

ILONA HELAVIRTA

Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis for Ulcerative Colitis

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Ileal Pouch-Anal Anastomosis
for Ulcerative Colitis

ACADEMIC DISSERTATION

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of Tampere University,
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ACADEMIC DISSERTATION

Tampere University, Faculty of Medicine and Health Technology
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Finland

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To Tuomo and Urho

Abstract

The first choice of management is medical treatment in ulcerative colitis (UC). UC is limited to the rectum and colon and can therefore be cured surgically in case of failure of medical therapy or if there is a risk of cancer. Traditionally it has been estimated that approximately 30% of UC patients will require surgery at some point. Preliminary population-based studies suggest lower rates of surgery in the era of new biological medication. Restorative proctocolectomy (RPC) and ileal pouch-anal anastomosis (IPAA) is the preferred procedure for most UC patients. With this operation permanent stoma is avoided and an acceptable bowel movement frequency can be achieved.

The main goal of IPAA surgery is high quality of life without permanent enterostomy and there is evidence that high volume units and surgeons achieve better results. Not only the surgery itself but also the postoperative complications and their care may have serious effects on the functional outcomes of these patients and therefore also on health-related quality of life (HRQoL). This thesis aimed to study the surgical outcomes of IPAA patients in the second biggest centre performing IBD surgery in Finland, Tampere University Hospital.

The first study examined how our surgical technique has evolved since its introduction in 1985. Indications for surgery and early and late morbidity after surgery are reported. We changed our anastomosis technique from hand-sewn to stapled anastomosis and the use of covering ileostomy has become a standard. Indications for surgery were acute colitis 45%, chronic colitis 48% and cancer or risk of cancer 7%. In our results, the serious pouch complications were comparable to those reported in the literature, with leakage occurring in 12.5%. We found that the use of covering ileostomy seemed to protect against major complications.

The second and third studies consist of questionnaires evaluating HRQoL and the functional outcomes of the IPAA patients. The generic Finnish 15D questionnaire was used to compare IPAA patients to general population. The majority of the patients had HRQoL comparable to that in general population. The disease-specific IBDQ questionnaire was

used to compare IPAA patients to non-operated UC patients not undergoing surgery. IPAA patients with good functioning pouch had HRQoL similar to those with non-operated UC patients in remission or with mildly active disease.

The functional outcomes were assessed by Öresland score. These were good for the majority (70%) of patients and remained stable over time. No statistically significant connection was found between early pouch complications and poor pouch function. Anastomosis stricture was twice as common in poorly functioning pouches as in well-functioning pouches.

The fourth part of the study is concerned with pouch failure rate. The reasons for this and the life cycle of the pouch were analysed. We found that out of 491 IPAA patients, 53 (10.8%) experienced pouch failure (10 women, 43 men). Half of the pouch failures occurred within the first five years and 70% within seven years of IPAA surgery. The typical reasons for pouch failure were septic events that led to poor function. No reasons were found to account for the preponderance of men in the failure group. In patients who had Crohn's disease diagnosed after IPAA 47% experienced pouch failure. We also explored the pouch excision operations, of which were 52 (98% of pouch failures) and found that morbidity after the operation is common but complications mainly minor in nature.

In conclusion, this thesis is a comprehensive research entity on long-term IPAA surgical results for UC in a tertiary referral centre in Finland. The results for complications after surgery and the functional outcomes of the J-pouches and HRQoL are in line with earlier reports and the technique we use is justifiable.

Tiivistelmä

Haavaisen paksusuolen tulehduksen ensilinjan hoitomuoto on lääkehoito. Tauti rajoittuu paksu- ja peräsuoleen ja on sen vuoksi parannettavissa leikkauksella. Perinteisesti on arvioitu, että noin 30% potilaista tarvitsee kirurgiaa jossain vaiheessa sairautta. Viimeaikaiset ensimmäiset väestöpohjaiset tutkimukset viittaavat kirurgisen hoidon vähentyneen biologisten lääkkeiden aikakaudella. Tavallisin leikkausmenetelmä on paksu- ja peräsuolen poisto ja ileumista rakennettu J-pussi ja ileoanaalinen anastomoosi (IPAA). Tällä leikkauksella vältetään pysyvä suoliavanne ja saavutetaan yleensä hyvä toiminnallinen tulos ja elämänlaatu.

J-pussileikkauksella ja etenkin sen jälkeisten mahdollisten komplikaatioiden hoidolla voi olla kauaskantoiset seuraamukset J-pussin toiminnallisiin tuloksiin ja sitä kautta elämänlaatuun. Tämän väitöskirjan tarkoitus on raportoida J-pussileikkausten tulokset Tampereen yliopistollisessa sairaalassa (TAYS), joka on Suomen toiseksi suurin IBD kirurgiaa suorittava keskus.

Väitöskirjan ensimmäisessä työssä tarkastelimme, miten käyttämämme kirurginen tekniikka on kehittynyt alun 1985 jälkeen. Raportoimme myös indikaatiot leikkaukseen sekä leikkauksen jälkeiset varhais- ja myöhäisvaiheen komplikaatiot. Olemme siirtyneet saumanteon tekniikassa alkuperäisestä käsisaumasta saumauslaitteella tehtävään anastomoosiin. Suojaavan avanteen teosta on tullut standardi. Indikaatiot J-pussileikkauksiin olivat akuutti koliitti 45 %, krooninen koliitti 48 % ja syöpä tai syöpäriski 7 %. Tuloksemme komplikaatioiden suhteen on verrattavissa kirjallisuudessa esitettyihin lukuihin. Anastomoosin lekaasiprosentti oli 12,5 %. Havaitimme, että suojaavan ileostooman käyttö näytti suojaavan merkittävimmitä komplikaatioilta.

Toinen ja kolmas työ olivat kyselytutkimuksia, joissa selvitettiin J-pussipotilaiden elämänlaatua ja J-pussin toiminnallisia tuloksia. Valtaosalla J-pussipotilaista havaittiin olevan yhtä hyvä elämänlaatu kuin väestöllä, yleisellä 15D elämänlaatukyselyllä mitattuna. Sairausspesifisellä kyselyllä mitattuna havaitimme, että niillä potilailla, joiden J-pussin

toimi hyvin, elämälaatu oli vastaava kuin leikkaamattomilla potilailla, joiden sairaus remissiossa tai taudinkuva lievä.

J-pussin toiminnallinen tulos tutkittiin käyttämällä Öreslandin kaavaketta. J-pussien toiminnalliset tulokset olivat hyvät 70 %:lla potilaista pitkässäkin seurannassa. Hyvin ja huonosti toimivien pussin välillä ei löytynyt tilastollisesti merkittävää eroa IPAA leikkauksen jälkeisissä varhaisissa J-pussi-komplikaatioissa. Anastomoosin striktuura oli lähes kaksi kertaa yleisempi huonosti toimivien pussien potilailla kuin hyvin toimivien.

