 (37.7)	
Hand-assisted laparoscopic	3 (4.2)	24 (10.9)	
Stage of pouch procedure			<0.001[§]
One stage	0	131 (59.5)	
Two stage	51 (71.8)	88 (40.0)	
Three stage	23 (28.2)	1 (0.5)	
Pouch type			0.027[¶]
J-pouch	57 (80.3)	146 (66.4)	
B-pouch	14 (19.7)	74 (33.6)	
Stapled ileo-anal anastomosis	64 (90.1)	209 (95)	0.158[¶]
Follow-up (months)**	68 [48-89]	76 [39-108]	0.318[†]

Data are presented as mean ± SD and median [IQR] or *n* (%). [§]Chi-square test / [¶]Fisher's exact Test / [†]Mann Whitney U test. UC = ulcerative colitis. FAP = familial adenomatous polyposis, IBDU = Inflammatory bowel disease unknown. * Missing data: 13 (4.5). ** Time between construction of the IPAA and returning the questionnaires (*n* = 77 and *n* = 143 respectively)

Surgical outcomes

Twenty-eight of 291 patients (9.6%) developed an anastomotic leakage; five patients in the IPAA-S (7%) and 23 patients (10.5%) in the IPAA-NS group (*Table 2*, P = 0.492). These were Grade B leakages in 1 patient in both groups and Grade C leakages in 4 vs 22 patients, respectively. A reoperation for other reasons than anastomotic leakage within 30 days was performed in 6 (8.5%) patients in the IPAA-S compared to 8 (3.6%) patients in the IPAA-NS (P = 0.114).

Overall complications graded according to the Clavien-Dindo classification did not differ between groups (*Table 3*, P = 0.172), although there were more Grade II complications in the IPAA-S group (P = 0.011). There were no perioperative mortalities.

In the IPAA-S group the ileostomy was reversed after a median of 3 months (iqr 2-4). In the 28 patients with an anastomotic leak, the ileostomy was reversed after a median of 6.5 months (iqr 3.8-13).

There was no difference in the prevalence of one or more episodes of pouchitis or chronic pouchitis between both groups (P > 0.05). Pouch failure occurred in 6 patients (8.5%) in the IPAA-S group versus 14 patients (6.4%) in the IPAA-NS group. Indefinite proximal diversion was done in 4 patients (5.6%) versus 6 patients (2.7%) , pouch excision had to be performed in 2 (2.8%) versus 8 (3.6%) patients, respectively (P > 0.5).

Table 2 Surgical characteristics

	IPAA-S n = 71	IPAA-NS n = 220	p-value
Anastomotic leakage	5 (7)	23 (10.5)	>0.05¶
Grade A	0	0	
Grade B	1 (1.4)	1 (0.5)	
Grade C	4 (5.6)	22 (10)	
Reoperation due to complications†	6 (8.5)	8 (3.6)	0.114¶
RPC related laparotomy	2 (2.8)	3 (1.4)	
Other surgery	4 (5.6)	5 (2.5)	
Total number of secondary ileostomies created‡	-	31 (14.1)	
Pouchitis			>0.05¶
One episode	7 (9.9)	14 (6.4)	
Multiple episodes	1 (1.4)	3 (1.4)	
Chronic pouchitis	17 (23.9)	30 (13.6)	
Long term pouch failure			
Indefinite proximal diversion	4 (5.6)	6 (2.7)	0.265¶
Pouch excision	2 (2.8)	8 (3.6)	1.000¶

Data are presented as median [IQR] or *n* (%). §Chi-square test / ¶Fisher's exact test (two-tailed)
Anastomotic leakages were classified as Grade A: no change in patients' management, Grade B: leakage requires active therapeutic intervention but is manageable without re-laparotomy/re-laparoscopy, Grade C: leakage requires re-laparotomy/re-laparoscopy
†RPC related reasons for reoperation within 30 days (other than anastomotic leakage) in the IPAA-S group were; abscess drainage (n = 2), in the IPAA-NS group these were; abscess drainage (n = 1), luxation of pouch drain through pouch (n = 1), pouch-vaginal fistula (n = 1). Other reasons for reoperation in the IPAA-S group were correction of ileostomy (n = 3), adhaesiolysis (n = 1), in the IPAA-NS group these were adhaesiolysis (n = 2) fascia dehiscence (n = 1), pouch retention (n = 1) luxation of small bowel through omentum majus (n = 1).
‡Ileostomy created at any time after IPAA creation due to pouch leakage (n = 23), abscess drainage (n = 2), adhaesiolysis (n = 1), pouch retention (n = 1), luxation of pouch drain through pouch (n = 1), pouch-vaginal fistula (n = 2), high defecation frequency (n = 1).

Functional outcomes

In 34 of 291 patients the questionnaires were not applicable; 20 patients (6.9%) had either pouch excision or indefinite proximal diversion and 14 patients (4.8%) died in the period between pouch procedure and the questionnaires (*Figure 1*). Of the 257 patients, 220 patients (86%) returned the questionnaires; 55 patients in the IPAA-S group and 165 patients in the IPAA-NS group. The response rate did not differ between the two groups (P = 0.725). Median follow up period (time between construction of the IPAA and returning the questionnaires) for the entire study population was 68 months (iqr 39-101).

The social impact subscore of the Vaizey score (*Figure 2*) was significantly higher in the IPAA-S group compared to the IPAA-NS group (P = 0.045), indicating more disturbance. The outcomes of the COREFO questionnaire are shown in *Figure 3*. The IPAA-S group had a significantly poorer score on the incontinence subscore (P = 0.011) and the medication subscore (P = 0.010) compared to the IPAA-NS group.

Table 3 Complications within 30 days graded according to Clavien-Dindo classification

Clavien-Dindo classification	IPAA-S n = 71	IPAA-NS n = 220	p-value
Grade I	5 (7.0)	8 (3.6)	
Grade II	7 (9.9)	5 (2.3)	0.011
Grade IIIa	7 (9.9)	15 (6.8)	
Grade IIIb	7 (9.9)	29 (13.2)	
Grade IV	0	0	
Grade V	0	0	

Grade I: Any deviation from the normal postoperative course without the need for treatment. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Included are blood-transfusion and total parenteral nutrition
Grade IIIa: Requiring surgical, endoscopic or radiological intervention without general anaesthesia
Grade IIIb: Requiring surgical, endoscopic or radiological intervention with general anaesthesia
Grade IV: Life-threatening complication requiring IC/ICU management
Grade V: Death of a patient
No difference in overall complications between groups was found, P = 0.172. A significant difference in complications Grade II between IPAA-S and IPAA-NS groups was found, P = 0.011). For all other complications P >0.05.

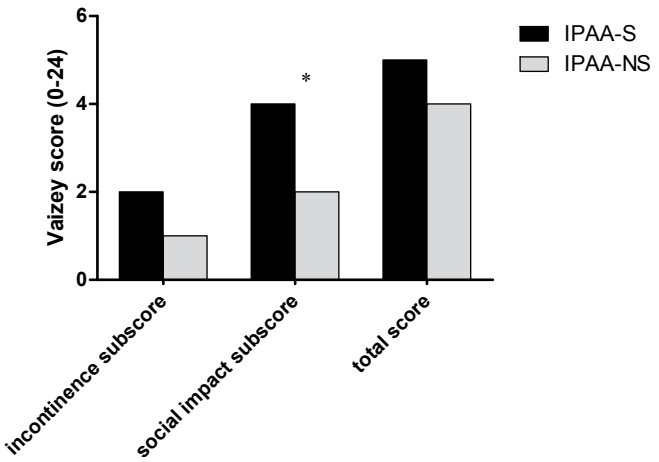


Figure 2 Vaizey scores
The total Vaizey score ranges from 0 (complete continence) to 24 (complete incontinence), with incontinence and social impact subscale scores from 0–12
IPAA-NS: patients without a primary defunctioning ileostomy after IPAA. IPAA-S: patients with a primary defunctioning ileostomy after IPAA. * = significant difference P < 0.05.

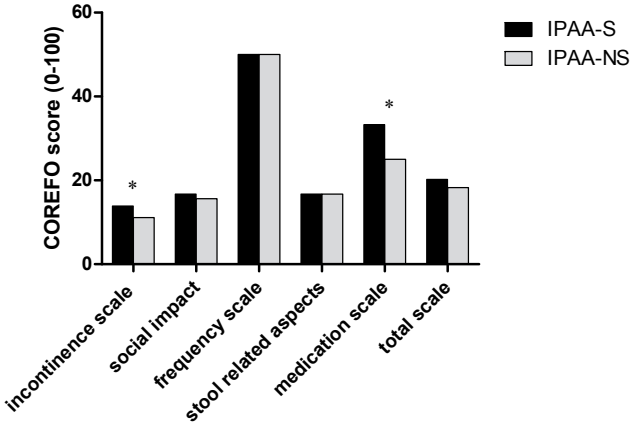


Figure 3 COREFO score
COREFO score: a higher score represents an increased level of continence disturbance. IPAA-NS: patients without a primary defunctioning ileostomy after IPAA. IPAA-S: patients with a primary defunctioning ileostomy after IPAA. * = significant difference P < 0.05.

No correlation between time to ileostomy reversal and better Vaizey or COREFO scores could be demonstrated.

In the IPAA-S group 13 patients (23.6%) used protective pads, compared to 17 patients (10.3%) in the IPAA-NS group (P = 0.021). For patients in the IPAA-S group, the OR for protective pad use was 2.69 (95% CI 1.10-6.41) compared to patients in the IPAA-NS group.

Constipating medication was taken by 34 patients (61.8%) in the IPAA-S group versus 60 patients (36.6%) in the IPAA-NS group (P = 0.002). For patients in the IPAA-S group, the OR for taking constipating medication was 2.81 (95% CI 1.43-5.56) compared to patients in the IPAA-NS group. No differences in daily or nightly stool frequency between the study groups were found.

Multivariable logistic regression analysis showed that treatment in the IPAA-S group was a predictive factor for protective pad use (OR 2.7, 95% CI 1.086-6.724). Predictive factors for taking constipating medication were treatment in the IPAA-S group (OR 2.28, 95% CI 1.136-4.606) and the occurrence of pouchitis (OR 2.240, 95% CI 1.191-4.916).

Quality of life

The groups did not differ in the eight general health dimensions of the SF-36 (P > 0.05). Vitality (energy and fatigue) and general health perception were scored the lowest compared to other dimensions in both groups (*Figure 4*).

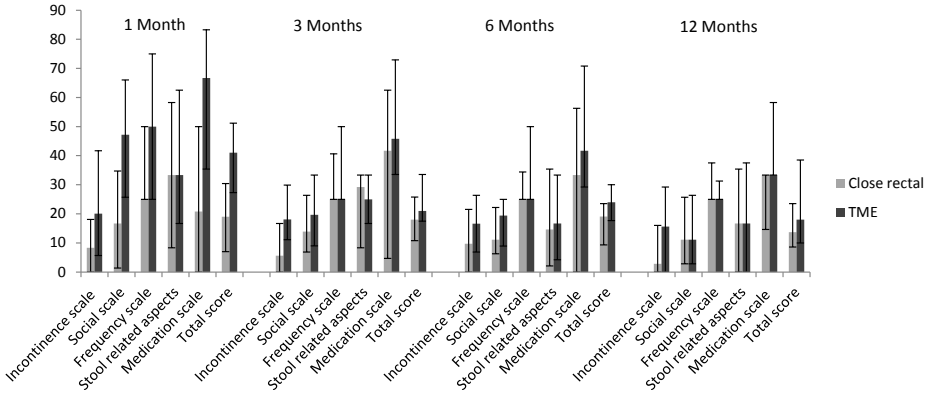


Figure 4 SF-36 score
The SF-36 score ranges from 0 (worst health) to 100 (best health). IPAA-NS: patients without a primary defunctioning ileostomy after IPAA. IPAA-S: patients with a primary defunctioning ileostomy after IPAA. For all differences P > 0.05. PF: physical functioning, RP: role physical, BP: bodily pain, SF: social functioning, MH: mental health, RE: role emotional, V: vitality, GHP: general health perceptions.

Functional outcomes and quality of life after anastomotic leakage

The functional outcomes of patients in the IPAA-C were separately analysed and compared with patients without anastomotic leakage in the IPAA-S group. The IPAA-C group had a significantly worse score on the CORFEO frequency subscale, for all other COREFO subscales and the Vaizey scores no significant differences were found. The number of patients using protective pads in the IPAA-C group was 10.5%. The number of patients taking constipating medication in the IPAA-C group was 44.4%. Furthermore, no differences in the SF-36 scores between the groups were found.

DISCUSSION

This study shows that primary defunctioning of an IPAA does not result in a lower leakage rate, overall postoperative complications or decreased pouch failure rates. It results in a higher rate of continence disturbances, indicated by more protective pad use, increased use of constipating medication, and impaired social functioning scores at long term follow up compared to patients with an IPAA without primary defunctioning ileostomy.

For this study, the functional outcomes and quality of life were assessed by validated questionnaires (Vaizey, COREFO and SF 36) [15-18]. Only patients in whom the pouch was functional for at least one year were included, as it is generally accepted that pouch function does not evolve any longer after one year. It is known that health related quality of life and health status improves in 12 months' time after restorative proctocolectomy

and becomes indistinguishable from the normal healthy population [20;21]. In our hospital, a pouch of approximately 10 cm is created. This is smaller than the J-pouches often created in other centres, which have a length of approximately 15 cm [22;23]. The smaller pouches created in our centre have similar quality of life and continence outcomes compared to the larger pouches [24-29]. Furthermore, almost all patients (92.8%) in our hospital undergo stapled anastomosis. This is suggested to be associated with a decrease risk on complications associated with omission of diversion .

The results of this study corroborate with the findings of earlier clinical studies that showed that omission of defunctioning ileostomy after IPAA in selected patients does not increase septic complication and pouch failure rates [8]. Patients with an ileostomy due to postoperative complications after IPAA are expected to have deteriorated function compared to IPAA patients with a primary defunctioning ileostomy, although the metanalysis by Weston-Petrides suggested that functional outcomes are equal in both groups [12;30]. This study confirms these findings, as the functional outcomes between patients with an anastomotic leak (IPAA-C) were comparable to patients with a primary defunctioning ileostomy without complications.

A possible explanation for the poorer functional outcomes in patients with a defunctioning ileostomy after IPAA compared to patients without defunctioning ileostomy can be the potential deterioration of anal sphincter function after (long-term) faecal deviation. Furthermore, it can be hypothesised that a defunctioned IPAA will be hampered in maturation due to fixation in the presacral space and will be more non-compliant compared to non-defunctioned IPAA's. Finally, it has been demonstrated that anastomotic strictures at the level of the pouch-anal anastomosis are more frequent in patients with a defunctioning ileostomy [12]. This can potentially contribute to worse functional outcomes.

The strength of this study is the use of different questionnaires and the long follow-up period in both patient groups. This study was a non-randomised, single centre study from a tertiary referral centre in the Netherlands, and has therefore potential biases that could influence the results. The largest drawback is the fact that the creation of a defunctioning ileostomy was at the discretion of the surgeon. It could be hypothesized that this group therefore represents patients more at risk of leakage (and therefore worse outcome). However, the 7% leakage rate found in this group compares favourably to the literature and the functional results of patients after anastomotic complications was not significantly different from the IPAA-S group. This study is furthermore limited by the partially retrospective design. Although it is known that the risk on pouchitis increases over time and could therefore still be underestimated in both groups, it is unlikely that with longer FU, significant differences will develop in both groups that could influence functional outcomes.

This study shows that defunctioning of the pouch will not prevent pouch leakage, overall postoperative complications and failure rates. Furthermore, primary defunctioning of

the IPAA is associated with disturbances in continence. Moreover, functional outcomes and quality of life of IPAA patients with anastomotic complications are comparable to IPAA patients with a primary defunctioning ileostomy. Therefore, we believe that creation of a protective ileostomy in all patients as standard procedure should be avoided. This will also prevent a standard subsequent hospitalisation with a surgical procedure for ileostomy closure which is known to be associated with clinically relevant morbidity [31]. Furthermore, the omission of an ileostomy after IPAA may offer cost savings [32]. However, a protective ileostomy will be needed in a selected group of patients with anticipated anastomotic complications. To accurately select patients at risk for pouch failure, a prognostic model of preoperative risk factors will be needed.

Primary defunctioning of the IPAA resulted in a higher rate of continence disturbances and impaired social functioning scores at long term follow up compared to patients with an IPAA without primary defunctioning ileostomy. We believe that construction of a defunctioning ileostomy in all patients as standard procedure should therefore be avoided; this must be a patient-tailored decision.

REFERENCES

1 Parks AG, Nicholls RJ. **Proctocolectomy without ileostomy for ulcerative colitis.** Br Med J 1978; 2(6130):85-88.

2 Heise CP, Kennedy G, Foley EF, Harms BA. **Laparoscopic restorative proctocolectomy with ileal S-pouch.** Dis Colon Rectum 2008; 51(12):1790-1794.

3 Hallgren T, Fasth S, Nordgren S, Oresland T, Hulten L. **The stapled ileal pouch—anal anastomosis. A randomized study comparing two different pouch designs.** Scand J Gastroenterol 1990; 25(11):1161-1168.

4 Oresland T, Fasth S, Nordgren S, Hallgren T, Hulten L. **A prospective randomized comparison of two different pelvic pouch designs.** Scand J Gastroenterol 1990; 25(10):986-996.

5 Lovegrove RE, Heriot AG, Constantinides V, Tilney HS, Darzi AW, Fazio VW et al. **Meta-analysis of short-term and long-term outcomes of J, W and S ileal reservoirs for restorative proctocolectomy.** Colorectal Dis 2007; 9(4):310-320.

6 Ziv Y, Fazio VW, Church JM, Lavery IC, King TM, Ambrosetti P. **Stapled ileal pouch anal anastomoses are safer than handsewn anastomoses in patients with ulcerative colitis.** Am J Surg 1996; 171(3):320-323.

7 Gorfine SR, Gelernt IM, Bauer JJ, Harris MT, Kreel I. **Restorative proctocolectomy without diverting ileostomy.** Dis Colon Rectum 1995; 38(2):188-194.

8 Remzi FH, Fazio VW, Gorgun E, Ooi BS, Hammel J, Preen M et al. **The outcome after restorative proctocolectomy with or without defunctioning ileostomy.** Dis Colon Rectum 2006; 49(4):470-477.

9 Sagar PM, Lewis W, Holdsworth PJ, Johnston D. **One-stage restorative proctocolectomy without temporary defunctioning ileostomy.** Dis Colon Rectum 1992; 35(6):582-588.

10 Ikeuchi H, Nakano H, Uchino M, Nakamura M, Noda M, Yanagi H et al. **Safety of one-stage restorative proctocolectomy for ulcerative colitis.** Dis Colon Rectum 2005; 48(8):1550-1555.

11 Heuschen UA, Hinz U, Allemeyer EH, Lucas M, Heuschen G, Herfarth C. **One- or two-stage procedure for restorative proctocolectomy: rationale for a surgical strategy in ulcerative colitis.** Ann Surg 2001; 234(6):788-794.

12 Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJ et al. **Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy.** Arch Surg 2008; 143(4):406-412.

13 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):339-351.

14 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):205-213.

15 Ware JE, Jr., Sherbourne CD. **The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.** Med Care 1992; 30(6):473-483.

16 Bakx R, Sprangers MA, Oort FJ, van Tets WF, Bemelman WA, Slors JF et al. **Development and validation of a colorectal functional outcome questionnaire.** Int J Colorectal Dis 2005; 20(2):126-136.

17 Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. **Prospective comparison of faecal inconti-**

nence grading systems. Gut 1999; 44(1):77-80.

18 McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. **The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups.** Med Care 1994; 32(1):40-66.

19 Maartense S, Dunker MS, Slors JF, Cuesta MA, Gouma DJ, van Deventer SJ et al. **Hand-assisted laparoscopic versus open restorative proctocolectomy with ileal pouch anal anastomosis: a randomized trial.** Ann Surg 2004; 240(6):984-991.

20 Heikens JT, de VJ, van Laarhoven CJ. **Quality of life, health related quality of life and health status in patients having restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review.** Colorectal Dis 2010.

21 Martin A, Dinca M, Leone L, Fries W, Angriman I, Tropea A et al. **Quality of life after proctocolectomy and ileo-anal anastomosis for severe ulcerative colitis.** Am J Gastroenterol 1998; 93(2):166-169.

22 Maggiori L, Michelassi F. **Ileal J-Pouch Construction.** J Gastrointest Surg 2012.

23 McCormick PH, Guest GD, Clark AJ, Petersen D, Clark DA, Stevenson AR et al. **The Ideal Ileal-Pouch Design: A Long-Term Randomized Control Trial of J- vs W-Pouch Construction.** Dis Colon Rectum 2012; 55(12):1251-1257.

24 Fazio VW, O'Riordain MG, Lavery IC, Church JM, Lau P, Strong SA et al. **Long-term functional outcome and quality of life after stapled restorative proctocolectomy.** Ann Surg 1999; 230(4):575-584.

25 Muir AJ, Edwards LJ, Sanders LL, Bollinger RR, Koruda MJ, Bachwich DR et al. **A prospective evaluation of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis.** Am J Gastroenterol 2001; 96(5):1480-1485.

26 Richards DM, Hughes SA, Irving MH, Scott NA. **Patient quality of life after successful restorative proctocolectomy is normal.** Colorectal Dis 2001; 3(4):223-226.

27 Wolf ND, Kadmon M, Wolf RC, Brechtel A, Keller M. **Quality of life after restorative proctocolectomy and ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: a matter of adjustment.** Colorectal Dis 2011; 13(11):e358-e365.

28 Heikens JT, de VJ, Goos MR, Oostvogel HJ, Gooszen HG, van Laarhoven CJ. **Quality of life and health status before and after ileal pouch-anal anastomosis for ulcerative colitis.** Br J Surg 2012; 99(2):263-269.

29 Tulchinsky H, Dotan I, Halpern Z, Klausner JM, Rabau M. **A longitudinal study of quality of life and functional outcome of patients with ulcerative colitis after proctocolectomy with ileal pouch-anal anastomosis.** Dis Colon Rectum 2010; 53(6):866-873.

30 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(1):37-44.

31 van Westreenen HL, Visser A, Tanis PJ, Bemelman WA. **Morbidity related to defunctioning ileostomy closure after ileal pouch-anal anastomosis and low colonic anastomosis.** Int J Colorectal Dis 2012; 27(1):49-54.

32 Joyce MR, Kiran RP, Remzi FH, Church J, Fazio VW. **In a select group of patients meeting strict clinical criteria and undergoing ileal pouch-anal anastomosis, the omission of a diverting ileostomy offers cost savings to the hospital.** Dis Colon Rectum 2010; 53(6):905-910.

6

Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem.

Tjibbe J. Gardenbroek[1,2], Gijsbert D. Musters[1], Christianne J. Buskens[1], Cyriel Y. Ponsioen[3], Geert R.A.M. D'Haens[3], Marcel G.W. Dijkgraaf[4], Pieter J. Tanis[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery, Academic Medical Centre, Amsterdam, the Netherlands, [2]Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, [3]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, the Netherlands, [4]Clinical Research Unit, Academic Medical Centre, The Netherlands

Submitted

ABSTRACT

Background

In this study we determined the effectiveness and direct medical costs of early surgical closure of the anastomotic defect after short course of Endo-sponge® therapy of the presacral cavity, compared to conventional treatment in patients with anastomotic leakage after ileal pouch-anal anastomosis (IPAA).

Methods

Patients with anastomotic leakage after IPAA undergoing early surgical closure of the anastomotic defect after short Endo-sponge® treatment were prospectively followed and compared with a consecutive cohort of IPAA patients with an anastomotic leak treated with the creation of a loop ileostomy and occasionally drainage of the presacral cavity.

Results

A total of 15 patients were treated with early surgical closure and 29 patients were treated conventionally. In the early surgical closure group, the Endo-sponge® treatment was continued for a median of 12 days (iqr 7-15), with a median of 3 (iqr 2-4) Endo-sponge® changes. Secondary anastomotic healing was achieved in all patients (n = 15) in the early surgical closure group, which was significantly higher compared to 52% (n = 16) in the conventional treatment group (P = 0.003). Closure of the anastomotic defect was achieved after a median of 48 days (25-103) in the early surgical closure group compared to 70 days (iqr 49-175) in the conventional treatment group (P = 0.013). A functional pouch was seen in 93% and 86% of the patients respectively. No significant differences in direct medical costs were found.

Conclusion

Early surgical closure after a short period of Endo-sponge® treatment is highly effective to treat anastomotic leakage after IPAA without increasing costs.

INTRODUCTION

Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) is the treatment of choice in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). The Achilles' heel of this procedure is anastomotic leakage. Even in the presence of a protective stoma, anastomotic leakage occurs in 4% of the IPAA patients, while the non-diverted pouches have a risk of leakage of up to 15% [1-3].

Anastomotic leakage in the non-diverted pouches will most often present with pelvic sepsis. The anastomotic leak in diverted pouches often presents subclinically as a presacral abscess. The presacral abscess may develop into a presacral sinus with a chronic low grade infection, or even fistula formation to the perineal or gluteal area [4]. The presacral sinus may postpone or even preclude stoma reversal. If it is possible to close the stoma, pouch function might be compromised due to the chronic pelvic inflammation and its subsequent fibrosis [5;6].

The goal of treating anastomotic leakage is the prevention of chronic sepsis and concomitant chronic sinus formation. Conventional management of anastomotic leakage after IPAA is faecal diversion by an ileostomy, which can be combined with transanal or percutaneous drainage of the presacral abscess cavity. Weidenhagen et al. described a novel approach to treat the presacral abscess with Endo-sponge® vacuum assisted drainage. The Endo-sponge® is endoscopically placed through the anastomotic defect into the presacral cavity and is connected to a low vacuum suction system [7]. By changing the Endo-sponge® two times per week and tapering the size of the Endo-sponge® systematically, the abscess cavity gradually collapses. This technique is labour-intensive, expensive and it takes several weeks until closure is achieved [7-13]. In addition, a small sinus may persist in the end with a risk of recurrent sinus after stoma reversal. We have proposed a modification of this technique. Instead of repetitive exchanges of the Endo-sponge® aiming at gradual collapse of the cavity, the Endo-sponge® is used to clean the cavity during two or three Endo-sponge® placements. When the cavity is clean and is surrounded by healthy granulation tissue, the anastomotic defect is closed surgically [14]. This innovative approach might overcome the drawbacks of the Weidenhagen technique.

The aim of this study was to determine if early surgical closure is feasible, results in a higher percentage of secondary healed anastomosis, reduces the time to anastomotic healing and leads to a higher percentage of functional pouches in patients with anastomotic leakage after IPAA for UC or FAP compared to the conventional management. In addition, we analysed the direct medical costs of both treatment modalities.

METHODS

We included all consecutive patients with anastomotic leakage after IPAA for UC or FAP in the period January 2003 – January 2014. Anastomotic leakage was defined as a symptomatic or asymptomatic leakage with an anastomotic defect confirmed by radiological imaging or during relaparotomy for abdominal sepsis. Patients undergoing early surgical closure after Endo-sponge® treatment of the anastomotic leakage between January 2010 and January 2014 were prospectively recorded and compared with a retrospectively identified cohort of IPAA patients with anastomotic leakage who underwent conventional treatment between January 2003 and December 2009. Since 2010, the anastomotic leakages were treated with a short course of Endo-sponge® followed by surgical closure of the anastomotic defect, when conservative treatment was not feasible. The Institutional Review Board (IRB) of the Academic Medical Centre in Amsterdam, the Netherlands, granted exemption from approval for this study.

