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ULCERATIVE COLITIS

DYSPLASIA AND CANCER, SURGICAL TREATMENT, AND FAECAL MICROBIOTA TRANSPLANTATION FOR CHRONIC POUCHITIS

Essi Karjalainen

ACADEMIC DISSERTATION

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To my grandmother

One of the advantages of
being disorganized is that
one is always having surprising
discoveries

Winnie the Pooh

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ABSTRACT

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown aetiology. UC is associated with increased risk of colorectal cancer (CRC). The risk of CRC has declined over recent decades, but the risk is still approximately 2-fold. CRC is one of the indications for surgery, but most UC patients undergo surgery due to medically refractory disease, suggesting that they often use immunomodulative medication and corticosteroids prior to surgery. The most common operation performed is proctocolectomy with ileal pouch-anal anastomosis (PC-IPAA), avoiding a permanent ileostomy. Controversy exists about whether or not a diverting ileostomy should be constructed. The most common long-term complication of PC-IPAA is pouchitis. Episodes of pouchitis are frequently successfully treated with antibiotics. However, a chronic antibiotic-refractory pouchitis can be difficult to manage.

Aims: The dissertation comprises four original studies. The aims of these studies were to determine the incidence and prognosis of UC-associated CRC (Study I), to assess the effect of preoperative anti-tumour necrosis factor (TNF) therapy and corticosteroids on postoperative complications and pouch failure (Study II), to determine the effect of covering ileostomy on postoperative morbidity after IPAA (Study III), and to investigate the efficacy and safety of faecal microbiota transplantation (FMT) in the treatment of chronic pouchitis (Study IV).

Patients and methods: All studies were carried out at Helsinki University Hospital, Finland. Studies I, II, and III were retrospective. Study I included all 71 patients with UC-associated CRC who were operated on at Helsinki University Hospital between 1991 and 2018. Moreover, 108 patients with dysplasia in the surgical specimen were analysed. Study III included all 510 consecutive patients who underwent PC-IPAA or proctectomy with IPAA between January 2005 and June 2016. A diverting ileostomy was constructed in 119 of these patients. Study II was a subgroup of Study III that excluded patients who underwent proctectomy or were using tacrolimus or vedolizumab prior to surgery. In total, 445 patients were included. Study IV was a randomized, double-blinded, placebo-controlled trial. We randomly allocated 26 patients in a 1:1 ratio to either donor FMT or autologous transplant (placebo). The recruitment was implemented between December 2017 and August 2018.

Results: In Study I, CRC was diagnosed preoperatively in 47 patients (66.2%). Altogether 34 patients (47.9%) had synchronous CRC or dysplasia. The incidence of CRC among patients undergoing surgery has not changed

during the 28-year study period (P = 0.113). The overall survival was 71.8%, while the 5-year CRC-specific survival was 81.5%.

In Study II, anti-TNF therapy was not associated with postoperative complications. Corticosteroids with a dose equivalent to prednisolone 20 mg or more increased the incidence of anastomotic leak (12.6% vs. 2.5%, P = 0.002) and wound dehiscence (4.2% vs. 0%, P = 0.019), but not pouch failure (2.1% vs. 0%, P = 0.141). Patients with a lower dose of corticosteroids had more pouch failures than patients without corticosteroid treatment (4.4% vs. 0%, P = 0.015).

In Study III, patients with a diverting ileostomy had more postoperative complications than patients without ileostomy (55.4% vs. 30.2%, P < 0.0001). Although clinical anastomotic leak was more common in patients without an ileostomy (6.6% vs. 1.7%, P = 0.04), the re-laparotomy rate due to an early complication did not differ between the groups (P = 0.58). Re-admission rate was higher among patients with an ileostomy (42.0% vs. 13.0%, P < 0.0001). Of patients, 43.4% had problems with an ileostomy after discharge. There was no difference in pouch failure rate between the groups (1.7% vs. 2.8%, P = 0.74).

In Study IV, relapse-free survival was similar between the groups (log rank P = 0.183; HR 1.90, 95% CI 0.73 to 4.98, P = 0.190). Patients reported no major adverse effects.

Conclusions: The incidence of UC-associated CRC has remained constant among patients undergoing surgery. The prognosis of patients with UC-associated CRC was no worse than the prognosis of all CRC patients in the Finnish population. The most important finding in Study I was that one-third of the CRCs were not diagnosed until surgery. Moreover, synchronous lesions were common. These findings are alarming and should be considered before the endoscopic management of UC-associated dysplasia.

Anti-TNF agents seem to be safe prior to surgery. By contrast, corticosteroids were associated with a higher incidence of anastomotic leak, wound dehishence, and pouch failure.

An ileostomy is associated with a considerable number of complications without any reduction in pouch failure rate. Based on our results, a single-stage PC-IPAA is safe in low-risk UC patients.

FMT was not effective in the treatment of chronic pouchitis with the FMT treatment protocol used in our trial. The safety profile of FMT was good with no major adverse effects.

TIIVISTELMÄ (FINNISH ABSTRACT)

Tausta: Haavainen paksusuolentulehdus eli ulseratiivinen koliitti on tulehduksellinen suolistosairaus, jonka etiologia on pääosin tuntematon. Haavaista paksusuolentulehdusta sairastavilla potilailla on noin kaksinkertainen riski sairastua paksusuolen syöpään kuin normaaliväestöllä. Syöpä on yksi leikkausindikaatioista, mutta yleisin syy on lääkehoidolle reagoimaton tulehdus. Potilailla on yleensä tuolloin käytössä useita immuunipuolustusta moduloivia lääkkeitä, jotka voivat lisätä leikkauskomplikaatioiden määrää. Yleisin leikkaus on paksusuolen poisto ja ohutsuolisäiliön liitos peräaukkoon, jolloin pysyvää avannetta ei tarvitse rakentaa. Tutkimustiedon perusteella ei ole selvää, pitäisikö leikkauksen yhteydessä nostaa väliaikainen suojaava ohutsuoliavanne vai ei. Yleisin tähän leikkaukseen liittyvä pitkäaikaiskomplikaatio on ohutsuolisäiliön tulehdus eli pussiitti. Useimmiten pussiitti voidaan hoitaa antibiootilla. Osalla potilaista pussiitti kuitenkin kroonistuu, jolloin sen hoito voi olla hankalaa.

Tavoitteet: Väitöskirja koostuu neljästä osatyöstä. Ensimmäisessä osatyössä selvitimme ulseratiiviseen koliittiin liittyvän paksusuolen syövän esiintyvyyttä ja ennustetta. Toisessa osatyössä tarkastelimme tuumorinekroositekijän estäjien sekä kortikosteroidien vaikutusta leikkauskomplikaatioihin. Kolmannessa osatyössä selvitimme suojaavaan ohutsuoliavanteeseen liittyvää sairastavuutta. Neljännessä osatyössä tutkimme ulosteensiirron tehokkuutta ja turvallisuutta kroonisen pussiittin hoidossa.

Potilaat ja menetelmät: Osatöihin I, II ja III tarvittavat tiedot on kerätty jälkikäteen potilasasiakirjoista. Potilaat leikattiin Helsingin Yliopistollisessa Sairaalassa vuosien 1991 ja 2018 välillä. Ensimmäinen osatyö sisälsi kaikki 71 kyseisellä ajanjaksolla leikattua potilasta, jolla oli ulseratiiviseen koliittiin liittyvä paksusuolen syöpä. Myös ne 108 potilasta, joilla todettiin syövän esiaste vuosien 2002 ja 2018 välillä, otettiin mukaan tutkimukseen. Kolmas osatyö sisälsi kaikki 510 peräkkäistä potilasta, joille rakennettiin ohutsuolisäiliö tammikuun 2005 ja kesäkuun 2016 välillä. Toinen osatyö sisälsi samat potilaat kuin kolmas osatyö, poissulkien ne, joille oli jo aiemmin tehty paksusuolenpoisto, tai joilla oli käytössä muita immuunipuolustukseen vaikuttavia lääkkeitä kuin tutkimuksen kohteena olevat. Näin ollen toinen osatyö sisälsi 445 potilasta. Neljäs osatyö toteutettiin satunnaistettuna, kaksoissokkoutettuna tutkimuksena, johon satunnaistettiin yhteensä 26 potilasta. 13 potilasta sai luovuttajan ulosteesta tehdyn ulosteensiirron ja 13 potilasta sai omaa ulostettaan (lume). Potilaat rekrytoitiin joulukuun 2017 ja elokuun 2018 välillä.

Tulokset: Paksusuolen syöpä oli tiedossa ennen leikkausta 47 potilaalla (66.2 %). 34 potilaalla (47.9 %) oli lisäksi muualla paksusuolen alueella syövän esiaste tai syöväksi luokiteltava kasvain. Syöpäpotilaiden osuus leikkauspotilaista ei ole muuttunut 28 vuoden tutkimusjakson aikana. Tutkimusjakson lopussa elossa oli 71.8 % potilaista. Viiden vuoden syöpään liittyvä eloonjäämisluku oli 81.5 %.

Tuumorinekroositekijän estäjän käyttö ei vaikuttanut komplikaatioiden määrään. Suoliliitos sekä leikkaushaava paranivat huonommin potilailla, jotka käyttivät kortikosteroideja yli 20 mg:n annoksella. Pienemmillä annoksilla vastaavaa eroa ei tullut esiin. Toisaalta ohutsuolisäiliö jouduttiin purkamaan useammin alle 20 mg kortikosteroideja käyttävillä verrattuna potilaisiin, joilla kortikosteroidilääkitystä ei ollut.

Potilailla, joille nostettiin suojaava avanne leikkauksen yhteydessä, todettiin enemmän leikkauksen jälkeisiä komplikaatioita (55.4 % vrt. 30.2 %). Suoliliitoksessa havaittiin enemmän ongelmia potilailla, joille avannetta ei tehty (6.6 % vrt. 1.7 %). Siitä huolimatta uusintaleikkausten määrä oli ryhmissä yhteneväinen. Avannepotilaat joutuivat hakeutumaan useammin takaisin sairaalaan kotiutumisen jälkeen (42.0 % vs 13.0 %). 43.4 %:lla potilaista oli ongelmia avanteen kanssa. Tutkimusjakson aikana ohutsuolisäiliön purkuleikkauksia tehtiin ryhmissä saman verran (1.7 % vs 2.8 %).

Kroonisen pussiitin oireet aktivoituivat tutkimusjakson aikana 9 potilaalla tutkimusryhmässä ja 8 potilaalla lumeryhmässä. Ero ei ollut tilastollisesti merkittävä. Ulosteensiirto ei aiheuttanut vakavia haittavaikutuksia.

Johtopäätökset: Ulseratiiviseen koliittiin liittyvän paksusuolen syövän ilmaantuvuus leikkauspotilailla on pysynyt ennallaan. Ennuste ei vaikuttaisi olevan huonompi kuin ulseratiiviseen koliittiin liittymättömän paksusuolen syövän. Kolmasosalla potilaista syöpä ei ollut tiedossa ennen leikkausta ja lähes puolella oli lisäksi toinen syöpä tai syövän esiaste. Näiden löydösten vuoksi hyvänlaatuisten muutosten poistoa paksusuolentähystyksessä koliittipotilailla tulee harkita tarkoin.

Tuumorinekroosi tekijän estäjien käyttö ei lisännyt leikkauskomplikaatioiden riskiä. Kortikosteroidit lisäsivät leikkauskomplikaatioiden ja ohutsuolisäiliön purkuleikkauksen riskiä.

Suojaavaan ohutsuoliavanteeseen liittyy huomattavaa sairastuvuutta, mutta se ei näyttäisi suojaavan ohutsuolisäiliön purkuun johtavilta komplikaatioilta. Ohutsuolisäiliön rakentaminen ilman suojaavaa avannetta on turvallista matalan riskin potilailla.

Ulosteensiirto ei ollut tehokas kroonisen pussiitin hoidossa meidän tutkimuksessamme. Ulosteensiirto oli turvallinen.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals:

I. Karjalainen E, Renkonen-Sinisalo L, Lepistö A. Dysplasia in the mucosal biopsy specimen is still a warning sign of cancer in ulcerative colitis. *Scand J Gastroenterol*. 55:1019–23, 2020.

II. Karjalainen E, Renkonen-Sinisalo L, Mustonen H, Färkkilä M, Lepistö A. Restorative Proctocolectomy in Ulcerative Colitis: Effect of Preoperative Immunomodulatory Therapy on Postoperative Complications and Pouch Failure. *Scand J Surg*. January 2020.

III. Karjalainen E, Renkonen-Sinisalo L, Mustonen H, Lepistö A. Morbidity related to diverting ileostomy after restorative proctocolectomy in patients with ulcerative colitis. *Colorect Dis*. 21:671-8, 2019.

IV. Karjalainen E, Renkonen-Sinisalo L, Satokari R, Mustonen H, Ristimäki A, Arkkila P*, Lepistö A*. Fecal Microbiota Transplantation in Chronic Pouchitis: A Randomized, Parallel, Double-blinded Clinical Trial. *Inflamm Bowel Dis*. January 2021.

* These authors share last authorship.

ABBREVIATIONS

ASUC	Acute severe ulcerative colitis
CADP	Chronic antibiotic-dependent pouchitis
CARP	Chronic antibiotic-refractory pouchitis
CD	Crohn's disease
cPDAI	Clinical Pouchitis Disease Activity Index
CRC	Colorectal cancer
ECCO	European Crohn's and Colitis Organisation
FMT	Faecal microbiota transplantation
IBD	Inflammatory bowel disease
IC/ICU	Intermediate care/Intensive care unit
IFX	Infliximab
IPAA	Ileal pouch anal anastomosis
IRA	Ileo-rectal anastomosis
mPDAI	Modified Pouchitis Disease Activity Index
NR	Not recorded
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
PC-IPAA	Proctocolectomy with ileal pouch anal anastomosis
PDAI	Pouchitis Disease Activity Index
PSC	Primary sclerosing cholangitis
py	Person-years
RCT	Randomized controlled trial
TME	Total mesorectal excision
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UICC	Union of International Cancer Control
5-ASA	5-aminosalicylic acid

1 INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by continuous mucosal inflammation that starts in the rectum and extends proximally to the colon. Up to one-third of the patients develop extra-intestinal manifestations, most commonly affecting the skin, joints, eyes, and liver (Feuerstein et al. 2019). Inflammatory bowel diseases (IBDs), including UC, Crohn's disease (CD), and indeterminate colitis, are traditionally regarded as diseases of westernized countries. However, the incidence of IBD is now accelerating in newly industrialized countries, and IBD has become a global disease (Ng et al. 2017). The burden of UC is especially high in Scandinavia, North America, and Australia.

Episodes of relapse and periods of remission characterize UC. The first-line therapy of UC is medical, consisting mainly of 5-aminosalisylates, corticosteroids, thiopurines, and biologics. The aim of the medical treatment is to induce and maintain steroid-free remission, defined clinically and endoscopically (Harbord et al. 2017). In addition, endoscopic surveillance is important because of the higher risk of colorectal cancer (CRC) in UC patients than in the general population. The risk of CRC has declined over recent decades, but UC patients still have a 1.7-fold increased risk for CRC (Olén et al. 2020). Moreover, patients with UC-associated CRC are often younger and have multifocal tumours. In the study of Olén et al., UC patients had a 1.6-fold increased risk of death from CRC.

New treatment modalities, such as biologics, might partly explain the declining incidence of UC-associated CRC. The surgery rate, however, has not declined. Up to 30% of UC patients need surgery at some point during the disease course (Biondi et al. 2012). The most performed operation is proctocolectomy with an ileal pouch-anal anastomosis (PC-IPAA), which is, however, vulnerable to numerous complications (Davies et al. 2007). It is especially important to identify potential risk factors for pouch-related complications, which could further lead to pouch failure, i.e. excision of the pouch or a permanent ileostomy (Kiely et al. 2012).

