Linköping University Medical Dissertation No. 1883

Reconstruction after Colectomy for Inflammatory Bowel Disease

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LINKÖPING UNIVERSITY

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Till Ida!

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I. Risto A, Hallbook O, Andersson P, Sjodahl R, Myrelid P. Long-term Follow-up, Patient Satisfaction, and Quality of Life for Patients With Kock's Continent Ileostomy. Dis Colon Rectum. 2021;64(4):420-8.

II. Risto A, Andersson RE, Landerholm K, Bengtsson J, Block M, Myrelid P. Reoperations and Long-term Survival of Kock's Continent Ileostomy in Inflammatory Bowel Disease Patients: A Population Based National Cohort Study from Sweden. Dis Colon Rectum. 2022.

III. Risto A, Nordenvall C, Deputy M, Hermanson M, Lindforss U, Block M, et al. Colectomy reconstruction for ulcerative colitis in Sweden and England: a multicenter prospective comparison between ileorectal anastomosis and ileal pouch-anal anastomosis after colectomy in patients with ulcerative colitis. (CRUISE-study). BMC Surgery. 2023;23.

IV. Risto A, Myrelid P, Söderling J, Olén O, Nordenvall C. Reconstructions after colectomy for ulcerative colitis based on pelvic pouch volumes at the colectomy hospital, a Swedish national cohort study. *Manuscript, Submitted.*

ABSTRACT

After colectomy there are four options available. The least complicated and most common is to leave the end ileostomy and not go for any reconstructive surgery. Then there is the ileal pouch anal anastomosis (IPAA) in which the rectum is removed, but the anal canal and a small rectal "cuff" is preserved. The pouch is created from the distal ileum and anastomosed to the rectal cuff. In the ileorectal anastomosis (IRA) the rectum is spared, and the distal ileum is anastomosed to the top of the rectum. In the continent ileostomy (CI), also referred to as the Kock pouch, the fecal flow is let out through the abdominal wall, but a pouch and a nipple valve mechanism is created making the stoma continent which needs to be manually emptied.

This thesis aims to investigate function, quality of life, satisfaction, complications, and aspects associated with the chance of having reconstructive surgery after colectomy for inflammatory bowel disease (IBD), i.e. ulcerative colitis (UC) or Crohn's disease (CD).

The first two papers focus on the continent ileostomy, the most uncommon of the options after colectomy. In *Paper 1* all patients who have received a CI at our center were identified and medical charts were reviewed for complications and CI patency. Function and quality of life were evaluated with the 36-item short form survey (SF-36), short health scale (SHS) and a local CI specific questionnaire for function and satisfaction. In *Paper II,* the Swedish national patient register (NPR) was used to identify all patients with an IBD diagnosis who had received a CI and data on diagnosis, demographics, reoperations, and excisions were obtained from the register.

Paper III describes an ongoing prospective non-randomized, multi-center, open-label, controlled trial between IRA and IPAA in UC patients subjected to colectomy. The primary endpoint is satisfaction but Quality of Life (QoL), sexual function, bowel function and complications are also evaluated.

In *Paper IV,* we investigated if the chance of getting reconstructed after colectomy was dependent on the IPAA volumes at the colectomy hospital using data from the national patient register. The hospitals were arranged in to four categories based on the average annual number of IPAA procedures: (0, 1-3, 4-7, >7 procedures per year).

In *Paper I* we found that 59 % of CI patients needed repeat laparotomy after a median follow up of 24 years and nipple detachment was the most common cause of repeat laparotomy. Fifteen patients (18 %) had their CIs converted to end ileostomies and the most common cause for this was fistulas. Eighty-four per cent of CI patients reported satisfaction with their reconstruction. The national study in *Paper II* identified 727 IBD patients with CI and the median follow-up time was 27 years. During follow-up, 1484 reoperations were performed on 536 patients (74 %). Twenty-six per cent of the patients did not have any reoperations, 24 % had one reoperation, 20 % had two reoperations and the remaining 30 % had between three and 15 reoperations each. The CIs were identified to have been removed in 77 (11 %) patients. In *Paper III* we have so far

included 47 patients in the intervention arms out of which 35 (74 %) have chosen IRA and 12 patients (26 %) have chosen IPAA. Another 44 (40 % of the whole group) patients have so far received an IPAA but were deemed non-eligible for both IRA and IPAA and were hence not eligible for the intervention arms. So far 18 patients (17 % of the whole group) have chosen an ileostomy. In *Paper IV* we first identified 4112 UC patients subjected to colectomy between 1997 and 2020. Out of these 4112 patients, 1932 (47 %) went through some kind of reconstruction, 964 (50 %) IRA, 927 (48 %) IPAA and 41 (2 %) CI. The proportion having restorative surgery was larger for patients subjected to colectomy at a high IPAA volume center (62 % vs 38 %) and the chance of getting an IPAA increased with each IPAA volume category (Hazard ratios (HR) were: 1; 1.49 95 % CI (1.25-1.78) ; 1.79 95 % CI (1.49-2.15) and 2.11 95 % CI (1.70-2.62) respectively)The IPAA volumes did not affect the chance of receiving an IRA or the risk of failure of reconstruction.

SVENSK SAMMANFATTNING

Inflammatorisk tarmsjukdom utgörs i princip av två olika sjukdomar, Ulcerös kolit och Crohns sjukdom. Ulcerös kolit drabbar drabbar tjocktarmen och ändtarmen. Den drabbar inte alltid hela tjocktarmen och utbreder sig från ändtarmen och uppåt. Ungefär 15 % av alla patienter med ulcerös kolit behöver operera bort tjocktarmen (kolektomeras). Detta beror antingen på ett akut sjukdomsskov som inte svarar på medicinsk behandling, kroniskt aktiv sjukdom trots medicinisk behandling, eller att det utvecklas cellförändringar eller cancer. Crohns sjukdom och kan drabba hela mag-tarmkanalen men kan i vissa fall drabba enbart tjocktarmen eller drabba tjocktarmen värst. Då kan kolektomi bli aktuellt även för patienter med Crohns sjukdom, men det är mycket minder vanligt än vid ulcerös kolit.

Det vanligaste efter kolektomi är att man inte gör någon ytterligare kirurgisk åtgärd och tarminnehållet töms då genom en tunntarmstomi till en påse på magen. Det finns dock tre olika alternativ till rekostruktiv kirurgi efter kolektomi. De alternativen är bäckenreservoar, ileorektal anastomos och kontinent ileostomi (en så kallad Kocks reservoar). När en bäckenreservoar konstrueras opereras först ändtarmen bort men analkanalen och de första en till två cm av ändtarmen sparas. Av sista biten på tunntarmen görs en reservoar vilken sedan kopplas, anastomoseras, till den lilla kvarvarande biten ändtarm. Ileorektal anastomos innebär att det sista tunntarmsavsnittet kopplas direkt till toppen på den bevarade ändtarmen uppe i bukhålan. Tillskillnad från vid bäckenreservoar görs ingen dissektion i bäckenet vid ileorektal anastomos. Båda dessa alternativ kräver att ändtarmens slutmuskel är välfungerande och att det inte finns några onaturliga gångar (fistlar) mellan ändtarmen och huden. En förutsättning för ileorektal anastomos är att ändtarmen kan behandlas tillräckligt inflammationsfri (vilket ofta är fallet) när övriga tjocktarmen är bortopererad. Vid en kontinent ileostomi tillverkas en reservoar och en backventil av sista biten av tunntarmen så stomin blir kontinent och måste tömmas aktivt med en plastkateter.

De första två studierna i avhandlingen handlar om kontinenta ileostomier. I det första delarbetet undersöktes förekomsten av komplikationer genom granskning av journalerna från alla patienter som fått en kontinent ileostomi konstruerad i Linköping mellan 1980 och 2016. Livskvalitet, funktion och nöjdhet undersökte därtill genom en enkätstudie. I delarbete II identifierades alla patienter med inflammatorisk tarmsjukdom som fått en kontinent ileostomi i Sverige genom sökning i svenska nationella patientregistret. Ur registret kunde vi sedan få information om kön, ålder vid kirurgi, diagnos, reoperationer och om den kontinenta ileostomin behövt tas bort och konverteras till en vanlig ileostomi. Delarbete III beskriver en pågående prospektiv jämförelse mellan ileorektal anastomos och bäckenreservoar hos patienter med ulcerös kolit som behövt kolektomeras. De patienter som bedöms lämpliga för båda de typerna av rekonstruktioner får standardiserad information om båda metoderna och får sedan välja om de vill genomgå någon rekonstruktiv kirurgi och i så fall med vilken av de två operations metoderna. Vi jämför sedan i första hand hur nöjda patienterna är med sitt val av operation men också tarmfunktion, sexuell funktion, livskvalitet och förekomst av komplikationer. I det

fjärde delarbetet utvärderade vi chansen att bli rekonstruerad efter kolektomi hos patienter med ulcerös kolit beroende på hur många bäckenreservoarer som årligen görs på det sjukhuset där kolektomin utförts. Vi utvärderar också betydelsen av bland annat ålder, kön, tidsperiod och tid från diagnos till kolektomi. Vi valde att klassificera centra baserat på antal utförda bäckenreservoarer eftersom det är den tekniskt mest avancerade operationen och alla sjukhus som kan erbjuda bäckenreservoar kan också erbjuda ileorektal anastomos men inte tvärt om. Även i denna studie samlades data in från det nationella patientregistret.

I det första delarbetet, med patienter som opererats med kontinent ileostomi i Lnköping, identifierade vi 85 patienter med en medianuppföljningstid på 24 år. Av dessa genomgick 67 (79 %) patienter totalt 237 reoperationer. Vissa reoperationer var bara mindre operationer i lokalbedövning runt stomin eller redan från början planerade operationer på så kallade avlastande loop-ileostomier, uppströms om den kontinenta ileostomin, men 50 (59 %) patienter genomgick större oplanerade reoperationer. De vanligaste orsakerna till reoperation var att reservoaren lossnat från bukväggen och/eller att nippeln som ska fungera som backventilen glidit tillbaka och förvunnit. Hos 15 (18 %) av patienterna hade man varit tvungen att ta bort den kontinenta ileostomin och åter anlägga en vanlig ileostomi och den vanligaste orsaken till detta var fistlar (oönskade gångar mellan reservoaren och huden). Åttiofyra procent av patienterna med kontinent ileostomi uppgav att de vara nöjda med sin rekonstruktion. I det andra delarbetet identifierade vi 727 patienter med en medianuppföljningstid på 27 år. Av dem hade 26 % klarat sig utan någon reoperation medan24 % hade genomgått en reoperation, 20 % två reoperationer och resterande 30 % mellan 3 och 15 reoperationer var. Sjuttiosju (11 %) patienter hade fått sin kontinenta ileostomi bortopererad. I den tredje studien har vi hittills inkluderat 47 patienter i behandlingsarmarna (d.v.s. de som bedömts tillgängliga för båda metoderna och fått kunnat välja själva). Av dem har 35 (74 %) valt ileorektal anastomos och tolv (26 %) valt bäckenreservoar. Därutöver har 44 patienter som inte bedömts lämpliga för båda metoderna fått bäckenreservoar och 18 patienter har valt att behålla sin ileostomi. I det fjärde delarbetet identifierades 4112 ulcerös kolit patienter som genomgått kolektomi. Av dem hade 1932 (47 %) genomgått rekonstruktion (964 (50 %) ileorektal anastomoser, 927 (48 %) bäckenreservoarer och 41 (2 %) kontinenta ileostomier). Chansen att få en bäckenreservoar, men inte en ileorektalanastomos, var större om man genomgått kolektomi på ett sjukhus som gör fler bäckenreservoarer eller om man var man.

Sammanfattningsvis är kontinent ileostomi en operation som är associerad med stort behov av reoperationer men som trots det renderar en hög andel nöjda patienter och patienterna är beredda att genomgå många reoperationer för att få behålla sin kontinenta ileostomi. Av patienter som bedöms lämpliga för både ileorektal anastomos och bäckenreservoar och får samma information väljer tre fjärdedelar ileorektal anastomos och en fjärdedel bäckenreservoar. Det finns för patienter med ulcerös kolit i Sverige en strukturell ojämlikhet i chansen att bli rekonstruerad som beror både på vilket sjukhus kolektomin utförts på och kön.

ABBREVIATIONS

5-ASA	5-aminosalicylic acid
A.D.	Anno Domin
ANOVA	Analysis of variance
ATZ	Anal transitional zone
BCIR	Barnett continent intestinal reservoir
BMI	Body mass index
CD	Crohn's Disease
CI	Continent ileostomy
CI*	Confidence interval *(only in tables)
CRC	Colorectal cancer
EQ-5D	EuroQol 5 dimensions
FAP	Familial adenomatous polyposis
FSFI	Female sexual function index
HGD	High grade dysplasia
HR	Hazard ratio
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IBD-U	Inflammatory bowel disease unclassified
IC	Indeterminate colitis
ICD	International classification of disease
IIEF	International index of erectile dysfunction
IL	Interleukin
IPAA	Ileal pouch anal anastomosis
IQR	Inter quartile range
IRA	Ileorectal anastomosis
IRR	Incidence rate ratio
JAK/STAT	Janus kinases/signal transducer activator of transcription proteins
LGD	Low grade dysplasia

NOMESCO	Nordic medico-statistical committee
NPR	National patient register
OR	Odds ratio
PSC	Primary sclerosing cholangitis
QoL	Quality of Life
RCT	Randomized controlled trial
SBO	Small bowel obstruction
SD	Standard deviation
SF-36	36-item short form survey
SWIBREG	Swedish inflammatory bowel disease register
TaTME	Trans anal total mesorectal excision
TIES	Transcutaneous implant evacuation system
TNFα	Tumor necrosis factor α
UC	Ulcerative colitis

INTRODUCTION

Inflammatory bowel disease

Inflammatory bowel disease (IBD) consists of ulcerative colitis (UC), Crohn's disease (CD) and cases of colitis that cannot be distinguished between UC and CD. These latter cases are denoted as inflammatory bowel disease – unclassified (IBD-U). This diagnosis is used if clinical and endoscopic investigations have not been able to distinguish between UC and CD. If the patient has been subjected to colectomy and the pathologist still, despite the entire colon specimen, cannot tell whether it is UC or CD, the condition is called indeterminate colitis (IC)[1]. This traditional division between UC and CD is challenged by recent genetic research, which suggest that CD should be divided into ileocolic and colonic CD[2]. In some definitions microscopic colitis is also included in the IBD concept but microscopic colitis is very rarely cause of colectomy and will not be further discussed here[3].

The prevalence of IBD is increasing and in 2017 there were 6.8 million cases of IBD worldwide and the age-standardized prevalence has increased from 79.5 to 84.3 per 100 000 people between 1990 and 2017[4]. The increase is reported from newly industrialized countries while the IBD prevalence in Europe and North America is stable or even decreasing[5,6].

The cause of IBD appears to be multi factorial, with genetic predisposition, dysregulation of immune responses, environmental changes, and abnormalities in gut microbiota. Despite knowledge of several factors the complete pathogenesis of IBD remains unknown[7-9].

The first descriptions of non-contagious diarrhea in literature dates back to the first centuries A.D. in writings from (the aptly named) Soranus of Ephesus (ca 117 A.D.) and Aretaeus of Cappadocia (approximately 300 A.D.)[10]. A more detailed description of what might have been UC was published by Baillie, M. in 1833 [11]. The term UC first appears in literature in 1859 in a case report by Wilks, M. (Later analysis of his description strongly suggest it was a case of CD)[12]. The current concept of IBD and the increasing distinction between UC and CD emerged during the first half of the 20th century with reports by Dalziel, T.K. and Crohn B.B among others[13-16].

Ulcerative colitis

Ulcerative colitis is a chronic remitting and relapsing disorder of the large intestine. The inflammation in UC is usually limited to the colonic mucosa except in very severe, and rare, cases when the inflammation spread to deeper layers of the large intestine, a clinical entity referred to as toxic megacolon[17-19]. The inflammation is continuously distributed in the colon in a distal to proximal fashion. UC patients do occasionally have inflammation of the distal ileum, referred to as back-wash ileitis, if this is actually due to back wash is, however, debated.[20]

UC is more prevalent than CD and most prevalent in northern Europe and in the US. The prevalence in the western hemisphere ranges between 156 to 505 cases per 100 000 people and the incidence between nine and 20 cases per 100 000 person years. There is not much difference in incidence and prevalence between the sexes, although there are slightly higher figures among men[21-23]. The incidence of UC is increasing in more recently industrialized regions, indicating that environmental factors play a role in the onset of UC[24].

UC is classified with regard to the extent of inflammation and severity of flare according to the Montreal classification (Table 1).[1] The severity axis in the Montreal classification is almost identical to the still widely used Truelove and Witts severity index from 1955[25]. However, neither the extent nor the severity of the flairs are constant over the course of the disease[26]. What is, on the other hand, remarkably constant is that half of the UC patients will be in remission at any given time and over the course of a five-year period 25 % will be in continuous remission, 18 % will have continuous active disease and 57 % will alter between periods of active disease and remission[27].

Montreal Classification for UC

Extent		**Anatomy**
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends to splenic flexure
Severity		Symptoms and signs
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity.
S3	Severe UC	Passage of at least six bloody stools per day, heart rate of at least 90 beats per minuit, temperature of at least 37.5ºC, haemoglobin of less than 10.5 g/100ml, and ESR of at least 30 mm/h

Table1.

The cornerstone of UC treatment is pharmacological. The drugs used in modern treatment of UC are 5-aminosalicylic acid (5-ASA), sulfazalasin, and steroids which can be

used in both systemic as well as topical forms, and systemic therapy with immunomodulators such as the thiopurines azathioprine and 6-merkaptopurin, and biologicals[28]. The term biologicals refer to synthetic antibodies that target and deactivates, for instance, inflammatory mediator proteins. The first introduced, and still most used, biological agent in UC treatment is the monoclonal anti-TNFα antibody infliximab. There are also two more biologicals used in UC targeting TNFα, adalimumab and golimumab. The integrin-inhibitor vedolizumab and the IL12/IL23 inhibitor ustekinumab are also used to treat UC[29-31]. The latest (commercially available) contributions to the pharmaceutical arsenal against UC are the non-receptor thyrosine-kinas JAK/STAT inhibitors tofacitinib and upadacitinib[32,33]. These are not antibodies thus technically not biologicals. From available comparisons it appears that upadacitinib is the more effective of the two[34].