Neljännessä työssä tutkimme mikä on leikkaamiemme J-pussien poistoprosentti, katsoimme syitä pussien poistoon ja analysoimme pussien elinkaarta. Havaitimme, että 491:stä J-pussipotilaasta 53 (10,8 %) pussi oli poistettu käytöstä; naisia 10 ja miehiä 43. Tyypillisimmät syyt poistoon olivat tulehdukselliset tapahtumat, jotka johtivat J-pussin toiminnan huononemiseen. Syytä siihen miksi pussinpoisto oli yleisempää miehillä ei löytynyt. Potilaat, joilla diagnosoitiin Crohnin tauti J-pussin teon jälkeen, 47 %:lla pussi ei ollut enää käytössä. Yhdellä potilaalla pussi jäi paikoilleen, mutta muilta 52 (98 %) potilailta pussi poistettiin kirurgisesti. Sairastavuus pussinpoistoleikkauksen jälkeen oli melko yleistä, mutta vakavia komplikaatioita oli vähän.

Tässä väitöskirjassa selvitetään J-pussileikkauksen pitkäaikaistuloksia isossa suomalaisessa keskuksessa. Yhteenvetona voimme sanoa, että sairaalamme J-pussikirurgian tulokset niin leikkauskomplikaatioiden, kuin J-pussin toiminnallisten tulosten kuin elämänlaadunkin suhteen ovat hyväksyttävät ja tekniikkamme perusteltua.

List of Original Publications

The thesis is based on the following original publications, referred to in the text by the Roman numerals (I–IV):

- I Restorative Proctocolectomy for Ulcerative Colitis in 1985-2009. Helavirta I, Huhtala H, Hyöty M, Collin P, Aitola P. *Scand J Surg*. 2016 Jun;105(2):73-7
- II Health-Related Quality of Life after Restorative Proctocolectomy: A Cross-Sectional Study. Helavirta I, Hyöty M, Oksanen P, Huhtala H, Haapamäki J, Aitola P. *Scand J Surg*. 2018 May 107(4):315-21
- III Long-term functional outcome after restorative proctocolectomy: a cross-sectional study. Helavirta I, Hyöty M, Huhtala H, Collin P, Aitola P. *Scand J Gastroenterol*. 2018 Oct 22:1-5.
- IV Pouch failures following restorative proctocolectomy in ulcerative colitis. Helavirta I, Lehto K., Huhtala H., Hyöty M., Collin P., Aitola P. (Submitted)

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Abbreviations

15D	15-dimensional
5-ASA	5-aminosalicylic acid
ATZ	Anal transitional zone
BMI	Body mass index
CCI	Charlson comorbidity index
CD	Crohn's disease
C-D	Clavien-Dindo
CI	Confidence interval
CRC	Colorectal cancer
DS	Double stapled
ECCO	European Crohn's and Colitis Organisation
FAP	Familial adenomatous polyposis
HRQoL	Health-related quality of life
HS	Hand-sewn
IBD	Inflammatory bowel disease
IBDU	Inflammatory disease unspecified
IBDQ	Inflammatory bowel disease questionnaire
IC	Indeterminate colitis
ICD-9 and ICD-10	International Statistical Classification of Diseases 9 th and 10 th versions
IMA	Inferior mesenteric artery
IPAA	Ileo-anal pouch anal anastomosis
IPF	Ileal pouch failure

IVF	In vitro fertilisation
mPDAI	modified pouchitis disease activity index score
NIHW	National Institute for Health and Welfare
NSAID	Nonsteroidal anti-inflammatory drug
NCSP	NOMESCO Classification for Surgical Procedures
OR	Odds ratio
PDAI	Pouchitis disease activity index score
PSC	Primary sclerosing cholangitis
RAL	Robot-assisted laparoscopy
RPC	Restorative proctocolectomy
SBO	Small bowel obstruction
SCCAI	Simple clinical colitis activity index
SMA	Superior mesenteric artery
TaTME	Transanal total mesorectal excision
TNF	Tumour necrosis factor
UC	Ulcerative colitis

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1 Introduction

Inflammatory bowel diseases (IBD) are divided into ulcerative colitis (UC), Crohn's disease (CD), unspecified inflammatory bowel disease (IBDU) and indeterminate colitis (IC) which are chronic inflammatory conditions of the gastrointestinal tract. The aetiology is unknown but is thought to be multifactorial (Ananthakrishnan, 2015). IBD may be associated with considerable morbidity and may also require expensive healthcare.

UC is restricted to the large bowel and rectum. Inflammation starts from the rectum and extends proximally in a continuous manner to a variable length. Clinical features of UC include bloody diarrhoea and abdominal pain. The clinical course of the disease is often relapsing (Baumgart & Sandborn, 2007).

UC is a global disease but the incidence varies geographically. The incidence is highest in the westernized countries and still rising. A North-South gradient has been identified for IBD and in Europe the highest incidence rates are in Northern countries. (Ananthakrishnan, 2015)

Patients with long-lasting UC are at increased risk of colorectal cancer (CRC). Chronic inflammation is an important factor in the pathogenesis of CRC. Young age at diagnosis, extensive disease and primary sclerosing cholangitis (PSC) have been shown to increase the risk. (Keller et al., 2019.)

The treatment of UC is primarily medical, although surgery is required in about 30% of patients. There is new population-based data to suggest that the percentage requiring surgery may be falling in the era of biological medication (Frolkis et al., 2013; Ronnblom et al., 2016). Indications for surgery are acute drug resistant disease, chronic refractory disease or cancer or risk of cancer. When surgery is considered a multidisciplinary approach in collaboration between the gastroenterologists and colorectal surgeon looking after the patient is essential.

In 1978 Parks and Nicholls introduced the ileal pouch anal anastomosis (IPAA) (Parks & Nicholls, 1978). Restorative proctocolectomy (RPC) with a J-pouch attached to the dentate line replaced previous techniques and offered the patients the option of a stoma-

free life with acceptable bowel movement frequency. This operation has become the most used in UC surgery and is suitable for most patients. Over the four decades of J-pouch the operation has undergone refinements in surgical technique. Even so, it is still associated with significant morbidity and failure (Sagar & Pemberton, 2012).

This thesis aimed to evaluate the overall long-term surgical outcome of Finland's second biggest centre performing pouch surgery for UC. The specific aims were to evaluate the evolution of the surgical techniques used and changes in these, to evaluate the long-term health-related quality of life (HRQoL) and functional results of the IPAA patients operated on in our hospital and finally to evaluate the percentage of pouch failure and analyse the reasons for this.

2 Review of the Literature

2.1 Ulcerative colitis

The 1875 case report of Wilks and Moxon describing ulceration and inflammation of the entire colon in a young woman who had died of severe bloody diarrhoea was an early instance of UC (Kirsner, 2001).

In UC, the inflammation is restricted to the large intestine. The inflammation may be limited to rectum but may also involve the entire colon. UC is characterized by a relapsing and remitting course (Silverberg et al., 2005). The disease may present at any age, but occurs more often in the second or third decade of life with another peak suggested in the 60s. Men and women are equally affected (Ananthakrishnan, 2015).

The chronic nature of UC exerts a major burden on patients in burden of therapy, hospitalizations, surgery, health-related quality of life, economic productivity and social functioning.