In most patients, the indication for surgery is chronic refractory UC, suggesting that they are using multiple immunomodulative and immunosuppressive medications prior to surgery. Evidence indicates that preoperative high-dose corticosteroids increase the risk for short-term surgical complications, more precisely infections and pouch-related complications (Magro et al. 2017). Data on preoperative use of biologics are conflicting.

Debate is ongoing about whether a covering ileostomy should be constructed for all patients undergoing PC-IPAA. Proponents claim that an ileal diversion decreases the risk of anastomotic leakeage (Weston-Petrides et al. 2008). However, a covering ileostomy is associated with significant

morbidity (Park et al. 2018). Furthermore, omitting the ileostomy seems to result in a better functional outcome in long-term follow-up (Lovegrove et al. 2008). Although most of the surgeons divert during pouch surgery, some centers, including Helsinki University Hospital, follow an approach in which a covering ileostomy is constructed only in selected patients with risk factors for pelvic sepsis.

Pouchitis is the most common long-term complication after PC-IPAA, occurring in up to 50% of patients in a 10-year follow-up (Lightner et al. 2017). While acute episodes of pouchitis typically respond to 2- to 4-week antibiotic therapy, chronic pouchitis can be difficult to treat and impairs the patient's quality of life. In some patients, it even leads to an excision of the pouch (Tulchinsky et al. 2003). Today, there is no well-established treatment for chronic pouchitis. The exact pathogenesis of pouchitis remains unclear. Gut microbiota seems to have an important role in the development of pouchitis, arousing an interest in faecal microbiota transplantation (FMT) in the treatment of chronic pouchitis.

2 REVIEW OF THE LITERATURE

2.1 HISTORY AND EPIDEMIOLOGY OF ULCERATIVE COLITIS

2.1.1 HISTORY

Sir Samuel Wilks was the first to describe "UC" in 1859 (Wilks et al. 1859). He presented a case report of a 42-year-old woman who suffered diarrhoea and fever for several months, eventually dying. Autopsy showed a transmural ulcerative inflammation of the colon and terminal ileum, which was first diagnosed as UC, but was subsequently identified as CD (Fielding 1985). In 1875, Wilks and Moxon described the first patient with actual UC in their book titled Lectures on Pathological Anatomy (Wilks et al. 1875).

The surgical treatment of UC was initially either proctocolectomy with ileostomy or colectomy and ileorectostomy with continuous surveillance of the retained rectum (Best 1952). In 1933, Rudolf Nissen performed the first proctocolectomy and ileoanal anastomosis with the construction of a double-barrelled loop of ileum (Ng et al. 2019). The end result was not long lasting. Afterwards, many attempts at successful ileoanal anastomosis were performed using the pull-through method. In 1969, Nils Kock introduced a continent ileostomy, which, when working well, significantly improved a patient's quality of life (Kock 1969, Lepistö et al. 2003, Berndtsson et al. 2005). A major step was taken in the field of surgical management of UC in 1978. Park and Nicholls (1978) and Utsunomiya et al. (1980) independently introduced an ileoanal anastomosis with ileal pouch. Parks and Nicholls used an S-shaped pouch, while Utsunomiya developed the J-pouch, which is the most used pouch configuration today. Later, the W-pouch was developed with the aim of improving functional results (Nicholls et al. 1987).

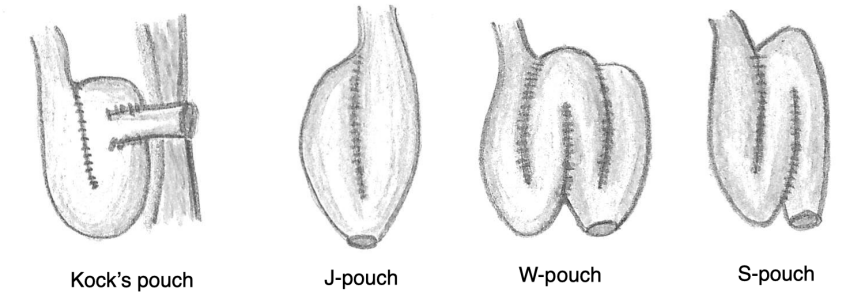

Figure 1 Different pouch configurations.

2.1.2 EPIDEMIOLOGY

UC occurs worldwide, but the incidence varies greatly. The incidence rates are highest in Northern Europe and North America, with UC more common in industrialized countries than in non-industrialized countries (Burisch et al. 2015). However, recent data show an accelerating incidence in newly industrialized countries of Asia and South America (Ng et al. 2017). Finland is one of the high incidence countries at 24.8 per 100 000 (Jussila et al. 2012). A higher incidence has only been reported in Faroe Islands. The highest reported prevalence is in Norway, 505 per 100 000, and the lowest in Malaysia, 6.6 per 100 000 (Ng et al. 2017).

Diagnosis of UC may occur at any age, but the peak incidence is between the ages of 15 and 30 years (Ordás et al. 2012). Some studies have suggested a second smaller peak between the ages of 50 and 70 years (Molodecky et al. 2012). No substantial sex preference exists, although several countries, including Finland, have found a slight predilection for men (Jussila et al. 2012, Burisch et al. 2015).

2.2 AETIOLOGY AND PATHOGENESIS OF ULCERATIVE COLITIS

The precise pathogenesis of UC is unknown. The dysbiotic gut microbiota, genetics, and environmental factors seem to be associated with the development of UC (Ananthakrishnan 2015).

More than 200 genes related to IBD have been identified, and one-third of the IBD-related genetic loci are shared between UC and CD (Khor et al. 2011). The majority of IBD-related genes code for immunological and epithelial barrier functions (Sheehan et al. 2017). A positive family history is more common in CD than in UC. Approximately 8% to 14% of patients with UC have a family history of IBD (Feuerstein et al. 2019). If both parents have IBD, the risk of children developing IBD before the age of 30 years is approximately 30% (Halme et al. 2006). Jewish ethnicity is associated with the highest risk for UC relative to all other ethnicities. The relative risk of developing UC for first-degree relatives is estimated to be 1.6% in non-Jewish patients and 5.2% in Jewish patients (Yang et al. 1993).

A reduction in the diversity of gut microbiota has been observed in patients with IBD compared with healthy individuals (Nishida et al. 2017). Nevertheless, whether microbiota dysbiosis is a cause or a consequence of IBD remains obscure. Multiple enteric infections leading to alterations in gut permeability and microbiota, most notably Escherichia coli and Campylobacter, have been associated with the development of IBD, but no single causative microbe has been identified (Satokari 2014). Probiotics and prebiotics have seldom been beneficial in IBD (Sheehan et al. 2017). However, recent randomized controlled trials (RCTs) on FMT in the treatment of UC to

restore the gut microbiota show promising results (Paramsothy et al. 2017, Costello et al. 2019).

Active smoking has a protective effect against UC. However, being a former smoker has been associated with an increased risk of UC compared with never-smokers (Mahid et al. 2006). Despite these findings, active smoking does not seem to have any effect on colectomy rates (To et al. 2016). Appendectomy before the age of 20 years is suggested to reduce the risk of UC (Andersson et al. 2001). The hygiene hypothesis claims that a high hygiene level is a risk factor for IBD. It seems that the risk is relevant only in migrants moving from low-hygiene countries to high-hygiene countries (Leong et al. 2016). In developed countries, the use of antibiotics increases the risk of IBD (Ananthakrishnan 2015, Leong et al. 2016). Other medications, such as oral contraceptives, non-steroidal anti-inflammatory drugs (NSAIDs), and hormone replacement therapy, might have a role in the development of IBD (Feuerstein et al. 2019). In addition, breastfeeding has a protective association against paediatric and adult-onset UC (Xu et al. 2017).

2.3 DIAGNOSIS

No standard diagnostic criteria exist for UC. Typical symptoms are diarrhoea, rectal bleeding, tenesmus, urgency, and faecal incontinence. Increased bowel frequency, abdominal pain, anorexia, and fever are seen in severe colitis. Characteristically, the inflammation begins in the rectum and extends proximally to the colon in a continuous manner. UC does not affect the small bowel, although a backwash ileitis may be present, especially in extensive disease. A skip lesion, known as a caecal patch, surrounding the appendiceal orifice might be present, breaking the rule of continuity (Zimmer et al. 2019). About 90% of patients have an intermittent course of disease characterized by periods of activity and remission (Langholz et al. 1994).

Histologically, the inflammation is limited to the mucosa. Biopsy specimens are typical in UC when the findings support chronic inflammation such as basal plasmacytosis and distortion of crypts and mucosa (Appleman 2008). Active inflammation, not always present, causes cryptitis and crypt abscesses. Histology is not specific for UC, but the diagnosis is made based on typical symptoms and findings on colonoscopy combined with typical histology (Feuerstein et al. 2019).

Differential diagnosis between UC and CD is sometimes difficult (Table 1). In 2-3% of patients, the diagnosis of UC may change to CD or indeterminate colitis during follow-up (Fumery et al. 2018). CD can affect any part of the gastrointestinal tract from mouth to anus, most commonly the terminal ileum and perianal area (Flynn et al. 2019). The discontinuous inflammation is transmural in CD, which leads to strictures and fistulas –not usually seen in UC. Histologically, granulomas are typical, but not alone diagnostic for CD (Maaser et al. 2018). Sometimes, a definite distinction between UC and CD

cannot be made. Most patients with indeterminate colitis ultimately represent UC and are therefore treated like UC patients.

Table 1. *Histopathological features used for diagnosis of IBD. Modified from Magro et al. (2013).*

Diagnostic feature	*Ulcerative colitis*	*Crohn's disease*
Macroscopic		
Localization	Rectum and colon	Whole gastrointestinal tract
Ileum	Only in backwash ileitis	Often involved
Rectum	Commonly involved	Typically spared
Pattern	Continuous	Segmental
Ulcers	Superficial	Deep, linear
Pseudopolyps	Common	Uncommon
Fistulas	Absent	Present
Strictures	Uncommon	Present
Microscopic		
Localization	Superficial	Transmural
Granulomas	Absent	Present
Crypt abscesses	Common	Uncommon
Mucin depletion	Present	Uncommon
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

2.3.1 CLASSIFICATION OF ULCERATIVE COLITIS

UC can be classified according to disease extent or disease severity, both of which influence the treatment modality and route of administration (Tables 2 and 3). Remission is defined as stool frequency of three or less per day, no bloody stools, and normal mucosa at endoscopy (Magro et al. 2017). Originally, a patient with severe colitis had to fulfil all criteria of Truelove and Witts (Table 3). Today, only one criterion in addition to elevated stool frequency and bloody stools is needed to define severe colitis, known also as fulminant colitis (Turner et al. 2007, Chen et al. 2016).

Table 2. *Montreal classification of UC according to disease extent Adapted from Silverberg et al. (2005) and Magro et al. (2017).*

Term	*Maximal extent*	*Description*
E1	Ulcerative proctitis	Inflammation limited to the rectum, i.e. distal to the rectosigmoid junction
E2	Left-sided UC (distal UC)	Inflammation limited to the portion of colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Inflammation extends proximal to the splenic flexure

Table 3. *Classification of UC according to disease severity using the Truelove and Witts Criteria. Adapted from Truelove et al. (1955).*

Parameter	*Mild*	*Moderate*	*Severe*
Stool frequency/day	< 4	between mild and severe	≥ 6
Blood in stool	none or small		present
Pulse rate	< 90 bpm		> 90 bpm
Temperature	< 37.5°C		> 37.8°C
Haemoglobin	> 11.5 g/dl		< 10.5 g/dl
Erytrocyte sedimentation rate	< 30 mm/h		> 30 mm/h

2.4 ULCERATIVE COLITIS-ASSOCIATED COLORECTAL CANCER

2.4.1 INCIDENCE

Crohn and Rosenberg described the first UC-associated CRC in 1925 (Crohn et al. 1925). Since then, the association of UC and CRC has been investigated in many studies, and today it is known that patients with UC are at increased risk for developing CRC.

In 2001, Eaden et al. published the first meta-analysis reporting the cumulative risk for CRC after UC diagnosis to be as high as 2% at 10 years, 8% at 20 years, and 18% at 30 years (Eaden et al. 2001). However, later studies have shown the incidence of CRC to be lower. In 2014, a meta-analysis by Castaño-Milla et al. revealed that the overall risk for CRC was 1.69 per 1000 person-years, and the cumulative incidence rates were 0.91 per 1000 person-years at 10 years, 4.07 per 1000 person-years at 20 years, and 4.55 per 1000 person-years at 30 years (Castaño-Milla et al. 2014). These rates are still considerably higher than the incidence of sporadic CRC. According to the

Finnish Cancer Registry, the incidence of CRC in the general population in Finland was approximately 0.6 per 1000 person-years in 2017 (https://cancerregistry.fi/statistics/cancer-statistics/). A recent Scandinavian population-based cohort study found that patients with UC have a 1.7-fold increased risk for CRC and a 1.6-fold increased risk of death from CRC (Olén et al. 2020). In Finland, the risk of CRC in patients with UC was highest among those under 45 years of age; about 20% of all CRCs were diagnosed in patients aged under 45 years (Jussila et al. 2013).

2.4.2 RISK FACTORS

It is important to recognize the risk factors for CRC in UC to better customize the surveillance and treatment of patients. These risk factors include pancolitis, young age at diagnosis, disease duration, primary sclerosing cholangitis (PSC), and family history of CRC (Yashiro 2014). In addition, a prior diagnosis of pseudopolyps increases the risk of CRC (Velayos et al. 2006).

In a meta-analysis, an overall increased risk of CRC among patients with extensive UC was 4.8 (95% CI 3.9-5.9), while in proctitis the risk was similar to that of the general population (Jess et al. 2012). In Finland, Manninen et al. (2013) reported similar results. During a 20-year follow-up the increased risk was 3.09 (95% CI 1.50-5.75) in extensive UC and 1.75 (95% CI 0.65-3.84) in left-sided UC. As in the meta-analysis, no additional risk was seen in proctitis. Young age at diagnosis of UC is an independent risk factor for CRC. Patients diagnosed in childhood or adolescence (age 0-19 years) had a relative risk of 43.8 (95% CI 27.2–70.7), and patients diagnosed in young adulthood (age 20-39 years) had a relative risk of 2.65 (95% CI 1.97–3.56) (Jess et al. 2012). UC patients with PSC have an approximately 4-fold increased risk for CRC relative to UC patients without PSC (Soetikno et al. 2002). Moreover, Thackeray et al. (2011) found that patients with IBD and PSC may develop CRC or dysplasia relatively soon. In their study, the occurrence of CRC or dysplasia was 21.5 per 100 person-years within 2 years of diagnosis of both diseases. UC patients with a positive family history of CRC have an over 2-fold risk of CRC. The risk is highest for those patients with a first-degree relative diagnosed with CRC before the age of 50 years (Askling et al. 2001).

2.4.3 CANCER SURVEILLANCE

European Crohn´s and Colitis Organisation (ECCO) recommends performing the first surveillance colonoscopy eight years after the diagnosis of UC (Magro et al. 2017). Subsequent colonoscopies are scheduled for one to five years, depending on the patient´s risk factors for CRC. If disease activity is limited to the rectum, regular surveillance is not necessary. If a patient is diagnosed with PSC, yearly surveillance colonoscopies are indicated. Table 4 presents the surveillance programme used at Helsinki University Hospital.

Table 4. *Cancer surveillance programme for patients with UC at Helsinki University Hospital. The first surveillance colonoscopy is performed in extensive colitis 8 years after the diagnosis of UC and in left-sided colitis 10 years after the diagnosis of UC. Subsequent colonoscopies are scheduled according to the table.*

Low risk	*Intermediate risk*	*High risk*
• Left-sided colitis • Extensive colitis without active inflammation	• Extensive colitis with mild active inflammation • Post-inflammatory polyps • A first-degree relative diagnosed with CRC at over 50 years of age	• Extensive colitis with moderate or severe active inflammation • Stricture or dysplasia detected within the past 5 years • PSC • A first-degree relative diagnosed with CRC at 50 years of age or under
Colonoscopy 5 years	**Colonoscopy 3 years**	**Colonoscopy 1 year**

For an efficient surveillance colonoscopy, good bowel preparation is essential to detect dysplastic lesions (Thomas-Gibson et al. 2006, Wong et al. 2016). Dye-based chromoendoscopy and high-definition colonoscopy improve dysplasia detection compared with standard definition colonoscopy (Bessissow et al. 2018).