The recommended medical treatment depends on the extension and severity of the inflammation (Table1) and previous response to treatment. Proctitis is generally treated with topical 5-ASA, in cases with more severe or therapy resistant inflammation topical 5-ASA is combined with systemic 5-ASA. Occasionally therapy resistant proctitis can require the full range of medical treatment, including systemic steroids, immunosuppressants and biologicals. Topical 5-ASA alone can be sufficient in left sided UC, but it is more likely that systemic treatment will be needed. For pancolitis, i.e. UC extending beyond the splenic flexure of the colon, 5-ASA enemas should be combined with at least systemic 5-ASA but more advanced treatment is often needed[28,35,36].

For severe UC flares, intravenous steroids are recommended as initial treatment and if the patient fail to respond to intravenous steroids, infliximab is often used to try to induce remission as a rescue therapy[28]. In contrast to the slower acting vedolizumab and ustekinumab, tofacitinib and upadacitinib has been shown to induce remission within a few days after administration[33,37]. This indicates that it may contribute to the treatment arsenal in severe UC flares.

Medical treatment for maintenance is recommended in periods of remission. As with active disease the strategy for maintenance treatment depends on extension and severity of the disease while active and what worked to induce remission[28]. All the above-mentioned drugs, apart from steroids, are reasonable to use for long-term maintenance treatment for UC. The side-effect pattern of long-term steroid use makes them a non-valid option since there are other ways to handle UC that will not stay in remission with less than steroid treatment[38]. Also, steroids have been shown less effective as maintenance treatment for UC than as induction treatment[39,40].

Crohn's Disease

CD is a transmural inflammatory bowel disease that can affect every part of the gastrointestinal tract[35,41]. The incidence of CD is between 3-20 per 100000 person-years with the higher figures in the high-income regions[42]. CD is classified according to the Montreal Classification based on age at diagnosis, anatomic location and behavior of the disease[1] (Table 2). In the early descriptions CD was referred to as regional ileitis or ileocolitis. Although there were descriptions of Crohn's like involvement of the colon from the same time and indeed the same research group who got to name CD the concept of isolated colonic CD was not widely accepted until the publications by Wells in 1952 and Lockhart-Mummery in 1960[14,16,43,44]. About 28 % of the CD patients have colonic CD at the time of diagnosis. However, both location and behavior often varies over time in the same patient[45].

Montreal Classification for CD		
Age at diagnosis	A1	Below 16 years
	A2	17-40 years
	A3	Above 40 years
Location (anatomic)	L1	Ileal
	L2	Colonic
	L3	Ileocolic
	L4	Isolated upper disease
Behavior (of disease)	B1	Non-stricturing, non-penetrating
	B2	Structuring
	B3	Penetrating
	p	Perianal disease modifier

Table 2.

Like in UC the mainstay of CD treatment is pharmacological, and the treatment arsenal is in part similar to that of UC[46]. However, 5-ASA is not effective against CD and instead azathioprine, 6-merkaptopurin and methotrexate are more widely used in CD. The same range of biologicals are used in CD as in UC. The JAK/STAT inhibitors have not been proven as effect in CD as in UC patients and only upadacitinib is in use for CD[47]

Cancer risk

The increased risk for colorectal cancer (CRC) among IBD patients is established since 1925[48]. Patients with UC have approximately a six times increased risk of developing CRC compared to the background population and develop their CRC at a younger age[49,50].The extent of colitis at diagnosis is strongly correlated to the CRC risk and the patients with only ulcerative proctitis do not have a significantly higher CRC risk than the general population[50]. A cancer incidence of 1.29 cases per 1000 person years compared to 0.82 cases per 1000 person years in a reference population was reported, in a recent large cohort study from Sweden and Denmark. This indicates that the CRC risk in UC may be a little reduced over time, possibly due to modern treatment[51]. The same

group also found and increased risk for CRC among CD patients, especially for patients with CD colitis[52].

Dysplasia in colorectal specimens is divided into three morphologic categories, i.e. indefinite, low-grade dysplasia (LGD), or high-grade dysplasia (HGD)[53,54]. Among UC patients with flat HGD, CRC is found in 42-67 % of colectomy specimens[55,56] and subsequent development of CRC is reported in between 25-32 % of cases who remain on surveillance[56,57]. For UC patients with flat LGD, CRC is reported to occur in 19-27 % of colectomy specimens. These figures are, however, from small studies (n=10, 11 and 16, respectively0)[56-58]. There are conflicting reports on the progression from flat LGD to HGD or CRC there are conflicting reports ranging from no difference in the CRC/HGD development in UC patients with or without LGD to an OR of 9.0 between the two (somewhat carelessly expressed as nine fold increased risk in the reference)[59-61]

Primary sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a condition with multifocal strictures of the bile ducts due to inflammation and fibrosis. PSC is tightly related to IBD and 50-80 % of PSC patients are reported to have concomitant IBD[62] and 2-8 % of IBD patients are correspondingly reported to have PSC[63-65]. PSC often progress towards end-stage liver disease with liver transplantation as the only potential cure[65]. There is a well-established relation between PSC and the development of cholangiocarcinoma and pancreatic carcinoma as well as CRC. Cholangiocarcinoma is reported in around 10-13% (160 times more common than in the general population) of PSC patients and the risk of developing pancreatic carcinoma is 14 times that of the general population [66,67]. In the Swedish PSC-UC population the cumulative risk of developing CRC is reported to be 9 %, 31 % and 50 % at 5, 10 and 25 years of disease duration, respectively, as compared to 2 %, 5 % and 10 % for patients with UC without PSC[68].

Colectomy

In the case of acute severe UC, colectomy is indicated if the patient fails to respond to emergency medical treatment. The effect of the first line of treatment, i.e., corticosteroids should be evaluated around the third day of treatment and second line, i.e. infliximab, no later than seven days after admission[69,70]. Further delayed colectomy is associated with increased rates of surgical complications[71,72]. This is also a reason that third line medical treatment is generally not recommended in acute severe UC[69]. Patients who have complications such as severe bleeding, toxic megacolon, or perforation at admission or during evaluation of the medical treatment are advised to undergo prompt surgery[70]. In the emergency or sub-emergency setting the procedure should always be a subtotal colectomy with an end ileostomy[73]. That is when the colon is removed but the rectum and most distal part of the sigmoid colon is spared.

Elective colectomy for UC is advised when it is not possible to obtain or sustain remission despite optimal medical treatment or when the patient remain steroid dependent to remain in remission[69]. Also in this setting subtotal colectomy is the most common choice also in this setting, but some argue the advantages of going for a proctocolectomy and possibly even reconstruction in the same operation[74,75].

HGD or manifest CRC is indication for proctocolectomy with oncologic lymphadenectomy with central ligations of mesenteric vessels. Due to conflicting evidence, it is not easy to balance the risk and benefit of colectomy in UC patients with LGD. If colectomy is not performed strict surveillance is, however, imperative[28].

For CD patients with treatment refractory acute pan- or multisegmented colitis subtotal colectomy is the treatment of choice. For segmental CD colitis segmental colonic resection is preferred over subtotal colectomy due to better functional outcome[76,77]. For pan- or multisegmented CD colitis in a more elective setting a deviating loop ileostomy without colectomy have been considered a valid option[78] and is still sometimes suggested[79,80], but lately the effect of deviating loop ileostomy without colectomy has been questioned[81]. For CD patients with colonic dysplasia or cancer the same strategy as in UC is applicable[79,80,82].

The colectomy rates among CD patients are not entirely well studied. In a population-based Canadian study of CD operations the total surgical resection rate was 3.8 per 100 person-years out of which 4.4 % were (sub)total colectomies and 33.6 % were segmental colectomies[83]. In an older study of 360 CD colitis patients, a resection rate of 76 % was reported[84].

There are several reports on the colectomy rates among UC patients. An early study of the Stockholm County cohort of patients diagnosed between 1955 and 1984 reported cumulative colectomy rates of 20 % at five years, 28 % at 20 years and 45 % at 25 years[85]. In subsequent studies colectomy rates have been reported between 0.5–6 %, at one year, 3–13 % at five years, 6–19 % at 10 years and 11–20 % at 20 years[63,86-98].

Reconstruction

Thank you for getting this far. Now we are closing in on the core of this thesis. Before we do, I would like you to adopt what I believe to be the proper mind set when scrutinizing different options after colectomy. The purpose is not to determine if one method is superior to the other, but to collect information on the pros and cons, risks and benefits with each option in any given circumstance. Providing the patient and care giver with the best possible information upon which to make their decision and thereafter accurate expectations.

After colectomy, there are four options available. The most obvious is to leave the end ileostomy and not go for any reconstructive surgery. If this is chosen one could either

go further with a completion proctectomy or, if there are no symptoms and no dysplasia, leave the rectum in situ. Then there is the ileal pouch anal anastomosis (IPAA), the ileorectal anastomosis (IRA) and the continent ileostomy (CI) i.e. Kock pouch. In Sweden less, than half of the patients subjected to colectomy gets reconstructed. If this is primarily because they are not offered reconstruction or if they actively refrain from reconstruction is unknown[99]. In reports from England and the United States only about one third of the UC patients subjected to colectomy gets reconstructed[100,101].

Historical aspects of surgical treatment for colitis

In the first half of the 20th century removal of colon was associated with considerable mortality and the general surgical option for colitis patients (the distinction between UC/CD colitis was not well established) was either ileostomy or appendicostomy. (An appendicostomy is when the appendix vermiformis of the caecum is let out through the abdominal wall and a small stoma is fashioned). Both methods primarily for irrigation of the colon and the ileostomy also for diversion of the fecal flow[102,103]. By the late 1940's colectomy, either primary or after initial ileostomy, had become safe enough to emerge as standard treatment for UC requiring surgical treatment why the appendicostomy went out of fashion[104]. The early ileostomies did not function very well due to the lack of both eversion technique and good stoma appliance material [105]. The modern way of creating an everted ileostomy was presented by Brooke in 1952 and by that time better stoma appliances had begun to emerge[106,107].

The first appearance in literature of an anastomosis between the ileum and rectum dates back to Lilienthal in 1903[108] and subsequent descriptions of similar operations for various conditions where proposed by Lane in 1909[109], Reinhoff in 1925[110], Devine in 1943[111,112], and Best in 1948 [113] The invention, or at least systematic introduction of the IRA, and hence the first successful restoration of fecal continuity after colectomy, is attributed to Aylett in his 1953 publication[114]. In his description, as also suggested by Devine[112], the IRA was performed first and the defunctioned colon was removed in a second stage several months later. This is the opposite order to the modern way of constructing an IRA. The concern for malignant development in the rectal remnant was mentioned, but partly dismissed, already in the original Aylett publication. In the subsequent decades the procedure earned a bad reputation for development of rectal cancers, which was probably largely due to inadequate surveillance programs[115,116]. The procedure has later regained popularity with better patient selection, topical treatment, and cancer surveillance[117,118].

The first reported attempt of an anastomosis between the ileum and anus was in a case report by Nissen in 1933[119]. In this case, a loop of ileum was anastomosed to the anus via an abdominal and sacral approach, but it was not successful. In the 1940's and 1950's several varieties of ileoanal anastomosis with or without ileal pouch formations, were suggested but the presented results were not very encouraging results. [113,120,121]. Something in between an IRA and an IPAA was presented by Peck in 1980[122]. Peck suggested that one should remove the rectal mucosa but preserve the rectal muscular layer and then

pull the distal ileum trough the rectal muscular tube and suture an anastomosis to a minimal rectal mucosal cuff. This method appears technically challenging and despite decent results only very few and small subsequent publications have been presented and the method have failed to gain widespread recognition[123]. The modern IPAA was first presented by Parks and Nicholls in 1978[124].

A continent ileostomy was presented by professor Nils G. Kock of Gothenburg in 1969 and is still often referred to as a "Kock Pouch" [125]. The surgical technique of the CI was refined in subsequent publications by Kock and colleagues and the present-day CI was established by the mid 1980's[126,127].

Ileal pouch anal anastomosis – IPAA

The IPAA is considered the gold standard for reconstruction[69]. The IPAA is also referred to as a "pelvic pouch" and in some cases even just a "pouch" (a parlance that might be confusing since there are other pouches, such as the Kock pouches, and should hence be used with caution). In the IPAA, the rectum is removed leaving only a small (not more than 2 cm) rectal remnant referred to as the "cuff". A pouch is then constructed from the terminal ileum, which in turn is connected to this rectal cuff either with circular staples or a sutured anastomosis. In this way, the fecal continuity is restored, and the patients will not need a stoma with associated appliance. The advantages of the IPAA are that almost all colon mucosa is removed, rendering both the CRC risk as well as the need for further pharmacological treatment eliminated. Any reconstruction that results in no need for a stoma appliance is also associated with a better bodyimagecomparedtoanendileostomy[128].

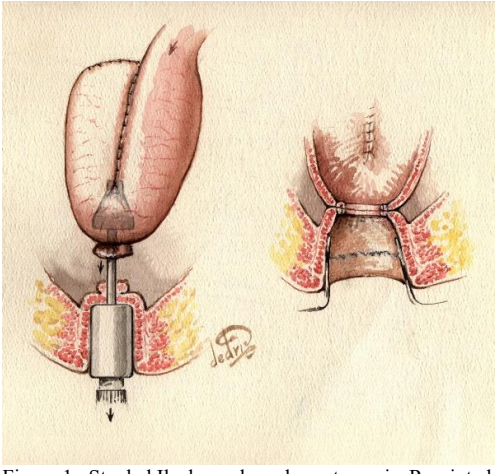


Figure 1. Stapled Ileal pouch anal anastomosis. Reprinted with permission from Tom Øresland and Leif Hultén.

Technical aspects – IPAA

Pouch types

In the original publication of the modern IPAA, Parks and Nicholls described a three-limbed "S" pouch with 5 cm untouched ileum distal to the pouch which was anastomosed to the rectal cuff[124]. The main problem with this "S" pouch was frequent need for active emptying of the pouch and in 1985 Nicholls reported that only 41 % their "S" pouch patients were able to defecate spontaneously[129]. A two-limbed pouch, later named, the "J" pouch was described by Utsunomiya et al. in 1980[130]. The solution to the emptying problems with the "S" pouches suggested by Nicholls and colleagues was the four-limbed "W" pouch with which they reported no need for intubation[129]. A pouch fashioned in the same way as a continent ileostomy named "K" pouch was presented with good functional outcome by Kock and colleagues in 1989[131]. Good long-term results of the "K" pouch has also been presented from the same institution[132]. Nevertheless, the "K" pouch IPAA never attracted much attention outside of Scandinavia, probably due to a more complex procedure than a "J" pouch. The development of surgical stapling devices from the 1980s and onwards have favored the "J" pouch since the it can be relatively fast and easily constructed with straight stapling devices, as compared to the "S", "K" and "W" pouches that requires hand-sewing[133]. A modification of the "J" pouch, called the "H" pouch have been proposed to handle problems with short mesentery, but has only been used in small numbers and predominantly in salvage surgery[134]. In a meta-analysis of 18 publications, Lovegrove and colleagues compared the "J", "S" and "W" pouches[135] and they found no significant differences in perioperative complications. They did, however, present a significantly higher number of daily stools and a significantly greater need for anti-diarrheal medications (J vs S: OR 2.80, P 0.01; J vs W: OR3.55, P < 0.001) for "J" pouches but significantly more frequent need for pouch intubation for the two other pouch types (S: 29.6%; W: 20.0 %; J:1.8%).

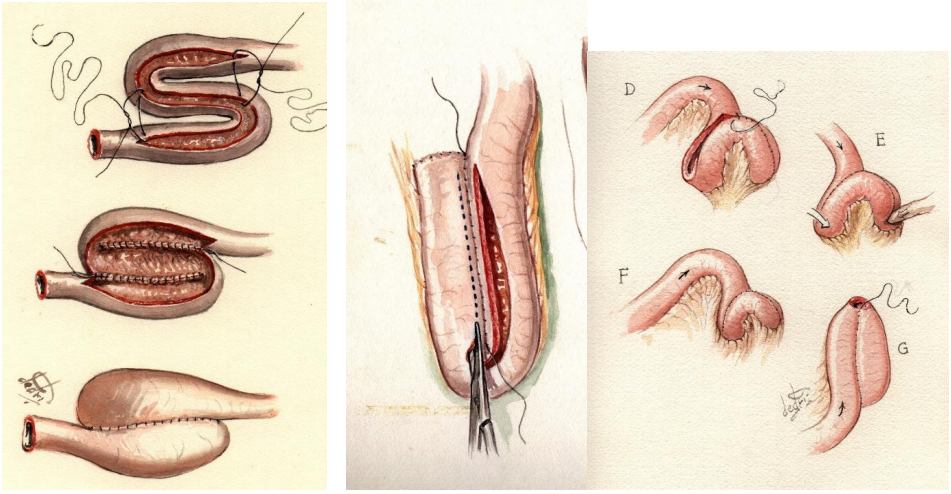


Figure 2. The "S", "J" and "K" pouches. Reprinted with permission from Tom Øresland and Leif Hultén.

Anastomosis

The anastomosis between the pouch and the rectal cuff or anus can be either hand-sewn or constructed with a circular stapling device. In the hand-sewn anastomosis option, which was first described[124], all rectal mucosa is removed and the ileal pouch is sutured to the dentate line[136]. The removal of all the diseased or potentially diseased mucosa is an advantage for this method. However, the mucosectomy requires more manipulation and hence potential damage to the anal sphincters[137]. The innervation anal transition zone (ATZ), which is important for the discrimination between flatus and stools[138,139], can be damaged by the mucosectomy. In support of this theory Saigusa et. al reported far worse ability to discriminate between stools and flatus among patients with a sutured compared to a stapled IPAA[140]. A meta-analysis regarding postoperative complications, functional outcomes, anorectal physiology, quality of life assessment, and neoplastic transformation between the two anastomotic techniques was published in 2006[141]. In the analysis of 4183 IPAA patients no difference in perioperative complications were detected. There was, however, a significant difference in continence and nocturnal seepage, favoring the stapled anastomosis, and a higher risk for pouch failure if the anastomosis was hand sewn, but the authors mainly contributed that to longer follow-up. There was no significant difference in neoplastic development reported, but the authors hesitate to recommend stapled anastomosis at least in patients with previous dysplasia in the distal rectum or any previous CRC, arguing that the follow-up was too short in the stapled group[141]. Al-Sukhni and colleagues compared cancer recurrence for 81 UC patients with dysplasia or CRC and found no significant difference between a stapled or sewn anastomosis over a median follow-up time of 76 months[142]. Further support for stapled anastomosis over hand-sewn was reported in 2009 when Kirat et al. compared the two anastomotic techniques in a retrospective study of 3109 patients and reported better functional outcome, less septic complications, anastomotic strictures, small bowel obstructions and pouch failures was reported for the stapled group[143]. Also, Lian et al. reported a significantly higher risk for pouch failure among patients with a manifested anastomotic leak if they had a hand-sewn rather than a stapled IPAA[144]. These functional benefits, combined with the lack of empiric confirmation of the theoretical disadvantages with a stapled anastomosis and a shorter operation time, have rendered the stapled anastomosis the recommended method in any circumstance and it has become the standard of care[69,145].