Early surgical closure

In patients with anastomotic leakage after IPAA creation without ileostomy, the first Endo-sponge® placement was combined with ileostomy creation under general anaesthesia. Subsequent Endo-sponge® changes were carried out under light sedation at the endoscopy room. First, the abscess cavity was examined and rinsed with saline (0.9%) using a flexible gastroscope (GIF-100 Video Gastroscope; Olympus, 9.8-mm diameter, Olympus Corp., Tokoyo, Japan). Next, one or more open-pored polyurethane Endo-sponge(s)® (B. Braun Medical B.V., Melsungen, Germany) were placed via a plastic overtube under the guidance of the gastroscope into the deepest point of the abscess cavity (*Figure 1*). Thereafter, the Endo-sponge(s) ® were connected to a low-vacuum suction bottle (Redyron® TRANS PLUS suction device, Melsungen, Germany). The Endo-sponge(s)® were endoscopically changed every 3-4 days to prevent tissue ingrowth or in case of vacuum depletion. When the abscess cavity was considered clean and the edges of the anastomosis were mobile, the anastomotic defect was closed surgically. Under general anaesthesia, the anastomotic dehiscence was transanally sutured with polydioxane 3-0 (PDS, Ethicon Endo-Surgery Inc., Cincinnati, Ohio, USA) over a vacuum drain by using the Lone Star Retractor System ™ (Lone Star Medical Products ®, Houston, Texas). The trans-anastomotic drain was removed on the 3rd postoperative day and antibiotics were given for 10-14 days postoperatively. All reconstructed anastomoses were evaluated by endoscopic inspection after two weeks or CT-scan with intraluminal contrast. Stoma closure was scheduled when anastomotic healing was confirmed. If there was a persisting anastomotic defect during radiological or endoscopic evaluation, continuation of Endo-sponge® treatment with a second attempt of defect closure, was considered.

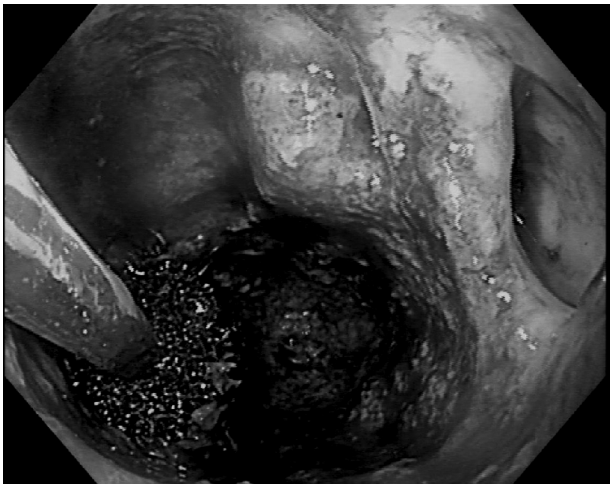


Figure 1 One of two endo-sponges® in situ in the presacral cavity.

Conventional treatment

After radiological confirmation of the anastomotic leakage, a diverted ileostomy was created, if not done so primarily. Depending on the size of the cavity, additional transanal or percutaneous drainage of the abscess cavity was performed, sometimes followed by regular irrigation via the drain, or a wait and see policy was adopted. During follow-up, secondary healing of the anastomosis was regularly checked endoscopically or by an x-ray with contrast enema of the pouch. Stoma closure was scheduled if anastomotic healing was confirmed.

Outcomes

Main outcome parameter was the percentage of secondary healed anastomosis at 6 months, without a persistent abscess or anastomotic defect assessed by imaging. Secondary outcome parameters were the time from diagnosis of the leakage to secondary anastomotic healing and the percentage of functional pouches at last date of follow-up. In addition, the size of the initial abscess cavity, the time to intervention, duration of Endo-sponge® treatment, the number of Endo-sponge® treatments, the number of patients with a chronic presacral sinus longer than one year, and the direct medical costs of both treatment modalities were calculated. Secondary healing of the anastomosis was defined as no signs of contrast leakage during contrast enema or abdominal CT scan with intravenous, oral and rectal contrast and an intact anastomosis during endoscopic inspection. Patients were classified as having a functional pouch when continuity was restored by ileostomy closure and no long term complications were reported (such as a persisting high defecation frequency, urgency incontinence or re-creation of a stoma).

Cost analysis

The direct medical costs per patient were calculated for both treatment groups. The direct medical costs were calculated from diagnosis of anastomotic leakage up to stoma reversal or up to 2 years of follow-up if ileostomy closure was not yet performed. The direct medical costs were calculated as the product sum of health care volumes involved and their unit costs. The direct medical costs included the costs of the index hospital admission, readmission(s), reoperation(s), visits to and telephone contacts with the outpatient departments (OPD) and the emergency room (ER), and endoscopic examination or radiological imaging from diagnosis of anastomotic leakage up to ileostomy reversal. In addition, we accounted for subsequent ileostomy care costs. For the early surgical closure group the costs of the Endo-sponge® treatment, Endo-sponge® changes, and surgical closure of the defect were incorporated as well.

The total medical cost consists of all patients that were successfully treated with early surgical closure and the successfully treated patients in the conventional treatment group. In addition, a separate cost analysis was performed up to two years after diagnosis of the leakage for the patients in whom no defect closure was observed at the end of follow-up or an ileostomy was present due to pouch failure. Unit costing was based on the Dutch costing manual for health care research[15] or was determined in cooperation with the hospital administration and pharmacy. The unit costs are determined for the year 2010, after price-indexing (based on general consumer price indices; www.cvz.nl, access date April 20, 2013) of unit costs stemming from different calendar years.

Statistical analysis

Descriptive data are reported as median with interquartile range (iqr) or mean ± standard deviation according to distribution. Categorical data were analysed with Fisher's exact test or Chi-square-test. Continuous variables were analysed using the Mann-Whitney-Wilcoxon test. $P < 0.05$ was considered statistically significant.

For the cost analysis the costs of both treatment modalities were compared by calculating the 95% confidence intervals (CI) for the mean differences after correction for bias, because of skewed distributions. Accelerated, non-parametric bootstrapping was used with stratification for Endo-sponge® treatment, drawing 10,000 samples of the same size as the original samples separately for each group and with replacement. All analyses were performed with IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Between January 2003 and January 2014, 393 patients underwent RPC and IPAA. Of these patients, 46 patients were diagnosed with an anastomotic leakage (11.7%). Five patients

were referred to our hospital for treatment of an anastomotic leak after IPAA. Of these 51 patients, 15 patients underwent early surgical closure and 29 patients received conventional treatment. The remaining 7 patients were excluded because they underwent other closing techniques; the original Weidenhagen technique (n = 4) and direct suturing of the defect without preceding Endo-sponge® therapy (n = 3). These procedures were performed in the period between the use of the conventional method and the adaptation of the early surgical closure technique.

Neither the location of the leakage nor the size of the abscess cavity differed between the study groups(*Table 1*). In the early surgical closure group, a diverting ileostomy was created during the RCP in four of the 15 (27%) patients. In nine patients (60%), an ileostomy was constructed after diagnosis of the anastomotic leakage. In two patients (13%), early closure after Endo-sponge® treatment was attempted without an ileostomy. In one of these two patients (7%) the early closure failed initially. After creation of a diverting

Table 1 Patient characteristics

	Conventional treatment n = 29	**Early surgical closure n = 15**	**p-value**
Age at surgery (years)	36 [22-47]	37 [25-56]	0.603
Sex (M)	15 (52)	12(80)	0.068
Diagnosis			0.552
- UC	20 (69)	9 (60)	
- FAP	9 (31)	6 (40)	
Indication for surgery			0.764
- Refractory	14 (48)	7 (47)	
- Dysplasia / carcinoma	8 (28)	3 (20)	
- Preventive	7 (24)	5 (33)	
Colectomy procedure			0.137
- Open	14 (48)	7 (47)	
- Total laparoscopic	5 (48)	4 (27)	
- Hand-assisted laparoscopic	10 (17)	4 (27)	
Stapled anastomosis	26 (90)	11 (73)	0.161
Abscess size (cm^3)*	141 [15-222]	161 [74-257]	0.291
- Length (cm)#	4 [2-6]	4 [3-6]	
- Height (cm)&	7 [3-8]	6 [5-8]	
- Width (cm)+	6 [3-7]	6 [4-7]	
Primary diversion	3 (10)	4 (27)	0.207
Mortality	1 (3)	0	1.00

Data are presented as median [IQR] or *n* (%). ¶Fisher's exact test (two-tailed) / †Mann Whitney U test
*Measurement of the abscess size was possible in 18 patients in the conventional treatment group and 11 patients in the early surgical closure group. *. All dimensions of the abscess cavity were measured from an abdominal CT-scan at their maximal size. #The length of the cavity was measured on the sagittal or axial plane &The height was measured on the sagittal or axial plane +The width of the cavity was measured on the coronal or axial plane.

stoma and a second period of Endo-sponge® treatment surgical closure was successful. In the conventional treatment group, three patients were primarily diverted during the RPC (10%) and the other 26 patients (90%) underwent secondary diversion after diagnosis of the leakage.

Early surgical closure

The Endo-sponge® was placed after a median of 2.0 days (iqr 0-8) following the diagnosis of anastomotic leakage. The Endo-sponge® treatment was continued for a median of 12 days (iqr 7-15), with a median of three (iqr 3-4) Endo-sponge® changes. After a median of 15 days (iqr 11-31) the anastomotic defect was surgically closed (*Table 2*). In two patients the surgical closure after Endo-sponge® treatment failed initially. A second period of Endo-sponge® treatment followed by surgical closure was successful in both of them.

Table 2 Treatment of anastomotic defect after IPAA

	Conventional treatment n = 28*	**Early surgical closure n = 15**	**P-value**
Time between diagnosis of leakage and surgical closure of defect (days)		15 [11-31]	
Time between diagnosis of leakage and observed closure of defect (days)	70 [49-175]	48 [25-103]	0.013
Time between pouch surgery and observed closure of defect (days)	84 [59-183]	59 [39-137]	0.081
Ileostomy reversed at end of follow-up	25 (89)	14 (93)	1.000¶
Long term pouch dysfunction (%)	4 (14)	1 (7.1)	1.000¶

Data are presented as median [IQR] or *n* (%). ¶Fisher's exact test (two-tailed) / †Mann-Whitney test. *In one patients the pouch was excised due to adenocarcinoma

Anastomotic healing

Secondary anastomotic healing after 6 months was achieved in all 15 patients in the early surgical closure group compared to 16 out of the 29 patients (52%) in the conventional treatment group (P = 0.003). Secondary anastomotic healing was achieved in the early surgical group after a median of 48 days (iqr 25-103) compared to 70 days (49-175) in the conventional treatment group (P = 0.013). A chronic presacral sinus was present in none of the patients in the early surgical closure group versus two patients (7%) in the conventional treatment group (P = 0.542). Patients in the early surgical closure group were followed for a median of 25 months (iqr 12-39) versus a median 104 months (iqr 60-122) in the conventional treatment group (P < 0.001).

One pouch in the early surgical closure group had to be diverted again, due to persisting high defecation frequency and urgency incontinence. Therefore, early surgical closure of the anastomotic defect resulted in a functional pouch in 14 of the 15 patients (93%), In the conventional treatment group, the pouch was excised in one FAP patient

due to the development of an adenocarcinoma, this patient was therefore excluded for the functional analysis. In the remaining 28 patients in the conventional treatment group, a presacral sinus persisted in four of the 28 patients (14%) after reversal of the ileostomy. Of these four patients, the persisting leakage resolved after extensive surgical treatment in one patient. The presacral sinus in the other three patients were observed during endoscopy but appeared to be not clinically relevant. Therefore, no treatment was instigated. In addition, one patient developed a dysfunctional pouch after stoma reversal in the conventional treatment group due to high defecation frequency. No diversion was performed in this patient. Thus, 24 of 28 patients (86%) in the conventional treatment group had a functional pouch at the end of follow up.

Cost analysis

The total treatment costs per patient were €27.627 (95 per cent c.i. €23.239 to €32.690) for the early closure group and €33.441 (95 per cent c.i. €24.955 to €46.728) for the conventional treatment group (P = 0.529). When patients with no observed secondary healed anastomosis and patients without ileostomy reversal are added with a follow-up of two years, the total direct medical costs were €27.879 (95 per cent c.i. 23.716 to 32.580) for the early surgical closure group, and €37.687 (95 per cent c.i. 27.592 to 51.007) for the conventional treatment group (P = 0.304).

DISCUSSION

Early surgical closure of a leaking IPAA following a short Endo-sponge® treatment resulted in a significantly higher percentage of secondary healed anastomosis at 6 months compared to the conventional treatment. Furthermore, early surgical closure significantly reduced the time to anastomotic healing with a median of 22 days compared to the conventional treatment. Early surgical closure resulted in a high percentage of functional pouches at the end of follow-up. Treatment costs per patient in both study groups were assessed and compared. This showed no differences in treatment costs.

Closing anastomotic leakage surgically is a paradigm shift, because traditionally this has been considered to fail by definition. The success of early surgical closure of the anastomotic defect as shown in the present study is probably explained by the preceding Endo-sponge® treatment, which resolves the pelvic sepsis behind the anastomosis. Subsequent surgical closure of the anastomotic defect is of great importance to prevent influx of mucus and debris in the cleaned cavity jeopardizing closure of the cavity. The short period of negative pressure via a vacuum drain is thought to be useful for drainage of contaminated fluids in the cavity enabling expansion of the pouch with collapse of the presacral cavity. Diversion of the pouch might be an essential component of this

treatment strategy, because if the anastomotic repair is not perfect the cavity will expand again due to the pressure of the intestinal contents. Closure failed initially in one of two patients without faecal diversion. The first results of early anastomotic reconstruction after a short period of Endo-sponge® treatment are very promising and compare favourably to the alternative strategies. Endo-sponge® treatment until closure as propagated by Weidenhagen has a mixed rate of success (56-94%)[7;11]. The median time of closure is more than 340 days in both patients undergoing low anterior resection and patients undergoing RPC [4]. Prolonged treatment using the Weidenhagen technique is associated with high costs due to a lot of Endo-sponge® exchanges and stoma materials [7-11], and is a logistic burden. No statistical significant difference in direct medical costs in both treatment strategies was found. However, early surgical closure seems to be less expensive than the conventional treatment. This is most likely due to the higher costs in stoma materials and outpatient clinic visits.

The early surgical closure treatment was successful in all patients after 6 months but resulted in a non-functional pouch in one patient (7%) due to high defecation frequency and urge incontinence. In the conventional treatment group the treatment was only successful in 52% of the patients after 6 months and in four patients (14%) a dysfunctional pouch was present at the end of follow-up. A chronic presacral abscess or presacral sinus formation after leakage is held responsible for delayed anastomotic healing or the inability for ileostomy reversal [5;6]. If eventually the defect has healed and the stoma is closed, the function of the pouch can be compromised due to fibrosis and scarring. Therefore, we think that the time interval between diagnosis of anastomotic leakage and the duration of subsequent treatment is essential and effects long term functional outcome. Endo-sponge® treatment according to Weidenhagen showed to be more successful if the treatment was started within six weeks after initial surgery with colo-anal or ileo-anal anastomosis, which is significantly higher than a 38% success rate if started after six weeks [11].

Ideally, pouch function was assessed with validated questionnaires to determine whether the pouch function of the early closure group is better preserved when the anastomotic leak is treated aggressively. We considered comparison with respect to function difficult due to the many confounders effecting pouch function e.g. the small group size, pouchitis, temporary ileostomy, mucosectomy and initial diagnosis.

This study is limited by the partially retrospective design. Definition of the moment of anastomotic healing in both groups was therefore difficult. In the prospective group all closures were checked endoscopically two weeks after surgical closure, while in the conventional group intermittent imaging was done to see whether the cavity was healed. This could have caused an overestimation of the time to heal.

Due to the difference in length of follow up the pouch failure rate of the early closure group might have shown more favourable, because it is well known that failure rates

increase over time. However, most of the failures were caused by the persistent sinuses that were prevented in the early closure group.

In conclusion, this study shows that early surgical closure after a short period of Endosponge® treatment is effective to treat anastomotic leakage after IPAA preventing chronic sinuses and permanent stomas.

REFERENCES

1 Gullberg K, Liljeqvist L. **Stapled ileoanal pouches without loop ileostomy: a prospective study in 86 patients.** Int J Colorectal Dis 2001; 16(4):221-227.

2 Wasmuth HH, Trano G, Endreseth B, Rydning A, Wibe A, Myrvold HE. **Long-term surgical load in patients with ileal pouch-anal anastomosis.** Colorectal Dis 2009; 11(7):711-718.

3 Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJ et al. **Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy.** Arch Surg 2008; 143(4):406-412.

4 van Koperen PJ, van der Zaag ES, Omloo JM, Slors JF, Bemelman WA. **The persisting presacral sinus after anastomotic leakage following anterior resection or restorative proctocolectomy.** Colorectal Dis 2011; 13(1):26-29.

5 Breen EM, Schoetz DJ, Jr., Marcello PW, Roberts PL, Coller JA, Murray JJ et al. **Functional results after perineal complications of ileal pouch-anal anastomosis.** Dis Colon Rectum 1998; 41(6):691-695.

6 Farouk R, Dozois RR, Pemberton JH, Larson D. **Incidence and subsequent impact of pelvic abscess after ileal pouch-anal anastomosis for chronic ulcerative colitis.** Dis Colon Rectum 1998; 41(10):1239-1243.

7 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(8):1818-1825.

8 Cresti S, Ouaissi M, Sielezneff I, Chaix JB, Pirro N, Berthet B et al. **Advantage of vacuum assisted closure on healing of wound associated with omentoplasty after abdominoperineal excision: a case report.** World J Surg Oncol 2008; 6:136.

9 D'hondt M, De HG, Malisse P, Vanden Boer J, Knol J. **Chronic pelvic abscedation after completion proctectomy in an irradiated pelvis: another indication for ENDO-sponge treatment?** Tech Coloproctol 2009; 13(4):311-314.

10 Mees ST, Palmes D, Mennigen R, Senninger N, Haier J, Bruewer M. **Endo-vacuum assisted closure treatment for rectal anastomotic insufficiency.** Dis Colon Rectum 2008; 51(4):404-410.

11 van Koperen PJ, van Berge Henegouwen MI, Rosman C, Bakker CM, Heres P, Slors JF et al. **The Dutch multicenter experience of the endo-sponge treatment for anastomotic leakage after colorectal surgery.** Surg Endosc 2009; 23(6):1379-1383.

12 Weidenhagen R, Gruetzner KU, Wiecken T, Spelsberg F, Jauch KW. **Endoluminal vacuum therapy for the treatment of anastomotic leakage after anterior rectal resection.** Rozhl Chir 2008; 87(8):397-402.

13 van Koperen PJ, van Berge Henegouwen MI, Slors JF, Bemelman WA. **Endo-sponge treatment of anastomotic leakage after ileo-anal pouch anastomosis: report of two cases.** Colorectal Dis 2008; 10(9):943-944.

14 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.

15 Hakkaart van Roijen L, Tan SS, Bouwmans CAM. **Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg (manual for cost research).** College voor zorgverzekeringen 2012.

7

Surgery for Crohn's disease: new developments

Tjibbe J. Gardenbroek[1], Pieter J. Tanis[1], Christianne J. Buskens[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Digestive Surgery 2012

ABSTRACT

Background

Crohn's disease is a chronic relapsing inflammatory bowel disease requiring surgery in a large number of patients. This review describes new developments in surgical techniques for treating Crohn's disease.

Results

Single-incision laparoscopic surgery decreases abdominal wall trauma by reducing the number of abdominal incisions, possibly improving postoperative results in terms of pain and cosmetics. The resected specimen can be extracted through the single-incision site or the future stoma site. Another option is to use natural orifices for extraction (i.e. transcolonic/ transanal), but actual benefits of these procedures have not yet been determined. In patients with extensive perianal disease or rectal involvement, transperineal completion proctectomy is often feasible, thereby avoiding relaparotomy. By using a close rectal intersphincteric resection, damage to the pelvic autonomic nerves is avoided. In addition, the risk of presacral abscess formation is reduced by leaving the mesorectal tissue behind.

Conclusion

Minimally invasive surgery and associated techniques have become standard clinical practice in surgical treatment of patients with Crohn's disease. New developments aim at further reducing the hospital stay and morbidity, and improving the cosmetic outcomes.

INTRODUCTION

Crohn's disease is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract. It is a relapsing disease with large variability in clinical presentation. The incidence of Crohn's disease is 5–10 per 100,000 people per year[1]. The initial therapy consists of medical treatment. Despite the current variety of available medications, between 70% and 90% of patients with Crohn's disease will require surgery during their lifetime[2;3], and nearly half of these patients will undergo repeat surgical interventions[4;5]. Indications for surgery are complications (acute or chronic), refractory disease despite optimal medical therapy, and side effects of medical therapy. Often, the initial presentation of Crohn's disease is early in life. Especially young patients and patients undergoing repeat surgery may benefit from bowel-sparing techniques and minimally invasive surgery with reduced adhesion formation. This review describes new developments in surgical techniques aiming at minimizing sequelae of surgical intervention in patients with Crohn's disease.

Single-incision laparoscopic surgery

Laparoscopic techniques have transformed colorectal surgery in the last decades, and meanwhile numerous studies have shown the safety and advantages of laparoscopic surgery in Crohn's disease with reduced hospital stays, shorter times to first postoperative bowel movements, lower complication rates, better cosmetic outcomes and comparable disease recurrence rates for laparoscopic and open surgery[6-14]. In our opinion, the laparoscopic approach is preferable in patients with inflammatory bowel disease.

Single-incision laparoscopic surgery (SILS) is a promising new development in the field of minimally invasive surgery. This technique has been developed to decrease abdominal wall trauma further by reducing the number of abdominal incisions compared with the standard laparoscopic approach. This might decrease postoperative pain, shorten the recovery period and improve cosmesis. SILS has already been applied in ileocolic resections, right and left hemicolectomies, total colectomies, sigmoid resections and restorative proctocolectomies[15-29]. In SILS, the umbilicus is most frequently used as the only access site through which the specimen is dissected and extracted. The scar virtually disappears in the shallow of the umbilicus (F*igure 1a, b*). In benign disease, close pericolic dissection of the mesocolic and omental attachments of the colon can be performed, thereby facilitating specimen removal through the small incision. In patients who will have an ostomy, the SILS port can be placed at the ostomy site.

Crohn's disease limited to the ileocolic region is a common indication for laparoscopic surgery. The SILS ileocolic resection has recently been described by Rijcken et al.[30] for medically refractory stenosis of the terminal ileum in 20 consecutive patients. A matched comparison was performed with patients who underwent standard laparoscopic ileocolic

resection. There were no differences in conversion rates (1/20 in the SILS group vs. 2/20 in the standard laparoscopic group). Similar major complication rates (2/20 in the SILS group vs. 1/20 in the standard laparoscopic group) and wound infection rates (2/20 in both groups) were reported. No differences in the postoperative pain scores, length of peridural anaesthesia or hospital stay were found. This study showed that the SILS ileocolic resection is feasible, safe and effective with the advantage of having less port sites and superior cosmesis although the latter was not formally studied.

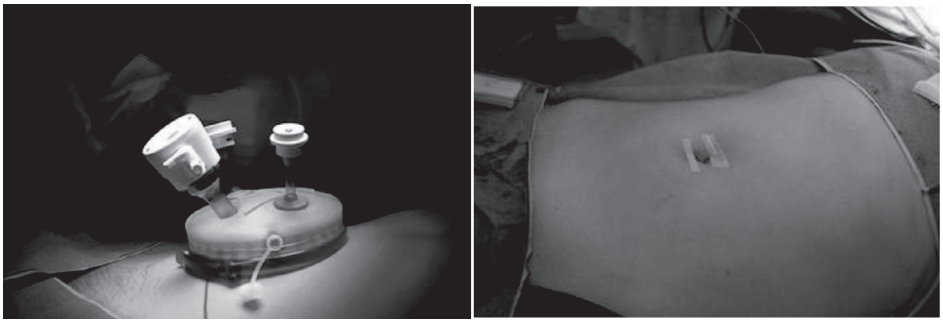


Figure 1a Single port placed at the level of the umbilicus during single port ileocolic resection.
Figure 1b Postoperative result after single-port ileocolic resection. The incisional scar virtually disappears in the shallow of the umbilicus.

SILS has also been described for ileocolic resections in complex Crohn's disease with previous surgery, fistulas and abscesses. Most reports describe single cases[31-34]; however, one study reported a consecutive series of 6 patients with an abscess, phlegmons or enterocutaneous fistulae[35]. There were no conversions to laparotomy, but 4 of 6 patients required diversion with a loop ileostomy. In all of these patients, the ileostomy site was used for placement of a single-site port. Mean operative time was 160 minutes and the median length of the hospital stay was 3 days. No 30-day readmissions or mortality has been reported in this study. These studies show that the benefits of the standard laparoscopic ileocolic resection are preserved in the SILS approach; the superiority of the SILS approach in improving postoperative results in terms of pain and cosmetics has yet to be proven.

SILS colectomy has also been described as a feasible and safe technique in a review article by LeBlanc et al.[22]. The review included 9 studies with a total of 17 patients and reported a mean operative time of 116 minutes, a mean hospital stay of 5 days and a mean final scar length of 31 mm. A series of 10 consecutive patients with inflammatory bowel disease undergoing (sub)acute emergency colectomy included three patients with Crohn's disease[29]. All 3 (emergency) laparoscopic colectomies were safe and feasible. However, larger series with specific data on SILS colectomy in patients with Crohn's disease are needed to verify the benefits of this procedure.

The safety of a new technique is an important issue if its application on a larger scale is considered. SILS is probably more difficult than conventional laparoscopy because triangulation is hampered. In addition, ergonomics are decreased due to the parallel insertion of the instruments. Therefore advanced laparoscopic skills and case selection are essential to minimize the risk of technique-related complications. The learning curve of the SILS procedures has not been described in patients with Crohn's disease. However, in SILS cholecystectomies and SILS ileocolic resections, several studies showed that the learning curve does not include the slow beginning and steep acceleration seen in standard multi-incision laparoscopy[27;36;37]. In SILS colectomy, a minimal learning curve in experienced laparoscopic surgeons is described[28;38]. New developments in the design of the SILS instruments and robotics in combination with SILS might overcome these issues in the future.

Specimen extraction techniques

Removal of the specimen from the peritoneal cavity requires an incision. Several different techniques have been developed to extract the colonic specimen with no or minimal additional surgical trauma to the abdominal wall, such as the previously mentioned SILS technique or the natural orifice specimen extraction techniques (*Table 1*). For removal of the colonic specimen after resection for a T1 tumour, endometriosis or ulcerative colitis, extraction of the specimen through the rectum has been described[39-42]. Since bowel mobilisation, dissection, transsection and creation of the anastomosis can be done by using a total laparoscopic approach, removal of the specimen is the only reason to extend one of the port incisions or to create a Pfannenstiel incision in a patient with Crohn's disease. Especially in patients with benign disease in whom close colonic dissection is sufficient and no large inflammatory mass is present, the specimen can be exteriorised through the anus. This technique has been successfully applied after total laparoscopic ileocolic resection[43] and after laparoscopic colectomy[29] for Crohn's disease. The study of Eshuis et al. [43] included 10 patients with ileocolic Crohn's disease. Nine patients underwent primary resection and one patient underwent resection of the neoterminal ileum. The ileocolic specimen was retrieved by an endoscopist through the uncompleted anastomosis and ultimately exteriorized through the anus. Transcolonic specimen removal was feasible in 8 out of 10 patients. The data of patients that underwent transcolonic specimen removal were compared to previously published data for laparoscopically assisted ileocolic resection. Results demonstrated a longer operating time in the transcolonic group (208 minutes versus 115 minutes) but a comparable length of hospital stay (5 days) for both techniques. No differences in pain scores or quality of life, body image and cosmesis were found between the two groups. In another study from our institution[29], 10 consecutive patients with inflammatory bowel disease that underwent laparoscopic (sub)acute emergency colectomy with extraction of the colectomy specimen through the anus or stoma

site were described. This series included 3 patients with Crohn's disease. In 1 of these patients, the colectomy specimen was successfully extracted transanally after laparoscopic subtotal colectomy, with no infectious complications or reoperations.