2.4.4 PROGNOSIS

It is well known from the literature that patients with UC-associated CRC are on average 10–15 years younger and have more multifocal, mucinous, and signet-ring cell carcinomas (Grade 3, poorly differentiated) than patients with sporadic CRC (Eaden et al. 2001, Watanabe et al. 2011, Keller et al. 2019). These factors are associated with poorer prognosis. However, data are conflicting regarding comparison of the prognosis of UC-related CRC and sporadic CRC. The 5-year survival was equal in some studies, while others reported worse prognosis in UC-associated CRC (Table 5). In Japan, 5-year overall survival rates between UC-associated CRC and sporadic CRC did not differ (64.2% vs. 68.7%, P = 0.58), but in stage III cancer UC patients demostrated lower 5-year overall survival (Watanabe et al. 2011). However, cancer-specific survival rates were similar in all stages. A matched-pair analysis from Germany found poorer prognosis in stage II cancer regarding recurrence-free survival in favour of sporadic cancers (Leowardi et al. 2016). In a subgroup analysis of UC patients, male sex was associated with poorer prognosis (57.4% vs. 76.9%, P = 0.005). A meta-analysis found poorer overall survival in UC-associated CRC than in sporadic CRC (HR 1.19, 95% CI 1.12-1.27) (Ou et al. 2015).

Recently, Vetter et al. (2021) reported that CD-associated CRC showed more advanced tumour stage and reduced survival relative to UC-associated CRC.

Table 5. *Different studies reporting 5-year survival comparing UC-associated CRC and sporadic CRC.*

	Overall 5-year survival				
Study	*UC-associated*	*Sporadic*	*P-value*	*HR (95% CI)*	*P-value*
Aarnio et al. (1998)	39%	59%		1.83 (1.07-3.13)	0.03
Jensen et al. (2006)	37%	31%		1.17 (1.01-1.36)	
Delaunoit et al. (2006)	55%	53%	NS	1.0 (0.79-1.25)	
Watanabe et al. (2011)	64.2%	68.7%	NS		
Ording et al. (2013)	41%	41%		1.14 (1.03-1.27)	
Leowaldi et al. (2015)	65.7%	63.2%	NS		

NS = not significant

2.5 MEDICAL TREATMENT OF ULCERATIVE COLITIS

The primary aim of medical treatment is to induce and maintain steroid-free remission (Harbord et al. 2017). The selection of a specific treatment is guided by disease severity and extent. A step-up approach is recommended while following the clinical and endoscopic response. First-line therapy in mild disease is 5-aminosalicylates (5-ASA), followed by corticosteroids administered orally or rectally (Ungaro et al. 2017). Moreover, 5-ASA may have a chemopreventive effect in patients with extensive disease (Carrat et al. 2017). Figure 2 presents a suggested treatment algorithm for mild to moderate disease based on Toronto Consensus and ECCO Guidelines (Bressler et al. 2015, Harbord et al. 2017).

In moderate to severe disease and in steroid-dependent disease, thiopurines and biologics (anti-TNF agents and vedolizumab) are indicated (Figure 3). Based on a recent network meta-analysis, infliximab and vedolizumab are superior for induction of remission in patients with moderate to severe UC (Singh et al. 2017). Methotrexate is not currently recommended in the maintenance therapy of UC (Harbord et al. 2017).

Adverse effects are common with all drugs used in the treatment of UC. Due to side effects, such as bone marrow suppression, hypersensitivity reactions, hepatotoxicity, and pancreatitis, 10–28% of patients discontinue

thiopurine therapy (Quezada et al. 2018). Anti-TNF agents are associated with increased risk of serious and opportunistic infections, demyelinating disease, and congestive heart failure. In addition, infusion reactions may occur in 3–17% of infliximab infusions. Both thiopurines and anti-TNF agents increase the risk of lymphoma.

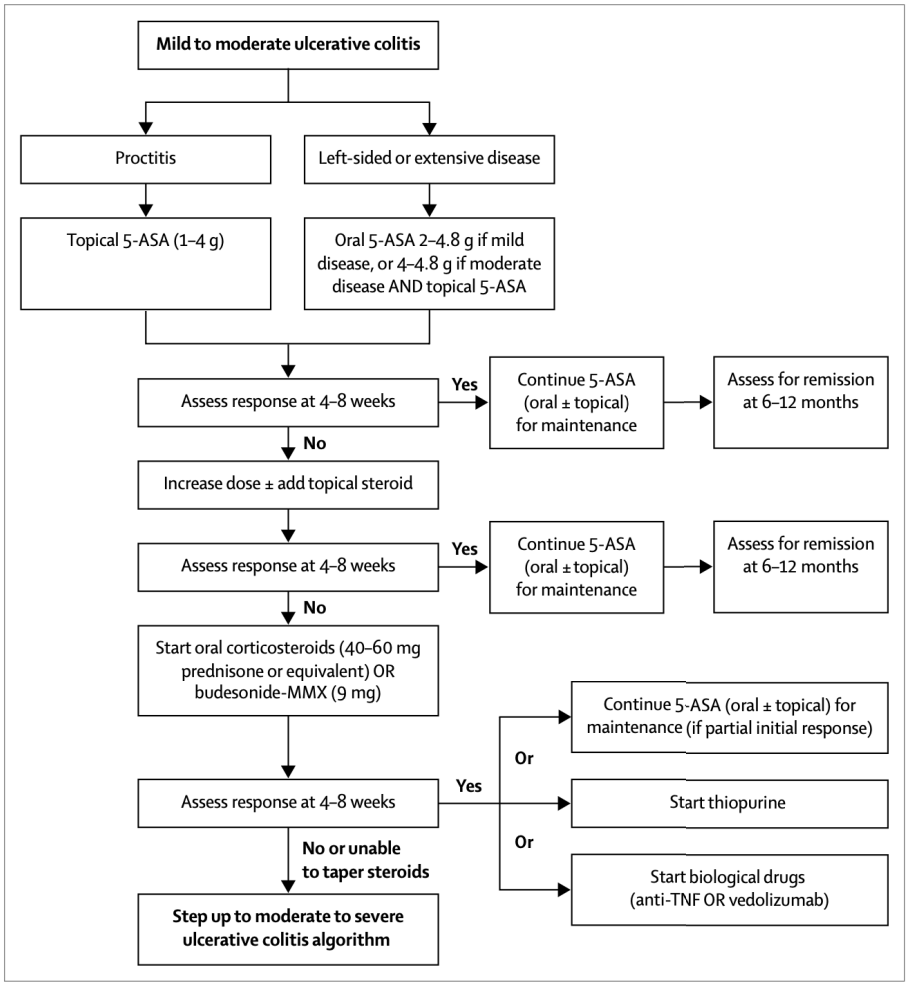

Figure 2 Medical treatment of mild to moderate UC. Adapted from Ungaro et al. (2017) by permission from Elsevier.

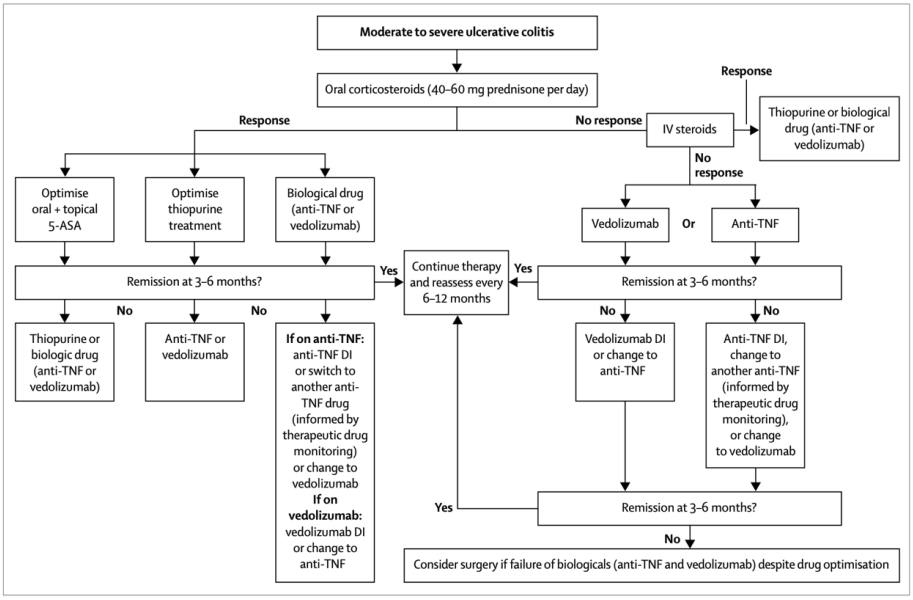

Figure 3 Medical treatment of moderate to severe UC. Adapted from Ungaro et al. (2017) by permission from Elsevier.

2.6 INDICATIONS FOR SURGERY

Overall, the need for operative treatment in UC has decreased over the past six decades. The risk of surgery in UC patients is 4.9% at 1 year, 11.6% at 5 years, and 15.6% at 10 years after the diagnosis of UC (Frolkis et al. 2013). The risk is higher in patients with extensive colitis than in patients with left-sided colitis or proctitis (Solberg et al. 2009). In addition, male gender, non-smoking, need for corticosteroids at least once, and hospitalization are risk factors for colectomy (Dias et al. 2015).

2.6.1 FULMINANT COLITIS

Fulminant colitis, also known as acute severe ulcerative colitis (ASUC), can be a life-threatening condition (Bernstein et al. 2013). Patients who meet the Truelove and Witts criteria for severe colitis should be admitted to hospital under the care of both a specialist gastroenterologist and colorectal surgeon (Øresland et al. 2015). In 10–34% of patients, fulminant colitis can be the first presentation of UC (Dinesen et al. 2010, Gallo et al. 2018). Approximately 15% of patients may experience an acute severe disease course (Fumery et al. 2018). The colectomy rate in hospitalized fulminant colitis has remained stable at 27% despite new treatment modalities (Turner et al. 2007).

Intravenous corticosteroids are the cornerstone of conventional therapy (Chen et al. 2016, Harbord et al. 2017). The response rate to corticosteroids is around 70% (Sedano et al. 2019). Prolonged conventional therapy is associated with an increased risk for postoperative complications (Randall et al. 2010). For this reason, response to corticosteroids should be assessed objectively around the third day (Øresland et al. 2015).

The second-line therapy with intravenous infliximab, ciclosporin, or tacrolimus can be considered in corticosteroid-refractory patients (Harbord et al. 2017). Colectomy is recommended if there is no improvement within 7 days of conventional therapy. In addition, the absolute indications for surgery are the complications of fulminant colitis: perforation, toxic megacolon, and severe gastrointestinal haemorrhage.

2.6.2 CHRONIC REFRACTORY ULCERATIVE COLITIS

In most patients, the indication for elective surgery is a chronic refractory UC, which includes corticosteroid-dependent disease and UC refractory to immunomodulators and biologics. The timing of the surgery has a key role also in the elective situation. Prolonging an evident surgery with new treatment modalities in the chase for an ideal medication may result in an anaemic patient with impaired nutritional status, which is not an ideal situation for major abdominal surgery (Gallo et al. 2018). Moreover, the use of immunomodulative or immunosuppressive medication may affect the outcome of surgery. The role of preoperative medication in postoperative complications is discussed later.

2.6.3 DYSPLASIA OR CANCER

Microscopically, dysplasia is classified as indefinite, low-grade, or high-grade dysplasia (Riddell et al. 1983). Macroscopically, dysplastic lesions are classified according to the shape of the lesion: polypoid (Paris type Ip and Is), non-polypoid (Paris type IIa, IIb and IIc), or endoscopically invisible (Endoscopic Classification Review Group 2005).

CRC is assumed to develop from previous dysplasia. It is accepted that dysplasia evolves along a continuous scale, which causes variation in interpretation of the grade of dysplasia among pathologists (Eaden et al. 2001). The presence of low- or high-grade dysplasia is recommended to be confirmed by two independent gastrointestinal pathologists (Magro et al. 2017).

The optimal treatment for polypoid lesions remains controversial. Neither pathologists nor endoscopists can with certainty state whether a dysplastic polypoid lesion is UC-associated or sporadic. Polypoid lesions occurring proximally to the microscopic level of inflammation are suggested to be considered sporadic adenoma and treated accordingly. ECCO Guidelines support an endoscopic treatment of polypoid lesions, but non-polypoid lesions

should be treated endoscopically only in selected cases (Magro et al. 2017). If a complete endoscopic resection cannot be achieved or non-polypoid or invisible dysplasia is present elsewhere in the colon, a patient with low-grade dysplasia or high-grade dysplasia should undergo colectomy. Odze et al. (2004) found no significant difference in the incidence of dysplasia detection in long-term follow-up between UC patients with endoscopically treated polypoid adenoma and non-UC patients with endoscopically treated sporadic adenoma. However, 59% of UC patients developed at least one additional adenoma during follow-up and one patient had CRC. According to a meta-analysis, the rate of developing further dysplasia after endoscopic treatment of polypoid dysplasia was 65 per 1000 person- years (Wanders et al. 2014).

Non-polypoid dysplasia, invisible dysplasia, lesion size ≥1 cm, and previous history of indefinite dysplasia showed a correlation with the risk of high-grade dysplasia or CRC in a follow-up study from St. Marks Hospital, United Kingdom (Choi et al. 2015). In their study, the cumulative incidence of high-grade dysplasia or CRC was 6.0% for polypoid lesions and 65.2% for non-polypoid lesions during the 5-year follow-up. Thus, endoscopic treatment of non-polypoid dysplastic lesions should be considered carefully. UC patient with endoscopically invisible low- or high-grade dysplasia should undergo colectomy.

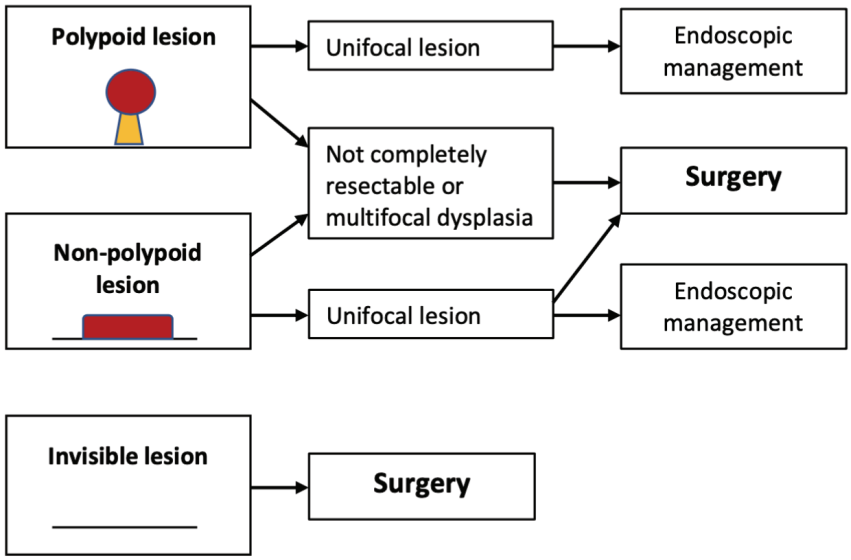

Figure 4 Management of dysplastic lesions according to ECCO Guidelines (Øresland et al. 2015, Magro et al. 2017).