Staging

The patient's way from having the colon in place to eventually ending up with an IPAA can take some different paths with the operation divided into different separate procedures or stages. There are four suggested ways to divide the total procedure into stages; one-stage, traditional two-stage, modified two-stage and three-stage[146]. In the one stage procedure the proctocolectomy and construction of the pouch is performed in one single procedure and no diverting loop ileostomy is constructed[147]. The traditional two-stage procedure, which was the suggested staging in the original description by Parks and Nicholls[124], is the same as the one-stage procedure with the addition that a diverting loop ileostomy is also constructed. Later, when the IPAA has been controlled with contrast

enema and endoscopy the loop ileostomy is reversed and that operation constitutes the second stage of the total procedure. The modified two-stage procedure consists of an initial subtotal colectomy followed by a completion proctectomy and creation of the IPAA without a diverting loop[148]. Just as the modified two-staged procedure the three-stage procedure consists of an initial subtotal colectomy followed by a completion proctectomy and IPAA construction but in addition a diverting loop ileostomy is constructed in the second stage and the third stage consists of closure of the loop-ileostomy.

Zittan et al. compared traditional to modified two-staged procedures and found that despite higher steroid use and more severe UC inflammation among the patients subjected to the modified two-stage procedure they still had significantly less anastomotic leaks[149]. Sahami et al. retrospectively compared all four staging options with focus on whether to use a primary deviating loop ileostomy or not[150]. They found differences in the rate of anastomotic leaks between the patients with or without a loop ileostomy but more severe leaks for the patients without loop. However, they also found a primary loop to be an independent risk factor for small bowel obstruction, strictures and fistulas and argue that a modified two-stage approach is preferable over a traditional two-stage approach in patients with risk factors for anastomotic leaks. In a large (n=2390) retrospective comparison between IPAA at colectomy (i.e. the one- and traditional two-stage procedures) and delayed IPAA (i.e. the modified two and three stage procedures), a significantly lower risk for reoperations was found in the latter group[151]. There is one randomized controlled trial (RCT) between one- and traditional two-stage procedures showing no difference in septic complications between the two, but the small sample size (n=45), a significantly larger proportion of women (with wider pelvises, which allows for easier surgery) in the one-stage group suggests that the results should be interpreted with cautioun.[152]. Some reports have shown that a three-staged strategy is associated with less pelvic sepsis and failure than the traditional two-stage operation[153-156]. In conclusion, from available data the modified two-stage strategy appears to be a good option in many cases.

Nevertheless, all but one of the available comparisons between the different staging options are retrospective observational studies and selection bias is very likely, i.e. patients in less favorable condition and with risk-factors for anastomotic complications are more likely to be found in the groups with more staged surgery[146]. Consequently, the more cautious (staged) approaches may from the available literature appear less favorable. risk of putting less favorable light on. There is an ongoing RCT comparing the modified two-stage and three-stage IPAA that hopefully will provide stronger evidence on how to stage the operation[157].

Open/laparoscopic

The first reports of laparoscopic IPAA procedures were published around the turn of the millennium[158,159]. There are some early reports of "laparoscopy assisted" IPAA where the laparoscopy part only extends to the colectomy, but the pelvic dissection is performed in an open manner. From today's point of view that would not count as a laparoscopic IPAA[160,161]. The intended benefits from laparoscopic IPAA, as compared to

open IPAA, are the cosmetic results and effects on sexual function and fertility[162]. In a retrospective series of 100 laparoscopic and 189 open IPAA procedures with a 43 % response rate Larson et al. reported no apparent benefit from laparoscopic over open IPAA regarding body image or sexual function[162]. In 2009, a Cochrane report of 11 studies including a total of 607 IPAA patients (41 % laparoscopic) found no significant difference in perioperative outcome, significantly longer operations time for laparoscopic procedures and some but questionable cosmetic advantages of laparoscopic operations and the long-term functional outcome poorly reported[163]. They concluded that larger and longer-term studies with specific endpoints were needed to prove any advantage with laparoscopic IPAA. Since then one single-center RCT comparing laparoscopic and open IPAA has been published[164]. It could unfortunately not reach the aspired number of included patients[165] because too many patients declined randomization and opted for a laparoscopic approach. Among the 41 patients (21 laparoscopic and 20 open surgeries) they found a tendency towards more frequent pouch failure in the open group. There was no difference in perioperative morbidity, hospital stay or postoperative pain. Better physical activity scores at three months after surgery were reported for the laparoscopy group, but otherwise there were no differences between the groups. Sexual function was not evaluated in that study. There are studies indicating that fertility is less affected in females after laparoscopic surgery than after open IPAA[166,167]. The suggested primary mechanisms for the impaired fertility after pelvic surgery are fimbrial damage and tubal obstruction[168], probably in part due to adhesions which are less frequent after laparoscopic surgery[169].

The use of robotic assisted laparoscopic IPAA have been suggested and proven safe and feasible[170]and some publications have indicated reduced postoperative hospital stay with robotic assisted IPAA[171,172]. Still, long-term systematic evaluations of possible benefits from robotic IPAA remains to be performed[170]. A transanal minimal invasive technique (TaTME) have been proposed but has so far not gained any wide-spread interest [173].

Ileorectal anastomosis

The IRA is a procedure after subtotal colectomy when the fecal continuity is restored by means of the terminal ileum being anastomosed to the rectal/sigmoid remnant in the abdomen without pelvic dissection [114,118]. This is technically an easy procedure compared to the IPAA and can be performed as a laparoscopic as well as an open procedure. Although other methods have previously been suggested the anastomosis is nowadays generally fashioned with a circular stapling device[118,174]. The avoidance of pelvic dissection is suggested to reduce the negative effects on sexual function and fertility, but the remaining rectal mucosa constitutes a risk for proctitis as well as CRC and topical UC treatment as well as surveillance for CRC. When comparing IRA to IPAA, one should also keep in mind that an IRA can later be converted to an IPAA, while the other way around is not possible.

Apart from IBD, colectomy and IRA is also used for hereditary carcinogenic conditions such as familial adenomatous polyposis (FAP) and Lynch syndrome and in some, rare

occasions in slow transit constipations[175,176]. In these patients without inflammation of the rectum it is reasonable to consider a primary IRA, i.e. constructing the anastomosis in the same operation as the colectomy. For the UC and CD colitis patients it is not possible to determine prior to colectomy if the rectum will be suitable for IRA, as it needs to be free of inflammation and compliant(which means have normal/adequate motility)[118]. Hence, primary IRA is to my point of view not a good option for colitis patients, (except maybe cases of CD without proctitis) but this is to my knowledge not clearly stated in literature.

Continent ileostomy - Kock pouch

The continent ileostomy (CI), also referred to as the Kock pouch was introduced by Nils G Kock in 1969[125]. With the CI the fecal continuity is not restored after colectomy or proctocolectomy. Instead, an ileal pouch is created, and the outlet ileum is intussuscepted and stapled forming an inward facing nipple into the pouch. This creates a valve mechanism which makes the construction continent[127]. The stoma is small, at the level of the skin on the abdomen, and no stoma appliance is needed. The pouch is instead emptied actively with a plastic tube[127]. Since the emerge of the IPAA, and also the revival of the IRA the CI is not to be considered a standard option for reconstruction after colectomy[69]. However, some patients subjected to colectomy are not suited for either IPAA or IRA. This could be due to perianal fistulas, poor anal sphincter function or short mesentery and for these patients the CI constitutes an opportunity to avoid a stoma appliance.

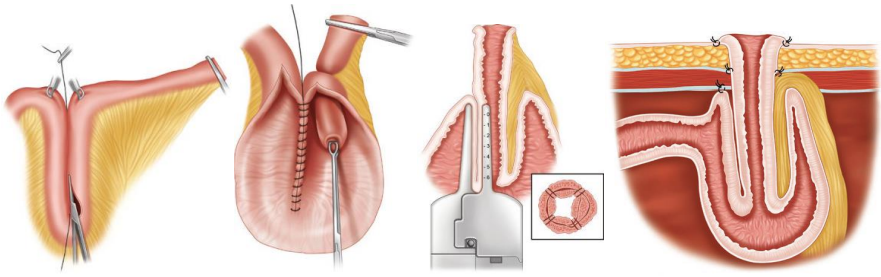


Figure 3. Construction of a CI. Reprinted with permission by Springer Nature, The Kock Pouch 2019[177].

Technical aspects – CI

The introduction of the CI is generally attributed to Kock's 1969 publication[125]. While that is true as far as it was the introduction of a continent ileostomy, it was not all that continent to begin with and required some modifications[126]. In the first version, a spherical ileal pouch was fashioned with the last 30 cm of the ileum and a corner of the pouch was opened and led trough the rectus muscle of the abdominal wall to form a stoma on the skin[125]. It was thought that the reduced pressure from the spherical construction and

the mixed ways of the peristaltic movements alongside the pressure from the rectus muscle would be sufficient to make the construction continent. It was indeed to some extent continent, but for the majority of patients this solution was not sufficient.

The next idea in order to improve the continence of the construction was to detach the inlet to the pouch and turn it around so the peristaltic movements would be directed back towards the pouch and anastomose it to the pouch and pull it through the rectus muscle of the abdominal wall creating a new outlet. Of course, also reconnect the divided inlet to the pouch. In the second modification, which by large rendered the CI used today, the pouch was created in the same spherical fashion from 30 cm of the ileum but 15 cm of the ileum distal to the pouch was kept to create the outlet. A part of the outlet was intussuscepted back into the pouch creating an inward facing nipple that was fixated with a stapling device. This nipple constitutes a valve mechanism, so when the pressure rises inside the pouch and it fills up the nipple will tilt and close. The system then needs to be emptied with a plastic tube through the stoma[126,127].

As we will find out in subsequent sections of this thesis, the CI is not free from problems even after the above-mentioned modifications and further modifications have been suggested and tested. Primarily in order to address the problem of nipple valve slipping Barnett suggested an intestinal collar surrounding the outlet[178,179]. Initially, a Marlex mash was also applied around the outlet of the Barnett continent intestinal reservoir (BCIR)[178]. At about the same time Kock and his colleagues in Gothenburg were also testing to stabilize the nipple construction with a surrounding Marlex or Mersilene mesh but that practice was soon discontinued due to an unacceptable susceptibility of nipple base fistulas among the patients operated with a mesh[127,180-182]. In later descriptions of the BCIR there is no mention of using any mesh[183]. There are only relatively short-term follow-up series presented on the BCIR, the longest follow-up is 3.6 years, and the latest publication is from 1999 [183,184]. From these publications the method does not appear to do worse than the conventional Kock CI but the lack of long-term data raises suspicion. There is also a modification suggested by Castillo in which the pouch is created much like the 3 limbed IPAA "S-pouch" and the nipple is stapled to the pouch wall[185].

Another suggestion to reduce the problems with valve slipping was proposed by Kaiser et al with the "T-pouch," in which a nipple is constructed by letting the pouch encircle a separate ileal outlet segment to avoid the intussusception moment[186]. There is one single center study with a median follow-up time of 6.2 years that did not show any apparent advantage of the "T-pouch" over the conventional Kock CI[187].

A continent ileostomy solution with a titan ileal implant (transcutaneous implant evacuation system TIES) and a plastic cap to fit over the implant to make it continent have been evaluated, first in animals in 2010 and subsequently in four humans, and "no major safety concerns" were reported [188]. However, one of the authors of the first report, professor Øresland, remarked in a follow-up comment that there were healing problems and that only one or two patients ever achieved continence. Since then, the developer have modified the device (TIES III), but from what Øresland reports there was no apparent improvement among the six patients operated with the modified device[189].

The majority of CI patients report satisfaction and good quality of life, but the procedure is nevertheless associated with a relatively high frequency of complications. Revisions have been reported in 21-72 % of patients and excision and conversion to conventional brook end ileostomy has been reported in 5-40 % of patients[190-192]. The most common cause for reoperations is failure of the valve mechanism[192]. The follow up time in these studies varies greatly and there are several of the eventually excised CI that had worked well for 20 years or more at the time of excision[191-193]. CI is an available option after failure of both IRA and IPAA.

Functional outcome

Bowel function - IPAA

There are several aspects on bowel function that need to be addressed when evaluating the bowel function in an IPAA patient, such as the number of daily bowel movements, the number of nocturnal bowel movements, urgency (i.e. the ability to defer bowel movements 30 minutes/until convenient), stool incontinence or degree of such, and the ability to discriminate between stools and flatus. In a large meta-analysis of 26 studies including a total of 5 321 IPAA patients, a mean stool frequency 5.9 (95 % CI 4.9–6.7) per 24 hours and a nocturnal stool frequency of 1.5 (95 % CI 1.0–2.1) was reported[194]. That is in line with other investigators and 4-8 stools per 24 h is generally considered "normal" after IPAA surgery[195-197]. The stool frequency appears to increase a little over time, but in the hardly relevant pace of 0.3 stools per decade[196]. About 75 % of the IPAA patients has at least occasionally nightly bowel movements[196,198]. Some degree of incontinence is reported in 14-39 % of patients during daytime and in up to 68 % of patients during nighttime[196,198,199]. The wide variety in reported incontinence is probably in part due to different definitions. In many papers, the use of protective pads is reported separately from incontinence although the need for protective pads must indicate some degree of incontinence. In the above-mentioned meta-analysis, the investigators tried to separate severe cases of incontinence and reported six percent of IPAA patients with severe incontinence[194]. It has been suggested that incontinence may increase with increasing age of the IPAA patient. In a meta-analysis of IPAA in the elderly, an incontinence rate of 14.2 % was reported in the age-group 50-65 years, as compared to 25.7 % among those over 65 years[200]. Urgency, as defined above, is by many colitis patients described as a very real and difficult problem. Among IPAA patients, it is reported in about 40 % of patients the first year after reconstruction, then decreasing over time to about 16-32 % of patients suffering urgency ten years after IPAA construction[196,198,199]. According to Michelassi and colleagues, a little less than half of the IPAA patients can often or always distinguish between stools and flatus [196]. In contradiction to Saigusa's findings, Michelassi found no difference between hand-sewn and stapled anastomosis in this regard[140,196].

Bowel function - IRA

The functional aspects to consider after IRA are obviously the same as after IPAA or indeed if the colitis afflicted colon was still in place. The number of bowel movements per 24 hours after IRA is reported to be between three and six and fewer when compared to patients after IPAA surgery[201-206]. There are three studies comparing the need for nighttime evacuation between IRA and IPAA and none of them found any significant difference. [201,207,208]. Da Luz Moreira reported a tendency towards less continence problems for IRA when compared to IPAA and a small, but statistically significant, difference in nighttime seepage to the advantage of IRA[207]. This is in accordance with findings of Abdalla et al[201]. Da Luz Moreira additionally reported significantly more urgency among IRA patients, as compared to IPAA patients (68 % vs. 21% $p< 0.001$)[207]. Abdalla et al. reported urgency among 34.2 % of IRA patients compared to 15.4 % among IPAA patients but the difference was only borderline significant($p=0.057$)[201]. Börjesson et al. reported urgency among 33 % of IRA patients and in a different publication from the same center among 16% of IPAA patients[209]. It is, to my knowledge, not studied if urgency, as for IPAA patients, is reduced over time also in IRA patients. Using the Øresland score as a global assessment of bowel function the IRA patients reports better scores than IPAA patients[201].

Bowel function - CI

While the bowel obviously does not function in a regular sense with a CI there are most certainly functional issues to address with the CI. These are how often the CI needs emptying, the need to empty the CI during night, problems intubating the CI and incontinence. Medians of four or five daily evacuations as well as a corresponding mean of 4.4 daily evacuations are presented in several reports [180,210-213]. In addition, Litle et al. reported that 18 % of their 129 CI patients evacuated their pouch more than six times in 24 hours and, in accordance, Aytac et al. reported a range of one to ten evacuations among their 67 CI patients with previous IPAA. Litle et al. also reported that 18 % needed to empty their pouch at least once every night[212]. Nessar et al. reported, among their 330 CI patients a median need for nightly evacuation of 0.5 (which I interpret as 50 % of patients need at least occasional nightly emptying)[180]. Difficulties intubating the pouch was reported in between 8 – 59 % of CI patients[211,212,214,215]. The wide range probably reflects different definitions of "difficulties". Flatus incontinence was reported in between 36 – 50 % of CI patients[185,211,212]. Castillo et al. reported 10 % fecal incontinence and 70 % mucus discharge problems[185] while Litle et al. reported 25% fecal incontinence[212] and Parc et al. reported 44 % incontinence or soiling[211]. Both the incontinence and intubation problems are partly subjective from the perspective of both the patient and the reporter. Moreover, when these problems occur it is most likely due to a mechanical complication or possibly pouchitis, both of which will be addressed below.

Sexual function - IPAA

The pelvic dissection required for an IPAA poses a risk to nerves controlling sexual function. Several investigators have evaluated the impact on sexual function after IPAA[162,216-220]. In a meta-analysis from 2007 of seven studies including a total of 419 female IPAA patients, dyspareunia was reported in eight % of patients before IPAA and 25 % after[218]. Larson and colleagues used the International index of erectile dysfunction (IIEF) and female sexual function index (FSFI) scores and compared both male and female patients after both open and laparoscopic IPAA. Comparisons were made both between the two approaches and to normal controls. The male IPAA patients reported better sexual function than the controls, while the female IPAA patients scored significantly worse than the controls. There was no difference in sexual function between the laparoscopic and open approach for either sex[162]. Hueting et al. found similar figures for female IPAA patients, but also self-reported impotence or retrograde ejaculation in 25.7 % of male IPAA patients[216]. Both Berndtsson et al. and van Balkom et al. reported a similar frequency of sexual function impairment among females, but, in accordance with Larson and colleagues, no adverse effect on male erectile function[217,220]. Berndtsson et al. also compared satisfaction with sexual life between the ileostomy period prior to IPAA and after the IPAA construction among the patients with an initial subtotal colectomy and found improved satisfaction for both sexes after IPAA, and more so among women[217]. In a Norwegian study from 2017, the dyspareunia among female IPAA patients was confirmed and was shown to correlate with pouch function, but sexual desire and the ability or likelihood to climax was not affected. In the same study, the male IPAA patients reported no impaired sexual function[219]. A small prospective study compared "sexual satisfaction" before and after IPAA and reported improvement for both male and female patients [221]. In a comparison between IPAA and end ileostomy patients, 13 % of the IPAA as compared to 30 % of the ileostomy patients, reported "sexual restrictions"[222].