2.1.1 Epidemiology and aetiology

The incidence and prevalence of UC have increased worldwide in the past 50 years and over the last 15 years also in developing countries (Cosnes et al., 2011). High prevalence of UC has been reported in Northern Europe (Manninen et al., 2010; Jussila et al., 2013), the United Kingdom and North America (Bernstein et al., 2006; Molodecky et al., 2012). The incidence of UC varies geographically. A North–South gradient has long been known for UC. In Europe, higher incidence rates have been found in Northern countries (Shivananda et al., 1996). In Finland a population-based study showed the highest reported incidence of 24.8 per 100,000 (Jussila et al., 2012) and a north-south gradient of prevalence has been reported (Jussila et al., 2013).

The precise aetiology for UC is unknown. The current hypothesis is a dysregulated mucosal immune response to commensal gut flora in genetically susceptible individuals (Xavier & Podolsky, 2007). Support for a role for genetics in the pathogenesis of IBD was initially derived from familial aggregation studies and twin studies, which suggested an important hereditary component (Ananthakrishnan, 2015). Since the identification first of a IBD risk gene in 2001, over 200 risk gene loci involved in IBD pathogenesis have been identified. The risk genes identified are those involved in regulating innate and adaptive immune responses or intestinal barrier functions. This strongly suggests that, in addition to genetics, the intestinal microbiota and environmental factors also play a critical role in IBD pathogenesis (Zhou et al., 2017; Ananthakrishnan et al., 2018).

Patients with IBD demonstrate a dysbiosis in their luminal microbiota, most consistently characterized by a reduction in the diversity of this microbial community compared with that in healthy individuals (Nagalingam & Lynch, 2012; Zhou et al., 2017; Ananthakrishnan et al., 2018). This could render the host more susceptible to colonization with pathogens (Ananthakrishnan et al., 2018).

Potentially relevant environmental influences start from mode of childbirth and early-life exposures to exposures later on in adulthood (Ananthakrishnan, 2015). Smoking and appendectomy have been shown to have a negative impact on the risk of developing UC (Lowenfels & Maisonneuve, 2001; Mahid et al., 2006; Myrelid et al., 2017). The use of antibiotics has been reported to correlate with IBD incidence. Nevertheless, the role of antibiotics seems to be more evident in CD than in UC (Shaw et al., 2011). Other medications have been thought to be associated with IBD including nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives and postmenopausal hormone therapy (Ananthakrishnan, 2015; Piovani et al., 2019). In studies concerning dietary factors in the risk of IBD, high dietary intakes of total fats, dietary n-3 polyunsaturated fatty acids, omega-6 fatty acids and meat are reportedly associated with an increased risk of UC. High vegetable intake was associated with decreased UC risk (Hou et al., 2011; Piovani et al., 2019).

2.1.2 Clinical presentation and diagnosis

UC is a relapsing non-transmural inflammatory disease that is restricted to the rectum and colon. UC primarily presents in late adolescence and early adulthood, although the diagnosis may be made at any age. Depending on the anatomic extent of involvement, patients can be classified as having proctitis, left-sided colitis (involving the sigmoid colon with or without the involvement of the descending colon), or pancolitis. The diagnosis is based on the clinical picture, endoscopy and histopathology findings (Baumgart & Sandborn, 2007). The most used classification system for UC is the Montreal classification, which takes into account the extent and severity of the disease (Silverberg et al., 2005). The Montreal classification is presented in Table 1.

Typical UC symptoms consist of bloody diarrhoea, passage of mucus and abdominal cramping during bowel movements. Severe attacks of illness present as fever, tachycardia, weight loss, abdominal distension or reduced bowel sounds. Patients with toxic megacolon usually have continuous bleeding, need for blood infusion, abdominal pain and tenderness and colonic distention in imaging. Severe symptoms are less common in left-sided colitis and proctitis. (Baumgart & Sandborn, 2007). In clinical practice, disease activity is typically described as mild, moderate or severe based on the severity of symptoms as mentioned above. (Kornbluth et al., 2010).

The endoscopic features of mild inflammation are erythema, vascular congestion, and partial loss of the visible vascular pattern. Moderately active colitis is characterized by a complete loss of vascular pattern, blood adhering to the surface of the mucosa and erosions, often with a coarse granular appearance and mucosal friability that bleeds on being lightly touched (Magro et al., 2017).

UC is a chronic inflammatory process limited to the mucosa. The microscopic features can be divided into mucosal architecture, lamina propria cellularity, neutrophil granulocyte infiltration, and epithelial abnormality (Magro et al., 2017).

Table 1. Montreal classification of ulcerative colitis
(Silverberg et al., 2005)

Extent of the disease	Anatomy
E1 Ulcerative proctitis	Involvement limited to the rectum
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 proximal to the splenic flexure
Severity	Definition
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 daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h

ESR, erythrocyte sedimentation rate

2.1.3 Medical therapy

Medical therapy is the first treatment of choice for UC. The pharmacodynamics, indications used to treat UC are summarized in Table 2. The treatment strategy for UC is mainly based on the severity, distribution and pattern of the disease (Harbord et al., 2017). The extent of inflammation influences the patient's management and the choice of delivery system for a given therapy. Suppositories or enemas are usually the first-line choice for proctitis and left-sided colitis respectively, whereas oral therapy is appropriate for extensive colitis (Magro et al., 2017). Currently the goal in medical therapy for UC is to induce and maintain remission both clinically and endoscopically that is mucosal healing (Boal Carvalho & Cotter, 2017).

Current treatment options for UC include 5-aminocyclic acids (5-ASAs), like sulphasalazine and mesalamine in both oral and rectal formulations, corticosteroids, thiopurines, calcineurin inhibitor (cyclosporine), anti-tumour necrosis factor (TNF)- α drugs (including infliximab, adalimumab and golimumab), more recently the anti-integrin drug vedolizumab and most recently tofacitinib, Janus kinase (JAK)-inhibitor (Feagan et al., 2013; Harbord et al., 2017; Antonelli et al., 2019).

The medical therapy can be divided into induction therapy and maintenance therapy. Induction therapy is tailored individually depending on the classification of the disease. Maintenance therapy is recommended for all patients with UC. (Magro et al., 2017.) Striking differences in the frequency, timing and degree of mucosal healing may be found in different UC patients, even under similar pharmacological approaches, underlining the importance of several genetic, epigenetic, environmental and microbiotic factors in this process (Rieder et al., 2012).