2.7 RESTORATIVE PROCTOCOLECTOMY WITH ILEAL POUCH-ANAL ANASTOMOSIS

Restorative proctocolectomy with IPAA is the procedure of choice for most UC patients because it removes all diseased mucosa and eliminates the need for permanent ileostomy (Bohl et al. 2015). The standard technique introduced by Parks et al. (1978) and Utsunomiya et al. (1980) includes excision of the colon and rectum, transanal mucosectomy of the anal stump, pouch formation from the terminal ileum, and a hand-sewn IPAA. Today, the most used pouch configuration is a J-shaped pouch. A meta-analysis showed an advantage for J- and W-pouches over the S-pouch regarding pouch function, but W-pouch had a lower frequency of defecation than the J-pouch (Lovegrove at al. 2007). The preference of the J-pouch might be explained by its simpler design. Sunde et al. (2017) compared functional outcome and quality of life between J- and K-pouch patients. The K-pouch was constructed according to the technique of continent Kock's pouch, but a hand-sewn IPAA was sutured instead of an ileostomy. Patients with K-pouch reported a slightly better pouch function.

An alternative to a hand-sewn anastomosis is a stapled anastomosis, first described by Heald and Allen (1986). A stapled anastomosis is believed to improve the pouch function by preservation of the anal transition zone. A meta-analysis of 4183 patients concluded that nocturnal continence was better in stapled IPAA (Lovegrove at al. 2006). However, another meta-analysis, including only RCTs, found no difference in the functional outcome between hand-sewn IPAA and stapled IPAA (Schluender et al. 2006). A disadvantage of the stapled technique is that a short segment of the rectal mucosa is left intact. The preserved mucosa might become symptomatic because of inflammation (cuffitis) and develop dysplasia or cancer. The incidence of cuffitis has been reported to be as high as 15% (Nobel et al. 2016). In a 10-year follow-up, dysplasia developed in preserved mucosa in 2.7% of patients (Remzi et al. 2003).

Many centres perform PC-IPAA laparoscopically. A meta-analysis comparing open and laparoscopic approaches concluded that both techniques result in similar long-term function and adverse events (Singh et al. 2013). Laparoscopic PC-IPAA was associated with less intra-operative blood loss, longer duration of surgery, reduced postoperative hospital stay, and lower risk of wound infection. Two retrospective studies reported better female fertility after laparoscopic PC-IPAA (Bartels et al. 2012, Beyer-Berjot et al. 2013). Gorgun et al. (2019) found that both pre- and postoperative infertility is common in patients undergoing PC-IPAA, and there was no significant difference in the infertility rate between open or laparoscopic PC-IPAA postoperatively. However, patients in the laparoscopic group became pregnant faster than those in the open surgery group (median 3.5 vs. 9 months). In a Finnish study, IPAA patients were compared with age-matched patients who had undergone appendicectomy (Lepistö et al. 2007). The cumulative incidence of pregnancy was 32% in IPAA patients compared with

67% in the control group after 6 months of trying, and increased to 73% in IPAA patients and 91% in the control group after 4 years of trying.

Quality of life is satisfactory in the majority of patients undergoing PC-IPAA (Berndtsson et al. 2007). With good pouch function, the quality of life is similar or slightly lower than in the general population (Lepistö et al. 2002, Heikens et al. 2011, Andersson et al. 2011). In the study of Abolfotouh et al. (2017), patients reported the most impaired quality of life in the dimensions of excretion, sexual activity, and sleeping. However, poor pouch function decreases the quality of life (Carmon et al. 2003, Helavirta et al. 2018). Patients report the most impaired quality of life after pouch failure (Berndtsson et al. 2007, Røkke et al. 2011). In a systematic review, Murphy et al. (2015) concluded that PC-IPAA and a proctocolectomy with a permanent ileostomy appear equivalent in terms of quality of life.

Although there is no specific age limit for the PC-IPAA procedure, functional results (e.g. continence) and quality of life are not as good in older patients (Delaney et al. 2003). PC-IPAA seems to be safe and effective in patients aged over 65 years (Pinto et al. 2011). However, elderly patients seem to have a greater tendency for dehydration and long-term complications such as pouchitis and anastomotic stricture (Chapman et al. 2005).

2.7.1 USE OF COVERING ILEOSTOMY IN RESTORATIVE PROCTOCOLECTOMY

PC-IPAA is most commonly performed as a two- or three-stage procedure with a loop ileostomy (de Zeeuw et al. 2012). The ileal diversion is also supported by ECCO Guidelines (Øresland et al. 2015). The arguments for an ileal diversion are to reduce the risk of anastomotic leak and its consequences. Leakage of ileal pouch-anal anastomosis might lead to pouch failure (Tulchinsky et al. 2003, Forbes et al. 2009). The results of different studies comparing IPAA with or without ileostomy are conflicting (Table 6). However, a diverting ileostomy is associated with significant morbidity (Park et al. 2018). A meta-analysis found that although anastomotic leak was more common when a stoma was omitted, pouch-related sepsis was not different between patients operated with or without a stoma (Weston-Petrides et al. 2008). Moreover, the rates of anastomotic strictures and pouch failures were higher in patients with a diverting ileostomy. In a recent study of 4031 patients from Cleveland Clinic, USA, Lavryk et al. (2017) found that omission of the ileostomy did not increase the pouch failure rate even if a patient had pelvic sepsis postoperatively.

Table 6. *Anastomotic leakage rate, re-operations, and pouch failure rate in different studies comparing one- and two-stage proctocolectomy.*

			Patients (n)		*Anastomotic leakage (%)*			*Re-operation (%)*			*Pouch failure (%)*		
Study	**Anastomosis**	**Total**	**IPAA with ileostomy**	**IPAA without ileostomy**	**IPAA with ileostomy**	**IPAA without ileostomy**	**P-value**	**IPAA with ileostomy**	**IPAA without ileostomy**	**P-value**	**IPAA with ileostomy**	**IPAA without ileostomy**	**P-value**
Järvinen et al. (1991)	HS	31	15	16				13.3%	6.3%	NR			
Cohen et al. (1992)	Stapled	158	87	71	6.9%	18.3%	< 0.05	3.4%	1.4%	NR			
Grobler et al. (1992)	Stapled	45	23	22	4.3%	4.5%	NS	39%	14%	NR			
Tjandra et al. (1993)	Stapled	100	50	50	4%	10%	< 0.05	0	8%	NR			
Gorfine et al. (1995)	HS	143	69	74	6%	8%	NS	14%	5%	NS			
Williamson et al. (1997)	Stapled	100	50	50	14%	22%	NR	2%	22%	0.006			
Ikeuchi et al. (2005)	HS	242	92	150	2.2%	4.7%	NS				2.2%	5.3%	NR
Remzi et al. (2006)	HS/Stapled	2002	1725	277	5.5%	4.3%	NS				4.5%	1.8%	0.022
Lovegrove et al. (2008)	Stapled	199	39	160	7.7%	2.5%	NS				5.6%	3.6%	NS
Mennigen et al. (2011)	HS/Stapled	122	89	33	5.6%	18.2%	0.031	4.5%	30.3%	<0.001	3.4%	3.0%	NS
Sahami et al. (2016)	HS/Stapled	621	305	316	16.7%	17.1%	NS	4.3%	10.4%	0.003	7.3%	6.3%	NS
Widmar et al. (2019)	HS/Stapled	987	317	670	13.6%	13.7%					4.4%	1.9%	0.01
Ellebæk et al. (2020)	NR	434	348	86	2.3%	10.5%	0.002				9%	15%	NS

HS = Hand-sewn, NS = Not significant, NR = Not recorded

2.8 ALTERNATIVE PROCEDURES

In patients not suitable for restorative surgery, a proctocolectomy with permanent ileostomy is the preferred option. Some specialized centres perform continent Kock's pouches with relatively good results. Approximately half of the patients with Kock's pouch require re-operations, mainly because of nipple valve sliding, but overall pouch survival is about 90% (Lepistö et al. 2003, Castillo et al. 2005, Lian et al. 2009). However, patients with a well-functioning Kock's pouch report a better quality of life than patients with conventional end-ileostomy (Kock 1969, Lepistö et al. 2003, Berndtsson et al. 2005). Kock's pouch can be offered to patients with failed IPAA, patients who have contraindications to restorative surgery, such as incontinence or anal canal disease, or patients with considerable problems with conventional ileostomy (Aytac et al. 2014).

In very selected patients, a colectomy with ileo-rectal anastomosis (IRA) is an alternative to IPAA (Magro et al. 2017). IRA is a much easier procedure and more common in countries without centralized IPAA surgery. Patients considered for IRA should meet several criteria: a spared rectum, a normal sphincter tone, good rectal compliance, no risk factors for CRC, and absence of dysplasia or cancer. Patients operated on with IRA have better anorectal function, except for urgency, than patients treated with IPAA (Abdalla et al. 2020). In addition, female fecundity is preserved after IRA (Myrelid et al. 2015). The risk of rectal cancer remains, thus routine endoscopic surveillance is required. About half of the patients with IRA need a subsequent proctectomy (Magro et al. 2017). In a Finnish study, the cumulative success rate of IRA was 69% at 10 years and 56% at 15 years (Lepistö et al. 2005).

2.9 COMPLICATIONS FOLLOWING RESTORATIVE PROCTOCOLECTOMY

PC-IPAA-related mortality rate is low in highly specialized centres. In a meta-analysis, mortality rates ranged from 0% to 2.9% (Peyrin-Biroulet et al. 2016). The occurrence of any early complication ranged from 9% to 65%, and the occurrence of any late complication ranged from 17% to 55%. In another meta-analysis, the most common pouch-related complications were pouchitis (26.8%, 95% CI 21.0-33.5), stricture (10.7%, 95% CI 8.2-13.8), pelvic sepsis (7.5%, 95% CI 6.1-9.1), and fistula (4.5%, 95% CI 3.5-5.7) (de Zeeuw et al. 2012). The pooled incidence of pouch failure in studies published since 2000 was 4.3% (95% CI 3.5-5.3). Table 7 presents the rate of pouch-related complications and cumulative pouch failure in different studies.

Table 7. *Different studies reporting pouch-related complications and cumulative pouch failure rate following PC-IPAA in UC patients.*

Study	*Patients (n)*	*Follow-up (years)*	*Pouchitis*	*Stricture*	*Pelvic sepsis*	*Fistula*	*Pouch failure*			
							1 year	5 years	10 years	Overall
Meagher et al. (1998)	1356	6.5 (2-15)	41.2%		6.0%		2.0%	5.0%	9.0%	
Dayton et al. (2002)	565	6.5	25.0%	4.8%		1.6%				1.2%
Lepistö et al. (2002)	486	2-16	35.6%			9.3%	1.0%	5%	7%	5.3%
Hahnloser et al. (2004)	409	15	47.0%	21.0%						
Chapman et al. (2005)	2002	10.1±5.7	44.2%	20.0%		7.1%		4.0%	5.9%	
Remzi et al. (2006)	1858	5		19.5%	6.4%	8.0%				4.3%
Lovegrove et al. (2008)	200	NR	28.6%	20.6%	7.0%	6.0%			4.9%	
Tekkis et al. (2010)	2491	4.5 (0.1-28.9)	14.2%	16.8%	11.8%	11.8%		9.3%	16.1%	7.7%
Fazio et al. (2013)	2959	NR	35.9%	16.5%	9.0%	4.0%				5.1%
Zittan et al. (2017)	758	NR		7.3%		3.4%				0.9%
Mark-Christensen et al. (2018)	1992	11.4						9.1%	12.1%	

In patients with stapled IPAA, a cuff of rectal mucosa remains. Inflammation of this rectal cuff is called cuffitis. In the study of Lavery et al. (1995), symptomatic cuffitis occurred in 14.7% of the patients. Most patients respond to medical therapy, but cuffitis may also lead to pouch failure (Wu et al. 2013).

Covering ileostomies are associated with considerable morbidity. Based on a systematic review of RCTs, the median overall incidence of loop ileostomy-related complications is 14.3% (Malik et al. 2018). There were no data about end-ileostomies in their analysis. In a recent study from Sweden, 49% of patients had loop ileostoma-related complications, parastomal skin irritation and high-volume output being the most common (Park et al. 2018). In a meta-analysis, overall mortality related to ileostomy closure was 16.5% (Mennigen et al. 2014).

2.9.1 ROLE OF PREOPERATIVE MEDICATION IN COMPLICATIONS

High-dose corticosteroids increase the risk of postoperative complications (Aberra et al. 2003, Ferrante et al. 2009). The risk of septic complications appears to be elevated in the early postoperative period, but not later (Lim et al. 2007). Two Japanese studies suggested that the greater risk factor was the total preoperative dosage of corticosteroids rather than the exact dose at the time of surgery (Miki et al. 2007, Uchino et al. 2010). Reduction of the dose of corticosteroids prior to surgery is advised (Øresland et al. 2015). ECCO Guidelines recommend performing a subtotal colectomy first and postponing pouch surgery to a second stage if the patient is using prednisolone 20 mg daily (or equivalent) for more than six weeks prior to surgery.

6-mercaptopurine or azathioprine alone or in conjunction with steroids does not increase the risk of postoperative complications (Mahadevan et al. 2002). A few studies suggest that preoperative use of methotrexate is not associated with postoperative complications (Mahadevan et al. 2002, Afzali et al. 2016).

There is no consensus about whether anti-TNF agents are a risk factor for postoperative complications. Currently, the recommendation is to avoid a single-stage proctocolectomy in anti-TNF-treated patients (Øresland et al. 2015). In a large, retrospective cohort study of 1172 patients, anti-TNF agents were associated with postoperative complications among patients undergoing PC-IPAA, but not among patients undergoing colectomy (Kulaylat et al. 2017). A Canadian study of 758 patients concluded the opposite (Zittan et al. 2016). Selvaggi et al. (2015) found in their meta-analysis an increased risk of short-term pouch-related complications and a trend towards higher risk of pouchitis at the 1-year follow-up in patients using infliximab. In another meta-analysis, no significant association between preoperative infliximab therapy and overall, infectious, or non-infectious complications were found (Yang et al. 2012).

Patients are often immunosuppressed with multiple agents prior to surgery. In Crohn's disease, the use of multiple immunosuppressive agents has been associated with intra-abdominal sepsis (McKenna et al. 2018). In a recent study on UC, anti-TNF therapy or immunosuppression with multiple agents did not affect surgical-site infections (Uchino et al. 2019).

2.10 POUCHITIS

2.10.1 PATHOGENESIS OF POUCHITIS

Pouchitis, a non-specific inflammation of the pouch, is the most common long-term complication after PC-IPAA. The incidence of pouchitis increases with the duration of follow-up. Approximately 50% of patients develop at least one episode of pouchitis over a 10-year follow-up (Lightner et al. 2017). By 30 years, the incidence is around 80%. Simchuk et al. (2014) reported an even higher incidence rate: 94% over a 6-year follow-up. In Finland, the cumulative risk for pouchitis was 28% over 11 years (Keränen et al. 1997). Pouchitis is not an isolated disease entity, rather the disease course varies greatly between affected patients (Shen 2013). Up to 60% of patients develop recurrent pouchitis after the first episode, and in 5–10% of patients the pouchitis becomes chronic (Landy et al. 2012).

In the majority of patients, pouchitis is considered idiopathic. In 20–30% of patients, chronic pouchitis might have a secondary cause (Navaneethan et al. 2010). Secondary causes include ischaemia, infections, and Crohn's disease of the pouch, among others, and these should be considered when treating a patient with chronic refractory pouchitis. The pathogenesis of an idiopathic pouchitis remains unknown. Gut microbiota seems to play a key role in the initiation and progression of pouchitis. The construction of the pouch alters the bowel anatomy, leading to faecal stasis and increased microbial load to the pouch mucosa. Colonic metaplasia, i.e. colon-like mucosa, develops, which creates an environment favourable for inflammation and induces a dysbiosis of the pouch towards colon-like microbiota (Luukkonen et al. 1988, de Silva et al. 1991, Kohyama et al. 2009). However, no individual bacterial species has been found to be related specifically to pouchitis (Shen 2013). Interestingly, patients who underwent PC-IPAA because of familiar adenomatous polyposis have much lower incidence of pouchitis, suggesting the contribution of genetic factors (Lovegrove et al. 2006).