Table 1 Overview of advantages and disadvantages of the different specimen extraction techniques

Laparoscopic techniques	Specimen extraction site	Advantages of extraction site	Disadvantages of extraction site
Hand-assisted laparoscopic surgery	Pfannenstiel	tactile feedback visibility	suprapubic scar incisional hernia
	trocar port incision	extraction of large specimen possible	large port site incision incisional hernia
Total laparoscopic surgery	Pfannenstiel	extraction of large specimen possible	suprapubic scar incisional hernia
	transanal	no additional scar possible reduction of adhesions and incisional hernia	intra-abdominal infectious complications technically difficult extraction of large specimen not possible
Single incision laparoscopic surgery	umbilicus	reduction in port sites cosmetics; scar disappears in shallow of umbilicus	technically difficult extraction of large specimen not possible
	stoma site	no additional incisions	parastomal hernia

Transstomal extraction of the colectomy specimen can be used in patients with a previously constructed ileostomy by placement of a balloon trocar or SILS port at the ileostomy site. This technique was used in two patients with Crohn's disease in this study [29].

These studies show the technical feasibility and safety of the different specimen extraction procedures. However, the actual benefits of these procedures have not been determined. The possible advantages on standard laparoscopic resection in the reduction of adhesions and incisional hernia on the long term have to be shown in larger series with longer follow up. Furthermore, the procedures are technically difficult and require a skilled team for their successful completion. The extraction can be complex in case of a large colonic tumour, a specimen with thickened mesentery or an en-bloc specimen with omentum or abdominal wall. From an oncological point of view, excessive manipulation of the specimen may induce tumour spillage. In transcolonic and transanal specimen removal, the anastomotic staple line is opened for a considerable period of time to facilitate specimen removal, which increases the possibility of faecal contamination, resulting in intra-abdominal infections or abscesses. Therefore, complicated extraction techniques with the avoidance of a minilaparotomy are expected to be predominantly useful if no future (mini)laparotomy is required, for instance in restorative procedures.

Transperineal completion proctectomy

In patients with extensive perianal disease and rectal involvement, where both medical management and (local) surgical treatment failed, the first surgical option is a defunctioning colostomy. If that does not provide sufficient relief, the 'last resort' option is completion proctectomy. Around 10 to 20% of patients with perianal Crohn's disease ultimately undergo completion proctectomy[44;45].

When proctectomy is opted for, either a low Hartmann's procedure or a transperineal intersphincteric resection of the rectum can be performed. A low Hartmann's procedure is defined as an anterior resection with total mesorectal excision in which the rectum is stapled at the dentate line or within the last centimetres of the lower rectum. A disadvantage of the low Hartmann's procedure is the residual distal rectal mucosa. This can cause persisting complaints of Crohn's disease and anastomotic breakdown will result in a presacral abscess draining and fistulising through the perineum[46-49]. Therefore, the intersphincteric resection procedure is preferred in our centre. This procedure usually comprises two consecutive phases; an abdominal and a perineal phase. However, the procedure can often be performed exclusively via a transperineal approach, with the patient in prone position. Using ultrasonic dissection, it is very feasible to dissect the rectum in a close rectal manner. With adequate haemostasis and retraction, rectosigmoidal stumps of up to 25 cm can be safely resected using a transperineal approach, thereby precluding an abdominal phase (*Figure 2*). Another advantage of the close rectal technique is preservation of the rectal mesentery, leaving only a minimal cavity. This not only reduces the risk of subsequent abscess formation due to natural filling of the presacral space, but it also avoids damage to the pelvic autonomic nerves.

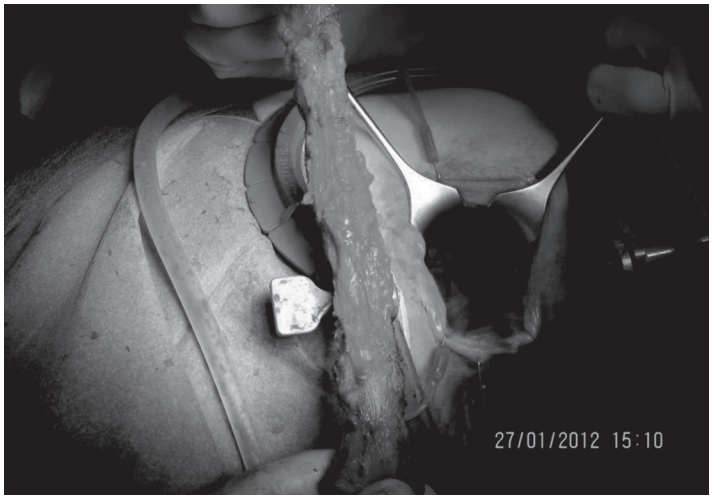


Figure 2 Intersphincteric resection of the rectum performed exclusively via a transperineal approach with a large rectosigmoidal stump after close rectal resection.

Known complications of completion proctectomy or proctocolectomy for Crohn's disease are poor perineal wound healing and a persistent presacral sinus, with an incidence of around 40% after proctectomy[50;51]. Possible contributing factors to the cause of the perineal sinus are postoperative perineal or pelvic infection and the failure to fill the pelvic cavity or perineal space with pelvic organs or adjacent musculoskeletal structures. The remaining cavity can be cleaned using vacuum-assisted drainage techniques with endo-sponge (*Figure 3*). The subatmospheric pressure drains the excessive fluid from the extravascular space, thereby improving the local blood flow and oxygenation[52]. The size of the remaining cavity is limited by using the close rectal dissection and leaving the mesorectal tissue behind, and pre-existing sepsis can be treated effectively by applying the endosponge. After endo-sponge assisted drainage of the perineal sepsis and stimulation of granulation tissue, the cavity can be closed surgically by suturing the external anal sphincter.

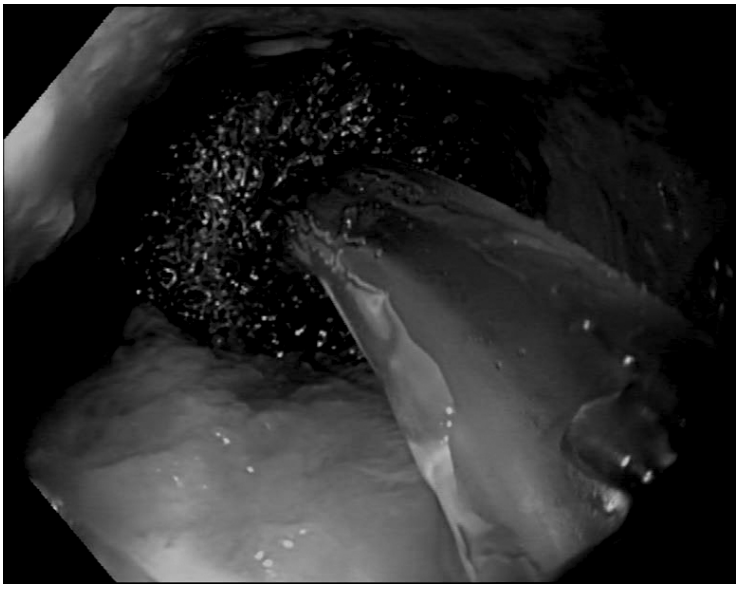


Figure 3 Vacuum-assisted drainage of the pelvic cavity after proctectomy.

CONCLUSION

In the surgical treatment of patients with Crohn's disease, minimally invasive surgery is currently recognized as standard treatment. New developments derived from existing minimal invasive techniques are SILS, natural orifice specimen extraction, close rectal dissection techniques and transperineal resectional surgery, all aiming at further reducing surgical trauma.

REFERENCES

1 Carter MJ, Lobo AJ, Travis SP. **Guidelines for the management of inflammatory bowel disease in adults.** Gut 2004; 53 Suppl 5:V1-16.

2 Baumgart DC, Sandborn WJ. **Inflammatory bowel disease: clinical aspects and established and evolving therapies.** Lancet 2007; 369(9573):1641-1657.

3 Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. **Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease.** Gut 2001; 49(6):777-782.

4 Duepree HJ, Senagore AJ, Delaney CP, Brady KM, Fazio VW. **Advantages of laparoscopic resection for ileocecal Crohn's disease.** Dis Colon Rectum 2002; 45(5):605-610.

5 Bernell O, Lapidus A, Hellers G. **Risk factors for surgery and postoperative recurrence in Crohn's disease.** Ann Surg 2000; 231(1):38-45.

6 Polle SW, Wind J, Ubbink DT, Hommes DW, Gouma DJ, Bemelman WA. **Short-term outcomes after laparoscopic ileocolic resection for Crohn's disease. A systematic review.** Dig Surg 2006; 23(5-6):346-357.

7 Dasari BV, McKay D, Gardiner K. **Laparoscopic versus Open surgery for small bowel Crohn's disease.** Cochrane Database Syst Rev 2011;(1):CD006956.

8 Eshuis EJ, Polle SW, Slors JF, Hommes DW, Sprangers MA, Gouma DJ et al. **Long-term surgical recurrence, morbidity, quality of life, and body image of laparoscopic-assisted vs. open ileocolic resection for Crohn's disease: a comparative study.** Dis Colon Rectum 2008; 51(6):858-867.

9 Rosman AS, Melis M, Fichera A. **Metaanalysis of trials comparing laparoscopic and open surgery for Crohn's disease.** Surg Endosc 2005; 19(12):1549-1555.

10 Tilney HS, Constantinides VA, Heriot AG, Nicolaou M, Athanasiou T, Ziprin P et al. **Comparison of laparoscopic and open ileocecal resection for Crohn's disease: a metaanalysis.** Surg Endosc 2006; 20(7):1036-1044.

11 Tan JJ, Tjandra JJ. **Laparoscopic surgery for Crohn's disease: a meta-analysis.** Dis Colon Rectum 2007; 50(5):576-585.

12 Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ et al. **Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial.** Ann Surg 2006; 243(2):143-149.

13 Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA et al. **Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease.** Br J Surg 2010; 97(4):563-568.

14 Polle SW, Bemelman WA. **Surgery insight: minimally invasive surgery for IBD.** Nat Clin Pract Gastroenterol Hepatol 2007; 4(6):324-335.

15 Bucher P, Pugin F, Morel P. **Single port access laparoscopic right hemicolectomy.** Int J Colorectal Dis 2008; 23(10):1013-1016.

16 Adair J, Gromski MA, Lim RB, Nagle D. **Single-incision laparoscopic right colectomy: experience with 17 consecutive cases and comparison with multiport laparoscopic right colectomy.** Dis Colon Rectum 2010; 53(11):1549-1554.

17 Boni L, Dionigi G, Cassinotti E, Di GM, Diurni M, Rausei S et al. **Single incision laparoscopic right colectomy.** Surg Endosc 2010; 24(12):3233-3236.

18 Bucher P, Pugin F, Morel P. **Transumbilical single incision laparoscopic sigmoidectomy for benign disease.** Colorectal Dis 2010; 12(1):61-65.

19 Chen WT, Chang SC, Chiang HC, Lo WY, Jeng LB, Wu C et al. **Single-incision laparoscopic versus conventional laparoscopic right hemicolectomy: a comparison of short-term surgical results.** Surg Endosc 2011; 25(6):1887-1892.

20 Geisler DP, Condon ET, Remzi FH. **Single incision laparoscopic total proctocolectomy with ileopouch anal anastomosis.** Colorectal Dis 2010; 12(9):941-943.

21 Katsuno G, Fukunaga M, Nagakari K, Yoshikawa S, Ouchi M, Hirasaki Y. **Single-incision laparoscopic colectomy for colon cancer: early experience with 31 cases.** Dis Colon Rectum 2011; 54(6):705-710.

22 Leblanc F, Champagne BJ, Augestad KM, Stein SL, Marderstein E, Reynolds HL et al. **Single incision laparoscopic colectomy: technical aspects, feasibility, and expected benefits.** Diagn Ther Endosc 2010; 2010:913216.

23 McNally ME, Todd MB, Brown KM. **Single-incision laparoscopic colectomy for malignant disease.** Surg Endosc 2011; 25(11):3559-3565.

24 Remzi FH, Kirat HT, Kaouk JH, Geisler DP. **Single-port laparoscopy in colorectal surgery.** Colorectal Dis 2008; 10(8):823-826.

25 Rieger NA, Lam FF. **Single-incision laparoscopically assisted colectomy using standard laparoscopic instrumentation**. Surg Endosc 2010; 24(4):888-890.

26 Vestweber B, Alfes A, Paul C, Haaf F, Vestweber KH. **Single-incision laparoscopic surgery: a promising approach to sigmoidectomy for diverticular disease.** Surg Endosc 2010; 24(12):3225-3228.

27 Waters JA, Guzman MJ, Fajardo AD, Selzer DJ, Wiebke EA, Robb BW et al. **Single-port laparoscopic right hemicolectomy: a safe alternative to conventional laparoscopy.** Dis Colon Rectum 2010; 53(11):1467-1472.

28 Papaconstantinou HT, Sharp N, Thomas JS. **Single-incision laparoscopic right colectomy: a case-matched comparison with standard laparoscopic and hand-assisted laparoscopic techniques.** J Am Coll Surg 2011; 213(1):72-80.

29 Gardenbroek TJ, Eshuis EJ, van Acker GJ, Tanis PJ, Bemelman WA. **Alternative specimen extraction techniques after laparoscopic emergency colectomy in inflammatory bowel disease.** Surg Endosc 2012; 26(2):408-412.

30 Rijcken E, Mennigen R, Argyris I, Senninger N, Bruewer M. **Single-incision laparoscopic surgery for ileocolic resection in Crohn's disease.** Dis Colon Rectum 2012; 55(2):140-146.

31 Heeney A, O'Connor DB, Martin S, Winter DC. **Single-port access laparoscopic surgery for complex Crohn's disease.** Inflamm Bowel Dis 2010; 16(8):1273-1274.

32 Scaringi S, Giudici F, Liscia G, Cenci C, Tonelli F. **Single-port laparoscopic access for Crohn's disease complicated by enterocutaneous fistula.** Inflamm Bowel Dis 2011; 17(2):E6-E7.

33 Gaujoux S, Bretagnol F, Ferron M, Panis Y. **Single-incision laparoscopic colonic surgery.** Colorectal Dis 2011; 13(9):1066-1071.

34 Chaudhary B, Glancy D, Dixon AR. **Laparoscopic surgery for recurrent ileocolic Crohn's disease is as safe and effective as primary resection.** Colorectal Dis 2011; 13(12):1413-1416.

35 Stewart DB, Messaris E. **Early experience with single-site laparoscopic surgery for complicated ileocolic Crohn's disease at a**

tertiary-referral center. Surg Endosc 2012; 26(3):777-782.

36 Hernandez J, Ross S, Morton C, McFarlin K, Dahal S, Golkar F et al. **The learning curve of laparoendoscopic single-site (LESS) cholecystectomy: definable, short, and safe.** J Am Coll Surg 2010; 211(5):652-657.

37 Ma J, Cassera MA, Spaun GO, Hammill CW, Hansen PD, Aliabadi-Wahle S. **Randomized controlled trial comparing single-port laparoscopic cholecystectomy and four-port laparoscopic cholecystectomy.** Ann Surg 2011; 254(1):22-27.

38 Huscher CG, Mingoli A, Sgarzini G, Mereu A, Binda B, Brachini G et al. **Standard laparoscopic versus single-incision laparoscopic colectomy for cancer: early results of a randomized prospective study.** Am J Surg 2012; 204(1):115-120.

39 Larson DW, Dozois E, Sandborn WJ, Cima R. **Total laparoscopic proctocolectomy with Brooke ileostomy: a novel incisionless surgical treatment for patients with ulcerative colitis.** Surg Endosc 2005; 19(9):1284-1287.

40 Whiteford MH, Denk PM, Swanstrom LL. **Feasibility of radical sigmoid colectomy performed as natural orifice translumenal endoscopic surgery (NOTES) using transanal endoscopic microsurgery.** Surg Endosc 2007; 21(10):1870-1874.

41 Wexner SD. **Restorative proctectomy with colon pouch-anal anastomosis by laparoscopic transanal pull-through: an available option for low rectal cancer?** Surg Endosc 2007; 21(9):1679.

42 Levitt MA, Martin CA, Falcone RA, Jr., Pena A. **Transanal rectosigmoid resection for severe intractable idiopathic constipation.** J Pediatr Surg 2009; 44(6):1285-1290.

43 Eshuis EJ, Voermans RP, Stokkers PC, van Berge Henegouwen MI, Fockens P, Bemelman WA. **Laparoscopic resection with transcolonic specimen extraction for ileocaecal Crohn's disease.** Br J Surg 2010; 97(4):569-574.

44 Basu A, Wexner SD. **Perianal Crohn's Disease.** Curr Treat Options Gastroenterol 2002; 5(3):197-206.

45 Williamson PR, Hellinger MD, Larach SW, Ferrara A. **Twenty-year review of the surgical management of perianal Crohn's disease.** Dis Colon Rectum 1995; 38(4):389-392.

46 Bernell O, Lapidus A, Hellers G. **Recurrence after colectomy in Crohn's colitis.** Dis Colon Rectum 2001; 44(5):647-654.

47 Lock MR, Fazio VW, Farmer RG, Jagelman DG, Lavery IC, Weakley FL. **Proximal recurrence and the fate of the rectum following excisional surgery for Crohn's disease of the large bowel.** Ann Surg 1981; 194(6):754-760.

48 Stern HS, Goldberg SM, Rothenberger DA, Nivatvongs S, Schottler J, Christenson C et al. **Segmental versus total colectomy for large bowel Crohn's disease.** World J Surg 1984; 8(1):118-122.

49 Guillem JG, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC, Schoetz DJ, Jr. **Factors predictive of persistent or recurrent Crohn's disease in excluded rectal segments.** Dis Colon Rectum 1992; 35(8):768-772.

50 Yamamoto T, Bain IM, Allan RN, Keighley MR. **Persistent perineal sinus after proctocolectomy for Crohn's disease.** Dis Colon Rectum 1999; 42(1):96-101.

51 Maeda Y, Heyckendorff-Diebold T, Tei TM, Lundby L, Buntzen S. **Gracilis muscle transposition for complex fistula and persistent nonhealing sinus in perianal Crohn's disease.** Inflamm Bowel Dis 2011; 17(2):583-589.

52 Schaffzin DM, Douglas JM, Stahl TJ, Smith LE. **Vacuum-assisted closure of complex perineal wounds.** Dis Colon Rectum 2004; 47(10):1745-1748.

8

Single-port versus multiport laparoscopic ileocecal resection for Crohn's disease

Tjibbe J. Gardenbroek[1], Tessa Verlaan[1,2], Pieter J. Tanis[1], Cyriel Y. Ponsioen[2], Geert R. A. M. D'Haens[2], Christianne J. Buskens[1] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery and [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Journal of Crohn's and Colitis 2013

ABSTRACT

Background

Several case series have demonstrated the feasibility of single-port laparoscopic ileocecal resection in Crohn's disease. However, only a few studies compared the single-port with a multiport laparoscopic ileocecal approach. The aim of this study was to compare short term surgical outcome parameters between single-port and multiport laparoscopic ileocecal resection for Crohn's disease.

Methods

Twenty-one patients who underwent single-port laparoscopic ileocecal resection between March 2010 and September 2012 were prospectively registered. A matched comparison on a 1:2 basis was performed with patients who underwent multiport laparoscopic ileocecal resection from January 1999 to March 2010. Matching parameters were BMI, length of diseased bowel resected and the presence of fistulas. Endpoints were the length of postoperative hospital stay, operative time, conversions, complications, postoperative pain scores and postoperative analgesia consumption.

Results

Twenty-one patients undergoing single-port resection were matched to 42 patients undergoing multiport resection. The postoperative stay (4 days, iqr 4-5 vs. 5 days, iqr 4-6; P = 0.033), operative time (103 min, iqr 94.0-121.0 vs. 123.5 min , iqr 100.0-157.0; P = 0.036) and morphine use on the first postoperative day (12.5 mg, iqr 5.0-33.3 vs. 28 mg, 15.0-50.0; P = 0.012) differed significantly. Postoperative pain scores and complications were similar in both groups. This study was limited by potential selection bias.

Conclusions

Single-port laparoscopic ileocecal resection is safe and feasible in Crohn's disease and is associated with less need for pain medication postoperatively as opposed to multiport laparoscopic ileocecal resection.

INTRODUCTION

Laparoscopic ileocecal resection in the management of ileocecal Crohn's disease has established short- and long term advantages[1-4]. Current guidelines by the European Crohn's and Colitis Organisation (ECCO) state the preference for a laparoscopic approach in patients undergoing ileocecal resection for Crohn's disease[5;6].

Single-port laparoscopic surgery facilitates the ileocecal resection to be performed entirely through one extraction site. This approach potentially reduces the abdominal trauma and postoperative pain, and improves cosmetic outcomes further. However, it may increase the operative time. Several reports have demonstrated the feasibility of the single-port laparoscopic ileocecal resection[7-9], but only a few studies compared the single-port with the multiport laparoscopic approach[10;11].

The objective of this study was to compare single-port laparoscopic ileocecal resection (SP-ICR) to case matched patients undergoing multiport laparoscopic ileocecal resection (ML-ICR) for Crohn's disease with respect to short term outcomes.

METHODS

Patients who underwent SP-ICR between March 2010 and September 2012 were prospectively registered. To compare these patients with a historical cohort, we retrospectively identified all patients who underwent ML-ICR for Crohn's disease from January 1999 to March 2010 in the Academic Medical Centre, Amsterdam, in The Netherlands. The Ethics Committee of the Amsterdam Medical Centre concluded that, according to local customs and practice, an official institutional review board approval for this study was not required.

Laparoscopic ileocecal resection

All surgeries were performed by experienced laparoscopic colorectal surgeons. Surgery was performed under general anaesthesia, and patients received intravenous antibiotic prophylaxis. Patients were placed in the French position on a bean bag, with the legs abducted. The SP-ICR procedures were conducted using the Single Site Laparoscopy Access System (Ethicon Endo-Surgery Inc., Cincinnati, Ohio, USA) or the GelPoint™ Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA, USA) positioned at the umbilicus (*Figure 1*). Mobilisation of the right colon was done laparoscopically. Devascularisation of the affected bowel was performed with ultrasonic dissection (Ultracision, Johnson and Johnson Medical, Inc., New Brunswick, NJ). The extraction of the specimen through the single port allowed the creation of a stapled antiperistaltic side to side anastomosis between the terminal ileum and the ascending colon extracorporeally with a linear stapler (2 cartridges of the PLC 75 mm stapler; Ethicon Endo-Surgery Inc., Cincin-

nati, Ohio, USA). After correctly orientating the neo-terminal ileum intra-abdominally, the umbilical port site was closed in layers (*Figure 2*). Additional ports placed during the operation were recorded as conversion to ML-ICR.

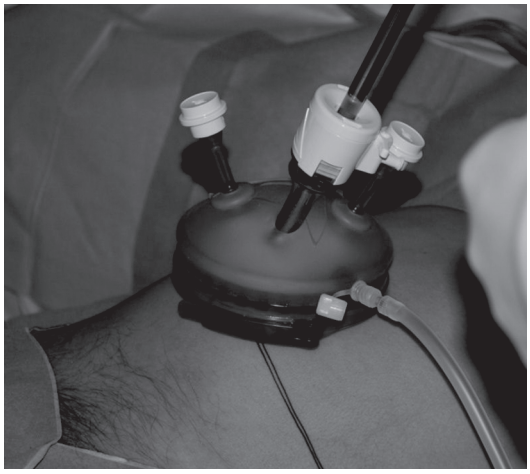


Figure 1 Single-port positioned in the umbilicus.

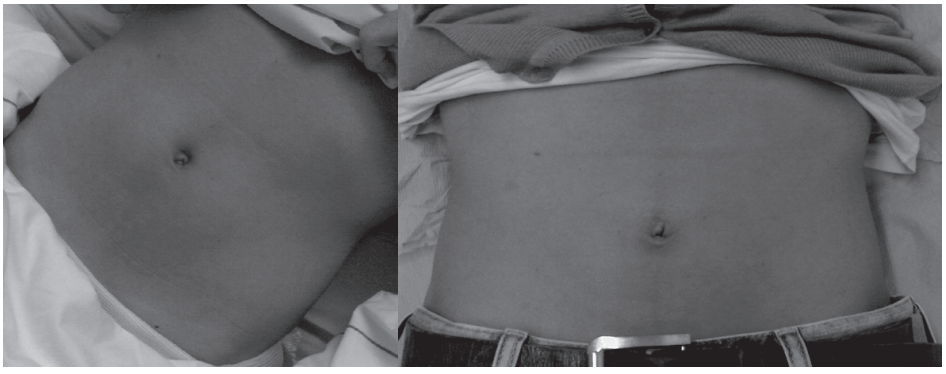


Figure 2a Abdomen of patient before single-port ileocecal resection
Figure 2b Postoperative result after single-port ileocecal resection

Standard ML-IRC included the insertion of up to 4 standard ports (1 in the umbilicus, 1 or 2 on the right side of the abdomen, 1 or 2 on the left side). For specimen extraction, the umbilical port incision was extended to 4 to 5 cm.

In case of entero-vesical or entero-sigmoidal fistula or large inflammatory mass, a Pfannenstiel incision was made and a hand-assisted laparoscopy was performed. Conversions to laparotomy were recorded. Lengthening of the midline incision greater than needed to extract the specimen was considered a conversion to laparotomy. The authors do not have

a conflict of interest. All devices mentioned were acquired by the Department of Surgery at the Academic Medical Centre.

Outcomes

The following variables were collected for both groups: age, sex, body mass index (BMI), indication for surgery, preoperative medical treatment, admission date, surgery date, operative time, additional procedures, conversions, intraoperative complications, postoperative complications (within 30 days of surgery), reoperation rate (within 30 days of surgery) and discharge date. Postoperative complications were defined as any deviation from the normal postoperative course within 30 days after ileocecal resection. An abscess was defined as an abscess confirmed by CT scan or during (radiological) re-intervention. Wound infection was defined as signs of infection or purulent discharge, requiring deliberate opening of the wound or antibiotic treatment. Postoperative pain was routinely assessed by means of a visual analogue scale (VAS), where 0 represented no pain and 10 the worst pain imaginable. This VAS was measured at days 1 to 3 after operation and was derived from anaesthetist' forms and/or nursing records. All patients received a comparable postoperative pain regimen including patient controlled analgesia (PCA) with intravenous morphine (loading dose 50-100 mcg/kg and 1 mg per pump activation with a maximum of 40 mg morphine/4h), if possible in combination with paracetamol and non-steroidal anti-Inflammatory drugs (NSAIDS). During this treatment pain scores and sedation scores were measured regularly. A VAS score of 4 or less was aimed for and guided the administering of pain medication.