Bengtsson et al. studied sexual function after failed IPAA and reported IIEF and FSFI scores below the cut-off levels for sexual dysfunction in both men and women[223].

Sexual function - IRA

Presumably, the IRA procedure itself would not affect sexual function since the pelvis is left untouched. Still the IRA patient may experience impaired sexual function related to bowel function or inflammation. There is one publication reporting no difference in "sexual restrictions" between the two operations among UC patients. Another publication on FAP patients only reports no difference in the ability to reach climax among the female patients subjected to IRA or IPAA procedures, but more frequent dyspareunia after IPAA (29 % vs 18 % no significance test presented). No male patient in either group had reported erectile dysfunction[224].

Fertility – IPAA

Female IBD patients have reduced fertility compared to the general population, especially those with CD or IBD-U, but to some extent also UC[225]. Male IBD patients of all subtypes have a subtle reduction of fertility as compared to the general population[226]. Colectomy alone further reduce fertility[227,228], but whether that is due to patient selection or effect of surgery is uncertain. In a large Swedish cohort obtained between 1964 and 2014 IPAA was associated with a further reduction of fertility for females of HR 0.67 (95 % CI 0.5-0.88), as compared to colectomy alone[227]. In a study from France, reduced fertility after colectomy was confirmed, but they reported no difference in fertility between IRA and IPAA, and better fertility after laparoscopic reconstruction, as compared to open reconstruction (OR 1.79, 95 % CI =1.20-2.63)[166]. In vitro fertilization is far more common among women subjected to IPAA than among women not subjected to IPAA. The success rate of in vitro fertilization is, however, not affected by IPAA surgery[229].

Fertility – IRA

Small studies on both IBD and FAP populations have suggested no further effect on female fertility after IRA [230,231]. This was confirmed by a recent large population-based study from Sweden, which also reported a subtle reduction in male fertility from colectomy, but no further reduction after either IRA or IPAA [227].

Quality of life

The sole aim of reconstruction after colectomy for IBD is to improve quality of life (QoL), since the disease is removed by the colectomy (possibly in conjunction with a completion proctectomy). QoL is a very universal term possibly effected by almost anything and it is often narrowed down to health related QoL or disease specific QoL. Health related QoL (HRQoL) or IBD specific QoL is what might be affected by the reconstructive operations or ileostomy and hence what is relevant in this context.

Quality of Life - IPAA

Several different validated and un-validated questionnaires have been used to assess QoL among IPAA patients. In 2015 a systematic review of all 13 studies comparing QoL in IPAA to ileostomy among UC patients up until 2014 was published [232]. The most common of the validated scores were SF-36, followed by EQ-5D and the IBDQ. Most of the non-validated scores or forms included yes or no questions concerning general satisfaction. Only one out of 13 studies found a better QoL for IPAA patients compared to end ileostomy UC patients and only in one of several validated forms. They concluded that global QoL scores were "virtually identical between the two groups"[233]. The only consistent finding in advantage of IPAA was a better body image[232]. One small prospective study investigated QoL before and after IPAA and reported significant improve-

ment[221]. Not surprisingly, some reports indicate a reduced QoL short after IPAA surgery, but improved values, to better than before IPAA, or "perfect health" after one year[234,235]. The QoL also appears to stay good for decades after IPAA surgery[198,236]

Quality of Life – IRA

While not as abundant as those on IPAA there are some reports on the QoL among IRA patients as well. In an Italian single center report from 2016 including 98 IRA and 98 IPAA patients, a higher percentage of IRA patients (97.9 %) than IPAA (87.7 %) reported that they were satisfied with their surgery (p=0.04). In the same report, a small but significantly larger proportion of the IPAA patients reported work and dietary restrictions but the IPAA patients scored significantly better in "current energy level"[237]. da Luz Moreira et el. Also found a tendency towards a higher proportion of satisfaction among the IRA patients but in their small IRA group (n=22) it did not reach statistical significance. In contrast to the above-mentioned Italian report Moreira found significantly more dietary restrictions among the IRA patients[206].

Quality of Life – CI

In the longest QoL follow-up on CI, Berndtsson et al. reported no difference in any domain of SF-36, as compared to age- and gender matched controls[193]. Hoekstra compared SF-36 results between CI, IPAA and Brook ileostomy patients and found no significant difference in the overall score between the groups but the in the subsection on sexual function the CI patients scored worse than the IPAA patients and in the subsection on gastrointestinal function the CI patients scored worse as compared to the end ileostomy patients[214]. In non-validated questionnaires presented Castillo et al. as well as Lian et al. 90 % and 97 % respectively of CI patients reported improvement in QoL compared to when they had their previous stomas[185,238]. Nessar et al. compared results on the Cleveland global QoL scale between CI and Brook ileostomy patients and reported better scores among the CI patients in all subscales (i.e. life, health and energy)[180].

Complications

Complications – IPAA

IPAA is an operation associated with considerable morbidity. In the largest available series to date, including 3707 IPAA patients with a median follow-up time of 84 months, early postoperative complications were found in 33.5 % of patients and late complications in another 29.1 %, (pouchitis not included)[199]. In that study, repeat laparotomy was reported needed in 14.9 % of patients, out of which 41.2 % were due to small bowel obstruction (SBO). In many publications concerning IPAA, complications are divided in early and late. An early complication is generally defined as a complication presenting within 30 days of surgery[239]. The Clavien-Dindo score[240] is used to grade complications occurring within 30 days of surgery. The cut-off for major complications is generally 3b

(i.e. intervention under general anesthesia) and Clavien-Dindo ≥ 3b is reported in between 6-18 % of IPAA patients [132,241-244]. However, a majority of publications concerning IPAA complications do not present the Clavien-Dindo score, or directly convertible information and, many possible complications can occur both early and late. A meta-analysis including 34 studies of complication rates in UC patients after/ IPAA in UC patients were recently presented[239]. All complications reported in more than five individual studies were subjected to meta-analysis and eight of them were defined as "early complications". Only seven studies, however, specified an early complication as occurring within 30 after surgery and for the rest the definition of early was arbitrary. Wound infection was reported in 13.4 % of patients, SBO in 11.3% (ileus was reported separately from SBO and occurred in 11.7 % of patients), anastomotic leak in 6.1 %, intraabdominal collection in 5.3 %, urinary tract infection in 4.1 % and pneumonia in 2.3 %[239]. Early pelvic sepsis was reported to have occurred in 9-19 % and pelvic abscess in 2-18 % and these entities, alongside "anastomotic leak" and "intraabdominal collection", probably refers to largely the same phenomenon. Hemorrhage was reported to occur in 3.2-8.3 % and sepsis in 1.3-7.9 %[239].

According to Gorgun, pouchitis, fistulas and strictures are the most common late complications[245]. Other reports also indicate that SBO, anastomotic leak and pelvic sepsis as frequent late complications[194,199,246]. Pouch failure is also in many publications referred to as a complication per se but in my opinion failure (as defined below) is not in itself a complication, but a consequence of one or several other complications. Many authors list functional problems after IPAA surgery as complications, I only partly agree with that and address them under separate headlines elsewhere in this text.

There is one large meta-analysis on all IPAA publications published between 2000 and 2012 in which strictures are reported to occur in about 10 % of IPAA patients, fistulas in 4.5 %, pelvic sepsis in 7.5 %, and SBO in 11.4 %[194]. In comparison to a very similar, earlier meta-analysis from the same research team[246], there were a tendencies towards reduction in all of the above mentioned complications over time, but no statistical significant differences. They do not distinguish between early and late complications in either of these reports.

Pouchitis is an inflammation of the pouch mucosa, resulting in more frequent bowel movements, looser stools, urgency and fever[247]. In a 2021 meta-analysis of 22 studies including 6 856 patients (not UC only) a pooled pouchitis incidence of 30 % and a range of 11-61 % were reported. The etiology of pouchitis is not clear and several mechanisms, including recurrence of UC, dysbiosis of the pouch microbiota, deprivation of nutritional short-chain fatty acids, mucosal ischemia, host genetic susceptibility and immune dysregulation have been suggested. Several of these factors are most likely working together in the same individual to cause the pouchitis[248]. The incidence of pouchitis appears to increase with the time from IPAA construction and the higher end of the range are probably from the studies with a longer follow-up[249-251]. Alongside follow-up time extent of colitis, back-wash ileitis and PSC have also been identified as risk factors for pouchitis[251,252]. In a study specifically addressing UC PSC patients with IPAA a signif-

icantly higher risk for pouchitis (63 % vs 30 %, OR 4.21, 95 % CI 2.86–6.18) was reported for the UC patients with PSC, as compared to those with UC only[253]. Initially, pouchitis is generally treated with antibiotics (metronidazole or ciprofloxacin). According to a 2019 Cochrane report ciprofloxacin might be a little more effective although the report states that the effect of either of the two is "uncertain"[254]. In a very recent RCT between vedolizumab and placebo, vedolizumab had effect on chronic pouchitis[255].

Apart from pouchitis, cuffitis can also occur. That is an inflammation in the small rectal mucosal remnant between the anastomosis and the ATZ. Cuffitis is reported in between 10-30% of IPAA patients and proposed risk factors are a long cuff (>2cm), a stapled anastomosis (which in turn is a risk for a longer cuff), and worse or more treatment refractory inflammatory conditions pre-operatively[256].

Pouch failure is generally referred to as excision of the pouch and creation of an end ileostomy or permanent (more than two years) deviation with a loop ileostomy. In the large meta-analysis by de Zeeuw et al. a pooled pouch failure rate of 4.3 % was reported when analyzing data from 43 studies including a total of 13 249 IPAA patients.[194] They also reported a significant reduction, as compared to the pooled pouch failure rate of 6.8 from a previous meta-analysis of 39 studies, published before the year 2000, which included 8 877 IPAA patients[194]. A more recent meta-analysis that specifically included studies on UC IPAA patients reported a total pooled pouch failure rates of 6 %, 5 % for studies with a median follow-up of ≥5 years and 9 % for studies with a median follow-up of ≥10 years [257]. A slightly higher pooled failure rate of 7.7 % for studies with a median follow-up of ≥5 years and 10.3 % for studies with a median follow-up of ≥10 years. In another recent meta-analysis of 22 978 IPAA patients, not limited to UC IPAA patients, an overall failure rate of 6.7 % was reported [258]. In a Swedish population-based national cohort of 1 720 UC patients with IPAA the failure rate was 6 % after a median follow-up of 12 years [259]. Time from IPAA construction to failure is a relevant aspect to consider when evaluating pouch failure. If the pouch is permanently deviated or removed very soon after construction, it is definitely to be considered a failure but if the IPAA provides the patient ten or more years of improved function and QoL before it is eventually removed than at least I am reluctant to call it a failure. In the series of 3707 IPAA patients (whereof 2 959 had UC) from the Cleveland clinic, 197 patients (5.3 %) eventually suffered from pouch failure and the median time to pouch failure was 30 months. Amongst those with, however 95 % had their IPAAs functioning after 10 years[199].

The possible reasons for pouch failure are another matter for scrutiny. In the meta-analysis by Heuthorst and colleagues, including 22 978 patients, the relationship between IPAA-related complications and pouch failure were analyzed and they presented a significant association between pelvic sepsis as well as fistula and pouch failure. [258]. When they separately analyzed the studies with ≥5 years of follow-up, only fistula remained significantly associated with failure. Similar findings were reported in a cohort study of 3468 patients, which reported an increased short-term risk for failure after anastomotic leak or pelvic abscess. If the IPAA was still functioning at five years after the compli-

cation though, the risk for failure had returned to that of subjects without a septic complication[260]. In line with these findings, the most common cause of the 197 failures from the 3 707 patients Cleveland series was fistulas (n=27), followed by pouch dysfunction (n=13), recurrent pouchitis (n=21), pelvic sepsis (n=12), anastomotic separation (n=9), stricture (n=10), incontinence (n=7), cancer (n=7), small bowel obstruction (n=2), bowel infarction or ischemia (n=2).The reason for twenty of the failures was reported as "other"[199]. The concept that septic complications and especially manifested fistulas, are the most common cause of IPAA failure is also supported by several other reports[156,249,261,262].

In an analysis of risk factors for IPAA failure in 391 UC patients male sex, older age and high body mass index (BMI) were found to be associated with an increased risk of IPAA failure[263]. In one study that specifically addressed UC PSC patients with IPAA a significantly higher risk for IPAA failure (7 % vs 10 %, OR 1.85, 95 % CI 1.08–3.17) was reported for UC patients with PSC, as compared to those with only UC [253].

Complications – IRA

Two studies report early postoperative complications after IRA according to Clavien-Dindo. Complications of grade 3a or worse were present in 9 % of patients in one report and in12 % in the other[202,264]. One of the studies specifies the early major complications and reports hemorrhage or hematoma to be the most common complication followed by anastomotic leak[202].

The IRA equivalent of pouchitis in IPAA/CI is proctitis. It is the most common IRA complication and reported (to some extent) in 59 % - 76 % of IBD IRA patients[265,266]. Functional problems related to proctitis are discussed under a separate headline. In a systematic review of 15 studies including a total of 907 IRA patients, a crude leakage rate of 3.9 % was reported[267]. That report did not only include IBD patients, but also series with FAP and slow transit IRA patients. In the largest publication including only subjects with IRA due to UC and which report leakage rate, a leakage rate of 2.9 % was reported[202].

Dysplasia or cancer in the retained rectum is a complication to the disease rather than the operation, but still a very relevant problem or concern to the IRA patients. For patients operated with IRA between 1955 and 1976, cumulative CRC rates of 6 % at 20 years and 15 % at 30 years was reported by Baker et al. [115]. No CRC was, however, found during the first 10 years of follow-up (corresponding to 3534 patient-years), and the risk of developing CRC in the first 10 years after IRA construction appears to be very low in UC patients without previous CRC or dysplasia. Andersson et al. reported cumulative CRC risk at 10, 20 and 25 years to be 0, 2.1 and 8.7 for UC IRA patients compared to 0.7, 1.8, 1.8 among IPAA patients[202]. There was no statistically significant difference between the two groups. Uzzan and colleagues reported the estimated CRC risk at 10 years of 2.1 % for patients without previous dysplasia or CRC, but 25 % if there were previous colonic dysplasia and 50 % in case of previous colonic CRC[268]. A systematic review of 1 234 IRA patients from 14 studies reported the crude risk of

dysplasia or CRC of 4.5 %, but follow-up time differed substantially between the studies[267]. The increased CRC risk among UC PSC patients is well known[269] and Abdalla et al. found an HR to develop CRC of 5.95 among UC IRA patients with PSC when comparing them to UC IRA patients without PSC[270].

IRA may in some instances be considered a "bridge to IPAA", especially in younger females who want to postpone the risk of impaired fertility that is associated with IPAA. In these instances, later conversion to an IPAA, or even Brook ileostomy should not necessarily be considered a failure, and one should keep this in mind when evaluating IRA failure rates. Failure of an IRA is generally defined as diversion with a stoma with or without a completion proctectomy[118]. In a Swedish population-based cohort of 1 112 UC IRA patients, the 10-year failure rate was 27 %[259]. A French multicenter study of 343 UC IRA patients reported estimated failure rates of 19 % at five years, 27 % at ten years, 35 % at 15 years and 40 % at 20 years and a median survival time without IRA failure of 26.8 years[271]. In the above-mentioned systematic review, failure was reported in 18 studies and a total of 2 447 patients and failure was reported in 20.4 % of cases [267]. In the French study, 67 % of failures were reported to be due to proctitis, 11 % due to dysplasia, 10 % due to manifested CRC, 7% due to functional reasons and the rest due to reasons reported as "other"[271]. Some of the failures reported as "other" are likely the ones who considered IRA as a "bridge to IPAA". Similar findings have also been presented by Berghog, Tonelli and Andersson[202,237,264]. In addition. Berghog et al. reported a significantly higher proportion of PSC among the patients with IRA failure.

Complications – CI

Early complications to the CI procedure may obviously include all possible complications of any major open abdominal procedure, such as bleeding, wound infection, anastomotic leak, wound dehiscence and SBO. Pouch or nipple specific complications such as valve necrosis and fistulas may also occur early after CI surgery[190]. Nipple slippage or pouch loosening may very well occur early in the post operative period, but it will not be evident until the tube is first removed from the pouch four to five weeks after surgery. Parc et al. reported early complications with a Clavien-Dindo grade of 3a or worse in 20 % in a series of 49 patients. Abscess formation was by far the most common, but there was also a case of each stoma necrosis, anastomotic leak and hemorrhage requiring surgery. Parc reported five cases of early fistulas which all healed on conservative treatment (although two later reoccurred)[211]. Aytac et al. reported a 30-day complication rate of 36 % in a series of 81 CI patients with previous IPAA (eleven ileus, eight wound infections, three abscesses and two hemorrhages), but classifications according to Clavien-Dindo were not reported[210].