Reported risk factors associated with the development of pouchitis include extensive UC before IPAA, presence of backwash ileitis, PSC, and other extraintestinal manifestations of UC, concurrent autoimmune disorders, and NSAID use (Quinn et al. 2018). Smoking seems to be associated with acute pouchitis, but protects against chronic pouchitis (Fleshner et al. 2007).

2.10.2 DIAGNOSIS OF POUCHITIS

Typical symptoms in pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus, nocturnal seepage, incontinence, blood per ani, and pelvic discomfort. Occasionally, fever may occur. In the presence of these symptoms, pouchoscopy should be performed to confirm pouchitis (Magro et al. 2017). Endoscopic findings range from mild erythema, oedema, granularity, and loss of vascular pattern to more severe changes such as friability, haemorrhage, ulcerations, and erosions. Routine biopsies from the pouch mucosa and from the afferent limb above the pouch are recommended. Sandborn et al. (1994) developed the Pouchitis Disease Activity Index (PDAI) to help in the diagnosis of pouchitis, but it is mainly used among researchers (Table 8). Modified Pouchitis Disease Activity Index (mPDAI), consisting of only clinical and endoscopic scores of PDAI, offers a similar sensitivity and specificity to PDAI in the diagnosis of acute pouchitis (Shen et al. 2003). Omission of the histological part of the PDAI reduces the cost and simplifies the diagnosis.

Pouchitis can be classified according to the duration of symptoms as either acute (< 4 weeks) or chronic (≥ 4 weeks). Chronic pouchitis can be further classified based on response to antibiotic treatment as antibiotic-dependent or antibiotic-refractory disease.

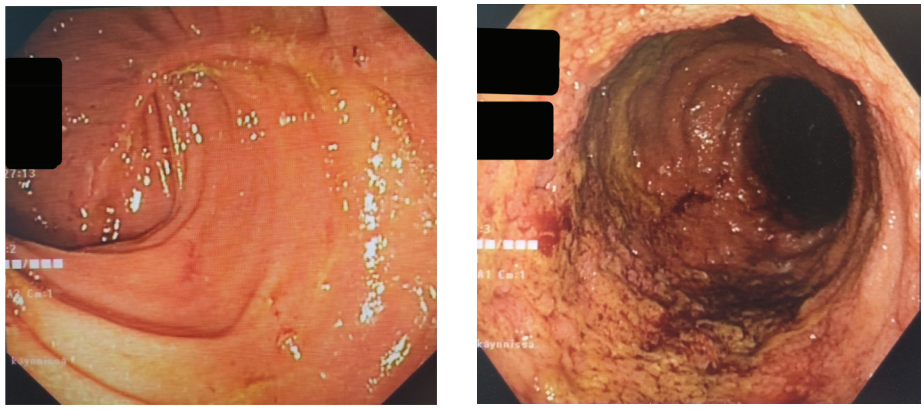

Figure 5 On the left, a normal pouch. On the right, a typical view of pouchitis.

Table 8. *Pouchitis Disease Activity Index develobed by Sandborn et al. (1994). Pouchitis is defined as a total score of 7 or more of a possible 18 points.*

Pouchitis Disease Activity Index	
Criteria	**Score**
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1-2 stools/day > postoperative usual	1
3 or more stool/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Faecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 37.8°C)	
Absent	0
Present	1
Endoscopic inflammation	
Oedema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudates	1
Ulceration	1
Acute histological inflammation	
Polymorphic nuclear leukocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
> 25%	1
25–50%	2
> 50%	3

2.10.3 TREATMENT OF POUCHITIS

Patients with acute pouchitis typically respond to antibiotic therapy, ciprofloxacin and metronidatzole being the most commonly used. Recently, a Cochrane review about treatment and prevention of pouchitis was published (Nguyen et al. 2019). Only four small RCTs assessed the treatment of acute pouchitis. Ciprofloxacin was more effective at inducing remission than metronidatzole, and adverse effects were less frequent (Shen et al. 2001). Metronidatsole and budesonide enemas were equally effective at inducing remission, but neither rifaximin nor *Lactobacillus GC* were superior to placebo (Sambuelli et al. 2002, Kuisma et al. 2003, Isaacs et al. 2007).

If symptoms persist for over 4 weeks, a combination of antibiotics is generally used as first-line therapy (Segal et al. 2016). Antibiotics have been shown to induce remission in 70% of patients with chronic pouchitis. Maintenance antibiotic therapy should be considered for patients who continue to have relapses of pouchitis at least three times a year (a chronic antibiotic-dependent pouchitis) (Dalal et al. 2018). VSL#3 has also been shown to be effective in secondary prophylaxis of pouchitis in RCTs (Gionchetti et al. 2000, Mimura et al. 2004).

A small proportion of patients who continue to have verified pouchitis despite antibiotics, probiotics, and maintenance therapy (a chronic antibiotic-refractory pouchitis) can be difficult to treat. Treatment options in these patients are corticosteroids, such as budesonide and beclomethasone, biologics, and tacrolimus. Evidence of their effectiveness is limited. In a meta-analysis, steroids induced remission in 77% of patients with chronic pouchitis, and tacrolimus in 72% of patients, but both failed to achieve significance (Segal et al. 2016). Biologics induced remission significantly in 53% of patients with chronic pouchitis. The only RCT in the treatment of chronic pouchitis compared adalimumab with placebo for 12 weeks (Dilling Kjær et al. 2019). Their primary outcome was reduction in PDAI score of 2 points or more at any time. There was no significant difference between the groups (50% vs. 43%, $P > 0.5$).

2.11 FAECAL MICROBIOTA TRANSPLANTATION (FMT)

FMT is defined as an infusion of faecal material from a healthy donor to the gastrointestinal (GI) tract of a recipient patient in order to alter the gut microbiota. FMT has been studied in multiple disorders such as IBD, irritable bowel syndrome, and metabolic syndrome. At the moment, the only clinical indication of FMT with sufficient clinical evidence is recurrent *Clostridioides difficile* infection (Cammarota et al. 2017). Based on four RCTs, FMT appears to be effective in inducing remission in UC (Narula et al. 2017). However, long-term outcome remains unclear. In CD, no RCT has yet been published. Overall, 50.5% of CD patients achieved remission in prospective uncontrolled trials (Paramsothy et al. 2017).

2.11.1 FMT IN TREATMENT OF CHRONIC POUCHITIS

Thus far, only case reports and prospective uncontrolled cohort studies have been published on FMT in the treatment of chronic pouchitis. Table 9 summarizes the main results of these studies. Overall, relatively few patients with chronic pouchitis benefit from FMT with the treatment protocols evaluated to date.

Herfarth et al. (2019) started a randomized, placebo-controlled, double-blinded trial consisting of a single FMT to the pouch, followed by oral FMT capsules for 14 days. However, the trial was halted after enrolment of six patients due to low clinical efficacy of FMT and poor engraftment of donor microbiota. All six patients relapsed within three weeks of FMT infusion (4 patients in FMT group, 2 patients in placebo group). All six patients were offered open label FMT, followed by daily oral FMT capsules for 14 days. One out of five open label participants achieved clinical remission and good engraftment of donor microbiota. Engraftment seems to be a problem. The best engraftment of the donor microbiota was achieved by Kousgaard et al. (2020): in six out of nine patients. They treated patients with FMT enemas for 14 consecutive days.

Table 9. *Studies evaluating efficacy of faecal microbiota transplantation in treatment of chronic pouchitis.*

Study	*Patients (n)*	*Inclusion*	*FMT route*	*Number of infusions*	*Primary endpoint*	*Follow-up*	*Clinical remission*	*Clinical response*
Landy et al. 2015	8	CADP and CARP, PDAI≥7	Nasogastric tube	1	cPDAI=0 or PDAI<5	4 weeks	0%	25%
Stallmach et al. 2016	5	CARP, PDAI 9-14	Jejunoscopy	1-7 (3- to 4-week intervals)	NR	at least 3 months	80% at 4 weeks, 60% sustained response	100%
Fang et al. 2016	1	CARP	Pouchoscopy	1	NR	3 months	100%	NR
Schmid et al. 2017	1	CARP	Pouchoscopy	3	NR	9 weeks	0%	0%
Nishida et al. 2019	3	PDAI≥7	Pouchoscopy	1	reduction in PDAI by ≥3 and PDAI <7	8 weeks	0%	33.3%
Herfarth et al. 2019	5	CADP, PDAI ≥7	Pouchoscopy and oral capsules	1 infusion and capsules for 14 days	mPDAI <4 and no antibiotics	16 weeks	20%	NR
Selvig et al. 2019	18	CADP and CARP	Pouchoscopy	1-2 (4-week interval)	Clinical improvement, reduction in PDAI by ≥3	4 weeks	bowel movement frequency improved, PDAI decreased in 1/11 (9%)	NR
Kousgaard et al. 2020	9	CADP and CARP, cPDAI≥3	Enema	14 consecutive days	PDAI <7	6 months	44% at 30 days, 33% sustained response	NR

3 OBJECTIVES OF THE STUDY

Specific aims of the study were as follows:

I. To determine the incidence and prognosis of ulcerative colitis-associated colorectal cancer.

II. To assess the effect of preoperative anti-tumour necrosis factor therapy and corticosteroids on postoperative complications and pouch failure.

III. To determine the effect of covering ileostomy on postoperative morbidity after ileal pouch anal anastomosis.

IV. To investigate the efficacy and safety of faecal microbiota transplantation in the treatment of chronic pouchitis.

4 MATERIALS AND METHODS

4.1 STUDY HOSPITAL

The study was carried out between 2017 and 2020 at Helsinki University Hospital, Finland. Helsinki University Hospital serves as a secondary and tertiary referral hospital, providing both elective and emergency care. At Helsinki University Hospital, the PC-IPAA was adopted for UC patients in 1985. The operative treatment of UC in Southern Finland is centralized to Helsinki University Hospital, and about 50–60 UC patients undergo proctocolectomy in our unit each year. Follow-up and pouchoscopies, if needed, are arranged mainly in Helsinki University Hospital by a colorectal surgeon. In addition, any further surgery, i.e. loop-ileostomy closures and pouch excisions, are performed in our unit. All patients in Studies I, II, and III underwent surgery at Helsinki University Hospital. In Study IV, two of the recruited patients were operated on in another tertiary referral centre in Finland.

4.2 PATIENTS

4.2.1 RETROSPECTIVE STUDIES I, II, AND III

In total, 1241 patients underwent surgery due to UC at Helsinki University Hospital during 1991–2018. All data were collected retrospectively from the medical records of patients included in each study. The institutional ethics committee of Helsinki University Hospital approved the study protocol. For retrospective parts of the study (I-III), written informed consent was not required.

Study I
This study included all 71 patients with UC-associated CRC who underwent surgery at Helsinki University Hospital between 1991 and 2018. In addition, we analysed those 108 UC patients who underwent proctocolectomy during 2002–2018 and had dysplasia but no cancer in the surgical specimen. Reliable data on patients with dysplasia before the year 2002 were not available.

Study II
Between January 2005 and June 2016, altogether 460 consecutive patients underwent PC-IPAA due to UC. Patients using immunosuppressive medication other than anti-TNF agents, corticosteroids, 6-mercaptopurine, azathioprine, or methotrexate were excluded. A total of 445 patients were included in the final analysis.

Study III
This study included all 510 consecutive UC patients who underwent proctocolectomy or proctectomy with IPAA between January 2005 and June 2016. Of these patients, 460 underwent PC-IPAA and 50 underwent subtotal colectomy due to fulminant colitis, and as a second-stage procedure proctectomy with IPAA.

4.2.2 RANDOMIZED PLACEBO-CONTROLLED TRIAL ON FMT FOR TREATMENT OF CHRONIC POUCHITIS (IV)

For this single-center, double-blinded, parallel group trial, we recruited patients at Helsinki Unversity Hospital between December 2017 and August 2018. Inclusion and exclusion criteria are presented in Table 10. The institutional review board and ethics committee of Helsinki University Hospital approved the study, and a written informed consent was obtained from all 26 patients. A study nurse randomly allocated patients in a 1:1 ratio to either donor FMT or placebo (autologous transplant) and had no further role in the study. The trial is registered with ClinicalTrials.gov (NCT03378921).

Table 10. *Inclusion and exclusion criteria for Study IV. All inclusion criteria had to have been met.*

Inclusion criteria	*Exclusion criteria*
Previous IPAA surgery for UC	Age <18 or >75 years
Endoscopically and histologically diagnosed pouchitis within 6 months	Use of immunosuppressive or immunomodulatory medication
Frequent or continuous use of antibiotics due to chronic pouchitis	Pregnancy
	Suspicion or established diagnosis of Crohn's disease

4.3 DEFINITIONS

Staging of UC-associated CRC is expressed according to the 7th Union of International Cancer Control's (UICC) TNM Classification (I). During the 30-year study period multiple different classifications were used, including Dukes' classification, and therefore, we were unable to report substaging (Tables 11 and 12). Histologically, grade I is well differentiated, grade II is moderately differentiated, and grade III is poorly differentiated CRC. Dysplasia was graded as low- or high-grade dysplasia by two independent and experienced gastropathologists.

Table 11. *7th UICC TNM Classification for colorectal cancer.*

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into pericolorectal tissue
T4a	Tumour penetrates the surface of the visceral peritoneum
T4b	Tumour invades or is adherent to other organs or structures
Regional nodal metastases (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 12. *TNM stages without substaging according to the 7th UICC TNM Classification and Dukes' Classification.*

Stage	T	N	M	Dukes
0	Tis	N0	M0	-
I	T1-T2	No	M0	A
II	T3-T4	N0	M0	B
III	Any T	N1-N2	M0	C
IV	Any T	Any N	M1	-

Postoperative complications were graded according to the Clavien-Dindo Classification (II,III). If a patient had multiple complications, we reported the highest Clavien-Dindo grade (Table 13). Symptomatic anastomotic leak was diagnosed by computed tomography scan with peranally administered contrast agent, in pouchoscopy or during the laparotomy. Determination of dehydration was based on a disturbance of electrolytes and a need for excess hydration postponing discharge. We assessed bowel obstruction as vomiting, need for nasogastric tube, or ileostoma malfunction postponing discharge. We defined pouch failure as excision of the J-pouch or a permanent loop-

ileostomy. Pouchitis was diagnosed by typical symptoms and confirmed in pouchoscopy. Pouchoscopy was not always performed if a patient had only one episode of acute pouchitis with typical symptoms. If symptoms persisted for more than four weeks, the pouchitis was defined as chronic. In Study IV, we defined a frequent use of antibiotics for chronic pouchitis as a need for antibiotic treatment more than once within the year prior to recruitment to the study.

Table 13. *Clavien-Dindo Classification (Dindo et al. 2004).*

0	No complication
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
2	Requiring pharmacological treatment, blood transfusions, or total parenteral nutrition
3a	Requiring surgical, endoscopic, or radiological intervention, not under general anaesthesia
3b	Requiring surgical, endoscopic, or radiological intervention, under general anaesthesia
4a	Life-threatening complication requiring IC/ICU management and single organ dysfunction
4b	Life-threatening complication requiring IC/ICU management and multiorgan dysfunction
5	Death

4.4 INTERVENTIONS

4.4.1 SURGICAL TECHNIQUE (II,III)

A proctocolectomy or a proctectomy with IPAA was performed through a low midline incision. The rectum was dissected close to the rectal surface, except in those patients with rectal cancer or a narrow pelvis, who were treated with total mesorectal excision (TME). A J-pouch (10 to 20 cm long) was created using multiple linear staples. In 90.1% of patients in Study II and in 89.8% of patients in Study III, the pouch-anal anastomosis was hand-sewn. The remaining rectal mucosa was removed transanally before suturing the anastomosis with interrupted sutures. The pouch was also anchored to the sphincters with four wall-through sutures. In a stapled pouch-anal anastomosis, the rectum was transected 1-2 cm above the dentate line.