Table 2. Medications used in the treatment of ulcerative colitis
(Harbord et al., 2017, Ruskoaho et al., 2018)

Medications	Mechanism	Indication
Aminosalicylates: mesalamine and sulphasalazine p.o. or topical	Likely local anti-inflammatory effect	<ul style="list-style-type: none"> – topical: proctitis and mild to moderate left sided colitis – oral: mild to moderate extensive colitis – inducing and maintenance of remission
Corticosteroids	Inhibit the expression of inflammatory genes, function of cytokines and function of inflammatory cells	<ul style="list-style-type: none"> – with moderate to severe activity with extensive disease inducing remission – mild active disease with no response to mesalamine inducing remission – acute severe colitis, first line therapy i.v.
Thiopurines: Azathioprine and mercaptopurin	Affect T-cell function and modulate cytokine function	<ul style="list-style-type: none"> – steroid-dependent or steroid-refractory disease alone or combined with anti-TNF alpha – inducing and maintenance of remission
Calcineurin inhibitor: cyclosporine	Immunosuppressant: effect on division and function of activated T-cells	<ul style="list-style-type: none"> – second line therapy in acute severe colitis – -inducing remission
Anti-TNF alpha: infliximab, adalimumab	Inhibits the pro-inflammatory cytokine TNF α	<ul style="list-style-type: none"> – steroid-dependent or steroid-refractory disease alone or combined with thiopurine – immunomodulator-refractory disease – inducing and maintenance of remission – infliximab second or third-line rescue therapy in acute colitis
anti-integrin: Vedolizumab	Inhibits the gut specific integrins	<ul style="list-style-type: none"> – first or second-line biological therapy – inducing and maintenance of remission
JAK-inhibitor: Tofasitinib	Inhibits JAK-1 and JAK-3 kinases and lowers the effect of interleukins and interferons	<ul style="list-style-type: none"> – moderate to severe colitis if prior biological treatment fails – inducing and maintenance of remission

2.2 Surgery for ulcerative colitis

Traditionally approximately 30% of UC patients have required surgery at some point (Hendriksen et al., 1985). Over the past 25 years, medical therapy for IBD has changed with the widespread use of immunosuppressive therapy and the introduction of anti-TNF α therapy and other biologics. Recent population-based studies demonstrate that the rates for surgery are decreasing (Frolkis et al., 2013; Ronnblom et al., 2016). A recent population-based study reported 5-, 10-, 15-, and 20-year cumulative colectomy rates after diagnosis to be 4.1%, 6.4%, 10.4% and 14.4% respectively (Parragi et al., 2018). A Finnish study reported lower colectomy rates but no change in indication for surgery before and during the biologics era (Kolehmainen et al., 2019). As to the new drugs (anti-integrins and JAK

inhibitors), studies are needed to show the trend (Olivera et al., 2017). The indications for surgery are fulminant colitis, chronic colitis with relapsing symptoms or cancer or risk of cancer. The risk of CRC over time especially in active chronic inflammation, approach risk level of up to 18% in 30 years (Eaden et al., 2001). Contraindications for pouch surgery are an incompetent sphincter mechanism and carcinoma in the lower rectum requiring excision of the anorectum. CD is generally contraindicated (Chang et al., 2017). A multidisciplinary approach between the gastroenterologists and colorectal surgeons looking after the patient is essential when considering surgery (Öresland et al., 2015).

2.2.1 History

Surgical treatment of UC emerged in the early 1900s but was initially sporadic and mostly experimental. Appendicostomy, caecostomy, and colostomy with colonic irrigations sought to eliminate a “noxious substance”. “Pelvic autonomic neurectomy” and distal vagotomy in the 1950s were futile efforts to correct “parasympathetic overactivity” (Kirsner, 1998). Subtotal colectomy with ileorectal anastomosis and partial colon resections during the 1950s and 1960s were discontinued because of recurrent disease (Kirsner, 1998). In the 1950s Bryan Brooke developed a better functioning everted end-ileostomy connected to one-stage proctocolectomy and this remained the surgical standard for many years (Parc et al., 1999). He stated that “if surgery is to be acceptable for UC it first must be reasonably safe and have a mortality lower than that of the disease itself (22–33%)”. He specified the indications for surgery and proposed that the surgery be done in stages depending on the nutritional and general condition of the patient (Brooke, 1952).

In 1969 a continent ileostomy (Kock pouch) was first described by Kock and was considered a major improvement over the conventional end ileostomy (Kock, 1969). Continent ileostomy allows planned evacuation of the small bowel through a reservoir equipped with a nipple valve and patients can live without an external appliance for stool. Today, continent ileostomy studies have revealed that this procedure has many short and long-term complications, mainly related to the valve mechanism. Despite many revisions, patients who retained their pouch were very satisfied and considered their quality of life to be good or excellent (Nessar & Wu, 2012). There are some centres, like the Cleveland clinic, which still perform continent ileostomy for certain indications but only a handful of surgeons familiar with the procedure can be found in practice (Aytac et al., 2014).

The description of IPAA in 1978 by Parks and Nicholls, however, quickly displaced the Kock pouch from a position of prominence in the surgical treatment of patients with UC (Parks & Nicholls, 1978). Nissen first described an ileal anal anastomosis as early as in 1933 but it was not until Parks and Nicholls created the ileal reservoir in the anastomoses that the functional results began to be acceptable (Parks & Nicholls, 1978). At first there were experiments with different shapes of pouches (Figure 1.) but today the J-pouch is the most used because it is straightforward to construct and has the fewest stapled lines and its

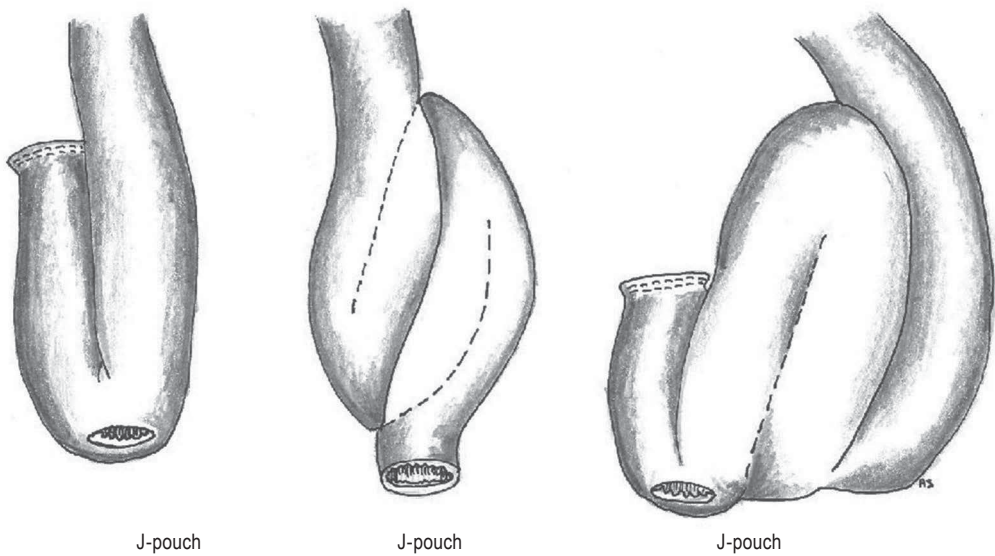


Figure 1. Various ileal pouch designs used

volume is suitable to allow acceptable function (Lovegrove et al., 2007; McCormick et al., 2012).