Statistical analysis

All SP-ICR patients were individually case matched for BMI (± 3 points), length of diseased bowel resected (± 5cm) and the presence or absence of internal fistulas to 2 patients undergoing ML-ICR. In all patients a similar postoperative enhanced care protocol was used[12]. Data was collected and analysed using IBM SPSS Statistics for Windows®, Version 19.0 (IBM Corp., Armonk, NY, United States). Data are presented as mean ± standard deviation in case of parametric data and as median with inter quartile range (iqr) in case of non-parametric data. Categorical data were analysed with Fisher's exact test or χ^2 test. Continuous variables were analysed using the Mann-Whitney-Wilcoxon test. $P < 0.05$ was considered significant.

RESULTS

Twenty-four patients underwent SP-ICR for Crohn's disease between March 2010 and September 2012. From January 1999 to March 2010 a total of 86 patients underwent ML-ICR. Of the 24 SP-ICR patients, 21 patients could be matched to 42 patients that underwent ML-

ICR. Three SP-ICR patients could not be matched to ML-ICR patients and were therefore not included in the analysis.

Both groups consisted predominantly of females and had a median age of 26 years at the time of surgery (*Table 1*). Matching was successful, considering that the SP-ICR group and the ML-ICR group both had a median BMI of 21.5 (iqr 18.8-23.3 and 19.8-23.9, respectively), a similar median length of diseased bowel resected of 28 (iqr 15.5-37.5) vs. 25.5 (iqr 19-33.5) centimetre and the presence of an enteric fistula in 1 (4.8%, terminal ileum to bladder and sigmoid colon) versus 2 (4.8%, terminal ileum to sigmoid colon and transverse colon) patients respectively.

Table 1 Patient demographics

	SP-ICR (n = 21)	ML-ICR (n = 42)	P-value
Female gender	14 (66.7)	31 (73.8)	0.568¶
Age at surgery	26 [21.5 - 40]	26 [23 – 35.5]	0.988†
BMI	21.5 [18.8 - 23.3]	21.5 [19.8 – 23.9]	0.374†
Disease duration (months)	56 [19 – 136.5]	17.5 [9 – 54.5]	0.009†
Medication at time of surgery			0.434§
Anti-TNF	3 (14.3)	4 (9.5)	
AZA / 6MP / MTX	6 (28.6)	7 (16.7)	
Steroids	6 (28.6)	13 (31)	
Previous abdominal surgery			0.576§
Appendectomy (McBurneys incision)	0	2 (4.8)	
Laparoscopic cholecystectomy	1 (4.8)	1 (2.4)	
Other*	0	1 (2.4)	
ERAS programme	21 (100)	3 (7.1)	<0.001¶

BMI: Body Mass Index (kg/m^2) Data are n (%) and median [interquartile range], SP-ICR: single-port laparoscopic ileocecal resection, ML-ICR: multiport laparoscopic ileocecal resection, ERAS: enhanced recovery after surgery, §Chi-square test / ¶Fisher's exact test (two-tailed) / †Mann Whitney U test. *Other procedure was refertilisation via laparotomy.

Operative time was shorter in the SP-ICR group compared to the ML-ICR group (103.0 minutes (iqr 94.0-121.0) versus 123.5 minutes (iqr 100.0-157.0), P = 0.036, *Table 2*). Operative time was also compared in patients with an umbilical incision between both groups; no difference in operative time was seen; 107.0 minutes (iqr 94.0-129.3) in the ML-ICR group versus 103.0 minutes (iqr 94.0-121.0, P = 0.447) in the SP-ICR group. One patient (4.8%) in the SP-ICR group and 2 patients (4.8%) in the ML-ICR group underwent hand-assisted laparoscopy (P = 1.000) due to a large inflammatory specimen or entero-sigmoidal fistula. No conversions to laparotomy were performed. The type of anastomosis and fashioning of the anastomosis (stapled or hand-sewn) differed between the groups; in all SP-ICR

cases a side-to-side stapled anastomosis was performed, whereas the anastomosis type and fashion varied for the ML-ICR cases.

There were no significant differences between the groups concerning complications, reoperations, or re-admissions, as outlined in *Table 2*. In the SP-ICR group, 1 patient (4.8%) was readmitted due to an intra-abdominal abscess. One other patient in this group was readmitted due to the development of a fluid collection. In both patients the collection

Table 2 Operative and peri-operative outcomes

	SP-ICR (n = 21)	**ML-ICR (n = 42)**	**P-value**
Operation time (minutes)	103 [94 - 121]	123.5 [100 - 157]	0.036†
HALS procedure	1 (4.8)	2 (4.8)	1.000¶
Conversion to laparotomy	0	0	
Extraction site			0.000§
Umbilicus	21 (100)	26 (61.9)	
Pfannenstiel	0	12 (28.6)	
Other*	0	2 (4.8)	
Type of anastomosis			0.003§
S-S	21 (100)	18 (42.8)	
E-S	0	15 (35.7)	
S-E	0	1 (2.4)	
E-E	0	3 (7.1)	
Anastomosis stapled / handsewn	21/0	6/36	0.000¶
Additional procedures			
Fistula closure	1 (4.8)	2 (4.8)	0.842§
Length of resected bowel (cm)	28 [15.5 - 37.5]	25.5 [19 - 33.5]	0.782†
Complications			0.638§
Anastomotic leakage	0	1 (2.4)	
Intra-abdominal abscess	1 (4.8)	0	
Intra-abdominal fluid collection	1 (4.8)	2 (4.8)	
Wound infection	0	1 (2.4)	
Ileus	1 (4.8)	1 (2.4)	
Other**	2 (9.5)	1 (2.4)	
Relaparoscopy	0	2 (4.8)	0.495¶
Postoperative hospital stay	4 [4-5]	5 [4-6]	0.033†
Readmission within 30 days	2 (9.5)	3 (7.1)	1.000¶
Mortality	0	0	

Data are n (%) and median [interquartile range], SP-ICR: single-port laparoscopic ileocecal resection, ML-ICR: multiport laparoscopic ileocecal resection, HALS: hand-assisted laparoscopy, variables containing missing data: anastomosis type: 6, anastomosis fashion: 7, §Chi-square test / ¶Fisher's exact test (two-tailed) / †Mann Whitney U test. *Other extraction site was a previously made McBurney incision in 2 patients **Other complications were bladder retention and aspiration after detubation in the SP-ICR group and urinary tract infection in the ML-ICR group

was percutaneously drained. In the ML-ICR group, 1 patient (2.4%) developed an anastomotic leakage. One other patient underwent relaparoscopy however no anastomotic leakage or abscess was found. Two patients in the ML-ICR group were readmitted due to the development of a postoperative fluid collection, but no intervention was needed. Hospital stay was significantly shorter in the SP-ICR group with a postoperative stay of 4 days (iqr 4-5), while this was 5 days (iqr 4-6) in the ML-ICR group (P = 0.033). Although median postoperative pain scores (VAS) did not differ between the groups (P >0.05, *Figure 3*), patients in the SP-ICR group required less morphine (12.5 mg, iqr 5.0-33.3 vs. 28 mg, iqr 15.0-50.0, P = 0.012) on the first postoperative day (*Figure 3*). When comparing morphine use on postoperative day one between the patients with an umbilical incision in both groups, the morphine use still differed significantly (SP-ICR 12.5 mg (iqr 5.0-33.3) vs ML-ICR 23 mg (iqr 15.0-55.0), P = 0.016).

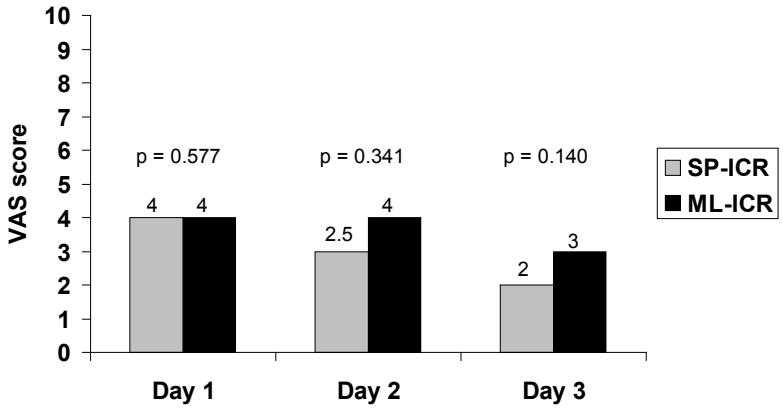


Figure 3 Postoperative VAS scores derived from anaesthesiologist records, on a scale from 1 (no pain) – 10 (worst pain).

DISCUSSION

Reductions in the postoperative length of stay, operative time and morphine use on postoperative day one were observed after SP-ICR. No difference in conversions, complications and postoperative pain scores were observed.

In colorectal surgery, a laparoscopic approach has been associated with better short-term outcomes compared to open surgery, consisting of reduced morbidity, reduced postoperative pain, shorter hospitalisation, and faster return to normal bowel function and normal daily activities[13;14]. Several studies have shown advantages of the laparoscopic ileocecal resection compared to the open procedure in Crohn's disease[1-4]. Single-port procedures in patients with inflammatory bowel disease are increasingly reported in the

recent years, even in complex procedures[15]. Recently, the feasibility and safety of SP-ICR in patients with ileocecal Crohn's disease was demonstrated, however few studies comparing SP-ICR with ML-ICR have been reported[7-11]. No significant differences in operative times, postoperative length of stay, and complications were found in these studies. Only one of these studies reported on postoperative pain scores after ileocecal resection[11], although no data on the postoperative analgesia requirement was provided.

Our study, in which perioperative SP-ICR data is compared to a larger matched control group than in previous studies, is consistent with the available data. In addition, we have observed a reduction in the postoperative length of stay, operative time and morphine use on postoperative day one in the single-port group. It is possible that the enhanced recovery after surgery (ERAS) programmes were more optimised in the later years of the study period, and influenced the reduction in postoperative hospital stay found in the SP-ICR group. However, for colon cancer, it is described that postoperative hospital stay is mostly influenced by type of surgery (laparoscopic surgery) instead of enhanced recovery after surgery programmes only[16]. A reduction of morphine use on the first postoperative day was found in the SP-ICR group only, although there were no significant differences in the postoperative pain scores (VAS). This is a very small difference and of unknown clinical relevance. One might consider that the incidence of Pfannenstiel incisions in the ML-ICR group affects morphine use. However, when comparing morphine use on postoperative day one only between the patients with an umbilical incision in both groups, day-1 morphine use still differed significantly. Morphine use could therefore be attributable to pain as a consequence of the lateral trocar incisions used with ML-ICR.

Our study differs from available literature in the selection of the matching criteria. These represent factors that are most likely to influence the procedure, hereby providing a more correct representation of the operative time than provided by other studies. On the other hand, more previous abdominal procedures were performed in patients in the ML-ICR group. This could have influenced the complexity of the procedure and extended the operative time in this group. A Pfannenstiel incision was performed in a considerable number of patients in the ML-ICR group and substantially more hand-sewn anastomoses were performed in this group. The difference in operating time between the two procedures is approximately 20 minutes. This could be explained by the larger amount of double layer, hand-sewn anastomoses in the ML-ICR group compared to the SP-ICR group, in which all patients had a stapled anastomosis. The stapled side-to-side anastomosis is most indicated in Crohn's disease[17]. When comparing the operation time in patients with an umbilical incision between both groups, no difference in operative time was seen. The shorter operative time in the SP-ICR group therefore presumably reflects changes in preferred surgical techniques over time. Furthermore, disease duration in the two groups differed significantly (56.0 vs. 17.5 months). This suggests a modification in the surgical approach of terminal ileitis that

is in line with current trends between gastroenterologist and surgeons. By performing an early resection, probably less pre-operative complications such as fistulas, have developed.

For the single-port procedure, one vertical incision is made in the umbilicus. During the procedure, the mesentery should be dissected intra-corporally to facilitate easier extraction of the bowel and to minimise the incision. Therefore, the single-port procedure is only advisable when the inflammatory mass is not too bulky; in that case a Pfannenstiel incision is necessary. Because the incision is made in the shallow of the umbilicus it is not easily visible. For this reason it is expected that the cosmesis improves compared to the multiport approach, although this is not yet proven. The single-port technique is a technically more difficult procedure due to the hampered triangulation. In addition to these technical challenges, the costs associated with the use of the disposable single ports are added to the general procedure related costs. However, if one takes into account that the average single port system in our hospital costs approximately 300 Euros and hospitalization for one day in our hospital costs 575 Euros[18], the single port surgery is not more expensive than the multiport procedure. Also important in single-port surgery for Crohn's disease is the feasibility of an accurate intraoperative staging of the disease and subsequent remission. The follow-up interval of the SP-ICR patients is brief compared to the ML-ICR group. Therefore, it is currently not possible to perform a justified comparison between remission rates. A long-term follow up evaluation of these patients should determine remission rate. However, a minimum follow-up interval of some years is needed to perform a valuable judgement. Eshuis et al. showed a clinical remission rate of 16-40% at 7 years after ileocecal resections for Crohn's disease [3].

With the single-port technique, various options for conversion are available if necessary; it can be converted to a multiport or hand-assisted procedure and if required a laparotomy can be performed by extension of the vertical umbilical incision.

The results of this study are limited by the single centre design of the study and the different time periods in which both treatments were performed. This creates potential selection bias. Furthermore, it can be expected that unmatched variables between the 2 groups might have induced selection bias in this study. Moreover, other outcomes such as costs, the effect on cosmesis and long-term outcomes on incisional hernias were not addressed.

This study demonstrates that with single-port laparoscopic ileocecal resection the advantages of the laparoscopic approach are preserved and that the procedure is feasible and safe in selected patients. Compared to multiport laparoscopic ileocecal resection, the single-port procedure was associated with a reduced length of stay, operative time and morphine use on postoperative day one and similar overall complications. These results encourage the use of the single port in ileocecal resection for Crohn's disease. Larger studies with longer follow-up that address technical details and cost of the procedure, cosmesis and incisional hernias will determine whether single-port ileocecal resection will earn a definite place in the treatment of Crohn's patients.

REFERENCES

1 Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ et al. **Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial.** Ann Surg 2006; 243(2):143-149.

2 Polle SW, Wind J, Ubbink DT, Hommes DW, Gouma DJ, Bemelman WA. **Short-term outcomes after laparoscopic ileocolic resection for Crohn's disease. A systematic review.** Dig Surg 2006; 23(5-6):346-357.

3 Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA et al. **Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease.** Br J Surg 2010; 97(4):563-568.

4 Dasari BV, McKay D, Gardiner K. **Laparoscopic versus Open surgery for small bowel Crohn's disease.** Cochrane Database Syst Rev 2011;(1):CD006956.

5 Dignass A, Van AG, Lindsay JO, Lemann M, Soderholm J, Colombel JF et al. **The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management.** J Crohns Colitis 2010; 4(1):28-62.

6 Travis SP, Stange EF, Lemann M, Oresland T, Bemelman WA, Chowers Y et al. **European evidence-based Consensus on the management of ulcerative colitis: Current management.** J Crohns Colitis 2008; 2(1):24-62.

7 Chaudhary B, Glancy D, Dixon AR. **Laparoscopic surgery for recurrent ileocolic Crohn's disease is as safe and effective as primary resection.** Colorectal Dis 2011; 13(12):1413-1416.

8 Gaujoux S, Bretagnol F, Ferron M, Panis Y. **Single-incision laparoscopic colonic surgery.** Colorectal Dis 2011; 13(9):1066-1071.

9 Ross H, Steele S, Whiteford M, Lee S, Albert M, Mutch M et al. **Early multi-institution experience with single-incision laparoscopic colectomy.** Dis Colon Rectum 2011; 54(2):187-192.

10 Maeda K, Noda E, Nagahara H, Inoue T, Takii M, Watanabe K et al. **A comparative study of single-incision versus conventional multiport laparoscopic ileocecal resection for Crohn's disease with strictures.** Asian J Endosc Surg 2012; 5(3):118-122.

11 Rijcken E, Mennigen R, Argyris I, Senninger N, Bruewer M. **Single-incision laparoscopic surgery for ileocolic resection in Crohn's disease.** Dis Colon Rectum 2012; 55(2):140-146.

12 Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF et al. **Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study).** Ann Surg 2011; 254(6):868-875.

13 Kolfschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J et al. **Successful and Safe Introduction of Laparoscopic Colorectal Cancer Surgery in Dutch hospitals.** Ann Surg 2012.

14 Schwenk W, Haase O, Neudecker J, Muller JM. **Short term benefits for laparoscopic colorectal resection.** Cochrane Database Syst Rev 2005;(3):CD003145.

15 Rijcken E, Mennigen R, Senninger N, Bruewer M. **Single-port laparoscopic surgery for inflammatory bowel disease.** Minim Invasive Surg 2012; 2012:106878.

16 Vlug MS, Bartels SA, Wind J, Ubbink DT, Hollmann MW, Bemelman WA. **Which fast track elements predict early recovery after colon cancer surgery?** Colorectal Dis 2012; 14(8):1001-1008.

17 Simillis C, Purkayastha S, Yamamoto T, Strong SA, Darzi AW, Tekkis PP. **A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease.** Dis Colon Rectum 2007; 50(10):1674-1687.

18 CVZ. **Handleiding voor kostenonderzoek (manual for cost research).** CVZ . 2012. 19-12-2012.

II

THE APPENDIX IN ULCERATIVE COLITIS

9

The effect of appendectomy on the course of ulcerative colitis: a systematic review

Tjibbe J. Gardenbroek[1], Emma J. Eshuis[1,2], Cyriel Y. Ponsioen[2], Dirk T. Ubbink[1,3], Geert R. A. M. D'Haens[2] and Willem A. Bemelman[1]

Affiliations

[1]Department of Surgery, [2]Department of Gastroenterology and Hepatology and [3]Quality Assurance and Process Innovation, Academic Medical Centre, Amsterdam, The Netherlands

Colorectal Disease 2012

ABSTRACT

Background

Previous studies have shown significantly lower appendectomy rates in ulcerative colitis (UC) patients compared with healthy controls. Evidence indicating that the appendix has an immunomodulatory role in UC has been accumulating. Aim was to examine the latest evidence on the effect of appendectomy on the disease course in patients with UC.

Methods

PubMed, The Cochrane library, and EMBASE were searched. Primary end-points were number of relapses, use of steroids, number of hospital admissions and number of colectomies.

Results

The search resulted in 6 observational studies (5 case control studies and one cohort study) totalling 2532 patients. Owing to clinical heterogeneity, no meta-analysis could be conducted. One study found lower relapse rates in patients appendectomised before the onset of UC (absolute risk reduction (ARR) = 21.5%; 95% CI: 1.71% - 45.92%). Another 2 studies found a reduced requirement for immunosuppression in appendectomised patients (ARR = 20.2%; 95% CI: 9.67% - 30.46% in the first study and ARR = 21.4%; 95% CI: 10.32%- 32.97% in the second study). In addition, one study found lower colectomy rates in nonappendectomised patients (ARR = 8.7%; 95% CI: 1.29% - 18.66%), and 2 studies found lower colectomy rates in appendectomised patients (ARR = 21.4%; 95% CI: 13.17% - 28.79% in the first study and ARR = 18.7%; 95% CI: 7.50% - 29.97% in the second study).

Conclusions

There are limited and conflicting data available regarding the effect of appendectomy on the disease course of UC. Most studies suggest a beneficial effect and the minority find no, or a negative, effect.

INTRODUCTION

Ulcerative Colitis (UC) diffusely affects the colonic mucosa, and is characterized by episodes of relapse and remission[1]. UC should be regarded as a multifactorial disease involving an interaction between genetic and environmental factors that give rise to an inappropriate immunologic response[2]. The disease activity is confined to the colon, and almost always involves the rectum. Patients can be classified as having proctitis (disease limited to the rectum), left-sided colitis (disease activity extending to the proximal bowel but not beyond the splenic flexure), or pancolitis (disease activity extending from the rectum proximally to the cecum). Most UC patients can be treated effectively with medical therapy. When the disease is unresponsive, surgery is indicated usually in the form of restorative proctocolectomy. Up to 30%-40% of patients with UC ultimately require surgery depending on local medical culture and availability of biologic therapies[3;4]. The complications of surgery have been studied in a meta-analysis[5].

The trigger for the development of UC is still unknown. However, cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells are considered to play an important role in the pathogenesis of UC. T-helper type 2 cells and their cytokines, particularly interleukin (IL)-4, have been suggested to enhance the development of UC[6]. Cytokine production within the appendix has been proposed to trigger an immunological cascade in the colorectum[7;8]. The appendix is therefore suggested to be a potential priming site in the development of UC[9].

There is growing evidence in the literature inversely linking prior appendectomy with the subsequent risk of developing of ulcerative colitis. This inverse association was first reported in 1987 as an unexpected finding in a study of childhood determinants of inflammatory bowel diseases[10]. Only when another study[11] reported a low incidence, of 0.6%, of appendectomy in UC patients compared with an incidence of more than 25% in controls from orthopaedic clinics, did this inverse relation attract major attention. Since then, various epidemiological and case-control studies have investigated the association between appendicitis, appendectomy and the risk of developing UC.

Furthermore, a study with a T-cell receptor α-chain knockout mouse model of colitis showed that the development of inflammation was suppressed in those animals that underwent appendectomies, particularly at 3-5 weeks of age[12]. Together with the findings that periappendiceal inflammation with a cecal patch occurs commonly as a skip lesion in UC, even in left-sided colitis[13-15], it has been suggested that the appendix is closely related to the pathogenesis of UC. The aim of this systematic review was to examine the latest evidence on the effect of appendectomy on the disease course of patients with UC.

METHODS

Search Strategy and study selection

The electronic databases PubMed, The Cochrane library, and EMBASE were searched up to 2 August 2010 by a clinical librarian. The search was performed with both keywords and MeSH terms. The search consisted of: ulcerative colitis OR colitis, ulcerative [MESH] AND (appendix OR appendectomy OR appendicectomy OR appendiceal).

Two reviewers (T.G. and E.E.) independently screened titles and abstracts for their relevance. In the event of disagreement between the two reviewers, a third reviewer (W.B.) was involved. In addition, the reference lists of all included articles were hand searched for other relevant references.

Studies designed to evaluate the effect of appendectomy on the disease course in patients with UC were included. No limits were applied to the reason for appendectomy or timing of appendectomy in UC patients. Cases were defined as patients with UC who had undergone an appendectomy at any time. Controls were defined as UC patients who had not undergone an appendectomy. Editorials and commentaries were excluded, as well as animal studies. All controlled trials and observational studies designed to investigate this effect were selected. Inclusion was not otherwise restricted by study size, language or publication type.

Outcome measures

Primary outcomes considered were the number of relapses, the number of hospital admissions, the use of steroids, and the number of colectomies. These measures were selected because of their clinical relevance. The number of relapses reflects the increase of disease activity, which can be measured in the outpatient clinic. The number of hospital admissions indicates a severe increase in activity of UC. The need for steroids is a good clinical marker for severe disease. Colectomy rates show patients with UC refractory to medical management.

Data extraction and assessment of methodological quality

Data were extracted by two reviewers independently and included the study design (cohort vs. case control), patient characteristics, total number of persons in each comparison group, disease specifications, duration of disease, medication type, potential confounders used for adjustment (e.g. smoking) and the 4 different outcome measurements compared between the appendectomised and non-appendectomised patients. Inconsistencies between the data extractions were resolved by consensus. Data reporting conformed to the Meta-Analysis of observational Studies in Epidemiology (MOOSE) group guidelines[16].

The methodological quality of the studies included was assessed by two reviewers independently using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-

randomised studies in meta-analyses[17], including the recruitment of cases and controls, the assessment of disease state, the description of potential confounders and other forms of potential bias. In this assessment, stars can be allocated for every item. Three broad perspectives are judged: the selection of the study groups (maximum 4 stars); the comparability of the groups (maximum 2 stars); and the ascertainment of either the exposure or outcome of interest (maximum 3 stars). The assessment of methodological quality and the data extraction was performed by two reviewers independently.

SPSS version 18.0 for Windows® (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. Results for continuous data were expressed as median with range or mean ± standard deviation (SD). Results for the primary outcome measurements were expressed as absolute risk reduction (ARR) with 95% CI.

RESULTS

A total of 359 potentially relevant titles were identified from the literature search, of which 63 were considered relevant based on title and abstract. Hereafter, 22 articles were excluded because they were commentaries, 7 articles were excluded because they did not present new data, and 23 articles were excluded because they reported on the inverse association between appendectomy and UC, not on the effect on the disease course of patients with UC.

Five articles were case reports or case series and were therefore not included in the analysis. However, the main results of these articles are shown in this review to give a complete view of all available data on this subject. One of these articles was only available in Korean; this was translated by a native speaker. A total of 6 full text articles remained for final analysis and data extraction[18-23]. Details of the search are shown in *Figure 1*.

Description of studies

Naganuma et al.[18] performed a case control study with UC patients from seven different hospitals. The studies from Radford-Smith et al.[19] and Florin et al.[21] collected patients with UC from a clinical database during the time-periods 1995-1999 and 1995-2002, respectively. The study of Selby et al.[20] included consecutive patients from a single practice. Hallas et al.[22] collected incident appendectomised UC patients from a national hospital registry during the time-period 1977-1999 and matched these patients by sex, age and age at diagnosis with UC patients who did not have had an appendectomy (controls). Each control patient was assigned an index date corresponding to the appendectomy date of the matched patient, and the disease activity of both cases and controls in the periods before and after this index date was compared. Cosnes et al.[23] included a cohort of consecutive patients with UC from 1997 to 2000 and retrospectively studied the patients

who had undergone appendectomy before disease onset and prospectively studied patients who had an appendectomy after the onset of UC.

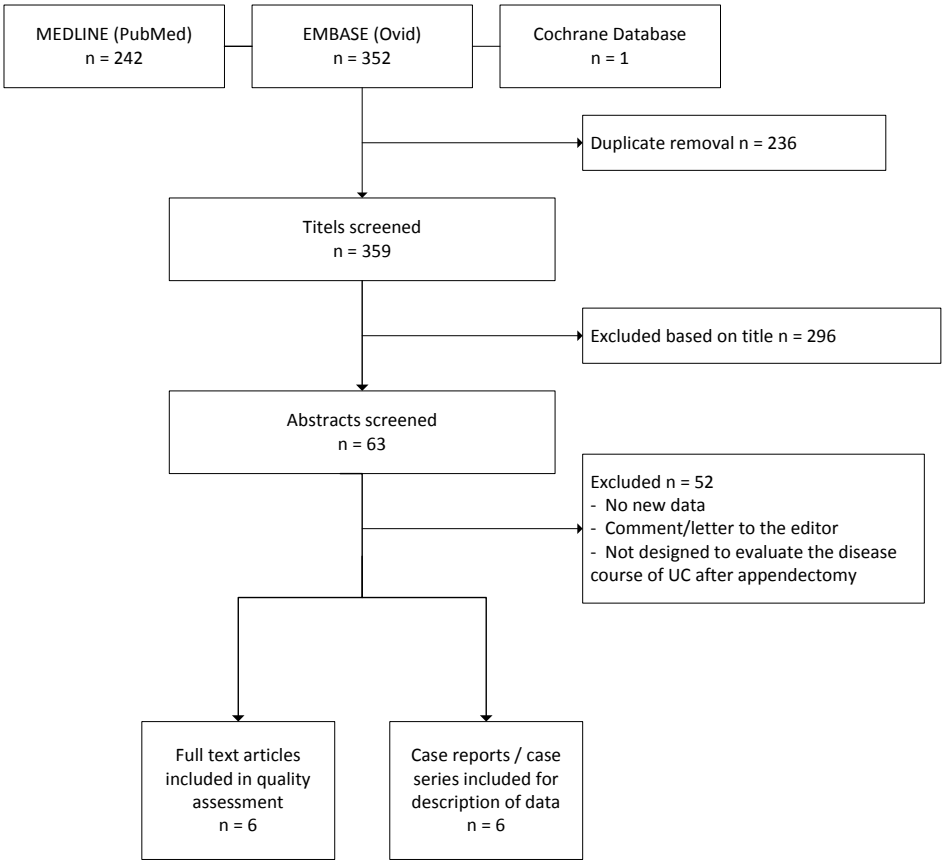


Figure 1 Flow chart of article inclusion

Methodological quality of studies

The methodological quality of the 6 included studies is summarized in *Table 1*. The overall quality of the studies was moderate. Of the 6 studies, five were case-control studies[18-22] and one was a cohort study[23]. The studies varied in the selection of cases and controls. Often there was no independent validation of cases[18;19;21;22] and no statement of potential selection bias[18;19]. Also, differences in comparability were present. A number of studies did not report any adjustment[18;20]; whereas in other studies adjustment was limited to age, sex and smoking[19], age, smoking status, immunosuppression and duration of disease[21] or duration of disease alone[22] or adjustment was extensively reported[23]. The exposure measurement was in all studies illustrated by the statement that medical charts, national registers, interviews and/or questionnaires were used.