Complications requiring revisional surgery or even CI extirpations are described in several reports and in a 2021 systematic review Deputy and colleagues presented a range of 21 % - 65 % for major revisions[272]. However, the follow-up time (median 1.5-31 years) differed substantially between the 12 publications reviewed by Deputy Only analyzing the publications with ten or more years of follow-up the, the rate of major revisions was at least 30 % and narrowing the scope down to publications with 15 or more

years of follow-up it was at least 45 %[193,211,212,215,273,274]. Moreover, a revision rate of 72 % over a median follow-up time of 16 years was reported in a series of 423 patients from the Cleveland Clinic, but that figure may also include minor revisions[190]. Nipple valve slipping refers to a condition when the nipple shortens, in part of the circumference or around the hole circumference. When the slipping is partial there may be difficulties intubating the pouch as part of the sliding nipple makes a turn between the pouch and the abdominal wall. As slipping proceeds and the nipple gets shorter the pouch gradually becomes less continent. Nipple valve slipping is reported to be the most common cause of major revisions in ten of 12 publications in the review by Deputy. In the two largest series of CI patients, from the Mayo clinic and Cleveland clinic, respectively, it was reported in 30 % of patients[180,213]. The Cleveland publication included both Kock and BICR CIs and there was no difference in valve slipping between the two. The second most common cause of major revisions are fistulas, reported in up to 25 % of patients[272]. Most of the larger and longer patient series includes a proportion of patients operated with a mesh including the one where fistulas were reported in 25 % of cases. Litle et al. reported that a mesh was used in 80 % of their patients presenting with fistulas[212]. Loosening of the pouch from the abdominal wall may occur simultaneously with valve slipping and in fact possibly cause the latter[275] (This is also my experience from reading the medical records for "*Paper 1*", and the clinical experience from our center.) Clinically, pouch loosening results in problems intubating the pouch rather than incontinence. Many reports do not specify pouch loosening but instead reports "difficulties intubating", when distinguished from stenosis this probably largely represents loosening[180]. Some authors have also interpreted stoma prolapse to be directly related to loosening[275]. When it is reported separately it appears to be the cause in around 15 % of major revisions[273]. Other complications reported to be responsible for major revisions are stoma prolapse, incisional or parastomal hernias, pouch bleeding and SBO[180,272]. Local skin level revisions or endoscopic dilatations for stoma stenoses are additionally reported in up 29 % of CI patients [276,277].

Failure, defined as excision and conversion to conventional Brook end ileostomy, has been reported in 5-40 % of patients[190-192]. In the largest series of 423 patients from the Cleveland clinic, a failure rate of 21 % is reported[190]. In the longest follow-up, with a median of 31 years, failure was only reported in 6 % of cases. Instead, the highest rate of major revisions (65 %) was reported[193]. This may reflect that whether to go for further revisions or conversion to an end ileostomy is not clear cut, but highly dependent on the attitudes and experiences of the responsible surgical team. In some publications, valve slipping[212,215,278] is reported to be the dominant cause of CI excision while other report fistulas to be the dominant cause[180]. Nessar and colleagues also reported an increased failure rate for CI patients with BMI over 30 (HR of 2.78 95 %CI 1.11–6.98).[180].

Pouchitis of the CI may present with excess excretion, excess pouch evacuation frequency, malodor, bleeding, abdominal pain, distention and fever[279]. The reported frequency of pouchitis in CI is similar to that of IPAA, ranging between 27 % and 46 %[180,211,212]. The pouchitis of the CI is most likely the same entity as that of the IPAA, which has been the subject to far more research, and it is treated in the same way with the possible addition of constant intubation.

Reconstruction in Crohn's Disease

It is not uncommon to compare the outcomes of a reconstructive method between patients with UC and CD[197]. However, such comparisons are hardly relevant since the patient cannot change his or her diagnosis. If anything, one should compare the different reconstructive options to one another within the CD population. One should also keep in mind that the CD colitis population contains more heterogeneity than the UC population. This heterogeneity is underlined in a Cleveland clinic publication describing their CD patients with IRA and IPAA, reporting more previous small bowel surgery and perianal disease in their CD IRA group[280].

IPAA – CD

In reports from the early 1990s, failure rates of 30-45 % were reported IPAA patients that were eventually deemed to have CD and performing IPAA in CD patients was considered questionable if not contraindicated[281,282]. Since then, the patient selection has improved and in 1996 Panis et al. presented a series of 31 patients with known CD colitis, but no small bowel or perianal disease, and reported only a 10 % failure rate after five years and similar functional results to a control group of 71 UC IPAA patients[283]. The suggested criteria for this patients selection is no perianal disease and no sign of small bowel CD[283]. Furthermore, Panis reported that two patients with CD recurrence in their pouches were successfully treated with azathioprine. Later, infliximab, ustekinumab, adalimumab and vedolizumab have also been found effective against CD recurrence in the pouch [284-287]. In 2021, Lightner and colleagues published a systematic review of six articles including a total of 345 CD IPAA patients[288]. They reported pelvic sepsis in 13 % of patients, SBO in 3 %, anal strictures in 18 %, urgency in 21 % and incontinence in 24 % of patients. IPAA failure was reported in between 6 % and 15 % between the studies and the pooled failure rate was 15 %, with a median follow-up of 69 months [280,283,289,290]. It should be mentioned that all studies were retrospective and included both patients with known CD at IPAA construction and patients that were believed to have UC at the time of IPAA construction. Among IPAA patients with perianal fistulas a failure rate of 21 % was reported[288].

IRA – CD

IRA is well established in CD colitis patients with mild or no proctits[280,291-293]. In a series of 81 CD IRA patients, O'Riordian et al. reported that 87 % had their IRA still functioning at five years and 72 % at ten years. Fourteen per cent had had a small bowel resection and redo IRA. Among the 18 patients who required proctectomy the mean time to proctectomy was 88 months[291]. In a report from the Cleveland clinic, the crude rate of indefinite stoma diversion was 23 % after a follow-up of 9.5 years[280]. From that publication Cleveland global Quality of life (CGQOL) scores were also reported and the CD IRA group scored worse than the CD IPAA group, but better than CD patients with total proctocolectomy and end ileostomy. However, the authors underline the diversity of the groups and points out that all groups achieved satisfactory QoL[280].

CI – CD

Much like the attitude at the time towards IPAA in CD patients, Handelsman et al. and concluded in 1993 that CD should be considered an absolute contraindication CI[294]. In a 2006 publication from Nessar and colleagues findings were, however, reported from a sub-population of 42 CD patients within their CI cohort. They reported a crude CI survival rate of 52 % (median follow up 11 years) and fistula formation in 43 % of the CD patients. Despite these numbers, they conclude that it should be reasonable to perform CI in well-informed and selected patients with CD colitis[180]. In 2017, Aytac et al. published their experience of 48 patients with CI in CD patients. They reported an estimated CI survival of 79 % at five years, 65 % at ten years and 48 % 20 years[295]. In that report, they also compared the patients with preoperatively known CD to those who had their diagnosis changed to CD during follow-up and found no relevant differences between the two. While they do not deem CI in CD unreasonable in all circumstances, they advocate a very cautious attitude and stresses the importance of proper preoperative risk information[295].

AIMS OF THE STUDY

Overall aim

The overall aim of this work is to provide more detailed information on the possible problems and benefits of the different reconstruction options to help tailor the best suited option for each IBD patient having had a colectomy.

Specific aims

- To assess long-term patient satisfaction, quality of life, complications, and failure rates as well as associated patient factors in patients subjected to continent ileostomy at our center.
- To assess long-term complications and failure rates and associated patient factors in IBD patients subjected to continent ileostomy in a population-based, Swedish national cohort.
- To assess what type of reconstruction UC patients chose after colectomy, their satisfaction with the choice of operation. The rate of complications, the postoperative function and QoL.
- To investigate the correlation between volumes of reconstructive surgery after colectomy for UC (defined as annual number of IPAA procedures) at the hospital performing the colectomy and the chance of reconstruction, type of reconstruction and outcome of reconstruction.

PATIENTS AND METHODS

Paper I

All patients who had received a *de novo* (that is a first time CI and not a redo CI) CI at Linköping University Hospital were identified from medical records. A total of 85 patients operated with a CI between 1980 and 2016 were identified. The medical records were surveilled for diagnosis, details of the primary surgery, patient demographics, reoperations (including CI excision) and pouchitis. Endoscopic confirmation of pouchitis was not always present and prescription of metronidazole was deemed sufficient to define occurrence of pouchitis. End of follow-up for pouch patency and reoperations was defined as death, CI excision or March 15, 2016.

All patients who were alive and possible to contact were invited to participate in the inquiry regarding satisfaction, QoL and pouch function. Satisfaction and aspects of CI function, such as incontinence, number of daily and nightly evacuations and intubation problems were assessed with a locally produced non-validated questionnaire. The validated eight domain, 36-item short form SF-36[296,297] and a stoma/CI modification of the IBD specific QoL instrument, Short health scale (SHS) were used to asses QoL[298].An evaluation of QoL using SF-36, was also conducted in 1998 and the results from then were compared with those of this study.

Paper II

There is a unique personal identity number assigned to all permanent Swedish residents[299]. This identity number is used in all official registers and allows for follow-up in nationwide health care registers. Data for this study was obtained from the Swedish National Patient Register (NPR), which holds information on discharge diagnoses, performed surgical interventions, and dates for admission and discharge. The NPR started in 1964 and is considered to have full coverage since 1987. Originally, it only held information from inpatient care, but since 2001 it has also been for specialist outpatient visits. The diagnoses are coded according to the international classification of disease (ICD) system. Between 1964 and 1996, surgical procedures were classified in a four-digit system based on the American system for the classification of surgical procedures. Since 1997, surgical procedures have been classified according to the Nordic medico-statistical committee (NOMESCO) classification of surgical procedures system.

All patients with two or more entries (to increase the reliability of the diagnosis) of an IBD diagnosis up until December 31th, 2014 were identified from the NPR. Patients were divided according to IBD subtypes; UC, CD and IBD-U. Patients with inconsistent diagnosing between CD and UC were categorized as IBD-U. This made the CD and UC diagnosis more reliable but putting a considerable number of patients that actually have

a well-defined diagnosis of either CD or UC in the IBD-U group. Among all patients who had received a CI, reoperations were identified and organized in the following categories: stoma revisions, hernia repairs, explorative operations/operations for SBO, operations for fistulas or perforations, stoma closures, and operations because of bleeding. Redo CI was not defined as failure but as any other reoperation and categorized by the cause of the reoperation.

Paper III

There was a previous attempt on an RCT between IRA and IPAA in UC patients deemed eligible for both procedures. However, after receiving standardized comprehensive information on both IRA and IPAA, the eligible patients insisted on choosing the procedure themselves, only one patient was ever included and unfortunately, nothing was published from this RCT. In this study, we try to mimic an RCT while still accepting that the patients will not consent to randomization if they are properly preoperatively informed.

Patients are enrolled at three tertiary referral centers in Sweden (Linköping University Hospital, Linköping, Karolinska University Hospital, Stockholm, and Sahlgrenska (Östra) University hospital, Gothenburg,) and one tertiary referral center in the United Kingdom (St Mark's Hospital and Academic Institute, Harrow).

There is to my knowledge only one study available on, our primary outcome, i.e. patient satisfaction between IRA and IPAA, and it reports 98 % and 88 % satisfaction for the methods respectively[237]. However, in that study they did not ask the patients having had IRA failure, making the report less reliable. De Buck van Overstraeten and colleagues compared quality adjusted life years (QALY) between IRA and IPAA and reported a mean of 33.42 QALYs for IRA and a mean of 31.57 QALYs for IPAA[300]. With a significance level 0.05 and 80 % power and an estimated standard deviation (SD) of 3 (2.8 for IRA and 4.5 for IPAA) one would require 43 patients in each group to demonstrate a difference. Lacking a perfectly well-suited study to base the power calculation on, we considered the de Buck van Overstraeten study most relevant and decided to aim at a minimum of 50 patients in each of the intervention arms. Reaching a little over the estimated 43 to hopefully compensate for possible loss to follow-up.

All adult UC patients subjected to colectomy and deemed eligible for both IRA and IPAA (Figure 4) at all participating centers are asked to participate. Standardized written and video recorded information on both reconstructive procedures are then presented to the patients who then get to choose between IRA and IPAA, or to keep the ileostomy. Adult UC patients that do not meet the inclusion criteria as well as patients choosing a stoma are also asked to participate as controls in order to obtain a comprehensive picture of the UC patients subjected to colectomy.

Inclusion criteria:

1. ≥18 years and <60 years
2. Good rectal compliance

Exclusion criteria:

1. PSC or colorectal cancer
2. Poor anal function
3. Mayo Score >1
4. Time gap between colectomy and restorative surgery >1 year
5. Uncertainties regarding UC-diagnosis

Figure 4. Inclusion and Exclusion criteria paper III

The primary endpoint is satisfaction with the choice of reconstructive method or stoma, which will assessed with a simple yes or no question. SF-36 and SHS will be used to assess QoL, Öresland score for bowel function, FSFI-6 and IIEF-5 for female and male sexual function respectively. Due to lack of validated instruments, fertility and reproductive outcomes will, alongside satisfaction, be assessed with locally produced, non-validated forms. Data will also be obtained on age at diagnosis, colectomy and reconstruction, indication for colectomy (chronic active disease, acute flare or dysplasia), UC medication, endoscopic status in pouch and rectum, BMI, smoking status, reoperations and for each operation the operation technique, operative time, bleeding, perioperative complications, and hospital stay. Postoperative complications will be graded according to the Clavien-Dindo classification. For the timeframe of the planned follow-up, see Figure 5

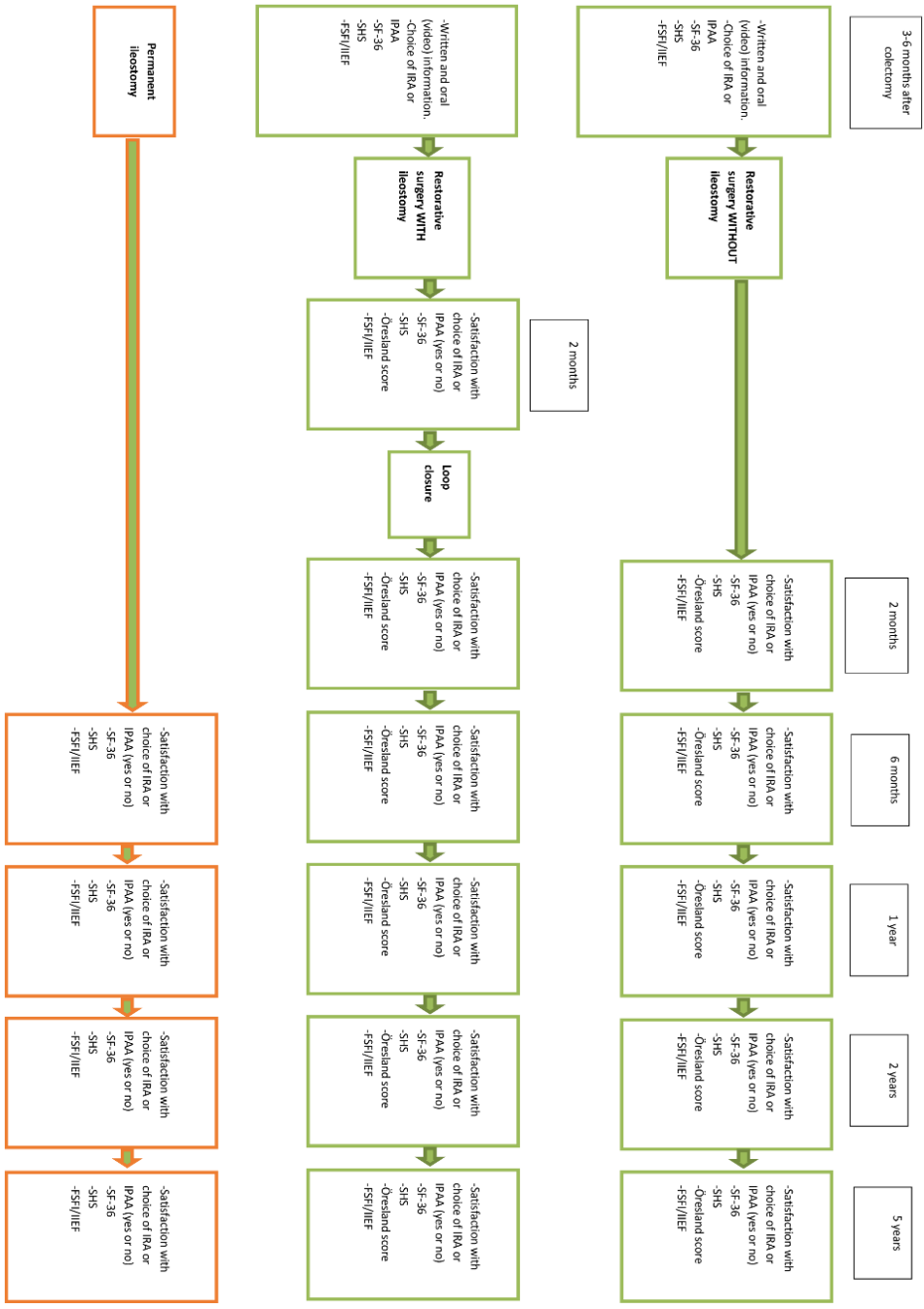


Figure 5. Timeframe for CRUISE follow-up

Paper IV

As in *Paper II,* data was primarily obtained from the NPR. Data but also from The Swedish Inflammatory Bowel Disease Register (SWIBREG).

We identified all patients with two or more UC entries in the NPR between 1987 and June 2020 in NPR. To avoid including patients that had already had a colectomy, we used a 10-year "wash out" period until 1997 and patients coded to have had a colectomy in that period were excluded. By means of NOMESCO procedure codes available in the NPR we identified all patients subjected to colectomy. Patients younger than 20 and older than 70 were at the time of colectomy were excluded. The exposure we sought to investigate was reconstructive volumes at the colectomy hospital. Patients were divided into four groups depending on the average annual number of IPAA procedures at the colectomy hospital during the three years prior to the colectomy: 0, 1-3, 4-7, >7 procedures per year. Consequently, the same colectomy hospital could be analyzed in different volume categories at different time points. The categorization was made based on the annual number of IPAA procedures rather than over all annual reconstructive procedures since, the former is the more technically challenging procedure and more relevant to estimate the ability and experience in reconstructive surgery. Codes for restorative surgery were noted from the NPR from colectomy discharge until admission for restorative procedures, migration, death or 30th of June 2020

The probability of restorative surgery was the primary outcome measure. In the analyses of IRA surgery, patients that received an IPAA were censored at the date of admission for IPAA surgery. Failure of restorative surgery was a secondary outcome measure. Failure was defined as need of new stoma or non-closure of existing stoma within two years of restorative surgery[99,301]. In the analyses of failure after reconstruction codes for failure (i.e. stoma surgery or two years after surgery in cases with non-closure of temporary stoma) were noted in the register from discharge date of restorative procedures or date for stoma closure if a temporary ileostomy was used in the restorative procedure events were noted until admission date for, date of migration, death or June 30th 2022, which ever occurred first.

Statistics

Continuous variables are presented as medians and range (*Paper I*), medians and IQR (*Paper II & IV*) or means and SD.