At Helsinki University Hospital, most of the patients undergo IPAA without a diverting ileostomy. The operating surgeon makes the decision to use or omit

the diverting ileostomy at the end of the operation. The indications for an ileostomy are presented in Table 14. When the decision was made to divert, a loop-ileostomy was raised as distally as possible, usually 20-50 cm above the pouch. A medena catheter was kept in the pouch postoperatively for five days in patients without an ileostomy and two days in patients with an ileostomy.

Table 14. *Indications for a diverting ileostomy in Studies II and III.*

Indication	***Study II***	***Study III***
Intention to treat, n/N (%)	101/445 (22.7%)	119/510 (23.3%)
Tension of IPAA	73.3%	69.7%
Morbidly obese patient	16.8%	17.6%
UC-associated CRC	6.9%	5.9%
Previous liver transplantation	Excluded	4.2%
Perianal fistula	2.0%	1.7%
Cirrhosis due to PSC	0%	0.8%
Because of the complication n/N (%)	24/445 (5.4%)	28/510 (5.5%)

4.4.2 FAECAL MICROBIOTA TRANSPLANTATION (IV)

The study protocol included two faecal transplants: the first transplant through flexible endoscopy on week 0 and the second transplant via a transanal catheter on week 4. In this trial, we used the faecal material of a single donor: a healthy 52-year-old woman of normal body weight (BMI < 25 kg/m^2). She had not used any antibiotics or probiotics within 6 months and had no gastrointestinal symptoms. The donor faecal material had previously been used successfully to treat patients with recurrent *Clostridioides difficile* infection.

Patients were followed up for 52 weeks, and no patient was lost to follow-up. Follow-up included a telephone interview on weeks 12 and 26 and a clinical visit with pouchoscopy on week 52. The clinical part of the PDAI (cPDAI) was calculated on weeks 4, 12, and 26, and the total PDAI was calculated at baseline and on week 52. In addition, faecal samples were collected before the first transplant and on weeks 4, 12, 26, and 52 post-transplantation. Patients filled in the health-related quality of life form (15D form) on weeks 0 and 26.

The primary outcome was remission, defined as PDAI less than 7, and no need for antibiotics due to pouchitis during the follow-up. Another objective was to analyse changes in the gut microbiota.

4.5 STATISTICAL ANALYSES

Continuous variables were compared using Mann-Whitney U-test or Student's t-test, and categorical variables were compared using Chi-square test or Fisher's exact test (I-IV). Normality of continuous variables was tested using Shapiro-Wilk test. We considered probability values below 0.05 to be statistically significant and used a two-tailed test. We compared the no-corticosteroid group, low-dose group, and high-dose group using the Jonckheere-Terpstra Trend test for continuous variables and the linear-by-linear association test for categorical variables (II). To compare early postoperative complications between the stoma and no-stoma groups, we created an age- and gender-adjusted univariate model using a binary logistic regression (III). We used a penalized maximum likelihood regression model based on the lasso method to select variables for the multivariate model. Bonferroni correction was used to account for multiple testing (II,III). For anastomotic leakage, we created an age-adjusted multivariate model using Firth's penalized likelihood logistic regression (II). Survival was analysed by the Kaplan-Mayer method and compared by log-rank test (I,IV). Hazard ratios and 95% confidence intervals for relapse-free survival time were estimated with Cox regression analysis (IV). The follow-up data of RCT were analysed pairwise, comparing each time point separately with baseline. The difference between each time point and baseline was measured, and the groups were compared using Mann-Whitney U-test or linear-by-linear association test (IV). We performed statistical analyses with SPSS software, version 24 or 25 (IBM Corporation, Armonk, NY, USA). An exception was the lasso method in Study III, where we used R software (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org).

5 RESULTS

5.1 INCIDENCE AND PROGNOSIS OF ULCERATIVE COLITIS-ASSOCIATED COLORECTAL CANCER (I)

Table 15. *Characteristics of patients with colorectal cancer or dysplasia in the surgical specimen.*

Variable	*CRC (n=71)*	*Dysplasia (n=108)*
Male gender	43 (60.6%)	81 (75.0%)
Age, years (mean±SD)	49.9 ± 11.3	44.5 ± 14.0
Primary sclerosing cholangitis	13 (18.3%)	24 (22.2%)
Median disease duration, years	19 (0-50)	11 (1-44)
Indication for surgery		
Cancer	47 (66.2%)	
Dysplasia	22 (31.0%)	70 (64.8%)
Medical therapy failure	0	38 (35.2%)
Fulminant colitis	1 (1.4%)	0
Pseudopolyposis	1 (1.4%)	0
Type of surgery		
PC+IPAA	55 (77.5%)	102 (94.4%)
Proctocolectomy with ileostomy	5 (7.0%)	4 (4.6%)
Colectomy with ileostomy or with IRA	10 (14.1%)	2 (1.9%)
Excision of pouch	1 (1.4%)	0
Pathological features		
Low-grade dysplasia		65 (60.2%)
High-grade dysplasia		36 (33.3%)
Dysplasia not classified		7 (6.5%)
Rectal cancer	20 (28.2%)	
Colonic cancer	51 (71.8%)	
Synchronous dysplasia	24 (33.8%)	
Synchronous colorectal cancer	10 (14.1%)	
Mucinous carcinoma	22 (31.0%)	
Grade 1/2/3/NA	18 (25.4%)/22 (31.0%)/ 14 (19.7%)/17 (23.9%)	
Stage I/II/III/IV	20 (28.2%)/24 (33.8%)/ 20 (28.2%)/7 (9.9%)	
Cancer recurrence	17 (23.9%)	
Death during follow-up	20 (28.2%)	6 (5.6%)
From colorectal cancer	14 (19.7%)	

A total of 71 patients with UC-associated CRC underwent surgery between 1991 and 2018. Patient characteristics are presented in Table 15. Of these patients, 58 (81.7%) were under routine surveillance. However, in one-third of the patients (n=24, 33.8%), CRC was not diagnosed preoperatively. In pathological examination, cancers expressed signs related to poorer prognosis; 31.0% were mucinous adenocarcinomas, 19.7% were poorly differentiated, 28.2% were spread to regional lymph nodes, and 9.9% were spread more widely. In addition, 34 patients (47.9%) had synchronous CRC or dysplasia.

We compared the incidence of CRC in our patient cohort by dividing the data into two equally long periods, from 1991 to 2004 and from 2005 to 2018. The incidence of CRC among patients undergoing PC-IPAA had not increased (5.2% vs. 6.2%, P = 0.56). The results remained the same even when the 108 patients with dysplasia in their surgical specimen were added to the analysis (20.3% vs. 17.3%, P = 0.26, years 2002 to 2018).

During follow-up cancer recurrence was diagnosed in 17 patients (23.9%), and 14 patients (19.7%) died due to CRC. Median follow-up time was 8.2 years (range 0.6-26.8), and the mean age of death was 55.7 years (±13.5). Overall survival was 71.8%. CRC-specific survival was 76.5%. Stage-specific survival is presented in Figure 5. The 5-year CRC-specific survival was 81.5%: 87.8% for women and 77.3% for men.

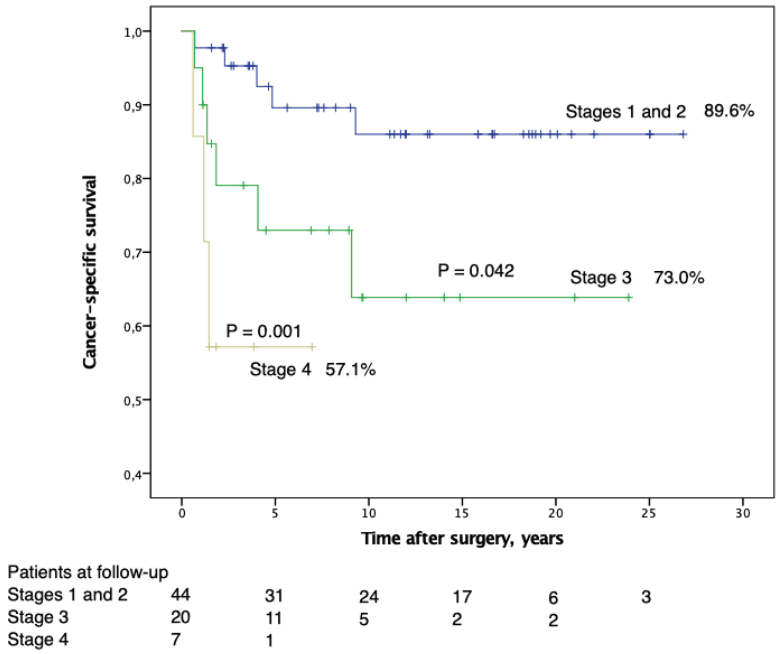

Figure 6 CRC-specific survival of 71 patients with UC-associated CRC.

5.2 EFFECT OF PREOPERATIVE ANTI-TUMOUR NECROSIS FACTOR (TNF) AGENTS, CORTICOSTEROIDS, AND USE OF A COVERING ILEOSTOMY ON COMPLICATIONS (II,III)

Between January 2005 and June 2016, altogether 510 consecutive patients with UC underwent proctocolectomy or proctectomy with IPAA. We included all of these patients in Study III, comparing patients who underwent surgery with or without a covering ileostomy. Study II is a subgroup of Study III, excluding patients who underwent only proctectomy or were using tacrolimus (patients with liver transplant) or vedolizumab. In Study II, we analysed the effect of preoperative anti-TNF agents and corticosteroids on postoperative complications. Patient characteristics are presented in Table 16.

5.2.1 ANTI-TNF AGENTS

The 33 patients who were treated with anti-TNF agents within 12 weeks preceding PC-IPAA were compared with all others. The anti-TNF agent used was infliximab in 29 patients, golimumab in two patients, and adalimumab in two patients. The median number of infusions was four (range 1-22), and the median time between last infusion and surgery was 6 weeks (range 3-11). In patients treated with anti-TNF agents, the median disease duration time was shorter ($P = 0.039$), and they were also using higher doses of corticosteroids ($P = 0.001$) (Table 16). The incidence of any postoperative complication did not differ between the groups (Table 17).

5.2.2 CORTICOSTEROIDS

We excluded patients with anti-TNF therapy from the analysis of corticosteroids. Of 412 patients, 255 (56.0%) were using corticosteroids. We categorized them further to either a low-dose (less than prednisolone 20 mg or equivalent) group (160 patients) or a high-dose (prednisolone 20 mg or more) group (95 patients). We compared both groups with the 157 patients who received no corticosteroids in the 6 weeks prior to surgery. Median disease duration was shorter in both corticosteroid groups ($P < 0.0001$). This difference may be explained by the indication for surgery. The majority of patients in the steroid groups were operated on due to refractory disease (91.0%), but in the no-corticosteroid group 43.3% of patients underwent surgery due to dysplasia or cancer. In addition, haemoglobin and albumin levels were lower in both steroid groups, as a sign of a more severe UC.

Table 16. *Patient characteristics in Studies II and III. * Difference is statistically significant between the groups.*

	Study II					*Study III*	
Outcome	**Anti-TNF agent (n=33)**	**Controls (n=412)**	**No corticosteroids (n=157)**	**Low-dose steroid (n=160)**	**High-dose steroid (n=95)**	**Stoma (n=119)**	**No stoma (n=391)**
Mean age (years±SD)	35.6±13.0	40.0±13.1	41.8 ± 12.6	40.6 ± 13.1	36.5 ± 13.4*	42.7±13.4	38.7±13.0
Male gender	25 (75.8%)	252 (61.2%)	97 (61.8%)	92 (57.5%)	63 (66.3%)	91 (76.5%)	221 (56.5%)*
Median disease duration in years	3 (1-31)	6 (0-50)*	10 (1-50)	5 (1-39)	4 (0-26)*	6 (0-50)	6 (0-47)
Mean preoperative hemoglobin (g/l)	127.5 ± 22.2	129.7 ± 18.0	134.1 ± 16.7	129.2 ± 16.8	123.2 ± 20.0*	133.3 ±20.3	128.3 ±17.0*
Mean preoperative albumin (g/l)	35.6 ± 6.0	37.5 ± 4.9	39.0 ± 4.1	37.9 ± 4.0	34.5 ± 6.2*	37.8 ±5.1	37.4 ±4.9
Steroid use (mg)		*		158 (100%)	91 (100%)		
<10	0 (0%)	53 (20.8%)		53 (33.5%)	0	18 (15.1%)	42 (10.7%)
10-20	5 (23.8%)	105 (41.2%)		105 (66.5%)	0	18 (15.1%)	93 (23.8%)
20-30	5 (23.8%)	50 (19.6%)		0	50 (54.9%)	12 (10.1%)	43 (11.0%)
>30	11 (52.4%)	41 (16.1%)		0	41 (45.1%)	14 (11.8%)	38 (9.7%)
Anti-TNF agents	33 (100%)	0	0	0	0	7 (5.9%)	21 (5.4%)
Other immunosuppressive therapy	14 (42.4%)	238 (57.8%)	88 (56.1%)	90 (56.3%)	60 (63.1%)	19 (16.0%)	76 (14.1%)
Prior colectomy						11 (9.2%)	39 (10.0%)
Mean operating time (hours:min)						3:49±0:40	3:03±0:31*
Pouch-anal anastomosis							*
Hand-sewn						87 (73.1%)	371 (94.9%)
Stapled						32 (26.9%)	20 (5.1%)
Proximal diversion	10 (30.3%)	115 (27.9%)	40 (25.5%)	39 (24.4%)	36 (37.9%)		
Intention to treat	9 (27.3%)	92 (22.3%)	36 (22.9%)	30 (18.8%)	26 (27.4%)		
Because of the complication	1 (3.0%)	23 (5.6%)	4 (2.5%)	9 (5.6%)	10 (10.5%)*		
Length of stay, days (median)	10 (6-28)	10 (5-57)	9 (6-42)	10 (5-57)	10 (6-43)	6-58 (12)	5-43 (9)*

Table 17. *Postoperative complications in patients treated with anti-TNF agents and corticosteroids (II). Significant P-values are bolded.*

Complication	***Anti TNF agent (n=33)***	***Control (n=412)***	***P-value***	***No corticosteroids (n=157)***	***Low dose steroid (n=160)***	***P-value***	***High dose steroid (n=95)***	***P-value***	***Trend analysis, P-value***
Anastomotic leak	1 (3.0%)	23 (5.6%)	1.00	4 (2.5%)	7 (4.4%)	0.542	12 (12.6%)	**0.002**	**0.002**
Other infectious complications	4 (12.1%)	44 (10.7%)	0.770	17 (10.8%)	17 (10.6%)	1.00	10 (10.5%)	1.00	1.00
Wound dehiscence	1 (3.0%)	6 (1.5%)	0.419	0	2 (1.3%)	0.498	4 (4.2%)	**0.019**	**0.012**
Haemorrhage	0	6 (1.5%)	1.00	1 (0.6%)	4 (2.5%)	0.371	1 (1.1%)	1.00	0.792
Thrombosis/Embolism	0	4 (1.0%)	1.00	0	4 (2.5%)	0.123	0		0.754
Occlusion/Ileus	4 (12.1%)	48 (11.7%)	1.00	21 (13.5%)	19 (11.9%)	0.736	8 (8.4%)	0.309	0.272
Dehydration	6 (18.2%)	38 (9.2%)	0.122	16 (10.3%)	17 (10.6%)	1.00	5 (5.3%)	0.240	0.268
Relaparotomy because of complication	2 (6.1%)	34 (8.3%)	1.00	7 (4.5%)	15 (9.4%)	0.121	12 (12.6%)	**0.025**	**0.020**
Because of anastomotic leak	1 (3.0%)	20 (4.9%)	1.00	4 (2.5%)	7 (4.4%)	0.542	9 (9.5%)	**0.020**	**0.017**
Pouch-related fistulas	0	32 (7.8%)	0.155	8 (5.1%)	15 (9.6%)	0.136	9 (9.7%)	0.196	0.153
Pouch failure	0	9 (2.2%)	1.00	0	7 (4.4%)	**0.015**	2 (2.1%)	0.141	0.189
Clavien-Dindo classification									0.078
No complication				105 (66.9%)	101 (63.1%)		60 (63.2%)		
Grades 1 and 2	9 (27.3%)	110 (26.7%)	0.943	44 (28.0%)	44 (27.5%)	0.899	22 (23.2%)	0.761	
Grade 3a	0	1 (0.2%)	1.00	0	0		1 (1.1%)	0.367	
Grade 3b	2 (6.1%)	33 (8.0%)	1.00	7 (4.5%)	15 (9.4%)	0.116	11 (11.6%)	0.072	
Grade 4	1 (3.0%)	2 (0.5%)	0.207	1 (0.6%)	0	1.00	1 (1.1%)	1.00	

High-dose steroids, but not low-dose steroids, increased the risk for anastomotic leak (P = 0.002, OR 5.7, 95% CI 1.87-17.32, P = 0.024) and wound dehiscence (P = 0.019), which led to a higher relaparotomy rate in the high-dose group (P = 0.025) (Table 17). A combination of anti-TNF agents and corticosteroids had no additive effect on anastomotic leak in logistic regression analysis (Table 18).