2.2.2 Surgical anatomy

The large intestine is approximately 1.5m long and consists of cecum, vermiform appendix, ascending, transverse, descending and sigmoid colon and rectum, Figure 2. The ileum enters the cecum obliquely and partly invaginates into it forming the ileocecal valve. This valve portions the ileal fluid into colon. The large intestine borders on the abdominal cavity below the liver, stomach and spleen. The ascending and descending colon lie retroperitoneally along the right and left sides of the abdominal cavity. The transverse colon is mobile and hangs down as a loop to a variable extent. The sigmoid colon is an S-shaped loop of variable length (usually about 40cm) that connects the descending colon to the rectum. The large omentum attaches the transverse colon to stomach with the gastrocolic ligament and hangs down covering the small bowel. The rectum (approx. 15cm long) is the terminal fixed part of the large intestine. The upper third is covered with peritoneum and below that the rectum is retroperitoneal and ends in the anal canal (4cm) at the level of the end of the coccyx before the anus in the perineum. In the anal canal the dentate line (mucocutaneous line) indicates the border where the intestinal mucosa becomes squamous epithelium and the skin starts, Figure 3. The arterial supply to the ileum and colon all the way to the splenic flexure drives from superior mesenteric artery (SMA) and its branches. The ileocolic artery is of specific importance because it supplies blood to the J-pouch. The

descending colon and rectum have blood supply from inferior mesenteric artery (IMA) and its branches Figure 2. The arteries that supply the colon anastomose in the marginal artery. (Moore et al., 2014; Hiltunen, 2018.)

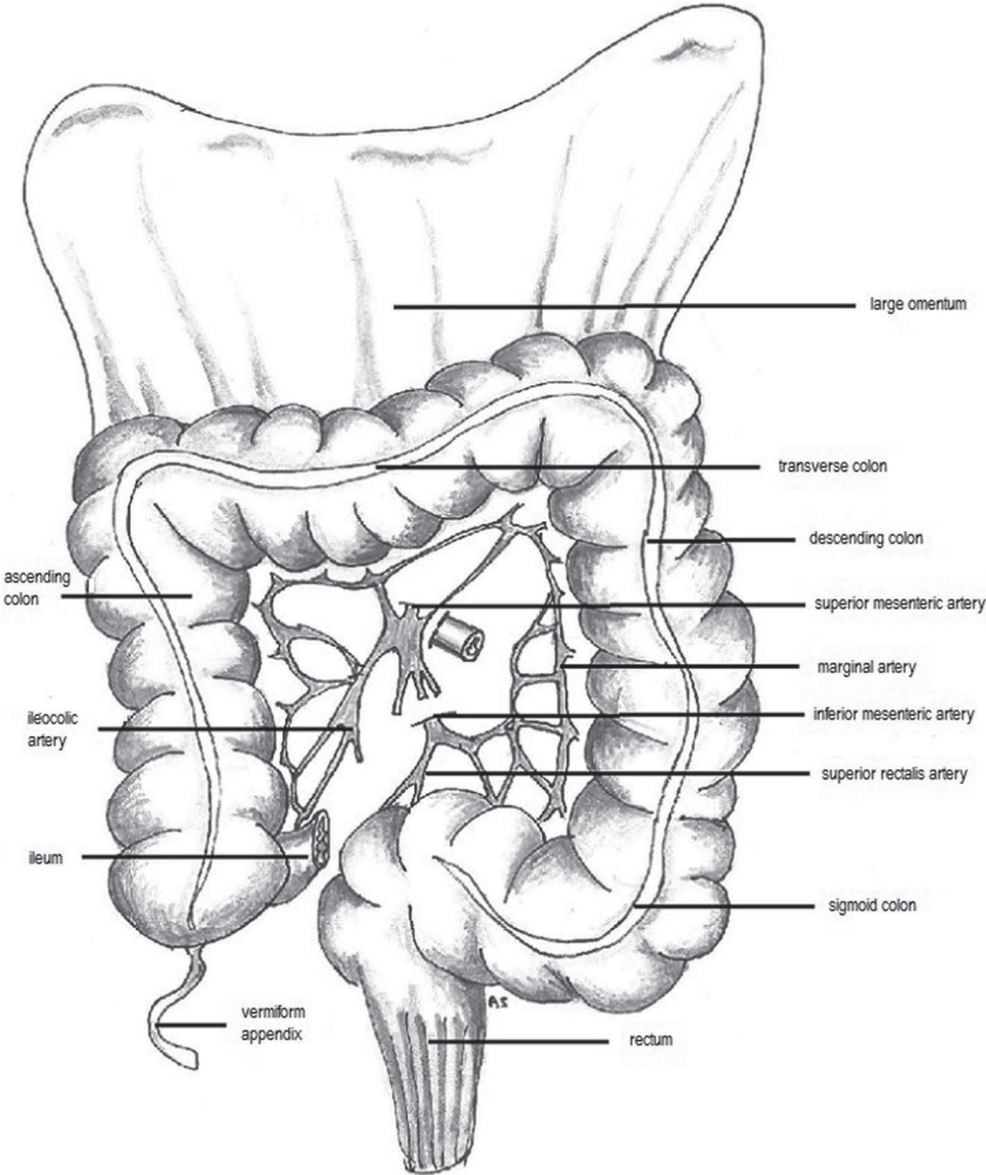


Figure 2. Surgical anatomy of the colon and rectum

2.2.3 Surgical technique

2.2.3.1 Subtotal colectomy

If surgery is performed in an emergency setting or if the risks for anastomoses are otherwise too high, colectomy with end ileostomy is performed first and the rectum is left *in situ*.

As the ascending and descending parts of the colon lie retroperitoneally, they have to be mobilized before dissecting the mesocolon. The transverse colon and its mesocolon are mobile, but attached to the large omentum. The omentum is preserved and detached from the transverse colon. If the surgery is not for malignant disease or if there is no high grade dysplasia and therefore risk of malignancy, the vessels and mesocolon can be divided near the bowel. The ileocolic artery should be preserved when possible for the J-pouch to have good circulation. A laparoscopic approach is associated with a lower postoperative complication rate and therefore should be preferred, also in emergency settings if the expertise needed is available (Öresland et al., 2015). The management of the remaining rectum following colectomy for acute severe colitis includes three options: 1) intra-peritoneal rectal stump closure, 2) creation of a mucous fistula in the rectosigmoid region 3) positioning the closed rectosigmoid remnant in the subcutaneous tissue in an attempt to prevent peritonitis in the event of a stump blowout. Rectal stump leakage resulting in pelvic sepsis occurs in 6–12% (Carter et al., 1991). The largest study on this matter during the laparoscopic era compared Hartmann's stump and subcutaneous placement of the rectosigmoid stump. There was no difference between groups between overall pelvic sepsis or reoperation rates but the leakage rate was twofold in the subcutaneous group although statistically it did not reach significance. Hartmann's procedure is easier to perform and was associated with decreased operating time and conversions. (Gu et al., 2013.)

2.2.3.2 Proctectomy

Most surgeons prefer to mobilize the rectum in the avascular mesorectal plane as this allows bloodless preparation in a clearly defined anatomical plane and because they are used to this technique from rectal cancer surgery. The technique of rectal dissection close to the rectum preserving the mesorectum may have effect on the rate of septic complications and the preservation of sexual function (Öresland et al., 2015). One series with 131 patients in which the mesorectum was preserved had fewer septic complications (1.5%) than the previously reported 3–15% (Rink et al., 2009). Sexual dysfunction has been reported to be as high as erectile dysfunction in 14% and retrograde ejaculation in 19% after RPC and is due to damage to pelvic nerves lying close beneath the mesorectum in the upper pelvis (Tiainen et al., 1999a; Hueting et al., 2004).