Table 1 Assessment of the quality of the studies using the Newcastle-Ottawa Scale (NOS)

Author	Study type	Selection	Comparability	Exposure
Naganuma et al	case control	◊		◊
Radford-Smith et al	case control	◊◊	◊◊	◊
Selby et al	case control	◊◊◊◊		◊
Florin et al	case control	◊◊◊	◊◊	◊
Hallas et al	case control	◊	◊	◊
Cosnes et al	cohort	◊◊◊	◊◊	◊

In the assessment of methodological quality, three perspectives are judged: the selection of the study groups (maximum four points); the comparability of the groups (maximum two points); and the ascertainment of either the exposure or outcome of interest (maximum three points).

Outcome of studies

An outline of the results are shown in *Table 2 and 3*. Meta-analysis was not feasible because the studies were heterogeneous in terms of variation in outcome measures, timing of appendectomy and timing of measurements.

Of the four outcome measurements, Naganuma et al.[18] studied the relapse rates of UC. In this study, a relapse was defined as hospitalization or an increase in clinical activity of UC. The study found a lower relapse rate in patients who had an appendectomy before the onset of UC (57.1%) compared with controls who had not undergone appendectomy (78.6%) (ARR = 21.5%; 95% CI: 1.71% - 45.92%).

The use of steroids in both the appendectomy and nonappendectomy patients was investigated in four of the six studies[19-21;23]. Radford-Smith et al. and Florin et al. found a lower requirement for immunosuppression (defined as therapy with azathioprine, 6-mercaptopurine, methotrexate or mycophenolate) in the UC patients who had an appendectomy (4.8% and 5.6%, respectively) compared with the controls (25% and 27%, respectively) (ARR = 20.2%; 95% CI: 9.67% - 30.46% and ARR = 21.4%; 95% CI: 10.32%-32.97%, respectively). Selby et al. found no differences in ongoing immunosuppression requirement (defined as therapy with azathioprine, 6-mercaptopurine, or cyclosporine) between patients who had an appendectomy before onset of UC (33.3%), patients who had an appendectomy after onset of UC (12.5%) or the control group (18%). The study of Cosnes et al. found no difference in the necessity for oral steroids in the appendectomised (67%) and nonappendectomised (70%) patients.

In the study by Hallas et al.[22], the number of hospital admissions in patients with UC before and after the appendectomy compared with hospital admissions in controls before and after the index date were reported. The number of hospital admissions in the appendectomy group was 171 before and 117 after appendectomy (a decrease of 47%). The number of admissions in the control group was 631 before and 424 after the index date (a decrease of 49%).

Table 2 Overview of included studies

Author	Country	Study type	N patients	N controls	Appendectomy		Age (mean)		Disease localizations	Duration of disease	Medical therapy	Follow up	Comments
					patients	controls	patients	controls					
Naganuma et al.	Japan	Case-control	325	325	21 (6.5)	53 (16.3)	38,9 (±13.70)	39.4 (±14.20)	All localizations	NA	ASA, CS	NA	
Radford-Smith et al.	Australia	Case-control	307	1016	21 (6.8)	286 (28.1)	32.7 (±0,85)	33.6 (±0.38)	All localizations	NA	ASA, CS, IM	NA	
Selby et al.	Australia	Case-control	259	280	12 (4.6)	70 (25.0)	43.1 (±0,89)	41.1 (±0,82)	All localizations	NA	ASA, CS, IM	NA	
					8 (3.1) ‡				All localizations				
Florin et al.	Australia	Case-control	294	1016	19 (6.5)	275 (27.1)	32.7 (±0.86)	33.6 (±0.38)	All localizations	NA	ASA, CS, IM	NA	
Hallas et al.	Denmark	Case-control	202	808	202 ‡	0	38.6 (±18.00)	38.7 (±17.70)	All localizations	NA	ASA, CS, IM	19 years	UC patients with appendectomy after onset of UC compared to UC patients without appendectomy
Cosnes et al.	France	Cohort retrospective	638	NA	49 (8.0)	NA	NA	NA	All localizations	NA	ASA, CS, IM	25 years	Significantly more female patients in appendectomised group
		Cohort prospective	507	NA	41 (8.1)	NA	NA	NA	All localizations	NA	ASA, CS, IM		

Data are given as n, n (%) and mean ± SD. ASA, salicylates; B, biological (tumour necrosis factor-α); CS, cortical steroids; IM, immunomodulatory; NA, data not applicable. All appendectomies were performed before the onset of ulcerative colitis (UC), those with a ‡ were performed after the onset of UC.

Table 3 Outline of results of UC patients

Author	Relapse		Hospital admissions		Steroid use		Colectomy		Comments
	A+ patients	A- patients	A+ patients	A- patients	A+ patients	A- patients	A+ patients	A- patients	
Naganuma et al.	12 (57.1%)	42 (78.6%)	NA	NA	NA	NA	NA	NA	Relapse=hospitalization or increase in clinical activity
Radford-Smith et al.	NA	NA	NA	NA	1 (4.8%)	71 (25%)	0 (0%)	60 (21.4%)	Immunosuppressive therapy with azathioprine, 6-mercaptopurine, methotrexate or mycophenolate
Selby et al.	NA	NA	NA	NA	4 (33.3%) 1 (12.5%)‡	43 (18,0%)	2 (16.7%) 1 (12.5%)‡	21 (8.8%)	Immunosuppressive therapy with azathioprine, 6-mercaptopurine or cyclosporine
Florin et al.	NA	NA	NA	NA	1 (5.3%)	74 (27%)	1 (5.3%)	67 (24%)	Immunosuppressive therapy with azathioprine, 6-mercaptopurine, methotrexate or mycophenolate
Hallas et al.	NA	NA	171/117‡	631/424	NA	NA	9 (4.5%)‡	42 (5.2%)	N° of admissions before/after appendectomy or index date
Cosnes et al.									
retrospective	NA	NA	NA	NA	33 (67%)	412 (70%)	7 (14.3%)	33 (5.6%)	
prospective	NA	NA	NA	NA	NA	NA	NA	NA	

Data are given as n (%) unless indicated otherwise. A+, appendectomised; A-, non appendectomised; NA, data not applicable. All appendectomies were performed before the onset of UC and those with ‡ were performed after the onset of UC.

In five studies the colectomy rate was investigated. Both Selby et al.[20] and Hallas et al.[22] found no differences in colectomy rates between the patients who had an appendectomy before onset of UC (12.5% and 4.5%, respectively), patients who had an appendectomy after onset of UC (16.7% in the study by Selby et al.) or the control group (8.8% and 5.2%, respectively). In the study by Cosnes et al.[23] a higher proportion of appendectomised patients required colectomy (14.3%) compared to the nonappendectomised patients (5.6%) (ARR = 8.7% for non-appendectomised patients; 95% CI: 1.29% - 18.66%). Radford-Smith et al.[19] and Florin et al.[21] both found a lower colectomy rate in the appendectomy group (0% and 5.3%, respectively) compared to the non-appendectomy group (21.4 and 24%, respectively) (ARR = 21.4%; 95% CI: 13.17% - 28.79% and ARR = 18.7%; 95% CI: 7.50% - 29.97%, respectively).

Case reports and case series

Two case reports and three case series have been published on the effect of appendectomy on the disease course in patients with UC (*Table 4*). Okazaki et al.[24] described a patient with distal ulcerative colitis whose symptoms resolved after appendectomy and was asymptomatic after three years of follow up. Kim et al.[25] described a patient with severe pancolitis whose symptoms decreased after appendectomy and was able to end the use of steroids.

Jarnerot et al.[26] performed a pilot study on laparoscopic appendectomy in 10 patients with refractory UC. This pilot study was stopped after six patients because of the difficulties in interpreting the results caused by confounding factors. These involved difference in medication used and duration of disease. No firm conclusions were drawn by Jarnerot et al.

Jo et al.[27] conducted a trial in nine patients who were compared with nine historical control patients (retrospectively matched). They found a transient decrease in the ulcerative colitis activity index (UCAI), which was only significant after 4 weeks ($P < 0.05$).

In a case series by Bolin et al.[28], 50 patients with ulcerative proctitis underwent appendectomy. The simple clinical colitis activity index (SCCAI) improved significantly from a median of nine to a median of two ($P < 0.0005$) in 40 patients (80%). From these patients, 15 (30%) had no need for continuing medical therapy. The SCCAI remained unchanged in 10 (20%) of 50 patients. The initial clinical response has been maintained in 37 (93%) of 40 patients for up to 3 years. Moreover, the appendiceal histology showed ulcerative appendicitis in 25 (50%) patients.

Table 4 Outline of results from case reports and case series

Author	Study type	N	Disease		Medical therapy	Disease activity		Full resolution	Col.	FU	Comments
			localizations	duration (range)		pre-appendectomy	post-appendectomy				
Okazaki et al.	Case report	1	Distal ulcerative colitis	3 years	None	Matt's grade IV	Matt's grade II	1 (100)	0	3 years	Microscopic grade
Jarnerot et al.	Case series	6	Refractory UC	Median 2.5 years (range, 4 months to 12 years)	ASA, CS, IM	NA	NA	2 (33)	0	2-4 years	Study stopped because of difficulties in interpreting the results
Jo et al.	Case series	9	All localizations (mild)	Median 49.4 months (range, 9-168 mo.)	ASA, CS, T	UCAI 147.2 (± 29)	UCAI 118.8 (± 29)	0	0	6 months	UCAI decrease was transient, only significant at 4 weeks after appendectomy
Kim et al.	Case report	1	Pancolitis	2 years	ASA, CS	Severe	Mild	0	0	NA	Activity was measured using the UCAI; exact scores could not be retraced
Bolin et al.	Case series	50	Ulcerative proctitis	Median 5 years (range, 8 months to 30 years)	ASA, CS, IM, B and T	SCCAI 9 (range, 7-12)	SCCAI 2 (range, 0-12)	15 (30)	0	14 months	

Data are given as median (range), mean (± SD) or n (%). ASA, salicylates; B, biological (tumour necrosis factor-α); Col., colectomy numbers; CS, cortical steroids; FU, follow up; IM, immunomodulatory; NA, data not applicable; SSCA, simple clinical colitis activity index; T, topical (CS or ASA); UCAI, ulcerative colitis activity index

DISCUSSION

This review shows limited and even inconsistent data regarding the effect of appendectomy on the disease course of UC. Of the six studies, one found a lower relapse rate in patients who had an appendectomy before onset of UC[18]. Two studies found a reduced requirement for immunosuppression in appendectomised patients [19;21]. However, another 2 studies found no differences in the requirement for immunosuppression[20;23]. In addition, 2 studies found no significant differences in colectomy rates between the appendectomised and nonappendectomised patients[20;22], one study actually found higher colectomy rates in appendectomised patients[23] and 2 studies found lower colectomy rates in appendectomised patients[19;21].

The results from this systematic review show the difficulties associated with case-control and cohort studies. The methods to recruit cases and controls were different among all the studies, varying from UC cases identified in databases[19;21;22], consecutive UC patients from one clinic[20] or from different hospitals[18], and controls from the community[20], from outpatient clinics[18] or from twin databases[19;21]. To establish comparability, cases and controls should be matched and/or confounders must be adjusted for in the analysis. The adjustment for confounders was insufficiently reported in all studies. Also, the median duration of follow up and median duration of disease was not always readily available[18-21]. For this review, four endpoints were chosen to identify the effect of appendectomy on the disease course of UC. At least one or more of these endpoints was investigated by the included studies. Nonetheless, the methodology was too heterogeneous and therefore it was not possible to pool the data from the studies.

Several other studies have described the effect of appendectomy on the influence of the disease course of UC. Okazaki et al.[24] and Kim et al.[25] both reported a case where appendectomy after UC onset beneficially influenced the clinical course of UC in a patient with distal ulcerative colitis and pancolitis, respectively. Jo *et al.*[27] concluded that their period of observation was too short to conclude whether appendectomy was beneficial. They also stated that periappendiceal inflammation in UC is a consequence of UC, rather than nonspecific inflammation. This suggests that the appendix is a site possibly involved in UC. In a case series by Bolin *et al.*[28], 80% of the 50 patients experienced significant improvement in clinical activity, with 30% having a complete remission of symptoms after appendectomy, without the requirement for any pharmacological treatment for up to three years of follow up. Moreover, the appendiceal histology showed ulcerative appendicitis in 25 (50%) patients. In these incident reports, one should be aware of the possible presence of publication bias because failed attempts of appendectomy as therapy for UC may not have been reported.

With the aforementioned remarks on the quality and comparability of the studies included for the review, the clinical relevance of the differences found in the studies

remains controversial. As illustrated by the prospective series published by Jarnerot et al.[26] and Jo et al.[27], a major shortcoming in the studies published to date is the divergence of patients and endpoints that were analysed. The patients differed with regard to duration and localisation of the disease, the medication used and whether the appendectomy was performed before or after UC was diagnosed. In addition, different end-points were analysed in the studies, varying from histological and disease-activity end-points to the unspecific end-point of admission rate.

All these aspects make it difficult to draw conclusions, but the studies by Naganuma et al.[18], Radford-Smith et al.[19], Florin et al.[21] and Bolin et al.[28] do suggest that appendectomy in patients with UC may have a beneficial effect on the disease course of UC. It is evident that more rigorous and prospective data is needed. A prospective randomized trial evaluating the disease-modifying effect of appendectomy on the disease course of UC is therefore justified.

REFERENCES

1 Baumgart DC, Sandborn WJ. **Inflammatory bowel disease: clinical aspects and established and evolving therapies.** Lancet 2007;369:1641-57.

2 Shanahan F. **Pathogenesis of ulcerative colitis.** Lancet 1993;342:407-11.

3 Hancock L, Windsor AC, Mortensen NJ. **Inflammatory bowel disease: the view of the surgeon.** Colorectal Dis 2006;8 Suppl 1:10-4.

4 Roses RE, Rombeau JL. **Recent trends in the surgical management of inflammatory bowel disease.** World J Gastroenterol 2008;14:408-12.

5 Hueting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. **Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients.** Dig Surg 2005;22:69-79.

6 Rachmilewitz D, Karmeli F, Takabayashi K, Hayashi T, Leider-Trejo L, Lee J, Leoni LM, Raz E. **Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis.** Gastroenterology 2002;122:1428-41.

7 Mizoguchi A, Mizoguchi E, Chiba C, Bhan AK. **Role of appendix in the development of inflammatory bowel disease in TCR-a mutant mice.** J Exp Med 1996;184:707-15.

8 Panaccione R, Sandborn WJ. **The appendix in ulcerative colitis, a not so innocent bystander.** Gastroenterology 1999;117:272-3.

9 Matsushita M, Takakuwa H, Matsubayashi Y, Nishio A, Ikehara S, Okazaki K. **Appendix is a priming site in the development of ulcerative colitis.** World J Gastroenterol 2005;11:4869-74.

10 Gilat T, Hacohen D, Lilos P, Langman MJ. **Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study.** Scand J Gastroenterol 1987;22:1009-24.

11 Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. **Appendectomy protects against ulcerative colitis.** Gastroenterology 1994;106:1251-3.

12 Mombaerts P, Mizoguchi E, Grusby MJ, Glimcher LH, Bhan AK, Tonegawa S. **Spontaneous development of inflammatory bowel disease in T cell receptor mutant mice.** Cell 1993;75:274-82.

13 D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. **Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study.** Am J Gastroenterol 1997;92:1275-9.

14 Perry WB, Opelka FG, Smith D, Hicks TC, Timmcke AE, Gathright JB Jr, Farr GH Jr, Beck DE. **Discontinuous appendiceal involvement in ulcerative colitis: pathology and clinical correlation.** J Gastrointest Surg 1999;3:141-4.

15 Groisman GM, George J, Harpaz N. **Ulcerative appendicitis in universal and nonuniversal ulcerative colitis.** Mod Pathol 1994;7:322-5.

16 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. **Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.** JAMA 2000;283:2008–12.

17 Higgins JPT, Green S. **Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2** [updated September 2009]. The Cochrane Collaboration, 2009. Available from: http://www.cochrane-handbook.org. (accessed 2 August 2010)

18 Naganuma M, Iizuka B, Torii A, Ogihara T, Kawamura Y, Ichinose M, Kojima Y, Hibi T; Tokyo Gut Club. **Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: Results of a multicenter case-controlled study in japan.** Am J Gastroenterol 2001;96:1123-6.

19 Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, Green A, Newman B, Florin TH. **Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease.** Gut 2002;51:808-13.

20 Selby WS, Griffin S, Abraham N, Solomon MJ. **Appendectomy protects against the development of ulcerative colitis but does not affect its course.** Am J Gastroenterol 2002;97:2834-8.

21 Florin THJ, Pandeya N, Radford-Smith GL. **Epidemiology of appendicectomy in primary sclerosing cholangitis and ulcerative colitis: Its influence on the clinical behaviour of these diseases.** Gut 2004;53:973-9.

22 Hallas J, Gaist D, Vach W, Sørenson HT. **Appendicectomy has no beneficial effect on admission rates in patients with ulcerative colitis.** Gut 2004;53:351-4.

23 Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. **Effects of appendicectomy on the course of ulcerative colitis.** Gut 2002;51:803-7.

24 Okazaki K, Onodera H, Watanabe N, Nakase H, Uose S, Matsushita M, Kawanami C, Imamura M, Chiba T. **A patient with improvement of ulcerative colitis after appendectomy.** Gastroenterology 2000;119:502-6.

25 Kim SW, Lee ST, Lee SO, Choi SC. **Clinical improvement of severe ulcerative colitis after incidental appendectomy: a case report.** Korean J Gastroenterol 2006;47:463-6.

26 Järnerot G, Andersson M, Franzén L. **Laparoscopic appendectomy in patients with refractory ulcerative colitis.** Gastroenterology 2001;120:1562-3.

27 Jo Y, Matsumoto T, Yada S, Nakamura S, Yao T, Hotokezaka M, Mibu R, Iida M. **Histological and Immunological features of appendix in patients with ulcerative colitis.** Dig Dis Sci 2003;48;99-08.

28 Bolin TD, Wong S, Crouch R, Engelman JL, Riordan SM. **Appendicectomy as a therapy for ulcerative proctitis.** Am J of Gastroenterol 2009;104:2476-82.

10

The ACCURE-trial: the effect of appendectomy on the clinical course of ulcerative colitis, a randomised international multicenter trial (NTR2883)

Tjibbe J. Gardenbroek[1], Dion Morton[2] , Thomas Pinkney[3], Christianne J. Buskens[1], Cyriel Y. Ponsioen[4], Marcel G. W. Dijkgraaf[5], Geert R. A. M. D,Haens[4] and Willem A. Bemelman[1], on behalf of the ACCURE Collaborative Study Group

Affiliations

[1]Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands, [2]Department of Surgery, University Hospitals Birmingham, Birmingham, United Kingdom, [3]Department of Gastroenterology, University Hospitals Birmingham, Birmingham, United Kingdom, [4]Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands, [5]Clinical Research Unit, Academic Medical Centre, Amsterdam, The Netherlands

Submitted

ABSTRACT

Background

Over the past 20 years evidence has accumulated confirming the immunomodulatory role of the appendix in ulcerative colitis (UC). This led to the idea that appendectomy might alter the clinical course of established UC. The objective of this study design is to evaluate the short-term and medium-term efficacy of appendectomy to maintain remission in patients with UC, and to establish the cost-effectiveness of the intervention compared to standard treatment.

Methods

This is an international phase III multicenter prospective randomised study that will include patients over 18 years of age with an established diagnosis of ulcerative colitis and a disease relapse within 12 months prior to randomisation. Patients need to be medically treated until complete clinical (Mayo score <3) and endoscopic (Mayo score 0 or 1) remission. Patients will then be randomised 1:1 to a control group (maintenance 5-ASA treatment, no appendectomy) or elective laparoscopic appendectomy plus maintenance treatment. The primary outcome measure is the one year cumulative UC relapse rate - defined both clinically and endoscopically as a total Mayo-score ffl5 with endoscopic subscore of 2 or 3. Secondary outcomes that will be assessed include the number of relapses per patient at 12 months, the time to first relapse, health related quality of life and treatment costs, and number of colectomies in each group.

Discussion

The ACCURE trial is an international multicentre randomised trial in patients with ulcerative colitis that will provide evidence on the role of appendectomy in the treatment of ulcerative colitis and the effects of appendectomy on the disease course.

INTRODUCTION

Ulcerative Colitis (UC) is an inflammatory bowel disease that diffusely affects the mucosa of the colon at variable distance from the anal verge. The aetiology of UC is not fully understood, although it is considered to be multifactorial with genetic and environmental factors leading to an inappropriate immunologic response [1,2]. Cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells are thought to play an important role in the pathogenesis of UC. T-helper type 2 cells and their cytokines are suggested to enhance the development of UC [1].

The primary treatment of UC is medical, first with 5-aminosalicyclic acids (5-ASA) and/or corticosteroids. More refractory patients need immunosuppression with thiopurines, calcineurin inhibitors or TNF alpha blockers. In disease refractory to medical treatment, a (staged) proctocolectomy with ileo-anal pouch anastomosis is usually performed. Approximately 20% of UC patients eventually require surgery [3-5].

A significant proportion of UC patients will remain on long term medication to maintain remission and prevent relapse, which carries significant morbidity and impacts considerably on quality of life and health resource utilisation. The peak age of onset of UC is 20-35 years old, which means that this condition has a significant impact on working life and potentially procreation and childcare.

Multicentre pooled data suggest that after a flare-up of UC, the annual relapse rate without medication ranges between 40-76%. Even on long-term maintenance therapy up to 40% of patients will still experience at least one relapse within the year, which will require treatment again often including corticosteroids with its incumbent risks and toxicity [6].

Over the past 20 years a substantial body of evidence has accumulated supporting the role for the appendix in the development and course of UC. There is a strong inverse relationship between prior appendectomy (most frequently for appendicitis) and the development of UC, documented through multiple epidemiological and case-control studies from diverse populations [7-9]. Several studies have also investigated the effect of appendectomy on established UC. In a systematic review we have shown that appendectomy might influence the disease course in UC patients, with possible reductions in relapse rates, need for immunosuppression and colectomy rates in UC patients who had an appendectomy, although the heterogeneity of the available studies and subjective nature of the endpoints made direct comparison difficult [10]. Furthermore, it was shown in a T-cell receptor knockout mouse model for colitis that an early appendectomy suppressed inflammation [11]. Another study showed that the proportion of CD4+CD69+ T cells was significantly increased in the appendix of UC patients, compared to the appendix of controls [12]. In addition, endoscopists have reported on 'skip lesions' around the caecal orifice of the appendix in UC patients (referred to as the caecal patch or PARP: peri-appendicular

red patch), which is seen even in distal colitis without caecal involvement in 48-86% of patients [9;12-17]. Consequently, the appendix is suggested to be a priming site in the development of UC.

This study will prospectively evaluate the role of the appendix in UC and the potential effect of appendectomy on the disease course.

METHODS

Study objective

The objective of this study is to evaluate the short-term and medium-term efficacy of appendectomy to maintain remission in patients with an established diagnosis of mild to moderate ulcerative colitis.

Study design

The study is designed as a multicenter randomised clinical trial aiming at patients with an established diagnosis of ulcerative colitis and a disease relapse within 12 months prior to randomisation, medically treated (for treatment with immunomodulators and biologicals a wash out period of 3 months before inclusion is required) until full clinical and endoscopic remission has been achieved as defined by the Mayo score.

Primary and secondary endpoints

The primary endpoint of the trial is the one year cumulative UC relapse rate, defined both clinically and endoscopically as Mayo-score ffl5 with endoscopy sub score of 2 or 3.

Secondary endpoints are the number of relapses per patient in the first year after randomisation, the time to first relapse, disease activity, health related quality of life and treatment costs, and finally the number of colectomies. During longer term follow up beyond one year, disease activity including number of relapses and number of colectomies will be measured.

Study population

Patients are eligible for this trial when they meet the following inclusion criteria:

(1) Aged ffl 18 years.
(2) Histologically confirmed diagnosis of UC.
(3) Disease relapse within 12 months prior to randomisation.
(4) In remission on 5-ASA or after a wash out period of at least 3 months after treatment with immunomodulators and biologicals (if given).
(5) Clinical (Mayo score <3) and endoscopic (Mayo score 0 or 1) remission at time of randomisation.

(6) Negative stool culture and C. Difficile toxin.

Patients will be excluded when:
(1) A prior appendectomy has been performed.
(2) Previous major abdominal surgery that may prevent safe and straightforward appendectomy has been performed.
(3) Any suspicion of Crohn's disease is present.
(4) A toxic megacolon or severe ongoing colitis is present at time of randomisation.
(5) Diagnosed with active extra-intestinal infections, liver or kidney failure, major lung or heart co-morbidity.

The participating Dutch centres will commence with the inclusion of a subset of patients. This subset will consist of patients treated with 5-ASA (oral and/or topical), steroids and/or when treatment with immunomodulators terminated at least 6 months prior to inclusion. Patients in The Netherlands will never have received biologicals at inclusion. Upon ethical approval in the UK, all potential patients according to the in- and exclusion criteria will be included.

Participating centres

Nine teaching hospitals in the Netherlands and six hospitals in the United Kingdom are participating in this trial, including 2 academic centres.

Ethics

This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Medical ethics approval has been obtained by the medical ethics committee from the Academic Medical Centre in Amsterdam dated April 12th, 2012. Separate ethical approval will be obtained in the UK via the National Research Ethics System (NRES) prior to UK sites opening. Before randomisation, written informed consent must be obtained from all patients.

Study outline

Participants will be recruited in the Inflammatory Bowel Disease outpatient clinics of the participating medical centres. Patients eligible for this study are randomised to undergo laparoscopic appendectomy in day care setting within six weeks of randomisation as opposed to no appendectomy (*Figure 1*). Surgery will be performed in the including centre or one of the coordinating centres; the Academic Medical Centre or University Hospitals Birmingham.