Table 18. *Age-corrected logistic regression analysis for anastomotic leakage. In patients, different immunosuppressive treatments are compared with no immunosuppressive medication.*

	OR (95% CI)	*P-value*
Low-dose corticosteroid group	1.75 (0.54-5.67)	0.686
High-dose corticosteroid group	5.69 (1.87-17.32)	0.024
Only anti-TNF agents	1.41 (0.07-29.92)	0.740
Anti-TNF agent and steroid	2.98 (0.43-20.82)	0.652
Thiopurines or methotrexate	1.03 (0.46-2.33)	0.938

5.2.3 DIVERTING ILEOSTOMY

Of 510 patients undergoing proctocolectomy or proctectomy with IPAA, covering ileostomy was constructed in 119 patients during the primary surgery (stoma group); thus, 391 patients underwent primary surgery without an ileostomy (no-stoma group). For 28 patients, a diverting ileostomy was constructed in a second laparotomy due to a complication, and these patients were included in the no-stoma group according to the intention-to-treat principle. Patients in the no-stoma group were somewhat younger (mean age 38.7 years vs. 42.7 years, P = 0.049), more likely to be women (P < 0.0001), and the pouch-anal anastomosis was more often hand-sewn (94.9% vs. 73.1%, P < 0.0001). In the stoma group, the mean operative time and median postoperative length of stay were longer (P < 0.0001) (Table 16).

Early postoperative complications. Overall, there were more early postoperative complications in the stoma group (66 patients, 55.4% vs. 118 patients, 30.2%, P < 0.0001). Anastomotic leaks were diagnosed in two patients (1.7%) in the stoma group and in 26 patients (6.6%) in the no-stoma group (P < 0.04). In the stoma group, pneumonias, wound dehiscence, intestinal obstruction, and tendency for dehydration were more common (Table 19). Relaparotomy rate did not differ between the groups (P = 0.58).

Re-admissions. The risk for re-admission within three months of the primary surgery was high in the stoma group relative to the no-stoma group (OR 4.3, 95% CI 3.1-5.9, P < 0.001). In the stoma group, the most common causes for re-admission were dehydration (19 patients, 16.0%), intestinal

obstruction (9 patients, 7.6%), and stoma complication (6 patients, 5.0%). In the no-stoma group, patients were re-admitted most commonly due to intra-abdominal abscess (17 patients, 4.4%) and dehydration (9 patients, 2.3%).

Table 19. *Early postoperative complications, re-admissions within three months of primary surgery before ileostomy closure, and late postoperative complications after ileostomy closure.*

Variable	***Stoma group (n=119)***	***No-stoma group (n=391)***	***P-value***
Early postoperative complications	66 (55.4%)	118 (30.2%)	<0.0001
Anastomotic leakage	2 (1.7%)	26 (6.6%)	0.04
Other infectious complications	15 (12.6%)	40 (10.2%)	0.47
Wound dehiscence	4 (3.4%)	4 (1.0%)	0.09
Occlusion/Ileus	27 (22.7%)	28 (7.2%)	<0.0001
Dehydration	30 (25.2%)	23 (5.9%)	<0.0001
Relaparotomy	9 (7.6%)	36 (9.2%)	0.58
Re-admissions	50 (42.0%)	51 (13.0%)	<0.0001
Median time to readmission, days	13 (1-92)	9 (2-92)	0.40

Table 20. *Comparison of early complications between the stoma and no-stoma groups with univariate and multivariate analyses.*

	Univariate		***Multivariate***	
	OR (95% CI)	***P-value***	***OR (95% CI)***	***P-value***
Early complications				
Anastomotic leak	0.2 (0.1-0.5)	0.001		
Other infectious complications	1.3 (0.9-1.9)	0.187		
Wound infection	2.9 (0.7-11.0)	0.126		
Intra-abdominal abscess	0.6 (0.2-1.7)	0.306		
Pneumonia	5.9 (2.0-17.4)	0.001		
Urinary tract infection	1.2 (0.7-2.0)	0.607		
Wound dehiscence	4.0 (1.5-10.5)	0.004		
Haemorrhage	0.6 (0.2-1.7)	0.339		
Thrombosis/Embolism	1.0 (0.2-4.3)	0.993		
Occlusion/Ileus	3.3 (2.2-4.9)	< 0.001	4.0 (2.6-6.0)	< 0.001
Dehydration	4.8 (3.2-7.3)	< 0.001	5.6 (3.6-8.5)	< 0.001
Re-admissions	4.3 (3.1-5.9)	<0.0001		

Complications related to the ileostomy. Of all 510 patients, 147 were discharged with a diverting ileostomy. All ileostomies were closed. The ileostomy was closed elsewhere in eight patients, and four of them were also followed up in another hospital. Therefore, we lack data on possible ileostomy-related complications in these patients. Both complications related to ileostomy itself (42.2%) and complications related to ileostomy closure (29.3%) were common (Table 21).

Table 21. *Complications related to the diverting ileostomy after discharge.*

Overall, before ileostomy closure (n=143)	
Yes	62 (42.2%)
No	81 (55.1%)
Complication	
Skin problems	17 (11.6%)
Difficulties with stoma products	26 (17.7%)
Dehydration	11 (7.5%)
Subcutaneous abscess	3 (2.0%)
Other	5 (3.5%)
Complication after ileostomy closure (n=139)	35 (29.3%)
Ileus	21 (14.3%)
Wound infection	6 (4.1%)
Anastomotic leak	3 (2.0%)
Dehydration	2 (1.4%)
Other	3 (2.0%)
Median length of stay after ileostomy closure, days	7 (3-39)
Median time to ileostomy closure, days	109 (23-391)
Clavien-Dindo Classification	
Grades 1 and 2	30 (85.7%)
Grade 3a	1 (2.9%)
Grade 3b	4 (11.4%)
Grade 4	0

Late postoperative complications. There was no difference between the groups regarding the late postoperative complications of fistulas, pouchitis, and pouch failure (Table 22).

Table 22. *Comparison of late complications between the stoma and no-stoma groups.*

Late complications	Stoma group (n=119)	No-stoma group (n=391)	P-value	*Univariate analysis* OR (95% CI)	P-value
Pouch-related fistulas	5 (4.3%)	31 (8.0%)	0.18	1.0 (0.6-1.6)	0.967
Pouchitis	51 (44.3%)	189 (48.8%)	0.40	0.8 (0.6-1.0)	0.041
Pouch failure	2 (1.7%)	11 (2.8%)	0.74	0.4 (0.1-1.0)	0.052

5.3 POUCH FAILURE (II,III)

Median follow-up time was 6.7 years (range 0.05-12.6). In 510 patients, the overall ileal pouch survival was 97.5%. Thirteen patients (2.5%) underwent pouch removal during the follow-up. Of these, 2 patients (1.7%) were in the stoma group and 11 patients (2.8%) in the no-stoma group (P = 0.74). All ileostomies were closed later. Therefore, there were no pouch failures due to a permanent ileostomy. Nine of the 13 pouch removals were analysed in Study II. Pouch failure was more frequent in the low-dose steroid group than in the no-corticosteroid group (7 patients vs. none, P = 0.015). The difference was not significant in the high-dose steroid group compared with the no-corticosteroid group (2 patients, P = 0.141), despite the higher anastomotic leakage rate. Patients treated with anti-TNF agents had no pouch failures.

5.4 FMT AND CHRONIC POUCHITIS (IV)

We assessed for eligibility 135 patients, of whom 86 met an exclusion criterion and 23 declined to participate. Thus, 26 patients were enrolled in the study and randomized in a 1:1 ratio to either donor FMT or autologous transplant. The groups were similar in baseline characteristics (Table 23).

Table 23. *Baseline characteristics of patients.*

	FMT (n=13)	***Placebo (n=13)***	***P-value***
Male gender	7 (53.8%)	8 (61.5%)	0.691
Mean age, years±SD	42.7±10.2	45.5±11.7	0.614
Median years from IPAA surgery	9.8 (1.6-21.9)	8.3 (3.0-26.6)	0.918
Antibiotic use at time of study enrolment			0.431
Continuous use	5	7	
Frequent use	8	6	
Probiotics	5	6	0.691

The relapse-free survival time was similar between the groups (P = 0.190, HR 1.90, 95% CI 0.73-4.98). During the 52-week follow-up nine patients relapsed in the FMT group and 8 patients in the placebo group (Log rank P = 0.183, Figure 6). Interestingly, five patients relapsed even before the second FMT; all five were in the FMT group, and two of them used continuous antibiotics before the trial. In the subgroup analysis of all patients who used antibiotics continuously before the trial, Cox regression analysis showed increased hazard for relapse in the FMT group (P = 0.021, HR 13.08, 95% CI 1.47-116.60). During the follow-up quality of life improved in the FMT group (P = 0.036). We found no significant difference in any other variable regarding the follow-up data: cPDAI, PDAI, subjective improvement, and faecal calprotectin.

The FMT was well-tolerated, and patients reported no major adverse effects. Within one week of FMT, one patient had fever, one had abdominal pain, and one had faecal urgency. In the placebo group, one patient had fever.

Table 24. *Cox regression analysis for relapse-free survival time comparing FMT and placebo groups.*

Relapse-free survival time (weeks)	*FMT (n=13)*	*Placebo (n=13)*	*HR (95% CI)*	*P-value*
All patients	10.7 (0.9-53.0)	42.0 (8.0-53.0)	1.90 (0.73-4.98)	0.190
Patients with continuous use of antibiotics	9.9 (0.9-24.7)	42.0 (8.0-53.0)	13.08 (1.47-116.60)	0.021
Patients with frequent use of antibiotics	39.1 (1.9-53.0)	40.0 (19.1-53.0)	1.246 (0.28-5.59)	0.774

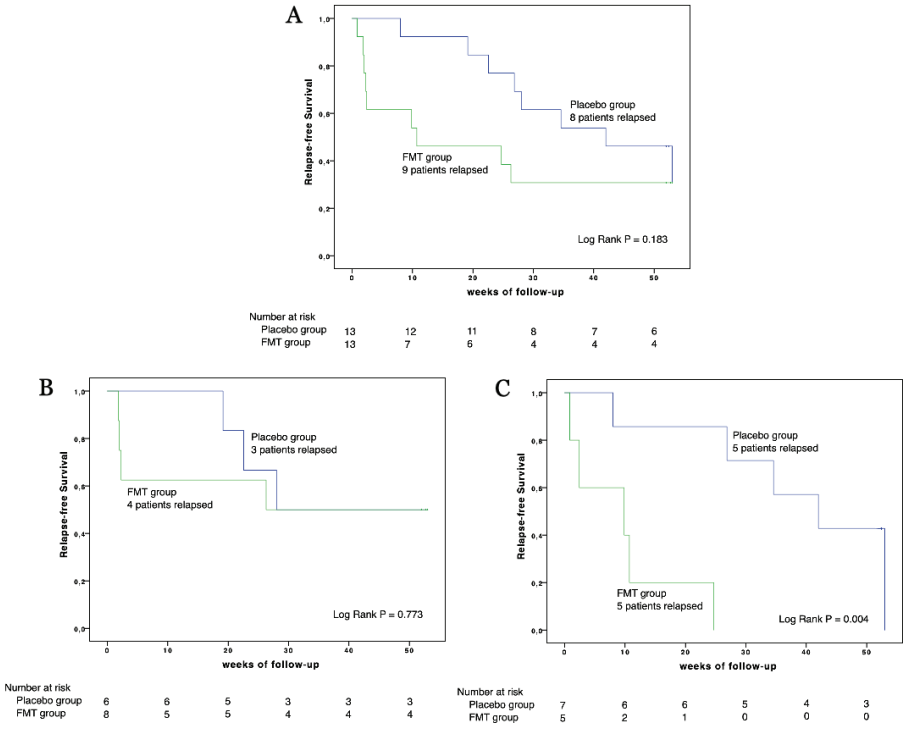

Figure 7 Kaplan-Mayer curves for relapse-free survival: A) in all patients, B) in patients using continuous antibiotics for chronic pouchitis before the trial, and C) in patients with frequent use of antibiotics for chronic pouchitis before the trial.

6 DISCUSSION

6.1 ULCERATIVE COLITIS-ASSOCIATED COLORECTAL CANCER (I)

Despite new treatment modalities, such as biologics, and the development of endoscopic equipment, the incidence of UC-associated CRC has not declined during the last three decades in our patient cohort. Still, approximately 6.5% of the UC patients undergoing surgery has CRC in the surgical specimen. The meta-analysis of Castaño-Milla et al. (2014) showed a decreasing incidence of UC-associated CRC over the last six decades. It may be that the need for surgery for other indications has decreased even more in Southern Finland, leading to the same proportion of CRCs for the first and second halves of the study period. Kolehmainen et al. (2019) found decreasing colectomy rates among UC patients in Southern Finland when the rising prevalence of UC was taken into account. During 2005-2007 the colectomy rate was 8.6 per 1000 person-years, and during 2014-2016 the colectomy rate was 5.1 per 1000 person-years. In their study, the proportions of indications for colectomy remained constant. Thus, it seems that the incidence of UC-associated CRC is decreasing also in Finland.

The main finding in our study was that one-third of the CRCs were not identified before surgery. In most of these patients, the indication for surgery was dysplasia without any endoscopic suspicion of cancer. Moreover, almost half of the patients with CRC had synchronous dysplasia or even another CRC. Our results indicate that endoscopic detection of dysplastic lesions in UC patients is challenging. In standard definition colonoscopy with random biopsies, the detection of dysplasia is very poor (van den Broek et al. 2014). ECCO Guidelines recommend the use of more advanced techniques: high-definition endoscopes and dye-based chromoendoscopy (Magro et al. 2017). According to a meta-analysis, dye-based chromoendoscopy seems to be the most efficient in detecting dysplasia (Bessissow et al. 2018). In our endoscopy unit, the use of chromoendoscopy is slowly taking a foothold, but most surveillance endoscopies are still standard colonoscopies. Time will tell whether chromoendoscopies really improve the detection of dysplastic lesions. Recently, there have been suggestions for endoscopic management of dysplasia, even high-grade dysplasia, if lesions are polypoid. However, the recognition of dysplasia, and, more importantly, the recognition of cancer are far from optimal, which makes us wonder whether endoscopic treatment of dysplastic lesions leads to more advanced cancers. Even one patient is too much.

The majority of the patients in our study were under routine surveillance. At Helsinki University Hospital, the surveillance protocol recommended in the ECCO Guidelines is followed, and the first surveillance colonoscopy is

scheduled 8 years after the UC diagnosis. The exception is patients with PSC, who are monitored annually irrespective of disease duration. Another important finding in our study was that 12.7% of CRCs were diagnosed within the first 8 years. This is not a new finding. Lutgens et al. (2008) reported that 20% of IBD-related CRCs developed within the first 8 years after IBD diagnosis. In a study from Denmark, the diagnosis of CRC was made in 41% of UC patients and in 58% of CD patients within one year of IBD diagnosis (Ording et al. 2013). Additional risk factors for CRC, i.e. active inflammation or positive family history, are incorporated in the surveillance protocol, but only after the first 8-year colonoscopy. This raises the question of whether the first surveillance colonoscopy should be scheduled earlier.