2.2.3.3 Anastomosis

During the early years of IPAA surgery anastomosis was performed hand sewn (HS). The idea is to do a total mucosectomy and sew the ileal pouch to the dentate line. This procedure has the advantage of removing all the diseased or potentially diseased mucosal tissue. Later on, double-stapled (DS) ileoanal anastomosis has been performed 1–2cm above the dentate line leaving the transitional mucosa in place. Stapled anastomosis is technically easier and results in less tension on the mesentery and this could be important in patients with shorter mesenteries. (Figure 3.)

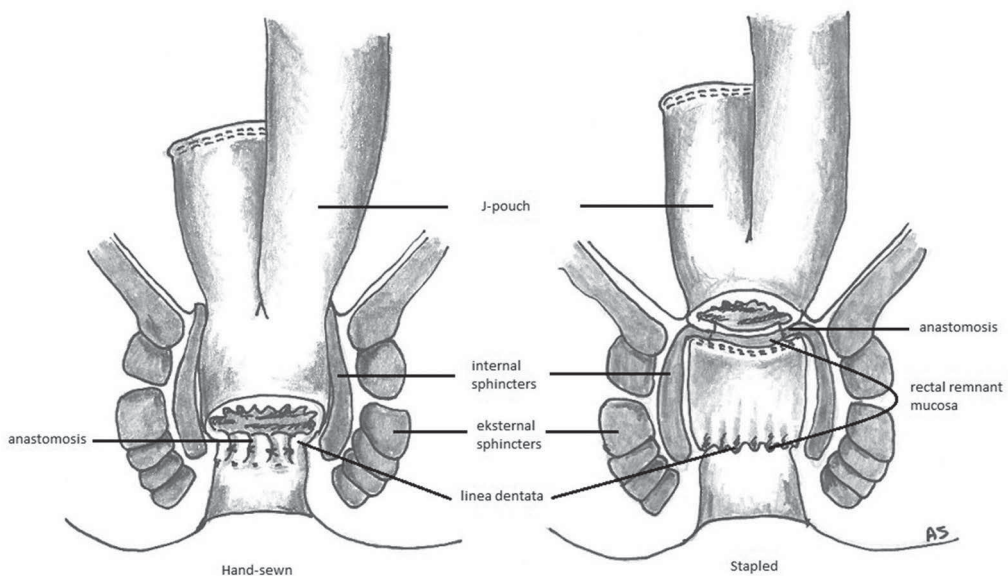


Figure 3. An illustration of the difference between hand-sewn and stapled ileal-pouch anal anastomosis

HS anastomosis has been reported to be more frequently connected with incontinence and pad use, especially at night time (Reilly et al., 1997; Lovegrove et al., 2006; Kirat et al., 2009). Preserving the rectal mucosa is important in the preservation of anal resting pressure (Gozzetti et al., 1994) and this is thought to explain the more frequent incontinence with HS technique.

Septic pouch complications and anastomotic stricture have reportedly been more frequent with hand-sewn anastomoses (Ziv et al., 1996; Fukushima et al., 2000; Kirat et al., 2009). In one meta-analysis including four prospective randomized studies no statistically significant differences were found in terms of functional outcome or manometric sphincter

continence (Schluender et al., 2006). Several large studies show that there is no difference in the likelihood of developing pouchitis after IPAA between HS and DS (Lovegrove et al., 2006; Kirat et al., 2009). However, cuffitis, in which the rectal stump is inflamed, is solely a DS problem and the incidence has been reported to be as high as 15% (Thompson-Fawcett et al., 1999).

Mucosectomy is performed to eliminate the possibility of inflammatory and/or neoplastic changes, but mucosectomy of the anal transitional zone (ATZ) is not always complete (Lovegrove et al., 2006). A large study on IPAA patients showed the pooled prevalence of dysplasia to be the same 1.13% in the pouch and the remnant and the cases of malignancy are very rare in the IPAA population (Borjesson et al., 2004; Scarpa et al., 2007). Risk factors for dysplasia of the pouch or rectal cuff include cancer or dysplasia in the proctocolectomy specimen, duration of UC preoperatively PSC and chronic pouchitis (Scarpa et al., 2007). No difference in the incidence of dysplasia in the residual rectal cuff has been detected (Lovegrove et al., 2006).

The European Crohn's and Colitis Organisation (ECCO) guidelines state that DS should be preferred but the rectal cuff left should be no more than 2 cm in length (Öresland et al., 2015). The American guidelines state that both anastomotic types are acceptable but that it is important for IBD surgeons to master both techniques (Ross et al., 2014).

2.2.3.4 *Covering stoma*

IPAA can be performed as a one-, two- or three-stage procedure. In emergency conditions, a total colectomy with end ileostomy will precede the pouch procedure. ECCO states that IPAA for ulcerative colitis should be covered with a loop ileostomy, especially in the presence of risk factors (Öresland et al., 2015). However, the issue about covering ileostomy is still under debate and practices vary between institutions.

Pelvic sepsis can not only have immediate potential life-threatening consequences but is also associated with pouch dysfunction and ultimate pouch failure (Forbes et al., 2009). Several risk factors for pelvic sepsis have been identified, such as high body mass index (BMI) >30, preoperative corticosteroid medications, the operating surgeon or the final pathology in the specimen being CD or IC (Kiran et al., 2010).

Only one randomized controlled study has been published with 23 diverted and 22 non-diverted patients, reporting that risk of pelvic sepsis was not increased by omitting diversion (Grobler et al., 1992) Some studies report that use of covering ileostomy reduces the morbidity of anastomosis leakage and pelvic sepsis (Tjandra et al., 1993; Williamson et al., 1997; Heuschen et al., 2001; Mennigen et al., 2011). Arguments against the routine use of a diverting ileostomy include the need for a subsequent surgical procedure, which entails an additional hospital admission and further re-operative morbidity (Grobler et al., 1992; Nastro et al., 2010; van Westreenen et al., 2012; Sahami et al., 2016; Karjalainen et al., 2019). Other authors conclude that closure of ileostomy after three-stage IPAA

is associated with a low rate of serious complications (Wong et al., 2005; Rottoli et al., 2018) and therefore routine use should be acceptable. A multicentre report reviewing the practice of pouch surgery in Great Britain and Ireland showed a slight decrease in the use of covering ileostomy: before 2013 it was 82.9% and in the period 2013–2017 it was 77.3% (Worley et al., 2018a).

In a recent large (n=621) retrospective multicentre study the leakage rates were quite high for both ileostomy and no ileostomy groups (16.7% vs. 17.1%, p=0.921). The higher leakage rate than previously reported was thought to be due to operating on only IBD patients excluding FAP patients and to the lack of a precise definition of anastomotic leakage. The authors found no benefit from the use of covering ileostomy but speculated that patients with known risk factors for leakage should be operated on with subtotal colectomy and end ileostomy and the IPAA should be postponed. (Sahami et al., 2016.) Therefore, these factors may serve to create a more selective trend based as regards the use of covering ileostomy (Lovegrove et al., 2011).