At inclusion, patients will undergo endoscopic mucosal visualisation, either by an ileocolonoscopy or a sigmoidoscopy in combination with a faecal calprotectin test that needs

to be < 100 ug/g, to confirm remission. At the time of relapse or at the end of the 12 month study period, patients will undergo a full colonoscopy to assess mucosal appearance. The clinical and endoscopic findings will be reported with the Mayo score. Using this 12-point scoring system, disease activity is evaluated based on stool frequency, rectal bleeding, the physician's global assessment, and endoscopic appearance. In the Mayo score, clinical remission is defined as a Total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing is defined as an absolute subscore for endoscopy of 0 or 1.

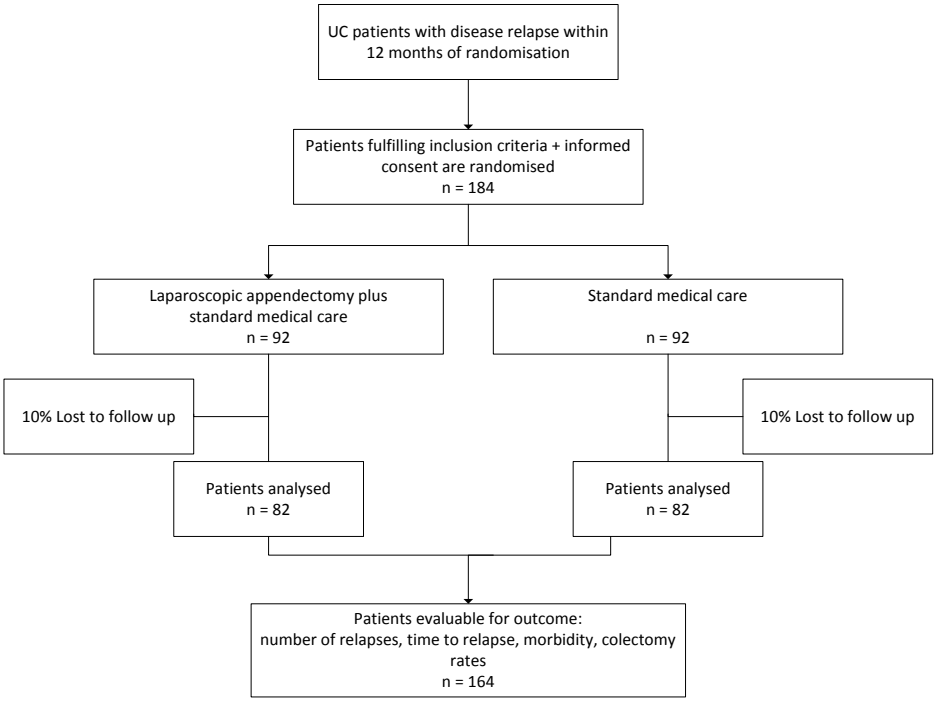


Figure 1 Study profile

During the first 12 months of follow up, all patients will receive oral maintenance therapy of 2 grams 5-aminosalicylic acid (Salofalk®, Dr Falk Pharma GmbH, Freiburg, Germany).

Outpatient clinic visits will be performed by the gastroenterologist or research team at 6 weeks and 3, 6, 9 and 12 months after appendectomy or randomisation in patients not undergoing appendectomy; other visits are scheduled on indication. During these contacts the non-invasive 9-point partial Mayo score will be assessed. Patients will complete health related quality of life questionnaires (EQ-5D, EORTC-QLQ-C30-QL and IBDQ) at inclusion and every 3 months thereafter for 12 months. In the 5 years following the study the gastroenterologist will be requested to measure the non-invasive 9-point

partial Mayo score every 6 months during outpatient clinic appointments. Three years after randomisation a further colonoscopy will be performed to assess long term mucosal healing in the patients with longstanding remission.

Laparoscopic appendectomy

Laparoscopic appendectomy is a relatively simple operation that can be done by most surgeons, in day care setting or with a single night stay in hospital. The normal reason to undertake an appendectomy is acute inflammation of the appendix (appendicitis). There is a lifetime incidence risk of 7% and patients diagnosed with this condition almost all undergo appendectomy [18;19]. It is in this forum that the laparoscopic (keyhole) method of removing the appendix has become established over the past 15 years and is now the recommended option owing to its proven faster recovery times and fewer wound complications [19].

The risks of removing a normal or non-inflamed appendix in an elective setting are not known, as published data exclusively refer to patients with confirmed or suspected acute appendicitis undergoing emergency operations by surgeons of variable seniority. It is reasonable to assume that the risk of post-operative complications will be significantly lower in our population than these published rates of 2.5-7.6% from patients with perforated appendicitis [19-21]. Specific complications that have been reported include wound infection, intra-abdominal abscess, iatrogenic bowel perforation, pneumonia and thrombosis. The laparoscopic appendectomy in this study will be carried out under general anaesthesia with the use of 3 trocars or a Single Port system. Laparoscopic appendectomy will be performed by a gastrointestinal or general surgeon with sufficient experience in laparoscopic procedures (>20 procedures/year). When participating centres lack a qualified surgeon the patient will be referred to the Academic Medical Centre, University Hospitals Birmingham or a surgeon that has enough experience in a collaborating hospital nearby.

Statistical analysis

Group size calculations are based on a clinically relevant reduction in relapse rate from an expected 40% in the control group to 20% in the intervention group. With a 5% two-sided significance level, 82 patients per study arm will be needed to achieve an 80% power to detect such a difference using a Chi-square test. Considering 10% patient drop out we expect to have to include 184 patients in order to analyse 164 patients.

All data-analyses will be performed according to the intention-to-treat principle.

The relapse rate, medication use and time to first relapse of the two groups will be compared with Chi-square testing, Mann Whitney U-testing and survival analysis. Additional mixed-models repeated measures analysis of variance will be used to investigate whether there is a different pattern of change over time between the two study arms in the Mayo score and the EQ-5D, EORTC-QLQ-C30-QL and IBDQ [22].

Randomisation

Patient data are entered into a computerized database and following the assignment of an unchangeable computer generated number, patients will be randomised to undergo laparoscopic appendectomy or no appendectomy. Randomisation will be performed stratified by disease localization (rectum, left sided colitis, pancolitis), number of years diagnosed and number of relapses in the past 12 months. Randomisation will take place after all inclusion and exclusion criteria have been verified and informed consent has been obtained.

Blinding

Blinding of patients and physicians during treatment is unfeasible in this study. Endoscopic follow- up for recurrence, however, will be performed by independent endoscopists blinded for the allocated treatment strategy. Endoscopic procedures will be recorded with photo documentation. Pathologists will also be blinded to the treatment allocation.

Data collection and monitoring

An electronic Case Report Form (eCRF) will include general patient data: sex, age, medical history, disease characteristics before and during the study period including Mayo score, appendectomy parameters, complications, mortality, duration of hospital stay and the patients' responses to the questionnaires. Patients will be followed for a period of 12 months. During this follow-up period patients will complete sets of questionnaires (EQ-5D, EORTC-QLQ-C30-QL and IBDQ). The questionnaires can be filled in online. For this a personal email with the invitation and access code will be sent to the patients by mail. Patients not willing or unable to complete the online questionnaires will receive identical paper questionnaires at their home address, accompanied by a free return envelope.

Patients will be contacted by telephone every 3 months by a study team member (i.e. trial nurse) to assess medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social in attendance and to ensure completions of the questionnaires.

Economic evaluation

The economic evaluation of appendectomy for established UC will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis with a time horizon of 12 months. Primary outcomes in these economic evaluations are the costs per patient without relapse and costs per quality adjusted life-year (QALY) respectively. Incremental cost-effectiveness ratios will be calculated as the extra costs per additional patient without relapse or per QALY gained. Furthermore, the cost-effectiveness per prevented relapse will be calculated. Additional sensitivity analyses will determine how changing treatment costs might impact the results.

Direct medical costs and indirect non-medical costs arising from losses in productivity will be assessed. National unit costs will be used for the various health care components, complemented by results from activity based costing when needed. Both, the human capital approach as well as the friction cost method will be applied to the indirect costs of sick leave from work.

The EQ-5D scoring profiles at successive measurements during follow-up will be used to derive the corresponding health utilities. This is done by applying computer algorithms available from the literature. These algorithms reflect preferences in the general population for various health states and have been determined using time trade-off elicitation techniques [23;24]. Having determined the health utilities, a QALY estimate for each patient can be calculated, accounting for the lengths of the periods in-between successive measurements.

Histopathological evaluation

Samples of appendicular tissues will be collected and investigated at the Tytgat Laboratory of the Academic Medical Centre Amsterdam according to a standard operating procedure. Resected appendices will be analysed by immunohistochemistry, FACS analysis and microbiota analysis will be performed. In the UK, translational research samples will be centralised to the University of Birmingham for analysis.

Patient safety

An independent Data and Safety Monitoring Committee (DSMC) has been established to assure proper data safety and relevance monitoring. The committee will guard the safety of the included patients, give advice on continuation of the study upon superiority of one of the types of treatment, and will guard the methodological quality of the study. An interim review will be performed at 25, 50 and 100 included patients. At 6 weeks after inclusion of these patients the trial's safety data will be evaluated. According to the Good Clinical Practice guidelines, a list of Serious Adverse events is defined. All events on this list have to be reported by the local investigators to the trial coordinators within 24 hours after the event. The DSMC will be supplied with the number of (serious) adverse events in both groups at the three mentioned time points. If there is a skewed distribution of the number of (serious) adverse events between the two groups and efficacy analysis can be performed at the discretion of the DSMC.

DISCUSSION

Chronic relapsing diseases such as ulcerative colitis (UC) incur a considerable long-term health burden to the patients and health care systems. Early interventions that reduce the

rate of relapse and colectomy would offer considerable benefit. Many patients with UC live with a substantial symptom burden despite medical treatment; three quarters report that symptoms affect their ability to enjoy leisure activities and two thirds of patients feel that symptoms affect their ability to perform at work [25]. Therefore, it is imperative to explore novel treatment options.

In as early as 1987 the appendix was suggested to play a role in ulcerative colitis, when an epidemiological study found a lower appendectomy rate in UC patients compared to healthy controls [26]. In the following years the involvement of the appendix in UC was confirmed by various other studies, suggesting the appendix' role in the immunologic cascade in the colonic mucosa of UC patients [9;12-17;27]. The available literature suggests a more preferable clinical course in appendectomised patients with UC, but strong evidence is lacking [10].

The primary outcome of this study is the proportion of patients with UC relapse, as defined by the Mayo score. All patients in the study will be treated with 2 grams 5-ASA maintenance therapy. With this maintenance therapy, approximately 40% of the patients with UC will have a disease relapse within one year [28;29].

If an appendectomy can protect UC patients from future use of expensive or potentially hazardous medication or even surgery, the initial additional costs and potential side effects of appendectomy will be offset by substantial gain in health and reduction in costs later on. This is especially true for appendectomy, as this is a relatively simple procedure that can be performed in day care.

Appendectomy is not currently employed as a therapeutic treatment for UC anywhere in the world. If the current trial is positive, and demonstrates cost-efficacy, widespread use of this approach can be anticipated.

Acknowledgements

The Dutch part of the study is funded by Nuts FondsOhra (project 2012-008) and an unrestricted grant from Dr Falk Pharma GmbH, Freiburg, Germany.

The Dutch part is approved by the Medical Ethics Committee from the Academic Medical Centre in Amsterdam. The UK part of the study is funded by the NIHR Research for Patient Benefit programme (project PB-PG-1112-29107) and will receive ethical approval from the National Research Ethics Service (NRES) prior to trial commencement.

ACCURE Collaborative Study Group

Pieter J Tanis[1], Esther CJ Consten[6], Menno A Brink[7], Rogier MPH Crolla[8], Tom Seerden[9], Maarten J Boom[10], Rosalie C Mallant[11], Robert EGJM Pierik[12], Juda Vecht[13], Alexander P J Houdijk[14], Michael Klemt-Kropp[15], Andreas W K S Marinelli[16], Robert J Verburg[17], Michael F Gerhards[18], Jeroen M Jansen[19], Ernst Jan Spillenaar Bilgen[20], Marcel J M Groenen[21], Yair Acherman[22], Annekatrien CTM Depla[23], Hein BAC Stockmann[24], Johan P Kuyvenhoven[25], John K Maring[26], Karlien F Bruin[27], Richard van Hilligersberg[28], Bas Oldenburg[29], Laurents

PS Stassen[30], Marieke Pierik[31], Guido HH Mannaerts[32], Rachel West[33]. Tariq Iqbal[3], Shrikanth Pathmakanthan[3], Jon Deeks[34], Phillipe Taniere[35], Andrew Sutton[36]

Authors' details

[1]Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands, [2]Department of Surgery, University Hospitals Birmingham, Birmingham, United Kingdom, [3]Department of Gastroenterology, University Hospitals Birmingham, Birmingham, United Kingdom, [4]Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands, [5]Clinical Research Unit, Academic Medical Centre, Amsterdam, The Netherlands, [6]Department of Surgery, Meander Hospital, Amersfoort, The Netherlands, [7]Department of Gastroenterology, Meander Hospital, Amersfoort, The Netherlands, [8]Department of Surgery, Amphia Hospital, Breda, The Netherlands, [9]Department of Gastroenterology, Amphia Hospital, Breda, The Netherlands, [10]Department of Surgery, Flevo Hospital, Almere, The Netherlands, [11]Department of Gastroenterology, Flevo Hospital, Almere, The Netherlands, [12]Department of Surgery, Isala Hospital, Zwolle, The Netherlands, [13]Department of Gastroenterology, Isala Hospital, Zwolle, The Netherlands, [14]Department of Surgery, Medical Centre Alkmaar, Alkmaar, The Netherlands, [15]Department of Gastroenterology, Medical Centre Alkmaar, Alkmaar, The Netherlands, [16]Department of Surgery, Medical Centre Haaglanden, Alkmaar, The Netherlands, [17]Department of Gastroenterology, Medical Centre Haaglanden, Alkmaar, The Netherlands, [18]Department of Surgery, Onze Lieve Vrouwe Hospital, Amsterdam, The Netherlands, [19]Department of Gastroenterology, Onze Lieve Vrouwe Hospital, Amsterdam, The Netherlands, [20]Department of Surgery, Rijnstate Hospital, Arnhem, The Netherlands, [21]Department of Gastroenterology, Rijnstate Hospital, Arnhem, The Netherlands, [22]Department of Surgery, Slotervaart Hospital, Amsterdam, The Netherlands, [23]Department of Gastroenterology, Slotervaart Hospital, Amsterdam, The Netherlands, [24]Department of Surgery, Kennemer Hospital, Haarlem, The Netherlands, [25]Department of Gastroenterology, Kennemer Hospital, Haarlem, The Netherlands, [26]Department of Surgery, Twee Steden Hospital, Tilburg and Waalwijk, The Netherlands, [27]Department of Gastroenterology, Twee Steden Hospital, Tilburg and Waalwijk, The Netherlands, [28]Department of Surgery, Utrecht University Medical Centre, Utrecht, The Netherlands, [29]Department of Gastroenterology, Utrecht University Medical Centre, Utrecht, The Netherlands, [30]Department of Surgery, Academic Hospital Maastricht, Maastricht, The Netherlands, [31]Department of Gastroenterology, Academic Hospital Maastricht, Maastricht, The Netherlands, [32]Department of Surgery, St. Franciscus Hospital, Rotterdam, The Netherlands, [33]Department of Gastroenterology, St. Franciscus Hospital, Rotterdam, The Netherlands, [34]Birmingham Clinical Trials Unit, University Hospitals Birmingham, Birmingham, United Kingdom, [35]Department of Pathology, University Hospitals Birmingham, Birmingham, United Kingdom, [36]Department of Health Economics, University Hospitals Birmingham, Birmingham, United Kingdom.

REFERENCES

1 Abraham C, Cho JH. **Inflammatory bowel disease.** N Engl J Med 2009; 361(21):2066-2078.

2 Shanahan F. **Pathogenesis of ulcerative colitis.** Lancet 1993; 342(8868):407-411.

3 Hawthorne AB, Logan RF, Hawkey CJ, Foster PN, Axon AT, Swarbrick ET et al. **Randomised controlled trial of azathioprine withdrawal in ulcerative colitis.** BMJ 1992; 305(6844):20-22.

4 Hueting WE, Buskens E, van dT, I, Gooszen HG, van Laarhoven CJ. **Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients.** Dig Surg 2005; 22(1-2):69-79.

5 Langholz E, Munkholm P, Davidsen M, Binder V. **Course of ulcerative colitis: analysis of changes in disease activity over years.** Gastroenterology 1994; 107(1):3-11.

6 Travis SP, Stange EF, Lemann M, Oresland T, Bemelman WA, Chowers Y et al. **European evidence-based Consensus on the management of ulcerative colitis: Current management.** J Crohns Colitis 2008; 2(1):24-62.

7 Andersson RE, Olaison G, Tysk C, Ekbom A. **Appendectomy and protection against ulcerative colitis.** N Engl J Med 2001; 344(11):808-814.

8 Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG et al. **Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease.** Gut 2002; 51(6):808-813.

9 Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. **Appendectomy protects against ulcerative colitis.** Gastroenterology 1994; 106(5):1251-1253.

10 Gardenbroek TJ, Eshuis EJ, Ponsioen CI, Ubbink DT, D'Haens GR, Bemelman WA. **The effect of appendectomy on the course of ulcerative colitis: a systematic review.** Colorectal Dis 2012; 14(5):545-553.

11 Mombaerts P, Mizoguchi E, Grusby MJ, Glimcher LH, Bhan AK, Tonegawa S. **Spontaneous development of inflammatory bowel disease in T cell receptor mutant mice.** Cell 1993; 75(2):274-282.

12 Matsushita M, Takakuwa H, Matsubayashi Y, Nishio A, Ikehara S, Okazaki K. **Appendix is a priming site in the development of ulcerative colitis.** World J Gastroenterol 2005; 11(31):4869-4874.

13 D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. **Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study.** Am J Gastroenterol 1997; 92(8):1275-1279.

14 Groisman GM, George J, Harpaz N. **Ulcerative appendicitis in universal and nonuniversal ulcerative colitis.** Mod Pathol 1994; 7(3):322-325.

15 Matsushita M, Uchida K, Okazaki K. **Role of the appendix in the pathogenesis of ulcerative colitis.** Inflammopharmacology 2007; 15(4):154-157.

16 Panaccione R, Sandborn WJ. **The appendix in ulcerative colitis: a not so innocent bystander.** Gastroenterology 1999; 117(1):272-273.

17 Perry WB, Opelka FG, Smith D, Hicks TC, Timmcke AE, Gathright JB, Jr. et al. **Discontinuous appendiceal involvement in ulcerative colitis: pathology and clinical correlation.** J Gastrointest Surg 1999; 3(2):141-144.

18 Addiss DG, Shaffer N, Fowler BS, Tauxe RV. **The epidemiology of appendicitis and appendectomy in the United States.** Am J Epidemiol 1990; 132(5):910-925.

19 Sauerland S, Jaschinski T, Neugebauer EA. **Laparoscopic versus open surgery for suspected appendicitis.** Cochrane Database Syst Rev 2010;(10):CD001546.

20 Margenthaler JA, Longo WE, Virgo KS, Johnson FE, Oprian CA, Henderson WG et al. **Risk factors for adverse outcomes after the surgical treatment of appendicitis in adults.** Ann Surg 2003; 238(1):59-66.

21 Neilson IR, Laberge JM, Nguyen LT, Moir C, Doody D, Sonnino RE et al. **Appendicitis in children: current therapeutic recommendations.** J Pediatr Surg 1990; 25(11):1113-1116.

22 Norman GR, Sloan JA, Wyrwich KW. **Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation.** Med Care 2003; 41(5):582-592.

23 Dolan P. **Modeling valuations for EuroQol health states.** Med Care 1997; 35(11):1095-1108.

24 Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. **[Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff].** Ned Tijdschr Geneeskd 2005; 149(28):1574-1578.

25 Ghosh S, Mitchell R. **Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey.** J Crohns Colitis 2007; 1(1):10-20.

26 Gilat T, Hacohen D, Lilos P, Langman MJ. **Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study.** Scand J Gastroenterol 1987; 22(8):1009-1024.

27 Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. **Effects of appendicectomy on the course of ulcerative colitis.** Gut 2002; 51(6):803-807.

28 Bresci G, Parisi G, Capria A. **Duration of remission and long-term prognosis according to the extent of disease in patients with ulcerative colitis on continuous mesalamine treatment.** Colorectal Dis 2008; 10(8):814-817.

29 Travis SP, Stange EF, Lemann M, Oresland T, Bemelman WA, Chowers Y et al. **European evidence-based Consensus on the management of ulcerative colitis: Current management.** J Crohns Colitis 2008; 2(1):24-62.

11

Immunological and histological characteristics of the appendix in ulcerative colitis

Tjibbe J. Gardenbroek[1], Saloomeh Sahami[1], Jan P. van Straalen[2], Hugo M. Horlings[3], Marc J. van de Vijver[3], Cyriel Y. Ponsioen[4], Gijs R. van den Brink[4], Geert R. A. M. D'Haens[4], Willem A. Bemelman[1] and CJ Buskens[1]

Affiliations

[1]Department of Surgery, [2]Department of Clinical Chemistry, [3]Department of Pathology, [4]Department of Gastroenterology and Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands

In progress

ABSTRACT

Background

Mucosal inflammation and cytokine production within the appendix has been suggested to play a causative role in the development and relapses of ulcerative colitis (UC). Objective of this study was to analyse if T-cell phenotype in appendiceal lavage fluid is associated with histological and immunohistochemical characteristics of UC appendices. Results were compared to the appendices of patients with Crohn's disease (CD), acute appendicitis (AA) and non-inflammatory controls, and correlated to clinical disease activity.

Methods

The appendix was removed from the surgical resection specimen and flushed with 2cc of phosphate buffered saline. Presence of CD4+ and CD8+ T-cells in the lavage fluid was determined by FACS analysis and the CD4/CD8 ratio was calculated. Histological analyses of the appendices assessed the degree of inflammation and mucosal ulceration. Furthermore, slides were immunohistochemically stained for CD4+ and CD8+ (grading 1-3), and T-cell infiltration grades were correlated to lavage results and clinical activity indices.

Results

Thirty-three patients were included; 13 with UC, 7 with CD, 5 with AA and 8 controls. In UC, an increased number of CD4+ cells was demonstrated in the lavage fluid, comparable to CD and AA. A relatively low number of CD8+ was found in UC, resulting in a significantly higher median CD4/CD8 ratio 7.1 (iqr 4.2-8.1) when compared to the median ratio of 3.2 (iqr 2.5-6.2) in the control group. At immunohistochemical evaluation the majority of UC (8/13 = 62%), CD (6/7 = 85.7%) and AA (3/5 = 60%) patients had increased levels of CD4+ lymphocytes (grade 2 and 3).
Immunohistochemical results correlated to CD4+ percentages in lavage fluid in 80% of UC patients, and was able to predict clinical disease activity in 90% of UC, 100% of AA, and 80% of CD patients.

Conclusions

Despite a macroscopically normal appearance, appendices of UC patients with active disease show immunological activation with inflammatory characteristics and increased numbers of CD4+ lymphocytes in lavage fluid and immunohistochemical analysis.

INTRODUCTION

The triggering factor for the development of ulcerative colitis (UC) is still unknown [1;2]. In the pathogenesis of UC, cytokine imbalance and production of inflammatory mediators by activated CD4+ T cells are regarded to play an important role [3-5]. Extensive infiltration of lymphocytes, especially CD4+ T cells, has been observed in the inflamed mucosa of UC patients [6]. Activated CD4+ T cells exhibit increased cytotoxic activity and produce cytokines, enhancing the inflammatory state which results in tissue injury [7-9].

Until recently the appendix was mostly seen as a rudimentary part of the human intestine, but nowadays it has been demonstrated that the appendix has distinct immunological functions. Reports are emerging linking this vermiform organ to the development of UC and a systematic review suggests that an appendectomy could modulate the course of the disease[10;11]. Although characteristic transmural histological changes in appendectomy specimens are hardly ever seen in UC, a quantitative and qualitative change of the lymphocyte phenotype in the appendix of UC patients has been described. Studies on T-cell subsets in the appendix have shown increased numbers of $CD4^+$ lymphocytes. Because it is predominantly the early activation antigen $CD4^+CD69^+$ and the activation marker $CD25^+$ that are increased, this could indicate that the appendix acts as a priming site for this particular disease[9;12;13]. Furthermore, UC mouse models suggest that the CD4/CD8 ratio in the mucosa of the appendix represents and influences the inflammation degree in the colonic mucosa [12;13].

In contrast, for patients with Crohn's disease (CD) higher incidence rates after appendectomy have been described, being highest within the first six months after resection. However, these data are difficult to interpret since the appendix is frequently involved as part of the terminal ileitis which could result in in overestimated incidence rates. The appendix as sole primary manifestation of the disease is rare [14-17]. Comparable to the affected terminal ileum, most specimens show macroscopically and microscopically affected appendices with transmural inflammation.

Acute appendicitis (AA) represents a different form of transmural inflammation. This non-autoimmuun coordinated inflammation has been linked to bacterial invasion, diet, familial aggregation and an obstructing appendiceal faecolith possibly play a role in the etiology of the disease[18-20]. To gain insight in the distinct role the appendix plays in the development in UC, it would be interesting to compare immunological changes to appendices from patients with CD, AA, and healthy controls. So far, lymphocyte phenotyping has been done predominantly in murine colitis models. The scarce literature on human UC appendices only discusses inflammatory characteristics in resection material. However, If T-cell infiltration and characterization could be clinically determined in the appendix, it might be possible to utilize this as a measurement for the inflammatory process, and guide clinical decision making.

The objective of this study was to analyse if T-cell phenotype in appendiceal lavage fluid was associated with histological and immunohistochemical characteristics of UC appendices. Results were compared to the appendices of patients with Crohn's disease (CD), acute appendicitis (AA) and non-inflammatory controls, and correlated to clinical disease activity.

METHODS

This prospective cohort study was performed in a tertiary IBD center (Academic Medical Center, Amsterdam) in The Netherlands. Patients over 18 years of age with therapy refractory UC scheduled for colectomy in an elective setting, or UC patients in remission participating in a study analysing the role of appendectomy in this disease, were eligible. The control groups consisted of patients with Crohn's disease (CD) undergoing ileocolic resection, patients with acute appendicitis (AA) undergoing laparoscopic appendectomy, and patients undergoing (partial) colectomy for colonic carcinoma or familial adenomatous polyposis (FAP). Patients were pre-operatively included in the MIC study ('In depth characterization of the mucosal microbiota in patients with IBD using novel, potent high-throughput approaches and their interaction with the immune system') in which the mucosal microbiota in the resection specimens of abovementioned patients was analysed. The study protocol was approved by the institutional review board of the Academic Medical Center and the trial was registered at Netherlands Trial Register (NTR2908). For the current study, we analysed the appendix of the included patients. Patients were included between August 2011 and January 2013.

Procedure

Surgical procedures were performed laparoscopically by two gastrointestinal surgeons. Care was taken not to touch the appendix during dissection. After resection, the specimen was extracted from the abdominal cavity and the appendix was removed from the resection specimen under sterile conditions. The mesentery of the appendix was removed and the appendicular tissue was cleaned of peri-appendicular fat. The distal tip of the appendix was cut off to enable flushing the appendix with fluid. The appendix was inserted in a transparent tube to provide circular pressure during flushing. Subsequently, the appendix was flushed with 2cc of phosphate buffered saline (PBS). In case of faecal contamination of the fluid, a second flush with 2cc of PBS was performed. The lavage fluid was collected in a container with a protein medium and analysed in the clinical chemical laboratory of the AMC. Subsequently, the appendix was transported to the department of pathology for histological evaluation and immunohistochemical staining according to a standardized protocol.