The overall 5-year survival in our study was 78.6%, which compares well with previous studies reporting overall 5-year survival of UC-associated CRC (Aarnio et al. 1998, Jensen et al. 2006, Delaunoit et al. 2006, Watanabe et al. 2011, Ording et al. 2013, Leowaldi et al. 2015). Few studies have reported CRC-specific survival rates. Debate is ongoing whether the prognosis of UC-associated CRC is similar or worse than that of sporadic CRC. A meta-analysis reported a poorer overall survival in UC-associated CRC than in sporadic CRC (Ou et al. 2015). Recently, in a large registry-based retrospective study from the United Kingdom, Arhi et al. (2020) concluded that patients with UC are more often diagnosed at an earlier stage but have a worse survival with stage III and stage IV cancer than patients with sporadic CRC. In Finland, the overall 5-year survival in all CRC patients is 66.2% according to the Finnish Cancer Registry; stage-specific survival data are not yet provided (cancerregistry.fi/statistics/cancer-statistics/). The comparison with our results is a bit unfair, though, because our study included only patients who underwent surgery, excluding some of the stage IV cancers. Thus, the survival of patients who undergo surgery is probably better than the survival of all CRC patients. However, the majority of patients with stage IV CRC undergo palliative surgery due to severe symptoms, i.e. occlusion or haemorrhage.

6.2 POSTOPERATIVE COMPLICATIONS AFTER IPAA

6.2.1 PREOPERATIVE USE OF ANTI-TNF AGENTS AND CORTICOSTEROIDS (II)

There is insufficient evidence about whether or not biologics increase postoperative complications after PC-IPAA. Yang et al. (2012) found no significant association between preoperative infliximab therapy and postoperative complications in UC patients undergoing any kind of surgery in their meta-analysis. In 2015, Selvaggi et al. conducted another meta-analysis to primarily clarify the effect of preoperative infliximab on IPAA-related complications (Selvaggi et al. 2015). They reported an increased risk of early IPAA-related complications in patients using infliximab prior to surgery (HR

4.12, 95% CI 2.37–7.15, P = 0.0001). However, when considering only papers reporting a cut-off value of 12 weeks between the last infliximab administration and surgery, the difference was not significant. Because of the uncertainty, the current recommendation is to avoid a single-stage proctocolectomy in anti-TNF-treated patients. Since these meta-analyses were published, two large retrospective studies have reported conflicting results (Zittan et al. 2016, Kulaylat et al. 2017). In our study, the preoperative use of anti-TNF agents within 12 weeks prior to PC-IPAA did not have an effect on postoperative complications. It is important to note that a single-stage proctocolectomy was not avoided in anti-TNF-treated patients in our unit if the patient was otherwise suitable. However, we had a relatively small group size (33 vs. 412 patients).

In previous studies, preoperative high-dose corticosteroids were associated with early postoperative complications after PC-IPAA, most importantly, pouch-related septic complications (Aberra et al. 2003, Lim et al. 2007, Ferrante et al. 2009, Utchino et al. 2010). Pelvic sepsis includes anastomotic leak, pelvic abscess, and pouch-related fistulas. What is not clear from the literature is the effect of preoperative corticosteroids on pouch failure rate. Previously, septic complications of the pouch have been shown to lead to poorer pouch function and quality of life (Kiely et al. 2012). Moreover, pelvic sepsis is a risk factor for later pouch failure. In the study of Helavirta et al. (2020), the most common reason for pouch failure was septic events, followed by pouchitis and functional problems. Sagap et al. (2006) found in their study that patients who used corticosteroids preoperatively had more anastomotic leaks, but unexpectedly, a lower pouch failure rate than patients without corticosteroids. In our study, only high-dose corticosteroids, but not low-dose corticosteroids or anti-TNF agents, were associated with anastomotic leak. On the other hand, pouch failures were more frequent in the low-dose corticosteroid group. There were also more pouch failures in the high-dose group than in the no-corticosteroid group, but the difference was not significant (2 vs. 0, P = 0.141), which could be expained by the relatively small group size and the short follow-up. Nevertheless, it seems that high-dose corticosteroids increase the risk of pouch-related septic complications and later pouch failure. However, the risk is small in highly specialized centres. In our patient cohort, the pouch failure rate was low even in the corticosteroid groups (4.4% and 2.1%), probably due to the centralization of the surgery.

Biologics are often combined with other immunosuppressive medication because of the risk of antibody development. We did not find any additive effect on anastomotic leakage rate when combining steroids and anti-TNF agents. Moreover, 6-mercaptopurine, azathiorine, or methotrexate was not associated with anastomotic leak. This is in line with previous studies (Mahadevan et al. 2002, Afzali et al. 2006).

6.2.2 MORBIDITY RELATED TO A DIVERTING ILEOSTOMY (III)

Debate is ongoing about whether or not a diverting ileostomy protects against pouch-related complications. The benefits of an ileostomy should be weighed against the morbidity related to a diverting ileostomy. As discussed above, anastomotic leakage increases the risk of poor pouch function and subsequent pouch failure. The only RCT comparing patients undergoing IPAA with or without a diverting ileostomy found no increased risk for anastomotic and septic complications by omitting the ileostomy (Grobler et al. 1992). A meta-analysis showed that, although anastomotic leakage was more common when a stoma was omitted, pelvic sepsis was not different between patients undergoing PC-IPAA with or without a diverting ileostomy (Weston-Petrides et al. 2014). Likely, anastomotic leaks are more often asymptomatic when a patient has a diverting ileostomy. This is supported by the fact that anastomotic strictures and pouch failures were more common in patients with a diverting ileostomy. This is consistent with our results; symptomatic anastomotic leaks were more common in patients without a diverting ileostomy, but there was no difference in the rate of pouch-related fistulas, strictures, or pouch failure. Further, a systematic review reported that 1.9% of patients developed pouch-related septic complications after closure of a diverting ileostomy, indicating subclinical pouch-related complications (Mennigen et al. 2014). In contrary, a recent registry-based Danish study of 1991 patients found a reduced risk of pouch failure in patients with primary diverting ileostomy (Mark-Christensen et al. 2018). A nationwide, randomized trial is ongoing in France comparing 6- and 12-month morbidity and pouch function between IPAA patients with or without a diverting ileostomy (IDEAL Trial, Beyer-Berjot et al. 2019).

In our study, relaparotomy rate was not elevated in the no-stoma group compared with the stoma group despite the higher rate of anastomotic leaks. In some studies comparing one- and two-stage PC-IPAA, however, there were more re-operations in patients without a diverting ileostomy (Williamson et al. 1997, Mennigen et al. 2011, Sahami et al. 2016). In the high-dose corticosteroid group, more relaparotomies were performed than in the no-corticosteroid group in our study, mainly due to anastomotic leak.

A diverting ileostomy itself is associated with considerable morbidity. In our patient cohort, a diverting ileostomy increased the incidence of early postoperative complications, primarily the incidence of dehydration and stoma-related bowel obstruction, which were also the most common causes for re-admissions in patients with an ileostomy. More than half of the patients in the stoma group had one or more early postoperative complications and their length of hospital stay was longer. Furthermore, 42.2% of the patients discharged with an ileostomy had stoma-related problems, and almost one-third of the patients had postoperative complications after ileostomy closure. Recent retrospective studies from Sweden and Denmark reported similar results (Park et al. 2018, Ellebæk 2020). In their hospitals, however, an ileal diversion is standard, which is also recommended by ECCO Guidelines (Magro

et al. 2017). In our centre, a diverting ileostomy is constructed only in selected patients.

We prefer the hand-sewn anastomosis due to the advantage of removing all diseased mucosa. The main indication for ileal diversion in our hospital was tension of the pouch-anal anastomosis or suboptimal suturing visibility of the anastomosis during surgery. In addition, an ileal diversion was performed on patients with a higher risk of lethal complications secondary to anastomotic leak, on patients with perianal fistula, and on patients with UC-associated CRC. Because of the selection, patients were probably more prone to complications in the stoma group. Our results suggest, however, that a diverting ileostomy itself accounts for the majority of the complications. We therefore prefer an one-stage PC-IPAA in low-risk patients. The advantage of an ileal diversion is a lower rate of clinical anastomotic leaks, and in high-risk patients a diverting ileostomy should be constructed because of the greater risk of severe complications.

6.3 FMT AND CHRONIC POUCHITIS (IV)

Chronic pouchitis is sometimes hard to manage, especially a chronic, antibiotic-refractory disease. Pouchitis is associated with poorer pouch function, which in turn impaires the patient's quality of life (Helavirta et al. 2018). Currently, there is no established treatment for chronic pouchitis with good long-term results, and chronic pouchitis is one of the causes of pouch failure. The pouch microbiota is differs between patients with pouchitis and patients with a normal pouch (Segal et al. 2018). The dysbiotic pouch microbiota is characterized by lowered bacterial diversity. In recent years, FMT for the treatment of chronic pouchitis has received increased attention, and several small studies have reported both positive and negative results. A systematic review noted that 31.8% of patients with chronic pouchitis achieved clinical remission (Cold et al. 2020). However, marked heterogeneity exists between studies and most of them are of low quality.

We conducted the first completed randomized, placebo-controlled, double-blinded trial of FMT for the treatment of chronic pouchitis. Unfortunately, the preliminary results suggest that FMT is not effective for chronic pouchitis with the treatment protocol used in our study. Patients treated with actual FMT relapsed even earlier than patients treated with placebo FMT. Inline with previous FMT studies, FMT was not associated with major adverse effects within the 52-week follow-up.

Herfarth et al. started a randomized, controlled, double-blinded trial consisting of a single FMT to the pouch via sigmoideoscopy followed by oral FMT capsules for 14 days (Herfarth et al. 2019). They stopped the trial after enrollment of six patients due to a low clinical efficacy of FMT; all six patients relapsed within three weeks after FMT infusion (4 patients in FMT group, 2 patients in the placebo group). All six patients were offered open label FMT

followed by daily oral FMT capsules for 14 days. One patient out of five open label participants achieved clinical remission and donor's microbiota was seemed to colonize only in this patient. The best engraftment of the donor's microbiota so far was achieved in a recent pilot study by Kousgaard et al. (Kousgaard et al. 2020). They treated patients with FMT enemas for 14 consecutive days. Microbiota engraftment was achieved in six out of nine patients. In a 6-month follow-up, three patients remained in remission. Stallmach et al. (2016) used multiple (1 to 7) FMT infusions into the jejunum via esophagogastroduodenoscopy, and four out of five patients achieve clinical remission with good microbiota encraftment. Three patients sustained the response for at least 3 months. The results were poorer in those case reports using a single FMT (Landy et al. 2015, Nishida et al. 2019).

Thus far, it is uncertain why some patients seem to benefit from FMT, while others do not. Based on the above-mentioned studies, donor microbiota engraftment is more likely achieved with multiple, frequent FMTs. In our study protocol, we treated patients with two FMTs with 4-week interval. However, five patients in the FMT group, but none in the placebo group, relapsed before the second FMT. For all patients, the second FMT was performed regardless of whether they relapsed or not between the first and second FMT. Perhaps, new microbes from the donor activated an inflammatory response in these patients. Unfortunately, the microbiota analysis was significantly delayed because of the COVID-19 pandemic and we are still waiting for the results. Therefore, we do not know yet how the donor's microbiota engraftment succeeded in our study. In addition, we did not use bowel preparation before FMT, which might have had an effect on the microbiota engraftment.

Another important factor in FMT studies is the donor. We used a single donor whose faecal material has been used successfully in the treatment of recurrent *Clostridioides difficile* infection. Moayyedi et al. (2015) conducted a study on FMT for active UC. Nine patients achieved remission, seven of whom received faecal material from a single donor, a so-called super donor. FMT from a pre-selected donor with specific gut microbiota composition could result in a better remission rate also in the treatment of chronic pouchitis. However, it is not possible to determine prospectively optimal donors for pouchitis, or any other indication, with the current knowledge.

Several studies used upper administration of FMT either through endoscopy or oral capsules (Landy et al. 2015, Stallmach et al. 2016, Herfarth et al. 2019). Stallmach et al. (2016) reported the most promising results to date, suggesting that future studies should also investigate whether a certain route of administration is more favourable than others.

Kousgaard et al. (2020) assessed the diet of the nine patients in their study. They found that patients in remission consumed more yoghurt than relapsed patients. In addition, reduced consumption of fruits has been associated with the development of acute pouchitis (Godny et al. 2019). Although the evidence

is low, these studies indicate that dietary habits may have a role in the clinical effect of FMT.

6.4 STUDY STRENGTHS AND LIMITATIONS

This dissertation was carried out at Helsinki University Hospital, which serves as a tertiary referral centre for UC patients in Southern Finland. Operative treatment of these patients is performed at our hospital. Studies I, II, and III were population-based, which we consider to be a strength. Moreover, Study I provides data extending over three decades. Study IV was a randomized, parallel, placebo-controlled trial. In addition, it was double-blinded without incidence of ineffective blinding. No patient was lost to follow-up.

The main limitation of Studies I, II, and III was retrospective design. During the long study period in Study I multiple cancer staging systems were used, which might have caused stage migration, but most probably downwards due to underdiagnosed lymph nodes and distant metastases. In addition, Study I lacks a control group of sporadic cancers. In Study II, group sizes, especially the anti-TNF group, were relatively small. Moreover, patients using anti-TNF agents or corticosteroids had presumably more severe UC, leading to a selection bias. The power calculations of RCT were done according to those few studies available when we were planning the trial. More studies have since been published according to which the remission rate might actually be poorer than expected, weakening the power of statistical analysis.

6.5 FUTURE PROSPECTS

Our next task is to analyse and report the results of the microbial analysis concerning the randomized, placebo-controlled trial. These results will show how well donor microbiota engraftment and long-term alterations in pouch microbiota were achieved. It will be interesting to see whether specific bacterial species were associated with remission and perhaps identify a subgroup of patients benefitting from FMT.

Quality of life and functional outcomes of the pouch are essential in evaluating the long-term results of PC-IPAA. Patients undergoing the procedure are young, making the quality of life even more important. Few studies have reported the effect of the operation on urogenital functions. A prospective single-centre study evaluating pouch functional outcomes is ongoing, in which our aim is to specifically assess whether PC-IPAA impairs urogenital functions, and further, report pouch function after one year of follow-up.

7 CONCLUSIONS

The following conclusions can be drawn from the current series of studies:

I
Among patients undergoing surgery, the incidence of UC-associated CRC has remained constant over three decades in Southern Finland. One-third of the CRCs were not diagnosed preoperatively, and synchronous dysplasia or even cancer were common. These findings are alarming and should be considered before endoscopic management of UC-associated dysplasia. A substantial proportion of CRCs were diagnosed before the first surveillance colonoscopy. The overall 5-year survival was 78.6%, and 5-year CRC-specific survival was 81.5%.

II
Preoperative anti-TNF therapy seems not to increase the risk of postoperative complications. Anastomotic leakage was more common in patients using prednisolone 20 mg or more (or equivalent) prior to surgery. Preoperative corticosteroids may also increase the risk of pouch failure.

III
A covering ileostomy is associated with considerable morbidity, a higher rate of re-admissions and a longer hospital stay. In high-volume centres, a single-stage PC-IPAA is safe in low-risk patients. Moreover, an ileostomy does not seem to prevent pouch failure. Therefore, a diverting ileostomy should be constructed only for patients at increased risk for severe complications such as anastomotic leakage.

IV
The FMT treatment regime used in our study was not effective in treating chronic pouchitis. Further microbial analyses are essential to select optimal study protocols and donors for future studies. The safety profile of FMT was good, with no major adverse effects.

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