Most centres plan ileostomy closure three months after RPC because earlier surgery is believed to be more difficult due to adhesions and therefore more dangerous (Mennigen et al., 2014). The largest study (n=1504) on outcome of ileostomy closure after RPC studied this matter and found wound infection to be significantly more frequent in early closers (Wong et al., 2005). The selected studies exploring the use of covering ileostomy are summarized in Table 3.

Study	Study design	Patients	Main results	Conclusions
Karjalainen et al., 2019	Retrospective	ileostomy 119, no ileostomy 391	More early leakage, SBO and dehydration in ileostomy group. Ileostomy closer, considerable morbidity. No difference in pouch failure.	Ileostomy only for high risk patients
Remzi et al., 2006	Retrospective	ileostomy 1725, no ileostomy 277	No difference in septic complications. Late SBO more common in ileostomy group. No difference in functional results or HRQoL	Omission of ileostomy in carefully selected patients.
Weston-Petrides et al., 2008	Review	17 studies ileostomy 721, no ileostomy 765	No functional differences. Significantly more leakages without ileostomy.	Omission of ileostomy in carefully selected patients.
Wong et al., 2005	Retrospective	1504 ileostomy closers	Complications 11.4% Hospital stay 3 (median)	Ileostomy closure with low morbidity and short hospital stay.
Ikeuchi et al., 2005	Prospective nonrandomized study	ileostomy 92, no ileostomy 150	No significant difference in complications Combined ileostomy closer complications raise the total morbidity of ileostomy group.	Omission of stoma superior for selected patients.
Grobler et al., 1992	Randomized controlled trial	ileostomy 23, no ileostomy 22	Omitting stoma did not increase pelvic sepsis. Loop ileostoma itself associated with complications.	
Järvinen & Luukkonen, 1991	Prospective	ileostomy 15, no ileostomy 16	Functional results did not differ nor did early complications. Hospital stay and operating time were shorter in no stoma group.	Ileostomy may be unnecessary for suitable cases with no technical difficulties
Mennigen et al., 2011	Prospective nonrandomized study	ileostomy 89, no ileostomy 33	Pouch-related septic complications significantly lower with ileostomy group as well as reoperations. The cumulative hospital stay was lower in ileostomy group	Covering ileostomy reduces pouch-related septic complications and early relaparotomies.
Widmar et al., 2019	Prospective nonrandomized study	ileostomy 317, no ileostomy 670	Ileostomy does not lower long-term risk of pouch failure in case of leakage.	Omitting ileostomy is a safe procedure for selected patients

Sahami et al., 2016	Retrospective, multicentre	ileostomy 305, no ileostomy 316	More SBO, stricture and fistula were seen in the ileostomy group. No effect on pouch failure. High complication rates associated with stoma closure.	Colectomy with ileostomy first, followed by completion proctectomy without an ileostomy for majority of patients improve outcome.
Mennigen et al., 2014	Systematic Review	26 studies, 2146 ileostomy closures	Overall morbidity 16.5%, reoperations 3%, SBO 7.6%. wound infection 4% in ileostomy closures	Considerable morbidity of ileostomy closure reduces the overall benefit of temporary fecal diversion.
Tjandra et al., 1993	Retrospective	ileostomy 50, no ileostomy 50	Pelvic sepsis and leakage more common in without ileostomy as well as reoperation. No difference in pouch function at 6 and 12 months but poorer HRQoL for without ileostomy group.	IPAA without diversion is not as safe as with covering ileostomy.
Heuschen et al., 2001	Retrospective case-control study	ileostomy 114, no ileostomy 57	Fever short- and long-term complications without ileostomy.	The one-stage procedure is clearly superior.
Williamson et al., 1997	Prospective nonrandomized study	ileostomy 50, no ileostomy 50	No difference in postoperative complications. More life-threatening complications among patients without ileostomy.	IPAA without covering ileostomy is associated with increased risk to life. Its routine use cannot be recommended.

Table 3. Characteristics of studies exploring the use of covering ileostomy in IPAA

2.2.3.5 *Laparoscopy and novel techniques*

Laparoscopy has been shown to be safe and effective in UC surgery in several studies. The major advantages are reduced blood loss and faster recovery and reduction in adhesion development (Tilney et al., 2007; Hull et al., 2012). In addition, the long-term functional results have been reported to be similar to open surgery (Mineccia et al., 2018; Lavryk et al., 2018). In a large case-matched study, laparoscopic IPAA was associated with better functional results and quality of life during the first two years and after that the results became similar (Lavryk et al., 2018). Due to reduction in adhesion formation after laparoscopic approach, the infertility rate has been reported to be significantly reduced in young women (Bartels et al., 2012; Beyer-Berjot et al., 2013). Remzi et al. found in a large pouch salvage surgery study that primary laparoscopy IPAAs tended to have longer rectal stump than open procedures (Remzi et al., 2015) and might cause obstructive problems. However, these results concerned solely the pouch failure group.

An alternative minimally invasive technique for IPAA in the approach to laparoscopic surgery includes the use of the da Vinci robot (Intuitive Surgical Inc., Sunnyvale, CA). Robot-assisted laparoscopy (RAL) provides improved 3-dimensional and high-definition visualization of the pelvis and multiple degrees of freedom, which greatly enhances performance, especially when working in narrow spaces. Robotic surgery has come to be used increasingly in colorectal surgery. The advantages of RAL over conventional laparoscopy have so far been limited to a lower conversion rate and lower intraoperative blood loss, as reported by two meta-analyses primarily based on data from studies on rectal cancer (Yang et al., 2012; Trastulli et al., 2012). The use of RAL for IPAA is still confined to single-centre studies with limited numbers of patients. These studies have used RAL for proctectomy after colectomy and then the colectomy was performed using traditional laparoscopy first because of the benefits afforded by robot in the pelvic area. Two studies concluded that RAL is safe and feasible for proctectomy and IPAA (Pedraza et al., 2011; McLemore et al., 2012) one states that the short-term outcome is comparable to that of laparoscopy (Miller et al., 2012) and one study compared RAL to open surgery and found the results acceptable (Mark-Christensen et al., 2016).

The last new innovative techniques in surgery such as single incision laparoscopic surgery, transanal total mesorectal excision (TaTME), and natural orifice specimen extraction surgery have also been introduced to UC surgery. These are not in general use and experiences are based on small single-institution series (de Lacy et al., 2019). Moreover, TaTME, for example is a challenging technique with a long learning curve and if not properly mastered can lead to devastating complications (Atallah et al., 2017).

2.2.4 Surgical outcome

The main goal of IPAA surgery is for the patient to have a well-functioning pouch and long-lasting good quality of life. These are the most important parameters when assessing the operative outcome.