When comparing two groups, assumed normally distributed means were compared with the Student's t-test (*Paper 1*), while assumed non-normally distributed means and medians were compared using the Mann-Whitney U-test (*Papers I & II*). When comparing more than two groups, non-normally distributed means and medians were compared using the Kruskal-Wallis test. Time to event (survival) analyses were made with both Kaplan-Meier estimates, tested for significance with log-rank test, and Cox proportional regression analysis (multiple univariable followed by multivariable). Results are presented as Kaplan-Meier graphs *(Papers I, II & IV)* and hazard ratios (HR) *(Papers II & IV)*. Risk factors for events that could reoccur several times in the same patient (i.e. reoperations) were analyzed with Poisson regression analysis and presented as incident rate ratios (IRR) in *Paper II*. Risk factors for reoperations were analyzed with a logistic regression model and presented as odds ratios (OR) in *Paper I*. Either p values or 95 % confidence interval or often both were presented. Significance was accepted at $p<0.05$ or 95 % confidence intervals not overlapping.

For *Paper III*, the primary outcome, i.e. the proportion of patients satisfied with their choice, will be compared using the Chi-square test. Secondary outcomes assumed to be normally distributed will be compared by the Student's t-test. Time to event (i.e. failure) will be analyzed with multivariable Cox regression analysis and Kaplan-Meier estimates. Risk factors for reoperations will be analyzed with Poisson regression, and functional as well as QoL variables will be analyzed with mixed model ANOVA analysis.

Ethics

All studies included in this thesis were approved by ethics review boards and the conduction of the studies was in line with modern ethical standards. The way we designed *Paper III* was largely due to the ethical consideration (which is very reasonable, and we unconditionally agree with) that the patients needed correct and equal information. All patients answering questionnaires in *Paper I* and all patients in the CRUISE study have provided written consent before entering the study.

RESULTS

Paper I

Of the 85 patients included in the study, 75 (88 %) had a UC diagnosis before CI construction and six (7 %) patients had a CD diagnosis before CI construction. Two patients had IC, one had familial adenomatous polyposis and one anal atresia. Five UC patients and one IC patient ended up with their diagnosis reevaluated to CD. There was no perioperative mortality. Patient characteristics are presented in Table 3.

Patients	**N=85**
Male n (%)	43 (51)
Female n (%)	42 (49)
Ulcerative colitis n (%)	69 (80)
Crohn's disease n (%)	12 (14)
Indeterminate Colitis n (%)	2 (2)
Familial adenomatous polyposis n (%)	1 (1)
Incontinence after surgery n (%)	1 (1)
Age at diagnosis* (years)	23 (7-64)
Age at colectomy (years)	31 (6-67)
Age at creation of CI (years)	36 (17-69)
Follow up time (years)	24 (0-35)
Prior to CI:	
Ileostomy n (%)	67 (79)
IPAA n (%)	8 (9)
IRA n (%)	2 (2)
Transverse colostomy n (%)	2 (2)
Primary CI n (%)	6 (7)
Diverting loop ileostomy at time of CI (n)	21 (25)

Table 3. Patient characteristics in 85 patients receiving a Kock's continent ileostomy at Dept of Surgery, Linköping University Hospital
Continuous variables are presented as median (range).
*One patient with anal atresia from birth was excluded

One-hundred-and-ninety-two re-laparotomies and 45 skin level revisions were performed in 67 (79 %) of the patients. Excluding the skin level revisions and planned stoma closures, 50 patients (59 %) underwent major reoperations including the CI excisions. The most common cause of reoperation was valve slippage and or pouch loosening, often occurring simultaneously and hard to distinguish between in the medical records. Details of the reoperations are presented in Table 4.

Reoperation	N (%)
Nipple slide/pouch loosening n (%)	67 (35)
Loop closure n (%)	37 (19)
Fistulas n (%)	26 (14)
Small bowel obstruction n (%)	16 (8)
Kock-excision n (%)	15 (8)
Hernia n (%)	7 (4)
Abscess n (%)	4 (2)
Stenosis n (%)	3 (2)
Other n (%)	17 (9)

Table 4. Major reoperations (n=192) in 85 patients receiving a Kock's continent ileostomy at the Dept of Surgery, Linköping University Hospital

Fifteen (17.6 %) patients had their CIs excised and converted to end ileostomies. Six (40 %) of the CI excision were due to fistulas, three (20 %) due to incontinence and one each one due to CD inflammation, nipple valve slippage and pouchitis, extreme sensitivity to bowel distension with fainting and intubation problems. In addition, one CI was excised because it had shriveled after long time deviation after SBO surgery and one patient had a perfectly well functioning CI but the patient simply did not like it and opted for conversion to an end ileostomy., CI survival is illustrated in Figure 6.

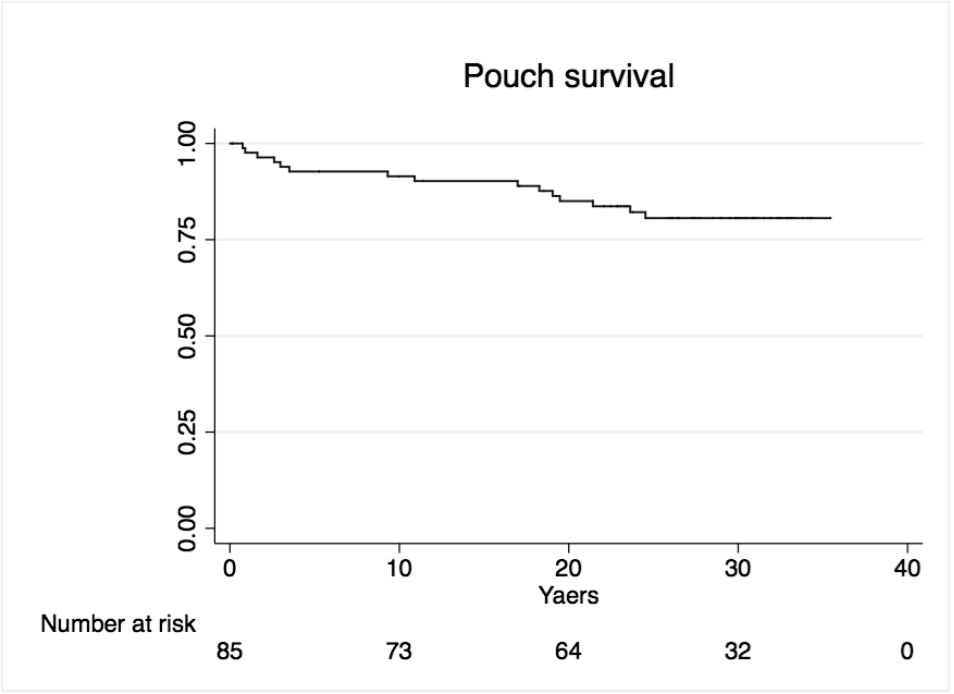


Figure 6. Kaplan-Meier regression to CI excision in 85 patients.

Neither the patients needing reoperations within the first 30 days nor the patients needing reoperation within the first year after CI construction had a significantly increased risk for CI excisions when compared to the rest of the CI population. Reoperation within the first year of CI construction was not associated with increased risk for further reoperations.

The CD patients had a higher crude rate of CI excisions, as compared to the rest of the CI patients, but the difference did not reach statistical significance (25 % vs. 16 %, p= 0.24), see Figure 7. The total rate of reoperations was significantly higher among the CD patients, but the risk for reoperations due to fistulas was significantly higher among the CD patients (83 % vs. 22 %, p=0.01).

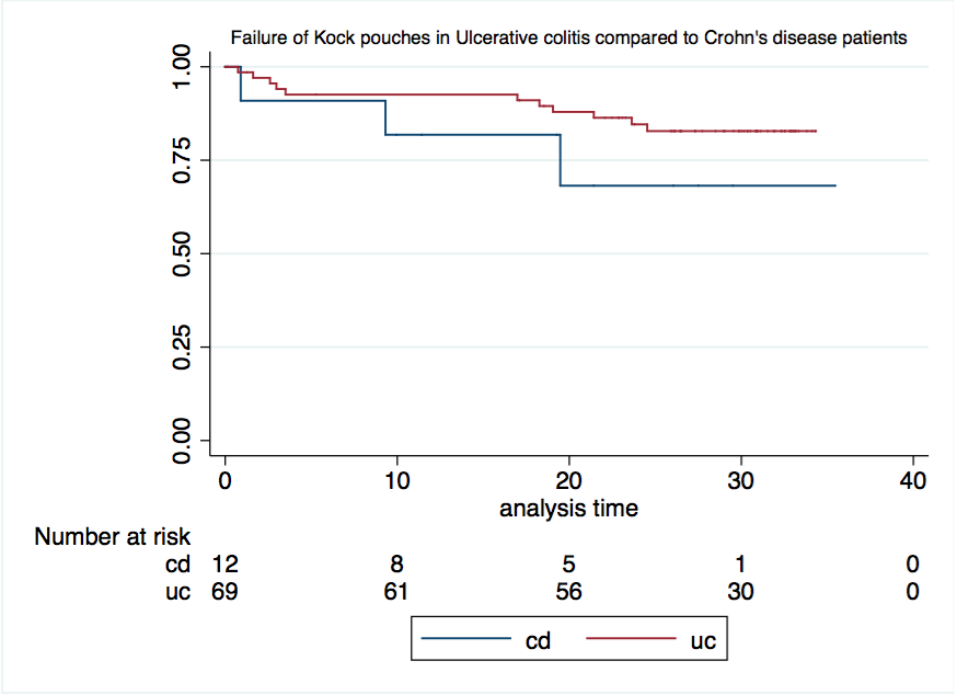


Figure 7. Kaplan-Meier regression to CI excision by diagnosis.
Log-rank p=0.24

Seven patients had IPAA prior to CI in our material. These patients had a significantly higher risk of CI excisions when compared to the patients with end ileostomy prior to CI (71 % vs. 11 % p=0.001) and among the patients with CI excision the mean time to extirpation was significantly shorter among those with previous IPAA (6.5 vs. 14 years p=0.015), see Figure 8.

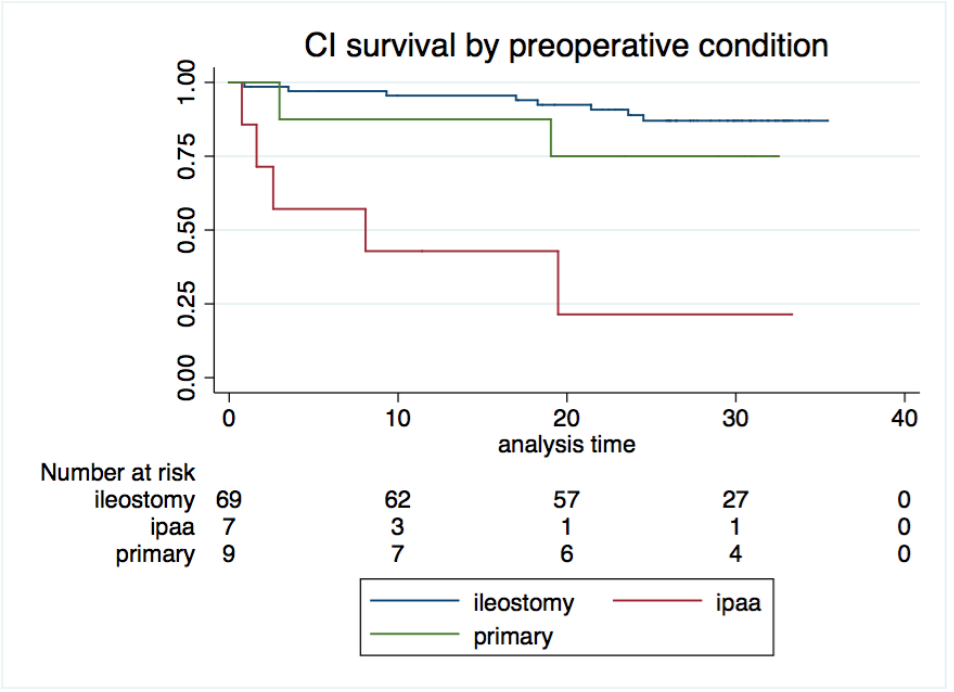
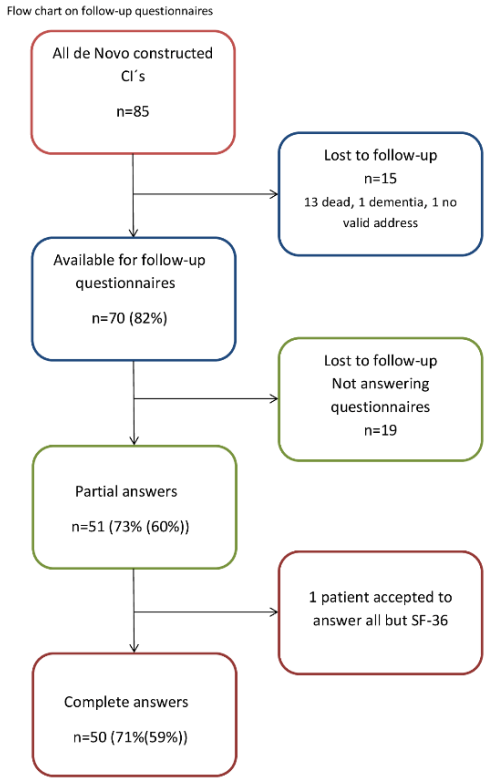


Figure 8. Kaplan–Meier regression illustrating the patency of the continent ileostomy (CI) depending on if the patient had the CI constructed at the time of colectomy, had an end ileostomy, or had an IPAA before the construction of the CI.
Log rank p=0.0001

A diverting loop ileostomy did not affect the risk for reoperations or CI failure. Pouchitis occurred in 56 % of patients and was more common among women (64 % vs. 47 %, p=0.05).

Seventy patients were available for questionnaires and 50 (71 %) replied, see Figure 9. Four of the available 12 CD patients answered and 43 (84 %) of the patients answering still had their CIs in function, see Table 5. Among the 36 patients answering SF-36 in 1998, 22 answered again in this present study. Forty-three (84 %) patients reported satisfaction with their CIs and 42 (82 %) reported that they would choose it again. Among the patients still having their CIs in function 91% reported satisfaction. Two of the four CD patients who replied to the questionnaire reported satisfaction, as compared to 87 % among the rest of the CI patients. Four patients reported dissatisfaction despite having their CI in place and all of them reported daily leakage problems. Four of the eight patients with removed CIs who answered the questionnaires reported satisfaction with their choice of CI.



Available for questionnaires	**n=70**
Answering n (%)	**50 (71)**
Male n (%)	23 (46)
Age at follow-up years (range)	66 (36-89)
Follow up time years(range)	27 (2-35)
Ulcerative colitis n (%)	43 (84)
Crohn's disease n (%)	4 (10)
Indeterminate Colitis n (%)	1 (2)
Familial Adenomatous Polyposis n (%)	1 (2)
Incontinence after surgery n (%)	1 (2%)

Figure 8 and Table 5. Loss to follow-up and answers among the 70 (82%) patients who were available for QoL questionnaires out of 85 patients receiving a Kock's continent ileostomy at Dept of Surgery, Linköping University Hospital.

There was no difference in the SF-36 score when comparing our CI population and the age-matched Swedish reference population, Table 6. Among the 22 patients who answered SF-36 in both 1998 and 2018 the scores on physical function were significantly

better in 1998 (85.9 vs 79.5; p = 0.05), but the scores on vitality were significantly better in 2018 (50.0 vs 59.8; p = 0.04).

The median CI evacuation rate was five times daily (range 2-20) and 60 % reported that they never or rarely needed to evacuate during night.

	CI patients n=50		**Age matched reference population n=286**	
	Mean	95 % CI	Mean	95 % CI
Physical functioning	81.7	75.3-88.1	74.9	72.2-77.6
Role physical	73	61.0-85.0	75.6	72.3-78.9
Bodily pain	63.2	51.7-74.6	65.7	62.6-68.8
General health	62.4	55.8-69.0	65.5	63.0-68.1
Vitality	60.4	53.6-67.2	65.4	62.7-68.1
Social functioning	81.5	74.4-88.6	84.7	82.0-87.4
Role emotional	80.0	69.5-90.5	80.3	77.2-83.4
Mental health	79.0	74.0-84.0	78.0	74.5-80.1

Table 6. SF-36 CI patients vs age match Swedish reference population

Paper II

We identified 727 patients, whereof 428 (59 %) had UC, 45 (6 %) had CD and 254 (35 %) had IBD-U. The median follow-up time was 27 years (interquartile range [IQR], 20.8–30.9). The yearly distribution of CI constructions is presented in Figure 10. The median age was 32 (IQR, 23–42) years at IBD diagnosis, 33 (IQR, 25–43) years at colectomy and 36 (IQR, 28–46) years at CI construction (Table 7). The proportions between the IBD subtypes among the patients subjected to CI changed over the time of the study. Of the patients receiving their CI before 1990, 64 % (328/511) had UC; between 1990 and 2000, 51 % (76/148) had UC, and after 2000, 35 % (24/68) had UC.

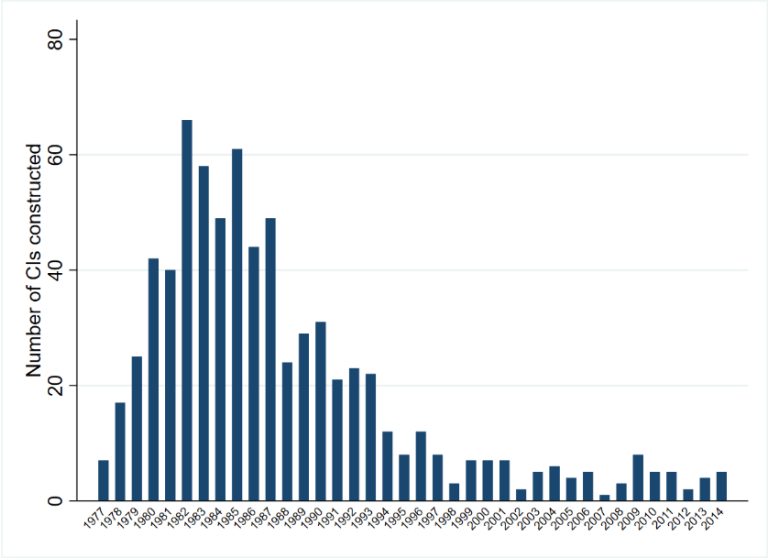


Figure 10.
Number of CIs constructed yearly in Sweden from 1977 to 2014.