Appendix lavage fluid analysis

The mononuclear cells in the lavage fluid were stained with fluorescein isothiocyanate (FITC) and phycoerythrin-conjugated (PE) monoclonal antibodies (anti-CD45, anti-CD3, anti-CD4, and anti-CD8). First the phenotyped cells were analysed by colour flow cytometry (FACS analysis). Cell suspensions were visualised in the forward scatter/side scatter profile, subsequently lymphocytes were gated. Then, the proportion of CD4+ and CD8+ T cells and relative ratio of CD4+ and CD8+ T-cells in CD3+ cells were calculated. Figure 1 shows an example of a result after FACS analysis of the lavage fluid. An ROC curve was created to determine the optimal cut-off value for increased CD4+ percentages.

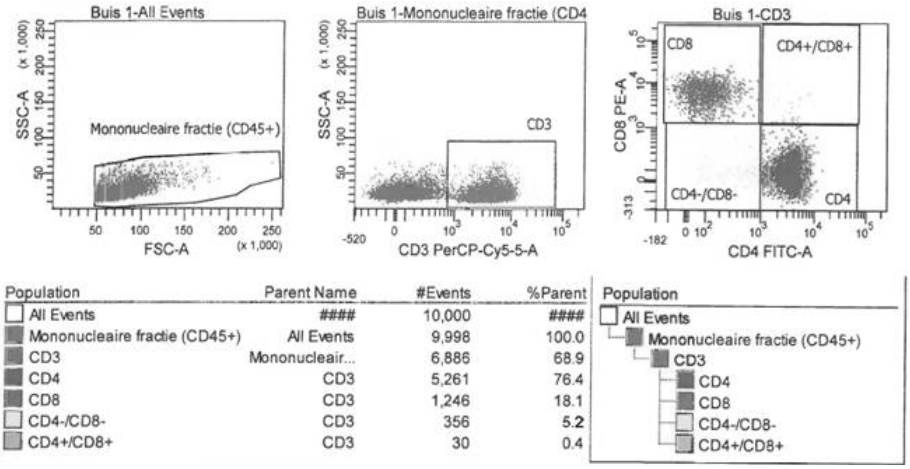


Figure 1 Image of a colour flow cytometry of appendix lavage fluid. Cell suspensions were visualised in the forward scatter/side scatter profile, subsequently lymphocytes were gated. The proportion of CD4+ and CD8+ T cells and the CD4/CD8 ratio in the total lymphocyte populations were calculated.

Histology and immunohistochemistry

The appendix was cut transversely and longitudinally, and serial sections were cut for staining and analysis. The hematoxylin and eosin stain sections of the appendix were evaluated, assessing the architecture and inflammatory features [21]. Architectural features included crypt atrophy, crypt distorsion and surface irregularities. Inflammatory features included increased cellularity of the lamina propria, plasmacytosis, crypt abscesses, granulomas and lymphoid aggregates, assessing the degree of inflammation (mucosal, submucosal or transmural) and mucosal ulceration.

Paraffin embedded slides were also immunohistochemically stained for CD4 and CD8, by routine staining with primary antibodies.

Results were assessed by three reviewers (SS, HH and CB) independently, blinded for the patients' clinical records and disease diagnosis, and scored according to the number of positive cells per high power field. A representative mucosal area was chosen which

was not directly covering a lymphoid follicle in the submucosa or lamina propria of the appendiceal wall. Scores were adapted from Stumpf et al. (grade 1 representing < 5 positive cells per HPF, grade 2 represents 6-19 cells per HPF and grade 3 >20 cells per HPF) [22].

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR) according to distribution. Categorical data are presented as frequencies and percentages. Independent t-test was used to compare means. Mann-Whitney-U test was used for continuous, not normally distributed data. To compare dichotomous data the $\chi 2$-test or Fisher's exact test were used. All tests were two-sided and a P-value of <0.05 was deemed significant. Statistical analysis was done with IBM SPSS Statistics for Windows®, Version 19.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Demographics

A total of 33 patients were included; 13 UC patients, 7 patients with CD, 5 patients with appendicitis and 8 patients with colonic carcinoma or FAP (non-inflammatory controls). The characteristics of all groups are summarized in *Table 1*.

Table 1 Baseline patient characteristics

	UC (n = 13)	CD (n = 7)	AA (n = 5)	Controls (n = 8)
Gender M/F	6/7	2/5	3/2	4/4
Age at surgery	43 [30.5-61]	26 [26-34]	40 [35-44.5]	60 [54-73.3]
Disease duration (months)	63 [23.5-183]	45 [17-116]	-	0 [0-1]
Disease location				
- Left sided	8 (61.5)			
- Pancolitis	5 (38.5)			
Medication at time of surgery			-	-
- Steroids	7 (53.8)	2 (28.6)		
- AZA / 6MP / MTX	1 (7.7)	2 (28.6)		
- anti-TNF	-	1 (14.3)		
- anti-TNF + AZA / 6MP / MTX	-	1 (14.3)		

Appendiceal lavage

In 26 of 33 patients, analysis of the lavage fluid could be performed. Since the amount of CD3+ T-lymphocytes per lavage was variable, only percentages of CD4+ and CD8+ cells were compared. An ROC curve demonstrated that the optimal cut-off for increased CD4+

was > 70% CD4+ lymphocytes per lavage (sensitivity 0.74 and specificity 0.65, data not shown). In UC patients, an increased proportion of CD4+ was seen in the lavage fluid when compared to the controls (75% versus 50%). This increase in CD4+ cells in the lavage fluid was also seen in CD and AA. Since the number of CD8+ cells remained relatively low in UC and CD, this resulted in high CD4/CD8 ratio's in the lavage fluid for these patients groups (median 7.1 (iqr 4.2-8.1) and 5.2 (iqr 4.2-7.0), respectively) when compared to non-inflammatory controls (median 3.2 (iqr 2.5-6.2), P = 0.042). In AA patients, the associated increase in CD8+ cells resulted in a relatively low CD4/CD8 ratio. The results are shown in *Table 2*.

Table 2 Proportion of CD4+ and CD8+ T cells, and the CD4/CD8 ratio in lavage fluid of the appendix.

	UC (n = 10)	CD (n = 5)	AA (n = 5)	Controls (n = 6)
CD4+	75.7 [62.9-81.9]	75.0 [63.3-80.5]	73.9 [60.6-80.9]	64.6 [52.4-80.3]
CD8+	11.0 [6.7-18.2]	13.5 [10.1-18.4]	19.8 [11.5-23.3]	20.0 [12.3-24.4]
CD4/CD8 ratio	7.1 [4.2-8.1]*	5.2 [4.2-7.0]	3.8 [3.1-6.0]	3.2 [2.5-6.2]*

* CD4/CD8 ratio UC patients versus controls P = 0.042, for all other comparisons P >0.05

Histology and immunohistochemistry

In all UC and control patients the appendices appeared macroscopically normal, but mucosal based inflammation with increased lymphocyte infiltration was seen in 9 of 13 UC patients (69%). CD and AA patients demonstrated macroscopically affected appendices with an increased diameter, thickened meso-appendix, and a fibrino-purulent exsudate covering the serosal surface. Histology confirmed the transmural inflammation with oedema and lymphocyte influx present in the macroscopically affected appendices. Immunohistochemistry demonstrated that the increased number of lymphocytes seen at histology were predominantly CD4+ cells.

The majority of UC (8/13 = 62%), CD (6/7 = 85.7%) and AA (3/5 = 60%) patients had increased levels of CD4+ lymphocytes (grade 2 and 3). In the control group, the majority of patients had no increased CD4+ cells (88% grade 1 CD4+). Extensive influx of CD4+ lymphocytes (grade 3) was seen in 4/13 UC patients (31%), in 5 CD patients (71%), 2 AA patients (40%) and was present in only 1 control patient (*Figure 2*).

Comparable to the lavage results, the amount of CD8+ lymphocytes in UC and CD appendices was found to be a relatively constant factor. Only 1 UC and 1 CD patient had increased CD8+ cells (grade 3). In the AA appendices with increased CD4+ cells, an accompanying increase in CD8+ cells (grade 3) was found.

Immunohistochemical results correlated to CD4+ percentages in lavage fluid in 80% of UC patients.

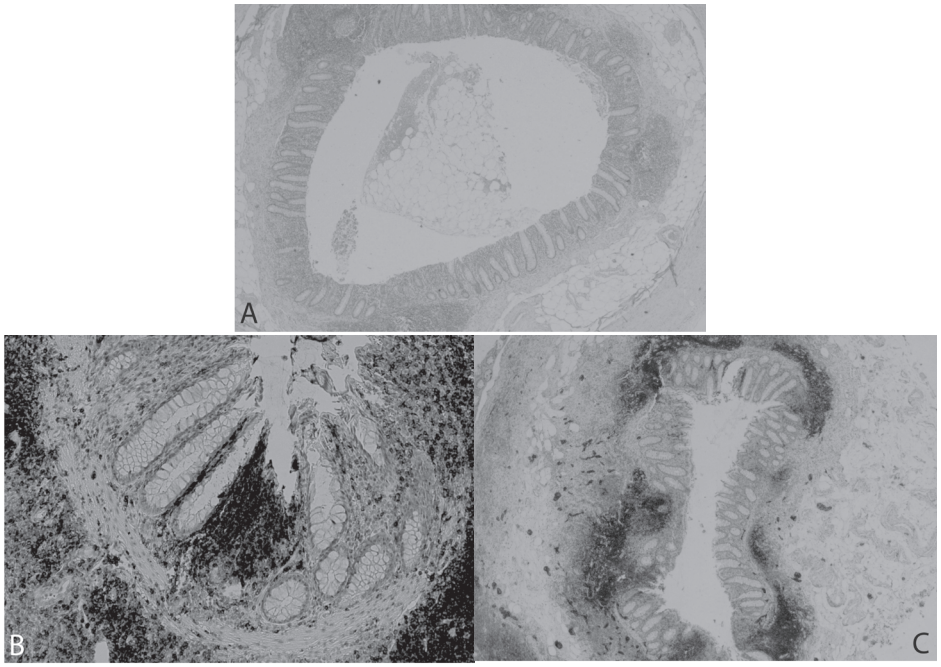


Figure 2 Immunohistochemical analysis, CD4+ T cell are stained in this image (brown coloured cells). In image A, a normal appendix is shown. The appendix of patients with appendicitis showed extensive influx (grade 3 or 4) of CD4+ cells (B). Also in the appendix of UC patients, extensive CD4+ influx can be seen (C).

Correlation with clinical disease activity

Increased CD4+ was able to predict clinical disease activity in 90% of UC, 100% of AA, and 80 of CD patients. Two UC patients were in remission at time of surgery, both patients had low CD4+ cells in the lavage fluid and both scored grade 1 in the immunohistochemical analysis. In three UC patients, a peri-appendicular red patch was seen on preoperative colonoscopy. Unfortunately, this could not be correlated to disease activity or increased CD4+ levels or CD4/CD8 ratio because lavage was performed in only one of these patients. Of the CD patients, one patient had a CD4+ level grade 1, in this patient indication for surgery was a stenosis. One other CD patient operated upon for stenosis had grade 2.

DISCUSSION

This study aimed to analyse if T-cell phenotype in appendiceal lavage fluid of UC patients was associated with inflammatory activation. Despite a macroscopically normal appearance of the appendix, patients with active disease showed inflammatory characteristics and increased numbers of mucosal CD4+ lymphocytes in lavage fluid and in immunohis-

tochemical analysis, comparable to CD and AA. This increase in CD4+ lymphocytes was predictive of disease activity in the majority of patients. The CD4/ CD8 ratio in lavage fluid was also significantly increased when compared to non-inflammatory controls. This elevated ratio in both UC and CD confirmed the difference in these auto-immune coordinated diseases when compared to AA, where a ratio comparable to non-inflammatory controls was found due to the associated increase in CD8+ cells.

In UC, the balance between T-helper cells and T-suppressor cells is shifted toward the T-helper cells. Infiltration of CD4+ T cells has been observed in the inflamed mucosa of UC patients, which results in enhancement of the inflammatory state by increased cytotoxic activity and cytokine production, eventually resulting in tissue injury [2-9]. The appendix is known to be part of the gut-associated lymphoid tissue system[23]. The mucosal lymphoid tissue of the appendix is predominantly composed of B cells and CD4 T-helper cells [24;25]. Here, T-lymphocytes are likely to get primed by various luminal antigens. A study by Matsushita et al. demonstrated an increased CD4/CD8 ratio in appendix biopsies of UC patients with active left sided colitis, when compared to non-inflammatory controls [13]. Interestingly, as the CD4/CD8 ratio in the appendix increased, the ratio in the rectum tented to increase as well. Furthermore, the proportion of early activated T cells (CD4+CD69+ T cells) in the appendix of UC patients, irrespective of disease extension or activity, was increased compared to non-inflammatory controls. Another study reported that the histological inflammation grade in the entire colon (both in inflamed and non-inflamed parts) was higher in patients with left sided colitis with appendiceal involvement [26]. In a murine UC model with T-cell receptor (TCR)-α deficient mice, CD4+ T-lymphocytes proliferate in the appendix, suggesting that the appendix is the priming site of cells involved in the disease process in these mice [10]. The results of these studies have led to the suggestion that the CD4/CD8 ratio in the mucosa of the appendix represents the inflammation degree in the colonic mucosa and cytokine production within the appendix is proposed to trigger an immunological cascade in the colorectum. In this respect, the finding of an elevated CD4/CD8 ratio in UC patients in remission is intriguing. If indeed this appendiceal immunological disbalance would contribute to the development of this disease, this could explain why reduced relapsing rates have been described after appendectomy [27-29]. The available literature suggests a more preferable clinical course with reduced need for immunosuppression therapy, reduced relapse rate and lower colectomy rates in appendectomised patients with UC, but strong evidence is lacking [30]. Currently, an appendectomy is sometimes offered as an experimental treatment in UC patients, even though the efficacy has not been evaluated in a randomized setting [31].

Involvement of the appendix in UC is also observed clinically. Endoscopists have described a cecal patch or peri-appendicular red patch (PARP) in UC patients. This patch of focal activity surrounding the appendiceal orifice is seen in up to 86% of patients with

a left sided colitis and an otherwise normal right-sided colon [26;32-34]. It has been hypothesized that this PARP could be used as a surrogate marker for ulcerative colitis.

In this study, we have prospectively identified patients with different inflammatory and non-inflammatory diseases and evaluated their appendicael tissue. The appendices were evaluated on all levels; macro- and microscopically and by lavage of the appendicael lumen. Assessment of the histological and immunohistochemical samples were blinded for diagnosis to avoid review bias. The intra- and inter-observer measurement error variability was restricted by independently repeating the sample scoring three times and by using three observers. This is a small exploratory study, that warrants further research. Currently, no objective measure of CD4+ cut off points in lavage fluid is available.

The results of this study indicate that despite a macroscopically normal appearance, appendices of UC patients with active disease show immunological activation with inflammatory characteristics and increased numbers of CD4+ lymphocytes in lavage fluid and immunohistochemical analysis. In contrast to AA there is no associated increase in the numbers of CD8+, resulting in a higher CD4/ CD8 ratio. An increased immunohistochemical CD4+ level was associated with active inflammation in UC, CD and AA patients, with CD4+ proportions in patients without active inflammation comparable to healthy controls. These results support the notion that the appendix may play a pathogenic role in UC. Future research should focus on the role of the appendix in UC, the implications of (endoscopical) appendicular lavage as measurement for the inflammatory process in the appendix, and the effect of appendectomy in UC. Accordingly, we have initiated several studies including an international multicentre randomized trial on the effect of appendectomy on the clinical course of UC (the ACCURE trial, Netherlands Trial Register NTR2883).

REFERENCES

1 Baumgart DC, Sandborn WJ. **Inflammatory bowel disease: clinical aspects and established and evolving therapies.** Lancet 2007; 369(9573):1641-1657.

2 Shanahan F. **Pathogenesis of ulcerative colitis.** Lancet 1993; 342(8868):407-411.

3 Rachmilewitz D, Karmeli F, Takabayashi K, Hayashi T, Leider-Trejo L, Lee J et al. **Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis.** Gastroenterology 2002; 122(5):1428-1441.

4 Davidson NJ, Fort MM, Muller W, Leach MW, Rennick DM. **Chronic colitis in IL-10-/- mice: insufficient counter regulation of a Th1 response.** Int Rev Immunol 2000; 19(1):91-121.

5 Papadakis KA, Targan SR. **Role of cytokines in the pathogenesis of inflammatory bowel disease.** Annu Rev Med 2000; 51:289-298.

6 Ueyama H, Kiyohara T, Sawada N, Isozaki K, Kitamura S, Kondo S et al. **High Fas ligand expression on lymphocytes in lesions of ulcerative colitis.** Gut 1998; 43(1):48-55.

7 Bhan AK, Mizoguchi E, Smith RN, Mizoguchi A. **Colitis in transgenic and knockout animals as models of human inflammatory bowel disease.** Immunol Rev 1999; 169:195-207.

8 Fiocchi C. **Inflammatory bowel disease: etiology and pathogenesis.** Gastroenterology 1998; 115(1):182-205.

9 Simpson SJ, Mizoguchi E, Allen D, Bhan AK, Terhorst C. **Evidence that CD4+, but not CD8+ T cells are responsible for murine interleukin-2-deficient colitis.** Eur J Immunol 1995; 25(9):2618-2625.

10 Mizoguchi A, Mizoguchi E, Chiba C, Bhan AK. **Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice.** J Exp Med 1996; 184(2):707-715.

11 Panaccione R, Sandborn WJ. **The appendix in ulcerative colitis: a not so innocent bystander.** Gastroenterology 1999; 117(1):272-273.

12 Jo Y, Matsumoto T, Yada S, Nakamura S, Yao T, Hotokezaka M et al. **Histological and immunological features of appendix in patients with ulcerative colitis.** Dig Dis Sci 2003; 48(1):99-108.

13 Matsushita M, Takakuwa H, Matsubayashi Y, Nishio A, Ikehara S, Okazaki K. **Appendix is a priming site in the development of ulcerative colitis.** World J Gastroenterol 2005; 11(31):4869-4874.

14 Haddad M, Azim F, Koren A, Stelman E, Mor C, Zelikovski A. **Crohn's disease of the appendix.** Eur J Surg 1993; 159(3):191-192.

15 Prieto-Nieto I, Perez-Robledo JP, Hardisson D, Rodriguez-Montes JA, Larrauri-Martinez J, Garcia-Sancho-Martin L. **Crohn's disease limited to the appendix.** Am J Surg 2001; 182(5):531-533.

16 Vanek VW, Spirtos G, Awad M, Badjatia N, Bernat D. **Isolated Crohn's disease of the appendix. Two case reports and a review of the literature.** Arch Surg 1988; 123(1):85-87.

17 Weston LA, Roberts PL, Schoetz DJ, Jr., Coller JA, Murray JJ, Rusin LC. **Ileocolic resection for acute presentation of Crohn's disease of the ileum.** Dis Colon Rectum 1996; 39(8):841-846.

18 Basta M, Morton NE, Mulvihill JJ, Radovanovic Z, Radojicic C, Marinkovic D. **Inheritance of acute appendicitis: familial aggregation and evidence of polygenic transmission.** Am J Hum Genet 1990; 46(2):377-382.

19 Jones BA, Demetriades D, Segal I, Burkitt DP. **The prevalence of appendiceal fecaliths in patients with and without appendicitis. A**

comparative study from Canada and South Africa. Ann Surg 1985; 202(1):80-82.

20 Walker AR, Segal I. **What causes appendicitis?** J Clin Gastroenterol 1990; 12(2):127-129.

21 Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K et al. **Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis.** J Crohns Colitis 2012; 6(10):965-990.

22 Stumpf M, Hasenburg A, Riener MO, Jutting U, Wang C, Shen Y et al. **Intraepithelial CD8-positive T lymphocytes predict survival for patients with serous stage III ovarian carcinomas: relevance of clonal selection of T lymphocytes.** Br J Cancer 2009; 101(9):1513-1521.

23 Spencer J, Finn T, Isaacson PG. **Gut associated lymphoid tissue: a morphological and immunocytochemical study of the human appendix.** Gut 1985; 26(7):672-679.

24 Thompson-Chagoyan OC, Maldonado J, Gil A. **Aetiology of inflammatory bowel disease (IBD): role of intestinal microbiota and gut-associated lymphoid tissue immune response.** Clin Nutr 2005; 24(3):339-352.

25 Kawanishi H. **Immunocompetence of normal human appendiceal lymphoid cells: in vitro studies.** Immunology 1987; 60(1):19-28.

26 Matsumoto T, Nakamura S, Shimizu M, Iida M. **Significance of appendiceal involvement in patients with ulcerative colitis.** Gastrointest Endosc 2002; 55(2):180-185.

27 Gilat T, Hacohen D, Lilos P, Langman MJ. **Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study.** Scand J Gastroenterol 1987; 22(8):1009-1024.

28 Hallas J, Gaist D, Sorensen HT. **Does appendectomy reduce the risk of ulcerative colitis?** Epidemiology 2004; 15(2):173-178.

29 Koutroubakis IE, Vlachonikolis IG, Kouroumalis EA. **Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review.** Inflamm Bowel Dis 2002; 8(4):277-286.

30 Gardenbroek TJ, Eshuis EJ, Ponsioen CI, Ubbink DT, D'Haens GR, Bemelman WA. **The effect of appendectomy on the course of ulcerative colitis: a systematic review.** Colorectal Dis 2012; 14(5):545-553.

31 Bolin TD, Wong S, Crouch R, Engelman JL, Riordan SM. **Appendicectomy as a therapy for ulcerative proctitis.** Am J Gastroenterol 2009; 104(10):2476-2482.

32 D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. **Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study.** Am J Gastroenterol 1997; 92(8):1275-1279.

33 Perry WB, Opelka FG, Smith D, Hicks TC, Timmcke AE, Gathright JB, Jr. et al. **Discontinuous appendiceal involvement in ulcerative colitis: pathology and clinical correlation.** J Gastrointest Surg 1999; 3(2):141-144.

34 Rubin DT, Rothe JA. **The peri-appendiceal red patch in ulcerative colitis: review of the University of Chicago experience.** Dig Dis Sci 2010; 55(12):3495-3501.

Summary and future perspectives

The research in the first part of this thesis focusses on the developments in the surgical treatment of patients with inflammatory bowel disease and familial adenomatous polyposis and it concentrates on new developments in surgical techniques. The second part of this thesis focuses on the appendix in and its role in UC. There is evidence that appendectomy protects against development of UC and may influence the disease course of UC. Furthermore, in the literature the appendix is suggested to be a potential priming site in the development of UC.

Part I

Chapter 1 presents a systematic review with meta-analysis in which short-term outcomes after laparoscopic and open colectomy for acute medically refractory colitis were compared. A total of nine non-randomized studies were included, comprising 966 patients in total. Meta-analysis showed a lower wound infection rate and a lower intra-abdominal abscess rate after laparoscopic colectomy compared to open colectomy. There were no significant differences observed in rates of reoperation, ileus, gastrointestinal bleeding or mortality. Together with the expected long-term benefits of the approach, such as fewer incisional hernias and adhesions, laparoscopic (sub)acute colectomy can be regarded as best practice in centres with sufficient technical experience.

Chapter 2 describes a study aimed to define predictors of postoperative complications in patients undergoing emergency colectomy for severe colitis in IBD patients. A review of 71 consecutive patients who underwent this intervention at the Academic Medical Centre was performed. In patients with a longer preoperative hospital stay the risk of complications increased. Furthermore, patients with postoperative complications had a higher age and a higher body mass index. The higher body mass index might reflect the use of more corticosteroids in this group. The results of this study underline that the presence of a multidisciplinary IBD team is essential in order to make a well-considered decision whether to continue medical therapy or to proceed to surgery, benefitting the results of both medical as well as surgical treatment.

Chapter 3 addresses a series of ten consecutive patients with IBD that underwent (sub) acute emergency colectomy with alternative specimen extraction techniques to remove the specimen from the abdominal cavity after emergency colectomy (natural orifice specimen extraction, NOSE). The study showed that the transrectal and transstomal extraction techniques were feasible and safe for retrieval of the colectomy specimen after laparoscopic subtotal colectomy characterized by low postoperative morbidity rates and few intra-abdominal adhesions. The foresights for these alternative extraction techniques are promising; however, the techniques still need refinement and are only applicable in selected patients.

The short term results of two surgical dissection techniques in the creation of an ileal pouch-anal anastomosis (IPAA) were compared in a randomized controlled trial presented in **Chapter 4**. The aim of this study was to compare morbidity and quality of life in patients having total mesorectal excision (TME) or close rectal dissection (CRD) during proctectomy followed by ileal pouch-anal anastomosis (IPAA) for benign disease. Patients having an IPAA were randomized to TME or CRD. Outcomes were 30-day morbidity and quality of life (QoL). Fifty-nine patients were included; 28 in the CRD group and 31 in the TME group. Operating time was longer in the CRD group. More TME patients had a primary defunctioning ileostomy and more severe complications occurred in the TME group. QoL life was better in the CRD group for several subscales of the questionnaires measured at 1, 3 and 6 months after surgery, but was similar on all subscales at 12 months.

In **Chapter 5** we compared the results of 2 cohorts of patients undergoing IPAA surgery with or without primary defunctioning ileostomy. Seventy-one patients were included in the group with a primary defunctioning ileostomy and 220 patients in the group without primary defunctioning ileostomy. Primary defunctioning of an IPAA did not result in lower leakage rates, lower overall postoperative complications or decreased pouch failure rates. It resulted in a higher rate of continence disturbances and impaired social functioning scores at long term follow up compared to patients with an IPAA without primary defunctioning ileostomy. Construction of a defunctioning ileostomy after IPAA should therefore be a patient-tailored decision instead of standard practice.

A novel solution for the treatment of anastomotic leakage after IPAA is presented in **Chapter 6.** In this study we determined the effectiveness and direct medical costs of early surgical closure of the anastomotic defect after a short course of Endo-sponge® therapy of the presacral cavity, compared to conventional treatment in patients with anastomotic leakage after ileal pouch-anal anastomosis (IPAA). A total of 15 patients were treated with early surgical closure and 29 patients were treated conventionally. The early surgical closure treatment resulted in a significantly higher percentage of secondary healed anastomosis at 6 months compared to the conventional treatment. Furthermore, early surgical closure significantly reduced the time to anastomotic healing with a median of 22 days compared to the conventional treatment. Early surgical closure resulted in a high percentage of functional pouches at the end of follow-up. No differences in treatment costs were found between both groups.

Chapter 7 describes a review discussing the developments in the surgical techniques in the treatment of patients with CD. In the surgical treatment of these patients, minimally invasive surgery is currently recognized as standard treatment. New developments derived from existing minimal invasive techniques are single-port laparoscopic surgery,

natural orifice specimen extraction, close rectal dissection techniques and transperineal resectional surgery, all aiming at further reducing surgical trauma and therewith further reducing the hospital stay and morbidity, and improving the cosmetic outcomes.

The single-port laparoscopic ileocolic resection was analysed in **Chapter 8**. Here, we compared short term surgical outcomes in 2 cohorts of patients who underwent either single-port or multiport laparoscopic ileocolic resection for CD. Twenty-one patients that underwent single-port resection were matched to 42 patients that underwent multiport resection. The single-port procedure was associated with a reduced length of stay, operative time and morphine use on postoperative day one and similar overall complications compared to multiport laparoscopic ileocolic resection. These results demonstrate that with single-port laparoscopic ileocolic resection the advantages of the laparoscopic approach are preserved and that the procedure is feasible and safe in selected patients.

Part II

Chapter 9 describes a systematic review of studies investigating the effect of appendectomy on the disease course of patients with UC. The search resulted in 6 observational studies (5 case control studies and one cohort study) totaling 2532 patients. One study showed a lower relapse rate in patients who had an appendectomy before onset of UC. Two studies found a reduced requirement for immunosuppression in appendectomised patients, however two studies found no differences in the requirement for immunosuppression. In addition, two studies found lower colectomy rates in appendectomised patients, one study actually found higher colectomy rates in appendectomised patients, and two studies found no significant differences in colectomy rates between the appendectomised and nonappendectomised patients. This study showed that the data regarding the effect of appendectomy on the disease course of UC are limited and conflicting. Most studies suggest a beneficial effect and the minority find no, or a negative, effect.

Chapter 10 presents the study protocol of the ACCURE trial, an international multicentre randomised trial in patients with UC that will provide evidence on the role of appendectomy in the treatment of UC and the effects of appendectomy on the disease course. The study will include patients over 18 years of age with an established diagnosis of UC and a disease relapse within 12 months prior to randomisation. Patients need to be medically treated until complete clinical (Mayo score <3) and endoscopic (Mayo score 0 or 1) remission. Patients will then be randomised 1:1 to a control group (maintenance 5-ASA treatment, no appendectomy) or elective laparoscopic appendectomy plus maintenance treatment. The primary outcome measure is the one year cumulative UC relapse rate - defined both clinically and endoscopically as a total Mayo-score ff15 with endoscopic subscore of 2 or 3.

In depth analysis of the appendix is performed in **Chapter 11**. In this study T cell infiltration in the appendices of UC patients was analysed and compared to the appendices of patients with CD, acute appendicitis (AA) and non-inflammatory controls. Despite a macroscopically normal appearance, appendices of UC patients with active disease show immunological activation with inflammatory characteristics and increased numbers of CD4+ lymphocytes in lavage fluid and immunohistochemical analysis.

FUTURE PERSPECTIVES

In the last decades, considerable progress has been made in the treatment of patients with IBD; surgical approaches have become less invasive thanks to laparoscopy and single port surgery. The medical treatment options also changed dramatically with the introduction of anti-tnf therapy and soon anti-integrin antibodies. Simultaneously, treatment goals have shifted from symptom control or steroid free remission, to mucosal healing. Future research should focus on early identification and stratification of patients benefitting from medical (biologic) therapy or early surgery. Randomised controlled trials comparing well-defined medical versus surgical treatment strategies will be of paramount importance to clarify optimal treatment strategies in IBD patients. Future paradigms could consist of early limited bowel resection or stricturoplasty followed by intensive follow-up with imaging and/or biomarkers and medical treatment in case of relapse or recurrence. Furthermore, future studies are warranted to determine the real impact of mucosal healing on the further disease course: will it really prevent the need for further resections in patients with IBD? In addition, more research is needed to clarify the impact of perioperative biologicals to potentially improve results of surgery, for example in perianal fistula surgery aiming at definitive closure of the fistula tract.

Future IBD research should also focus on the assessment of biomarkers for the future behaviour of CD and response to treatment. By analysing serologic, histopathological and genetic biomarkers, diagnostic tests may allow to determine the risk probability for severe disease or may be used to predict response to medical therapies.

Finally, laparoscopic appendectomy may be beneficial in the treatment of early or treatment-refractory ulcerative colitis. Further immunological characterisation of the appendix and research into the role of mucosal microbiota in the appendix and their interaction with the immune system will potentially lead to further insights into the aetiology of UC. Identification of UC patients potentially benefitting from appendectomy could lead to a more personalized treatment approach.

Specialised IBD care should be centralised in referral centres. In non-specialised IBD centres, routine care should be standardised and optimised using IBD care networks in collaboration with tertiary high-volume centres.

Nederlandse samenvatting

Het onderzoek in het eerste deel van dit proefschrift richt zich op de ontwikkelingen in de chirurgische behandeling van patiënten met inflammatoire darmziekten (IBD; de ziekte van Crohn en colitis ulcerosa) en familiaire adenomateuze polyposis (FAP) en concentreert zich op nieuwe ontwikkelingen in chirurgische technieken. Het tweede deel van dit proefschrift richt zich op de rol van de appendix en in colitis ulcerosa (CU). Er zijn aanwijzingen dat het verwijderen van de appendix beschermt tegen de ontwikkeling van CU en dat een appendectomie het ziektebeloop van CU kan beïnvloeden. Verder wordt in de literatuur gesuggereerd dat de appendix een potentiële basis is in de ontwikkeling van CU.

Deel I

Hoofdstuk 1 bevat een systematisch review met een meta-analyse waarin de korte termijn resultaten na laparoscopische en open colectomie voor medicamenteus refractaire colitis werden vergeleken. Een totaal van negen niet-gerandomiseerde onderzoeken werden geïncludeerd, met gegevens over totaal 966 patiënten. De meta-analyse liet zien dat er na laparoscopische colectomie minder wondinfecties en minder intra-abdominale abcessen voorkwamen. Er was geen verschil in het aantal patiënten dat een heroperatie nodig had, het aantal patiënten met een ileus, het aantal patiënten met gastro-intestinale bloeding of in de mortaliteit. In ervaren handen heeft laparoscopische (sub) acute colectomie belangrijke voordelen.

Hoofdstuk 2 presenteert een studie die was opgezet om voorspellers voor een gecompliceerd postoperatief beloop bij een colectomie vanwege een ernstige colitis te bepalen. Daartoe werd een serie van 71 opeenvolgende patiënten die vanwege een ernstige colitis een colectomie in het AMC ondergingen beschreven. De resultaten toonden dat een langere preoperatieve opnameperiode resulteerde in een toename van het risico op complicaties. Patiënten met postoperatieve complicaties hadden een hogere leeftijd en een hoger BMI in vergelijking met patiënten zonder complicaties. De aanwezigheid van een multidisciplinair IBD team is essentieel om een weloverwogen beslissing te maken om medicamenteuze behandeling voort te zetten of over te gaan tot een operatie.

Hoofdstuk 3 beschrijft tien IBD patiënten die een colectomie ondergingen waarbij er alternatieve methoden zijn gebruikt om het preparaat uit te nemen, zoals via het rectum of een stoma opening. Deze studie toonde aan dat het uitnemen van het preparaat via het rectum of via een stoma opening na laparoscopische subtotale colectomie haalbaar en veilig was, met weinig postoperatieve morbiditeit en beperkte intra-abdominale verklevingen bij een heroperatie. De mogelijkheden van deze alternatieve extractie technieken lijken veelbelovend. De technieken hebben echter nog verfijning nodig en zijn alleen van toepasbaar bij geselecteerde patiënten.

De resultaten van twee verschillende chirurgische dissectie technieken bij het creëren van een ileo-anale pouch anastomose (IPAA) werden vergeleken in een gerandomiseerde trial. Deze vergelijking wordt gepresenteerd in **Hoofdstuk 4**. Doel van dit onderzoek was de morbiditeit en kwaliteit van leven (KvL) te vergelijken in patiënten die een proctectomie ondergingen met een totale mesorectale excisie (TME) of close rectal dissectie (CRD), waarna een IPAA werd aangelegd. Patiënten werden gerandomiseerd voor TME of CRD techniek. Uitkomstmaten waren morbiditeit na 30 dagen en KvL. Negenenvijftig patiënten werden geïncludeerd; 28 in de CRD-groep en 31 in de TME groep. De operatietijd was langer in de CRD-groep, in de TME groep hadden meer patiënten een primair ontlastend ileostoma. In de TME groep traden meer ernstige complicaties op. KvL was beter in de CRD groep in verschillende subschalen van de vragenlijsten gemeten op 1, 3 en 6 maanden na de operatie. Na 12 maanden was er geen verschil in KvL tussen beide groepen.

In **Hoofdstuk 5** worden de resultaten van twee cohorten patiënten waarbij een IPAA werd aangelegd met of zonder primair ontlastend ileostoma vergeleken. Eenenzeventig patienten werden opgenomen in de groep met een primair ontlastend ileostoma en 220 patiënten in de groep zonder primair ontlastend ileostoma. Het aanleggen van een primair ontlastend ileostoma na IPAA chirurgie leidde niet tot een lager aantal naadlekkages, algemene postoperatieve complicaties of het aantal pouches dat niet functioneerde. Het resulteerde daarentegen in een hoger percentage continentie stoornissen en een verminderd sociaal functioneren op de lange termijn. Het aanleggen van een primair ontlastend ileostoma na IPAA moet een geïndividualiseerde beslissing zijn in plaats van standaard praktijk.

Een nieuwe methode voor de behandeling van een naadlekkage na IPAA wordt beschreven in **Hoofdstuk 6**. In deze studie zijn de effectiviteit en de directe medische kosten van twee verschillende behandelingen bij patiënten met naadlekkage na IPAA met elkaar vergeleken. Een groep van 15 patiënten onderging vroege chirurgische sluiting van het defect in de anastomose na een korte behandeling middels endo-spons® therapie van de presacrale holte. De andere groep van 29 patiënten werd behandeld volgens de conventionele behandeling. Vroege chirurgische sluiting van het defect resulteerde in vergelijking met de conventionele behandeling in een significant hoger percentage secundair genezen anastomoses na 6 maanden, een kortere duur van genezing van de anastomose en in een hoog percentage van functionele pouches. Er was geen verschil in de kosten voor behandeling tussen beide groepen.

Hoofdstuk 7 bevat een review van de ontwikkelingen in chirurgische technieken bij de behandeling van patiënten met de ziekte van Crohn. Minimaal invasieve chirurgie is de huidige standaard in de chirurgische behandeling van deze patiënten. Nieuwe ontwikke-

lingen die zijn afgeleid van bestaande minimaal invasieve technieken zijn single-port laparoscopische chirurgie, natural orifice specimen extraction (uitnemen van het chirurgisch preparaat via natuurlijke openingen), close rectal dissectie technieken en transperineale resectie. Deze technieken zijn allen gericht op het verder verminderen van het chirurgisch trauma en daarmee op een verdere afname van de duur van het ziekenhuisverblijf en morbiditeit, met tegelijkertijd een verbetering van de cosmetische uitkomsten.

Een studie van de single-port laparoscopische ileocecaalresectie wordt gepresenteerd in **hoofdstuk 8**. Hierin vergeleken we de korte termijn resultaten in twee cohorten patiënten met ziekte van Crohn die of een single-port of een multiport laparoscopische ileocecaalresectie ondergingen. Eenentwintig patiënten die een single-port resectie ondergingen werden vergeleken met 42 patiënten die een multiport resectie ondergingen.

Patiënten die een single-port ileocecaalresectie ondergingen hadden een korter ziekenhuisverblijf, kortere operatieduur, minder morfine gebruik op de eerste postoperatieve dag en een gelijk aantal algemene complicaties in vergelijking met de multiport laparoscopische ileocecaalresectie. Deze studie toonde aan dat bij de single-port laparoscopische ileocecaalresectie de voordelen van de laparoscopische behandeling behouden blijven en dat de procedure uitvoerbaar is in geselecteerde patiënten.

Deel II

Hoofdstuk 9 bevat een systematisch review van studies naar het effect van appendectomie op het ziektebeloop van patiënten met CU. Zes observationele studies (vijf case-control studies en een cohortstudie) met in totaal 2532 patiënten werden geïncludeerd. Eén studie vond een lager ziekterecidief bij patiënten die vóór aanvang van CU een appendectomie hadden ondergaan. Twee studies vonden een verminderde behoefte aan immunosuppressie in patiënten die een appendectomie hadden ondergaan, twee studies vonden geen verschil in immunosuppressie. Daarnaast vonden twee studies een lager aantal colectomieën in patiënten die een appendectomie hadden ondergaan, een studie vond een hoger aantal colectomieën in patiënten die een appendectomie hadden ondergaan en twee studies vonden geen verschillen in het aantal patiënten waarbij een colectomie werd uitgevoerd. Deze review liet beperkte en tegenstrijdige resultaten zien van het effect van een appendectomie op het ziektebeloop van CU. De meeste studies wijzen op een gunstig effect, de minderheid vindt geen of een negatief effect.

In **Hoofdstuk 10** wordt het onderzoeksprotocol van de Accure trial gepresenteerd. Dit is een internationale multicentrische gerandomiseerde studie bij patiënten met CU. Deze studie is opgezet om duidelijkheid te verkrijgen over de rol van de appendix in colitis ulcerosa en over de effecten van appendectomie op het ziekteverloop. De studie betreft patiënten ouder dan 18 jaar met CU en een ziekterecidief binnen 12 maanden

voorafgaand aan randomisatie includeren. Patiënten worden medicamenteus behandeld tot volledige klinische (Mayo score <3) en endoscopische (Mayo score 0 of 1) remissie is bereikt. Vervolgens worden de patiënten 1:1 gerandomiseerd naar een controlegroep (onderhoudsbehandeling met 5-ASA, geen appendectomie) of interventiegroep (electieve laparoscopische appendectomie plus onderhoudsbehandeling). De primaire uitkomstmaat is het cumulatieve aantal ziekterecidieven - zowel klinisch als endoscopisch gedefinieerd als een totale Mayo-score ffl 5 met endoscopische subscore van 2 of 3 - na een jaar.

Hoofdstuk 11 beschrijft een onderzoek naar inflammatoire en immunologische aspecten van de appendix van patiënten met CU. In deze studie werd de T-cel infiltratie in de appendix van patiënten met CU geanalyseerd en vergeleken met de appendices van patiënten met de ziekte van Crohn, acute appendicitis en niet-inflammatoire controles. Ondanks een macroscopisch normaal uiterlijk vertoonden de appendices van CU patiënten met actieve ziekte immunologische activering met inflammatoire eigenschappen en een verhoogd aantal CD4 +-lymfocyten in lavagevloeistof en immunohistochemische analyse.

TOEKOMSTPERSPECTIEVEN

In de laatste decennia is er veel vooruitgang geboekt in de behandeling van patiënten met IBD; chirurgische benaderingen zijn minder invasief geworden dankzij laparoscopische en single port chirurgie. De medicamenteuze behandelopties zijn ook drastisch veranderd met de introductie van anti-TNF-therapie en de ontwikkeling van anti-integrine antilichamen. Tegelijkertijd zijn de behandeldoelen verschoven van symptoomcontrole of steroïd vrije remissie naar mucosale genezing. Toekomstig onderzoek moet zich richten op de vroege identificatie en stratificatie van patiënten die profiteren van medische (biologische) therapie of van vroege operatieve behandeling. Gerandomiseerde studies waarin goed gedefinieerde medicamenteuze met chirurgische behandeling strategieën vergeleken worden, zullen van doorslaggevend belang zijn om de optimale behandeling strategieën in patiënten met IBD te bepalen. Toekomstige paradigma's kunnen bestaan uit vroege, beperkte darm resectie of stricturoplastiek gevolgd door intensieve follow-up met beeldvorming en / of biomarkers en medicamenteuze behandeling in geval van terugval of terugkerende ziekte. Bovendien zijn studies noodzakelijk om de impact van mucosale genezing op het verdere beloop van de ziekte vast te stellen: voorkomt dit de noodzaak tot (verdere) resecties bij patiënten met IBD? Daarnaast is meer onderzoek nodig naar het effect van perioperatieve biologicals op de verbetering van de resultaten van de procedure, bijvoorbeeld bij perianale fistel chirurgie gericht op definitieve sluiting van de fistel.

Toekomstig IBD onderzoek moet zich ook richten op de evaluatie van biomarkers als voorspellers van het ziektebeloop en de respons op de behandeling. Door het analyseren van serologische, histopathologische en genetische biomarkers kunnen diagnostische tests ontwikkeld worden die de kans op een ernstig ziektebeloop voorspellen of kunnen deze biomarkers worden gebruikt om respons op medicamenteuze therapie in te schatten. Tenslotte kan laparoscopische appendectomie een rol spelen in de vroege behandeling van CU of in geval van refractaire CU. Verdere immunologische karakterisering van de appendix en het onderzoek naar de rol van mucosale microbiota in de appendix en de interactie met het immuunsysteem zal mogelijk leiden tot verdere inzichten in de etiologie van CU. Identificatie van patiënten met CU die mogelijk profiteren van een appendectomie zou kunnen leiden tot een meer gepersonaliseerde behandeling.
Gespecialiseerde IBD zorg moet worden gecentraliseerd in verwijzingscentra. In niet-gespecialiseerde IBD centra moet routine zorg worden gestandaardiseerd en geoptimaliseerd met behulp van IBD zorgnetwerken in samenwerking met tertiaire hoog-volume centra.

Portfolio

Name PhD student: T. J. Gardenbroek
PhD period: September 2010 - June 2013
Name PhD supervisor: Prof. dr. W.A. Bemelman

	Year	Workload (ECTS)
General courses		
- Practical Biostatistics	2011	1.1
- Clinical data Management	2011	0.3
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	0.9
- Scientific writing in English for Publication	2011	1.5
Specific courses		
- Clinical Epidemiology	2011	0.6
- Advanced Topics in Biostatistics	2013	2.1
Seminars, workshops and master classes		
- Weekly department seminars	2010-2013	3
- Master class by Prof. J. Powell	2012	0.2
- ICH en EU Directives on Good Clinical Practice	2010	0.2
Oral Presentations		
- Active inflammation of the appendix in ulcerative colitis.		
NVGE Voorjaarsdagen, Veldhoven	2013	0.5
- Early closure of anastomotic leakage after ileal pouch-anal anastomosis: a novel solution to an old problem		
NVGE Voorjaarsdagen, Veldhoven	2013	0.5
NVvH Chirurgendagen, Veldhoven	2013	0.5
- The LIRIC trial; laparoscopic ileocolic resection or infliximab for Crohn's disease.		
European Crohn & Colitis Organisation, Barcelona	2012	0.5
Swedish IBD organization symposium, Stockholm	2010	0.5
- The effect of appendectomy on the clinical course of ulcerative colitis, the ACCURE trial.		
European Society of Coloproctology, Kopenhagen	2011	0.5
- Alternative specimen extraction techniques after laparoscopic emergency colectomy in Inflammatory Bowel Disease.		
NVGE Voorjaarsvergadering, Veldhoven	2011	0.5
NVvH Chirurgendagen, Veldhoven	2011	0.5
Poster Presentations		
- Early closure of anastomotic leakage after ileal pouch-anal anastomosis: a novel solution to an old problem,		

Digestive Disease Week, Orlando	2013	0.5
- Active inflammation of the appendix in ulcerative colitis. European Crohn's & Colitis Organisation, Wenen.	2011	0.5
- Pouch design and long term functional outcome after ileal-pouch-anal anastomosis.		
United European Gastroenterology Week, Stockholm	2011	0.5
European Society of Coloproctology, Kopenhagen	2011	0.5
- Alternative specimen extraction techniques after laparoscopic emergency colectomy in Inflammatory Bowel Disease.		
Nederlandse Vereniging voor Endoscopische Chirurgie, Leiden	2011	0.5
- The effect of appendectomy on the clinical course of Ulcerative Colitis, a systematic review.		
European Crohn's & Colitis Organisation, Dublin	2011	0.5
Nederlandse Vereniging voor Endoscopische Chirurgie, Leiden	2011	0.5
(Inter)national conferences		
- NVEC Jaarcongres, Leiden	2011	0.25
- European Society of Coloproctology, Kopenhagen	2011	0.25
- United European Gastroenterology Week, Stockholm	2011	0.25
- European Crohn's and Colitis Organisation, Dublin	2011	0.25
- NVGE Voorjaarscongres, Veldhoven	2012	0.25
- NVvH Chirurgendagen, Veldhoven	2012	0.25
- IBD Today & Tomorrow, Amsterdam	2012	0.25
- Update on colorectal cancer, Amsterdam	2012	0.25
- European Crohn's and Colitis Organisation, Barcelona	2012	0.25
- NVvH Najaarsdag, Rotterdam	2012	0.25
- United European Gastroenterology Week, Amsterdam	2013	0.25
- European Crohn's and Colitis Organisation, Wenen	2013	0.25
- NVGE Voorjaarscongres, Veldhoven	2013	0.25
- Digestive Disease Week, Orlando	2013	0.25
- NVvH Chirurgendagen, Veldhoven	2013	0.25
Teaching , Tutoring, Mentoring:		
Tutoring 3rd year medical students	2011-12	1

Bibliography

Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis. D.A. Sloothaak, T.J. Gardenbroek, J. Crezee, W.A. Bemelman, C.J. Punt, C.J. Buskens, P.J. Tanis. Eur J Surg Oncol. 2014 Jul 18

Health-related quality of life and disability in patients with ulcerative colitis and proctocolectomy with ileoanal pouch versus treatment with anti-TNF agents. S. Meijs, T.J. Gardenbroek, M.A. Sprangers, W.A. Bemelman, C.J. Buskens, G.R. D'Haens, M. Löwenberg. J Crohns Colitis Jan 2014 Jul 1;8(7):686-92.

Risk factors for complications after emergency colectomy for severe colitis. S.A.L. Bartels, T.J. Gardenbroek, L. Bos, C.Y. Ponsioen, G.R.A.M. D'Haens, C.J. Buskens, P.J. Tanis, W.A. Bemelman. Colorectal Dis. 2013 Nov;15(11):1392-8.

Single-incision versus multiport laparoscopic ileocolic resection for Crohn's disease. T.J. Gardenbroek, T. Verlaan, P.J. Tanis, C.J. Buskens, C.Y. Ponsioen, G.R.A.M. D'Haens, W.A. Bemelman. J Crohns Colitis. 2013 Nov 1;7(10):e443-8.

A systematic review and meta-analysis of laparoscopic versus open subtotal colectomy in patients with inflammatory bowel diseases. T.J. Gardenbroek, S.A.L. Bartels, D.T. Ubbink, C.J. Buskens, P.J. Tanis, W.A. Bemelman. Br J Surg. 2013 May;100(6):726-33

Surgery for Crohn's Disease: New Developments. T.J. Gardenbroek, P.J. Tanis, C.J. Buskens, W.A. Bemelman. Dig Surg. 2012;29(4):275-80.

Alternative specimen extraction techniques after laparoscopic emergency colectomy in Inflammatory Bowel Disease. T.J. Gardenbroek, E.J. Eshuis, G.J.D. van Acker, P.J. Tanis, W.A. Bemelman. Surg Endosc. 2012 Feb;26(2):408-12.

The effect of appendectomy on the disease course of Ulcerative Colitis, a systematic review. T.J. Gardenbroek, E.J. Eshuis, C.Y. Ponsioen, D.T. Ubbink, G.R.A.M. D'Haens, W.A. Bemelman. Colorectal Dis. 2012 May;14(5):545-53.

The Proximal Femur Nail Antirotation, an identifiable improvement in the treatment of unstable pertrochanteric fractures. T.J. Gardenbroek, M.J.M. Segers, R.K.J. Simmermacher, E.R. Hammacher. J Trauma. 2011 Jul;71(1):169-74.

Re-excisies bij borstsparende chirurgie. Een analyse en discussie naar aanleiding van eigen data. T.J. Gardenbroek, B.A.N. Verhoeven, R. Koelemij. Nederlands Tijdschrift voor Heelkunde 2009 Dec;18(9):310-15.

Pseudoarthrosis of the ribs treated with a locking compression plate. T.J. Gardenbroek, M. Bemelman, L.P.H. Leenen. J Bone Joint Surg Am. 2009 Jun;91(6):1477-9.

Dankwoord

Graag wil ik alle mensen bedanken die hebben bijgedragen aan mijn promotieonderzoek. Een aantal personen wil ik in het bijzonder bedanken.

Prof. dr. W.A Bemelman. Beste Willem, veel dank voor deze leerzame periode. Ik bewonder je gedrevenheid voor zowel het klinische werk als het onderzoek, en de invulling die je daaraan geeft. Dank voor alle mogelijkheden, het vertrouwen en de begeleiding van de afgelopen jaren. En zeker ook veel dank voor de mooie congressen, bbq's en tripjes op de plassen.
Prof. dr. G.R.A.M. D'Haens. Beste Geert, halverwege mijn promotietraject kwam de Belgische wervelwind naar het AMC. Je bent een inspirerend persoon met een passie voor onderzoek, dank voor de zeer nuttige en goede samenwerking.
Dr. Cyriel Ponsioen. Beste Cyriel, jij en Willem hebben me aangenomen op een uniek project van de chirurgie en maag-, darm- en leverziekten in het AMC, veel dank daarvoor. Onze ontelbare LIR!C tripjes waren leerzaam en gezellig, ik zal ze niet snel vergeten.
Dr. Christianne Buskens. Beste Chris, vrolijk en gedreven, altijd beschikbaar voor overleg en altijd met een scherpe en verhelderende blik. Het is fijn om samen te werken met jou, je hebt me nu al veel geleerd en ik kijk uit naar onze klinische tijd.

Prof. dr. Gouma, prof. dr. van den Brink, prof. dr. Stassen, prof. dr. Cuesta, prof. dr. van den Brink, prof. dr. Boermeester en dr. Löwenberg; hartelijk dank dat u zitting heeft willen nemen in mijn commissie.

Dank aan alle mede auteurs, alle leden van de LIR!C en ACCURE studiegroepen en alle collega's van de IBD Unit van het AMC. Florien Toxopeus, bedankt voor de prettige samenwerking.

Sanne Bartels, Emma Eshuis, Joline de Groof, Gijsbert Musters, Salomeeh Sahami, Didi Sloothaak en Hilko Swank en alle andere onderzoekers van G4, het was een mooie tijd. Shan, van de eerste letters op papier tot samen bij de drukker, het was super.
Niets is mogelijk zonder de toppers van G4; Carla, Coos, Els, Ingrid, Joke, Jacqueline en Trudi.

Playa Barrio del Mar, dit is pas het begin.

Dank aan alle chirurgen en assistenten van het AMC, het Antonius, het OLVG en het Gelre.

Al m'n vrienden, bedankt voor de afleiding tijdens deze periode. Jan en David, speciale dank voor jullie creativiteit.

Brinn, Cliff, Daan, Geert, Jip, Kuyt, Mark, Matty en natuurlijk Jasper: helden.

Mijn paranymfen Willem van der Sar en Jip Tolenaar. Willem, maatje! Al ons leven lang vrienden. Natuurlijk sta je naast me. Jippie, samen de wereld gezien, inmiddels drie boekjes verder. Mooi dat we er samen weer staan.

Liefste Lot, high-five! Je bent fantastisch.

Lieve pa en ma, bedankt dat jullie er altijd voor me zijn en voor de kansen die jullie mij geboden hebben.

Curriculum vitae

Tjibbe Gardenbroek was born on the 4th of November 1983 in Gouda. In 2002 he graduated from the Goudse Waarden and was admitted to medical school at the University of Utrecht. After graduating from medical school, he started working as a non-training resident at the St. Antonius Hospital in Nieuwegein (dr. P.M.N.Y.H. Go). In September 2010 he started the research that led to this thesis at the Academic Medical Centre Amsterdam under the supervision of his promotores prof. dr. W.A. Bemelman and prof. dr. G.R.A.M. D'Haens and co-promotores dr. C.Y. Ponsioen and dr. C.J. Buskens. In July 2013 he started his training in General Surgery at the Onze Lieve Vrouwe Gasthuis (dr. M.F. Gerhards). Currently he is working at Gelre Ziekenhuizen (dr. P. van Duijvendijk) and will continue his training at the Academic Medical Centre Amsterdam (prof. dr. O.R.C. Busch).