Patients	**n = 727**
Male n (%)	378 (52)
Ulcerative colitis n (%)	428 (59)
Crohn's disease n (%)	45 (6)
IBD-U n (%)	254 (35)
Primary sclerosing cholangitis n (%)	51 (7)
Age at diagnosis* (years) median [IQR]	31 [23-42]
Age at colectomy (years) median [IQR]	33 [25-43]
Age at creation of CI (years) median [IQR]	36 [28-46]
Follow up time (years) median [IQR]	27 [21-31]
Previous IPAA n (%)	22 (3)

Table 7. Demographics of the cohort including 727 Swedish patients with inflammatory bowel disease restored with Kock'scontinentileostomy1977–2014.
IQR – Inter Quartile Range

A total of 1484 reoperations were performed in 536 (74 %) patients. There were 1033 stoma revisions, 283 explorative laparotomies or operations for bowel obstruction, 215 stoma closures, 58 operations for fistulas or leakage, 51 hernia operations, and five operations for bleeding. The incidence rate for reoperations was 0.085 reoperation per person year and the median number of reoperations per patient was one (IQR, 0-3). Twenty-six per cent of the patients did not have any reoperations, 24 % had one reoperation, 20% had two reoperations and the remaining 30 % had between three and 15 reoperations each, see table 9. Risk factors significantly associated with an increased risk for reoperations were an IBD-U diagnosis (IRR 1.30, $p < 0.001$), reoperation within the first

year after CI construction (IRR 3.20; p < 0.001) and CI construction after the year 2000 (IRR 2.75, p < 0.001). The association between reoperation within the first year after CI construction and further reoperations was still significant when excluding reoperations that occurred during the first year of CI construction (IRR 0.81; p = 0.001), see Table 9.

		Number of reoperations			Proportion with no re-operation at follow-up [%]		Proportion with CI left in place at follow-up [%]	
Patients	n	Median	IQR	P	5 years	15 years	5 years	15 years
All	727	1	0-3		46.0	37.4	94.5	91.5
Sex				0.19*				
Female	349	2	1-3		42.8	31.2	94.7	91.0
Male	378	1	0-3		49.1	43.0	94.2	92.0
PSC	51	1	1-3	0.60*	42.2	35.3	95.7	88.7
IBD type				0.027**				
UC	428	1	0-3		47.3	39.5	95.0	93.5
CD	45	1	0-2		54.3	41.7	95.5	85.8
IBD-U	254	2	1-3		42.4	32.9	93.3	89.0
Previous IPAA***	22	2	0-4	0.70*	36.4	32.0	95.5	90.1
Age > 40	281	1	0-3	<0.001*	47.5	41.5	93.3	91.7
Reop first year	457	2	1-4	<0.001*	0	0	91.2	87.0

Table 8. Number of reoperations, proportions with no re-operations and proportions with no CI excision. The proportions without reoperations and excision at follow-up was calculated with Kaplan-Meier estimates.
* p values are from individual Mann-Whitney U-test to the rest of the population.
**Kruskal-Wallis test between all 3 IBD types.
*** Unreliable due to inconsistent IPAA coding, probable underestimations.

	Univariable			Multivariable		
Risk factor	IRR	95% CI	p	IRR	95% CI	p
Male	1.07	0.97-1.18	0.20	0.93	0.85-1.04	0.24
PSC	1.28	1.06-1.54	0.01	1.13	0.93-1.36	0.20
UC	0.70	0.64-0.78	<0.001	1		
CD	1.11	0.88-1.39	0.38	1.13	0.89-1.43	0.33
IBD-U	1.41	1.27-1.57	<0.001	1.30	1.17-1.45	<0.001
Age > 40	0.79	0.71-0.88	<0.001	0.81	0.72-0.91	<0.001
Reop first year	3.35	2.92-3.83	<0.001	3.20	2.80-3.67	<0.001
Previous IPAA	1.93	1.44-2.59	<0.001	1.22	0.90-1.67	0.193
– 1990	1			1		
1990–2000	1.01	0.88-1.17	0.87	0.95	0.82-1.10	0.51
2000–	3.57	2.96-4.32	<0.001	2.75	2.24-3.37	<0.001

Table 9. Uni- and multivariable Poisson regression analysis of risk factors for reoperations to the continent ileostomy.

The CI had been excised in 77 (11 %) patients and the median time to excision was 6.6 (IQR 1.8-18.8) years among them. Significant risk factors for CI excision were reoperation within the first year of CI construction (HR 2.35, 95 % CI 1.48-3.71), IBD-U (HR 1.56, 95 % CI 1.00-2.46) and CI construction after the year 2000. Only one patient with previous IPAA was identified to have had the CI removed. Time to CI excision by IBD subtype is illustrated in Figure 11 and risk factors for CI excision are summarized in table 10.

	Univariable			Multivariable		
Risk factor	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Male	1.12	0.73-1.72	0.59	1.11	0.72-1.71	0.64
PSC	1.48	0.72-3.07	0.29	1.37	0.66-2.89	0.40
UC	0.61	0.40-0.94	0.023	1	N/A	N/A
CD	1.36	0.59-3.13	0.47	1.40	0.57-3.43	0.46
IBD-U	1.55	1.01-2.38	0.05	1.56	1.00-2.46	0.05
Age > 40	0.99	0.64-1.55	0.99	1.07	0.68-1.69	0.75
Reop first year	2.38	1.51-3.75	<0.001	2.35	1.48-3.71	<0.001
– 1990	1			1		
1990–2000	1.31	0.74-2.32	0.35	1.19	0.66-2.14	0.55
2000–	3.15	1.46-6.79	0.003	2.74	1.24-6.03	0.013

Table 10. Uni- and multivariable Cox regression analysis of risk factors for excision of the continent ileostomy.

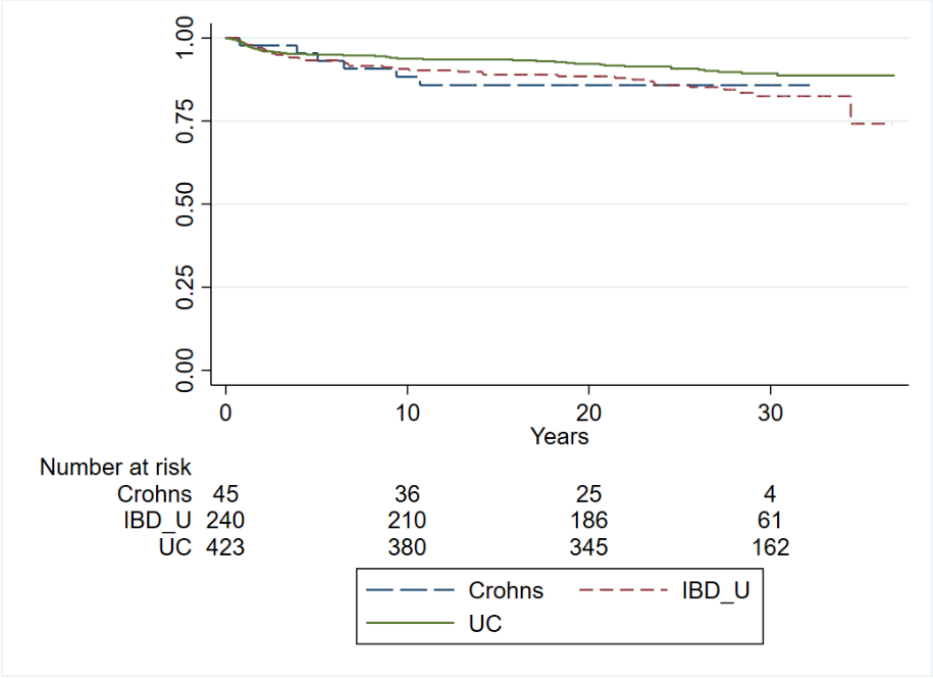


Figure 11. Kaplan-Meier regression to CI excision by diagnosis.

Paper III

Until now we have included 47 patients in the study arms out of which 35 (74 % of the intervention population) have chosen IRA and 12 patients (26 % of the intervention population) have chosen IPAA. In addition, 44 patients have received IPAA, but were not being deemed eligible for both IRA and IPAA, and therefore not eligible for the intervention arms. Eighteen patients (17 % of the whole group) chose an ileostomy, see Figure 12.

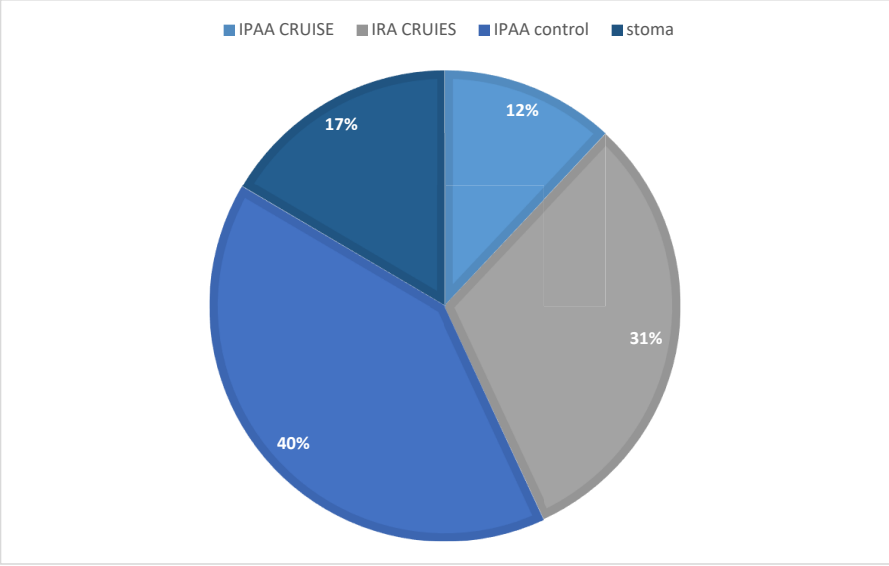


Figure 12. Distribution of patients in CRUISE.

Paper IV

From an initial cohort of 66 143 patients identified with incident UC between 1987 and 2020, 5 194 were subjected to colectomy between 1997 and 2020. Of these, 327 (6.3 %) had their colectomy before the age of 20 years, 615 (11.8 %) after the age of 70 years and 140 (2.7 %) were reported to already have been subjected to colectomy before the onset of UC, leaving a cohort of 4 112 patients for analysis. Reconstruction during the study period was identified in 1 932 (47.0 %) patients, see Figure 12.

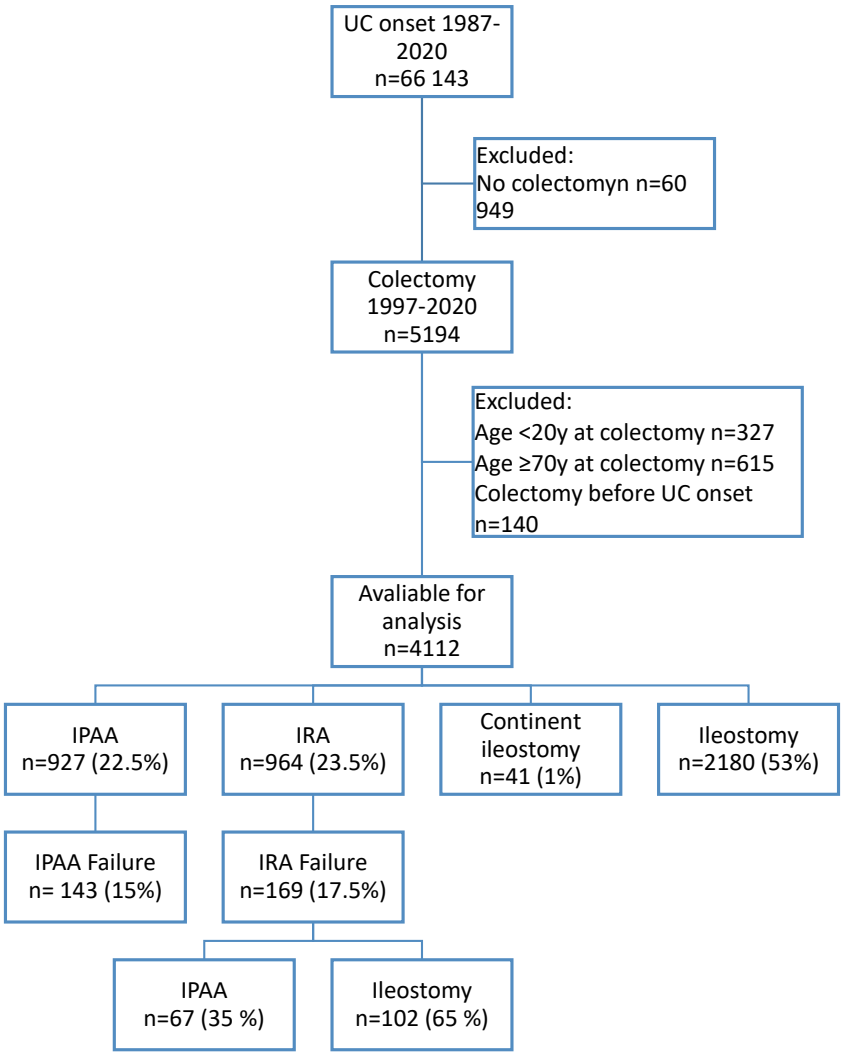


Figure 12. Flow-chart over the UC colectomy cohort studied to evaluate the relationship between IPAA volumes at colectomy hospital and the chance of getting reconstructed.

The reconstructions consisted of 964 (50 %) IRA, 927 (48 %) IPAA and 41 (2 %) CI. Due to the negligible proportion, the CIs were not included in the further analysis.

The chance of getting an IPAA significantly increased with every volume category (HR: 1; 1.49 95 % CI (1.25-1.78); HR 1.79 95 % CI (1.49-2.15); HR 2.11 95 % CI (1.70-2.62)). Other factors associated with an increased chance of getting an IPAA were male sex (HR 1.15, 95 % CI 1.00 – 1.31), and age 30-39 at colectomy (HR 5.59, 95 % CI 4.00-7.82, as compared to a HR of 1.0 in the reference group between 60 and 69 years of age). The chance of receiving an IPAA decreased, while the chance of receiving an IRA increased from the period between 1997-2003 to 2004-2010 and then remained

virtually unchanged throughout the remaining study period. There was no significant association between the average number of IPAAs performed and the chance of getting an IRA. Factors associated with an increased chance of getting an IRA were a diagnosis of PSC (HR 1.25, 95 % CI 1.00 – 1.57) and an age between 20-29 years (HR 1.93, 95 % CI 1.55-2.41). There was a tendency towards higher chance of getting an IRA among men. Results from uni- and multivariate Cox regression models with factors associated with the chance of getting an IPAA or an IRA are displayed in Table 11 and 12, respectively.

Variable	N	N IPAA (%)	Univariate model		Multivariate model	
			HR (95%CI)	p	HR (95%CI)	p
Mean annual IPAA						
0 (reference)	1137	180 (15.8%)	1.00	-	1.00	-
0< - ≤3	1421	311 (21.9%)	1.48 (1.24-1.78)	<0.001	1.49 (1.25-1.78)	<0.001
3< - ≤7	1098	286 (26.0%)	1.87 (1.56-2.25)	<0.001	1.79 (1.49-2.15)	<0.001
>7	456	150 (32.9%)	2.46 (1.99-3.04)	<0.001	2.11 (1.70-2.62)	<0.001
Sex						
Female (reference)	1528	331 (21.7%)	1.00	-	1.00	-
Male	2584	596 (23.1%)	1.09 (0.96-1.25)	0.19	1.15 (1.00-1.31)	0.047
Age						
20-29y	998	268 (26.9%)	5.27 (3.78-7.35)	<0.001	4.74 (3.39-6.64)	<0.001
30-39y	904	278 (30.8%)	6.17 (4.42-8.60)	<0.001	5.59 (4.00-7.82)	<0.001
40-49y	780	214 (27.4%)	5.29 (3.77-7.42)	<0.001	4.88 (3.47-6.86)	<0.001
50-59y	766	127 (16.6%)	2.95 (2.07-4.22)	<0.001	2.74 (1.92-3.92)	<0.001
60-69y (reference)	664	40 (6.0%)	1.00	-	1.00	-
Year						
1997-2003 (reference)	1437	430 (29.9%)	1.00	-	1.00	-
2004-2010	1273	288 (22.6%)	0.81 (0.70-0.94)	0.005	0.80 (0.69-0.94)	0.006
2011-2020	1402	209 (14.9%)	0.56 (0.47-0.66)	<0.001	0.57 (0.48-0.68)	<0.001
PSC			0.96 (0.72-1.27)	0.76	0.84 (0.63-1.12)	0.24
No (reference)	3849	877 (22.8%)	1.00	-	1.00	-
Yes	263	50 (19.0%)	1.01 (0.75-1.35)	0.96	0.92 (0.68-1.23)	0.56
Time from UC diagnosis to colectomy						
<30 days (reference)	684	150(21.9%)	1.00	-	1.00	-
30-365 days	637	149 (23.4%)	1.15 (0.92-1.43)	0.22	1.25 (1.00-1.56)	0.055
>365 days	2791	628 (22.5%)	1.19 (1.00-1.42)	0.045	1.34 (1.12-1.61)	0.002

Table 11. Univariate and multivariate Cox proportional hazard regression models for the chance of IPAA surgery after colectomy (n=4112)

Variable	N	N IRA (%)	Univariate model HR (95%CI)	p	Multivariate model HR (95%CI)	p
Mean annual IPAA						
0 (reference)	1137	257 (22.6%)	1.00	-	1.00	-
0< - ≤3	1421	326 (22.9%)	1.08 (0.92-1.27)	0.34	0.98 (0.84-1.15)	0.81
3< - ≤7	1098	279 (25.4%)	1.25 (1.06-1.48)	0.008	1.15 (0.97-1.36)	0.10
>7	456	102 (22.4%)	1.14 (0.91-1.43)	0.24	1.14 (0.91-1.43)	0.26
Sex						
Female (reference)	1528	342 (22.4%)	1.00	-	1.00	-
Male	2584	622 (24.1%)	1.09 (0.96-1.24)	0.19	1.08 (0.95-1.23)	0.25
Age						
20-29y	998	284 (28.5%)	1.91 (1.54-2.38)	<0.001	1.93 (1.55-2.41)	<0.001
30-39y	904	216 (23.9%)	1.65 (1.31-2.07)	<0.001	1.64 (1.30-2.06)	<0.001
40-49y	780	185 (23.7%)	1.58 (1.25-2.00)	<0.001	1.64 (1.30-2.08)	<0.001
50-59y	766	168 (21.9%)	1.39 (1.09-1.76)	0.007	1.42 (1.12-1.81)	0.004
60-69y (reference)	664	111 (16.7%)	1.00	-	1.00	-
Year						
1997-2003 (reference)	1437	218 (15.2%)	1.00	-	1.00	-
2004-2010	1273	386 (30.3%)	2.09 (1.77-2.46)	<0.001	2.03 (1.71-2.40)	<0.001
2011-2020	1402	360 (25.7%)	1.78 (1.51-2.11)	<0.001	1.71 (1.43-2.03)	<0.001
PSC						
No (reference)	3849	881 (22.9%)	1.00	-	1.00	-
Yes	263	83 (31.6%)	1.60 (1.29-1.99)	<0.001	1.25 (1.00-1.57)	0.046
Time from UC diagnosis to colectomy						
<30 days (reference)	684	129 (18.9%)	1.00	-	1.00	-
30-365 days	637	127 (19.9%)	1.12 (0.89-1.43)	0.33	1.03 (0.82-1.31)	0.78
>365 days	2791	708 (25.4%)	1.52 (1.26-1.82)	<0.001	1.23 (1.02-1.49)	0.027

Table 12. Univariate and multivariate Cox proportional hazard regression models for the chance of IRA surgery after colectomy (n=4112)

We did not detect any significant relationship between IPAA volumes at colectomy hospital and the risk for failure in either of the reconstructive methods, although there was a tendency towards decreasing risk for IPAA failure with increasing IPAA volumes at the colectomy hospital. Primary IRA construction (i.e., IRA in the same procedure as the colectomy) was associated with an increased risk for IRA failure.

Of the 169 patients with IRA failure during the study period, 67 (35 %) were converted to an IPAA.

DISCUSSION

This thesis is focused on evaluating different aspects of the available methods of reconstruction after colectomy for IBD. To be considered a balanced and comprehensive work on that subject this piece is obviously disproportionately CI heavy. This is due to the assessment that both papers on CI contributed substantially to the available literature on reconstruction after colectomy even if only addressing the outskirts of the subject. *Paper I* is the longest and largest follow-up including QoL and function and *Paper II* is, to my knowledge, the only population-based study on CI and with that by far the largest and also almost with the longest follow-up.

More to the very core of the subject, at least from a Swedish or Scandinavian point of view, is the prospective controlled comparison between IRA and IPAA. An RCT would have been preferable in ruling out bias effects on the primary outcome measure and indeed, had we thought it possible, we would most likely have aimed at performing an RCT. However, as previously mentioned, such RCT have already been tried and failed it because the patients insist on choosing method of reconstruction after receiving proper information on their options and we deemed it almost certain that would happen again. There are, however, some benefits to this present approach over an RCT. The most obvious is that we get to know the proportions who choose the different options and if the patients who choose one or another option share certain characteristics. Alongside what we refer to as the intervention arms, i.e. the patients meeting all inclusion criteria and who get to choose method of reconstruction, in the study we will also follow all UC patients subjected to colectomy that chooses to keep their ileostomy or are not considered eligible for both IRA and IPAA (which is an exclusion criteria). This allows us to obtain a comprehensive prospective overview of the UC colectomy cohort.

The sole purpose of reconstruction after colectomy for IBD is to improve the QoL since the disease is already cured by the colectomy or proctocolectomy. However, QoL is subjective and not easy to objectively measure and it is neither easy to relevant comparisons. We found that our CI patients scored in the same range as the age-matched reference population and so did Berndtsson et al[193]. The available option to CI patients is an end ileostomy. In a German study of 783 ileostomy patients an impaired QoL (SF-36), compared to the general population, was reported in the summary score and especially in the physical and mental domains, the latter partly attributed to vitamin b12 deficiency[302] The large proportion (38 %) of CD patients in that study needs to be taken in to account. A prospective comparison of QoL (non-validated forms) on 31 patients before and after CI construction reported improvement after CI construction[303]. Nessar et al. reported better QoL among the patients who had their CIs in place, as compared to their patients who had had their CIs converted back to end ileostomies[180]. We made the same comparison in our local study (*Paper I*) and while there were too few patients (n=8) to reach statistical significance, we saw a strong tendency towards worse QoL among the ileostomy patients. One should keep in mind that ours as well as Nessars comparisons may select the “trouble cases” to the ileostomy group, but may still be an indication of CI provides an improved QoL. Although not proven in a larger prospective

controlled trial, available evidence indicates that CI may improve QoL in patients subjected to colectomy. The comparison to the above-mentioned ileostomy QoL study should of course be equally relevant to IRA or IPAA patients. Somewhat in contradiction, Murphy however reported only subtle QoL benefits of IPAA over ileostomy in a systematic review based on 13 studies including 1 604 patients[232]. The only consistent benefit of IPAA over ileostomy reported by Murphy was an improved body image. Only three of the 13 studies were, however, prospective and no one was randomized. Only one of the studies included in the review was prospective, a single-center comparison of 35 IPAA and 24 ileostomy patients, reported an improvement in overall QoL in IPAA patients but so only according to one of the five instruments. They still concluded that the global QoL was "virtually identical" between the groups, but the IPAA patients reported a better sexual function, body image, energy and work/social function[233]. Three studies that compared QoL before and at multiple times after IPAA construction reported improved QoL one year after surgery[221,234,235]. Concerning QoL in IRA, Tonelli reported better satisfaction among 98 IRA patients compared to 98 IPAA patients. It appears, however, as if they disregarded the patients with a failed IRA. In that same report IPAA patients reported more dietary restrictions, but better energy level[237]. Another small study also found better satisfaction among IRA patients[206]. Although the ambition is not to establish the superiority of one method over the other, there is definitely relevant new knowledge to be gained from the CRUISE trial *(Paper III)*.

Considering functional outcomes in IRA and IPAA, the knowledge comes mainly from retrospective studies, as discussed under a previous headline, and it is reasonable to think that the CRUISE trial will provide further insight in the matter. To gain information on functional outcome in CI patients, the most relevant group to compare against would be end ileostomy patients but even that is, in my opinion, of limited interest. What might be of some interest is the number of nighttime evacuations vs. need to change stoma appliance during nighttime and stoma incontinence vs. risk of leakage from stoma appliance. There is considerable heterogeneity in available studies on leakage from stoma appliances and rates between 17 and 87 % are reported.[304,305], more indicating a wide variety in definitions than such variety in actual problems. Hoekstra reported "stoma problems" in 21.8 % of end ileostomy patients vs. 9.9 % of CI patients[214]. Nessar et al. reported a median 5 (0.5 nighttime) CI evacuation compared to 8 (2 nighttime) appliance changes among the ileostomy patients.[180] However, in that paper there were only 9 end ileostomy patients.

We found a total reoperation rate among CI patients of 71 % in the local study (*Paper I*) and 72 % in the national one (*Paper II*). This corresponds well to the 72 % reported in the largest (n=423) single-center material published[190]. The only study with longer follow-up (a median follow-up of 31 years), Berndtsson et al. reported a need for "Major revisions" in 65 % of CI patients, they did not report on "minor revisions". In our local study, we found a fairly similar 59 % need for major revisions. In the national study we could not reliably distinguish major revisions from either skin level revisions or planned stoma closures, and this probably rendered an overestimation (of unknown size) regarding the need for revisions.

Causes of reoperations were not possible to determine from the population-based study and did actually in part prove a little hard even in the local study with access to medical records. From the medical records it appears that valve slipping and pouch loosening often occur simultaneously. Moreover, it is not of much consequence to neither the patient nor the surgeon to distinguish between the two since both, if severe enough, require repeat laparotomy. Consequently, we grouped them together in the local study. In line with most previous authors[127,180,190,193,212,214,215,238,273,306], we found valve slippage and/or pouch loosening to be the most common cause of major revisions in the local material, responsible for some 35 % of reoperations. Our finding that while valve slippage or loosening causes most reoperations fistulas causes most CI removals is in line with Nessar and colleagues report of 330 CI patients from the Cleveland Clinic[180].

Wasmuth et al. reported a significantly increased risk for further revisions among the CI patients reoperated within the first year of CI construction[273]. In the local study, we saw no such tendency but in our national cohort we found a significantly increased risk for both further revisional surgery as well as eventual CI excision among those with a reoperation within the first year after surgery. Given that the national cohort is almost ten times the size of the local one it appears confirmed that early CI problems demanding surgical revisions are a risk factor for further CI problems. Still, this information is not likely to have much impact on how to handle patients needing reoperations within the first year. If anything, in cases with several early complications it may be advisable to consider CI excision rather than multiple early revisions.

As previously mentioned, it has been debated whether or not it is advisable to offer CI to patients with CD. The way to address that question should not primarily be to compare the CI outcomes between CD and UC patients. Instead, it should be addressed in a more absolute way. Are the outcomes among the CD patients acceptable, regardless of how they are compared to the UC patients? In our local study, only four CD patients answered the questionnaires and only half of them reported satisfaction. This is obviously a too small specimen to make any definite conclusions, but at least some CD patients will be satisfied with CI. Also, in the local study 80 % of the 12 CD patients still had their CI in place after 20 years, indicating reasonable satisfaction since they would probably have been removed otherwise. This was confirmed in the national cohort including 45 CD patients, 96 % of which had their CI in place after 5 years and 86 % after 15 years. Both Nessar et al. and Aytac et al. argue that it is reasonable to offer CI to carefully selected, well-informed CD patients at highly specialized centers. Our findings support this statement[180,295]. With regards to IPAA in CD patients, the argument is very much the same as for CI. From initial poor outcomes[281,282] reported in the early 1990s improved patient selection alongside improved medical treatment of CD in pouches have rendered IPAA reasonable, provided careful patient selection and preoperative information, to suggest to some CD colitis patients[283-287].

CI as an option after failed IPAA has been investigated by some previous authors[238,307-309]. In the largest publication of which, from the Cleveland Clinic in 2009, they reported, among their 64 patients, revision rates in the range of other CI publications and an estimated 5-year CI retention rate of 95 %. On the other hand, the median follow-up was

only 4.2 years[238]. Lian and colleagues alongside the other authors on the subject also give a fairly enthusiastic view[238,307]. All of the other publications being far smaller and of similar follow-up time. In our local study the CIs converted from IPAAs had a far worse excision rate of 71 %. The mean time CI extirpation was 6.5 years (as compared to 14 years for the rest of the excised CIs I our study), a little longer than the follow-up in the Cleveland Publication, but the shape of our Kaplan-Meir curve indicates that hardly made any difference. We do not have any reasonable explanation to why the CIs converted from IPAA fall out far worse from our center when every other aspect of our CI management appears to be going well. This will be the subject of thorough future scrutiny. In the national study previous IPAA was the strongest risk factor for reoperations but there were too few excisions among the CIs converted from IPAA to allow for further analysis. Although there are somewhat conflicting data, I think it is safe to say that one should be very careful with patient selection and thorough in information before suggesting conversion from IPAA to CI.

In the national CI cohort, we found that CI created after the year 2000 was associated with a significantly increased risk for reoperations as well as CI excisions, as compared to CIs created earlier. During the same period, CI had gone from being a standard reconstruction to a rare procedure saved for exceptional cases. Correspondingly, the proportion of UC patients went from 64 % before 1990 to 35 % after 2000. Moreover, it has been suggested that the use of infliximab and other advanced medical therapies might have either selected worse cases to colectomy or postponed an inevitable colectomy putting the patient in worse condition before colectomy. In support of this theory, Uzzan and colleagues found worse outcome after IRA among patients previously subjected to infliximab[271]. While the above-mentioned factors most likely have contributed to the worse outcomes in later years one must be humble to the possibility that decreased volumes and the subsequent decrease in fresh experience and training could have a negative impact on the CI outcomes.

Larger hospital colectomy volumes have been shown to be associated with reduced morbidity and mortality associated to the colectomy[100,310,311]. Higher IPAA volumes have also been shown to be associated with lower IPAA failure rates[312]. One study investigating the chance of getting an IPAA based on the IPAA volumes at the colectomy hospital reported a significantly higher chance of receiving an IPAA if having the colectomy at a high volume (>20) IPAA hospital[313]. Another study, primarily addressing colectomy outcomes, reported 47 % IPAA in high (>11) colectomy volume centers compared to 17 % in low (≤3) colectomy volume centers[100]. However, both those studies were conducted in the USA with a healthcare system substantially different from the Swedish and total reconstructions rates around 30-35 % compared to 47 % in Sweden[100,101,313]. Our study is the first to investigate the chance of any reconstruction based on the reconstructive volume at the colectomy hospital. We chose to let the number of annual IPAA procedures represent “reconstructive volume” since IPAA is the technically more challenging procedure and any center or surgeon that can perform IPAA can perform IRA, but not necessarily the other way around. Hence, had we used the annual number of any reconstruction, hospitals not able to perform IPAA might have ended up in the “high volume” category. Our finding that the chance of getting an IPAA increased

with every volume category is in line with the findings of both Aquina and Kaplan[100,313]. I do not believe that patients with contraindications to IPAA surgery are more common at low-volume hospitals. If anything, patients with comorbidities and severe disease are more common at high volume hospitals. Subsequently, our suggestion is that there is an inequality in the care provided to UC patients in Sweden based on which hospital is providing them primary surgical care.

PSC is viewed as a relative contraindication to IRA due to the increased CRC risk among PSC-UC patients[270,314,315]. Still, we found a significantly increased chance of getting an IRA among PSC patients compared to the non-PSC UC patients. Available data do not offer a clear explanation for this but leave room for guesses and our guess is that in the small volume hospitals, performing a larger proportion of IRA may suggest that this is the locally available method rather than the best suited option.

We also found a greater chance of getting an IPAA among men. That might have been explained by concern for reduced fertility in women, but if that was the cases one would assume to see a corresponding increase in IRA among women, which we did not. Instead, this suggests a structural inequality based on sex.

My suggestion to address these and any structural inequalities would be that all patients subjected to colectomy would be assessed and considered for reconstructive options by a multidisciplinary board including experienced gastroenterologists and surgeons experienced in all methods of reconstructive surgery.

Strengths and Limitations

Paper I

The single-center approach with access to medical records provides good control over the data. The addition of questionnaires on QoL, function and satisfaction provide an interesting extra layer of information. The relatively large cohort and long follow-up time are also to be considered strengths.

The retrospective design and the lack of any control or comparator population is on the other hand a limitation. The single-center design also makes the outcome less generalizable.

Paper II

The population-based design with a large cohort and long follow-up time are strengths. The "real world" data not solely derived from highly specialized centers may also provide more generalizable results. On the downside, the quality of the data is dependent on the register and while the register is proven to be fairly reliable, there is a higher for erroneous reporting of rare procedure codes. Moreover, detailed demographic data, such as smoking habits and BMI was not available. Data on QoL or functional data were furthermore not possible to obtain. The retrospective design is also a limitation.

Paper III

The prospective, controlled setting and the multi-center, multi-national approach are to be considered strengths with the CRUISE trial. Also, the inclusion of a wide range of UC patients subjected to colectomy as controls is a strength. The lack of randomization is indeed a considerable limitation to the study, but as repeatedly stated, that would probably not be possible. The lack of good data upon which to base the power calculation is also a limitation, posing a risk of under-powering of the study. However, we do not expect any of the two restorative procedures to be superior, rather equally good when it comes to patient satisfaction in well-informed and selected patients.

Paper IV

The primary strength is the nationwide population-based design with very limited loss of follow-up and a long follow-up time. The included registers are reliable both regarding diagnosis and surgical procedure codes[316,317]. The primary weakness is the lack of information on whether permanent stoma was an active choice or the result of inadequate information on the available reconstructive options. Since the study solely relied on register data, information on factors such as disease severity, presence of low-grade dysplasia and anal incontinence were not available.

CONCLUSIONS

CI is a reconstructive option associated with a considerable need for revisional surgery, but which offers offering a high degree of satisfaction and a good quality of life.

Despite the above-mentioned substantial need for revisional surgery a large majority of the CI patients get to keep their CIs for several decades.

There is a need for further prospective comparison between IRA and IPAA and since an RCT has been deemed unfeasible the CRUISE approach appears to be a good way forward.

There is structural inequality among UC patients in Sweden subjected to colectomy. This is based on the hospital providing primary surgical services and sex.

FUTURE ASPECTS

With a large and, as it appears, ever increasing arsenal of advanced pharmacological treatments for UC and CD colitis, I think the most relevant research area for these patients in the near future is to build and define the algorithm for which treatment to use when and of course fit colectomy and subsequent reconstruction into such an algorithm.

To contribute to this effort, we are right now starting up a prospective study named TRIOCOL, in which UC patients that have failed on their second line of advanced medical treatment will get standardized information on third line medical treatment as well as colectomy and get to choose between the two. The patients will be followed-up for five years with satisfaction as primary endpoint but QoL, function and complications will also be investigated. We are also investigating the impact of infliximab and other biologics on reconstructions after colectomy in UC patients. With data from the NPR, SWIBREG and prescribed drug register UC patients subjected to colectomy will be identified and divided into two groups depending on whether or not they at any point have received treatment with biologics. We will compare the proportions who have received any type of reconstruction, the type of reconstruction (IRA/IPAA/IC), reoperations after reconstruction, complications, and failure between the two groups.

The rather discouraging finding that CIs converted from IPAA at our center seems to do far worse than CIs converted from IPAA at other centers demands further investigation. We intend to, once more, review the medical records of these patients to look for other factors, surgical or demographic, that might explain this finding.

On the outcome of reconstructions, the ongoing CRUISE study (Paper III) will cover QoL, functional aspects and complications and hopefully provide both patients and surgeons a better overview over what to expect from the different options after colectomy.

Considering technical aspects of the existing reconstruction techniques, the CI appears to be fairly well established and while there have been attempts to address especially issues with the nipple valve non have yet proved any advantage over the “Kock” way of fashion a CI. It should be mentioned that CI, being a very niche procedure with small numbers of annual procedures even at the largest centers, do not have the optimal prerequisite for method improvement. The TIES, continent ileostomy implant is still under investigation, but from what is published yet it does not appear very promising.

On the staging of IPAA, the results from the French GETAID Chirurgie IDEAL trial, randomizing between 3-stage and modified 2-stage IPAA will be very interesting and possibly change our (normally 3-stage) approach[157]. Another interesting future aspect of IPAA surgery is the use of robotic assisted laparoscopy. While yet to scientifically prove any advantage over conventional approaches[170], the access to the pelvic floor for narrow rectal dissection seems appealing.

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