2.2.4.1 Early morbidity

IPAA surgery is considered major abdominal surgery and therefore a certain number of other than pouch-related complications are inevitable even though everything is done according to good surgical practice. The patients are typically young and otherwise healthy and operations are performed in tertiary centres so mortality is low – usually less than 1% (Tulchinsky et al., 2003; Fazio et al., 2013).

Although mortality is very low the IPAA procedure has an appreciable postoperative morbidity of 35% (Fazio et al., 2013). Morbidity after IPAA is traditionally divided into early complications (< 30 days after surgery) and late complications.

The most important complications considering the functional results are pouch-related complications 6–25% (de Zeeuw et al., 2012; Sagar & Pemberton, 2012). Pouch-related septic complications include anastomotic leakage, abscesses and fistulas (Heuschen et al., 2002a; Shen et al., 2006). A recent long-term study from Belgium reported the overall leakage rate for patients operated on in 1990–2015 (n=335) to be 14.9% (Germain et al., 2017). Different definitions of pelvic sepsis or septic complications or how a leakage is diagnosed sometimes makes it difficult to compare the results of different studies. Risk factors for pouch-related septic complications include steroid use, BMI >30, patient's age older than 50 years and surgeon's experience (Kiran et al., 2010). The risk of preoperative use of anti-TNF α and anti-integrin agents is unclear.

A large review study calculated the pooled incidence from 46 studies for pelvic sepsis to be 7.5% (95% CI, 6.1–9.1). In this study the fistula was apart from pelvic sepsis and the pooled incidence was 4.5% (95% CI 3.5–5.7) (de Zeeuw et al., 2012). Because patients who experience early leakage or other pelvic sepsis have a higher risk of subsequent pouch dysfunction and failure, aggressive management is required (Heuschen et al., 2002b). Recently, endo-cavitational vacuum therapy (Endo-SPONGE[®]) with early perineal closure of the leak has been reported to be more effective than the previously mainly used passive strategy with diversion and drainage. A German study reported no difference between early closure treated patients and control patients without leakage in pouch function ($p = 0.647$) and pouch failure rates (0/18 versus 5/133, $p > 0.99$) were also similar. Conventional treatment resulted in poorer pouch function ($p = 0.016$) and a higher pouch failure rate (5/22 versus 5/107, $p = 0.013$) than in control patients (Wasmann et al., 2019).

Another early pouch-related complication is haemorrhage, but this is quite uncommon (Fazio et al., 1995). Pouch endoscopy with clot evacuation and irrigation with adrenaline solution is often successful (Lian et al., 2008).

In addition to the morbidity caused by ileostomy closure, the early complications of ileostomy patients must be born in mind. Some have reported no difference in overall complication rates after the initial RPC (ileostomy 29.2% vs. no ileostomy 42.4%, $p=0.167$), but fewer second laparotomies for the management of complications in the ileostomy group (4.5% vs. 30.3%, $p<0.001$). (Mennigen et al., 2011.) In a recent Finnish study where covering ileostomy was used, patients reported having more early leakage (6.6% vs. 1.7%, $P=0.04$), SBO (22.7% vs. 7.2%, $p<0.0001$) and dehydration (25.2% vs. 5.9%, $P<0.0001$) as an early complication than did those without ileostomy. Readmission to hospital was also more frequent among ileostomy patients. (Karjalainen et al., 2019.)

2.2.4.2 Late morbidity

The most common late complication is pouchitis, which affects 7-46% of patients depending on the definition (Dalal et al., 2018). It is an idiopathic inflammation in the pouch that leads to urgency, increased frequency of bowel movements and abdominal pain. Patients with coexisting PSC have been shown to have an increased incidence of pouchitis, reaching up to 79% ten years after IPAA (Penna et al., 1996). Pouchitis may be acute or chronic relapsing pouchitis. The exact aetiology is unknown, but interestingly it does not appear to affect pouches formed for familial adenomatous polyposis (FAP) (Barton et al., 2001). The most used and validated scoring system for pouchitis is the Pouchitis Disease Activity Index (PDAI). The index consists of stool frequency, rectal bleeding, urgency, fever and endoscopic and histologic findings. A total score of 7 or higher is defined as pouchitis. (Sandborn et al., 1994.) (Table 4.) A simpler modified pouchitis disease activity index (mPDAI) has also been created and has been proven to work well. This index omits the histology and is therefore faster and less costly (Shen et al., 2003). First-line therapy for acute pouchitis should be a 2-week course of metronidazole or ciprofloxacin (Shen et al., 2001). In the case of relapsing pouchitis evaluation of secondary reasons such as use of NSAIDs, Clostridium or cytomegalovirus infection, evaluation of surgical complication (leak, stenosis and fistula) or CD should be ruled out with tests and endoscopy. If no secondary cause can be found antibiotic maintenance therapy or in some cases immunosuppressive therapy is used. (Dalal et al., 2018.) Patients with severe chronic pouchitis should be reviewed together with gastroenterologists.

Table 4. Pouchitis Disease Activity Index
(According to Sandborn et al., 1994)

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

The risk for small bowel obstruction (SBO) is high for IPAA patients due to combined abdominal and pelvic dissection, the need for multiple operations and higher risk for septic complications (Gorgun & Remzi, 2004). Large studies report an incidence of 13–25% (Fazio et al., 1995; Erkek et al., 2008). Most episodes can be treated conservatively, whereas about 25% require surgery (Fazio et al., 1995). One would expect the laparoscopic approach to entail less adhesion and therefore less SBO, yet this was not shown in a meta-analysis comparing laparoscopic and open pouch surgery (Singh et al., 2013).

Anastomotic strictures are not uncommon and are seen in 14% (Fazio et al., 1995) and are usually related to a local complication. Studies have demonstrated that lower rates of stricture follow stapled anastomoses than hand-sewn anastomoses (Rossi et al., 2002; Prudhomme et al., 2003). If severe, the stricture may obstruct the outlet of the pouch and

result in evacuation problems and pouch dilation. Short and soft strictures can be gradually dilated with Hegar's dilators.

Pouch-related fistulas may be vaginal, perineal, cutaneous or presacral (Gorgun & Remzi, 2004). Fistula may occur in 5-10% of patients (Fazio et al., 2003; Tekkis et al., 2005). Fistulas may develop after IPAA as a result of inflammation within the perianal tissues around the pouch. A large cohort study with comprehensive follow-up identified five independent predictors of pouch-related fistula: gender, previous anal pathology, final pathology especially CD, anorectal physiology and pelvis sepsis (Tekkis et al., 2005). Another large study reported no predictive value for gender nor type of anastomosis used but UC versus FAP as the initial disease type was a risk factor for developing fistula (Gecim et al., 2000). Management of the fistulae depends on the severity of the symptoms. Some minimally symptomatic fistulae may require only a seton placement, others may require diversion with an ileostomy and subsequent fistula repair (Ng et al., 2019). Perineal approaches include fistulectomy and endoanal advancements flaps and are suitable for low fistulas.

Pouch-vaginal fistula is of special importance because these fistulas are a source of considerable morbidity and impair the patient's quality of life. Usually late presentation of pouch-vaginal fistula is due to CD or erosion from the staple line (Maslekar et al., 2012). The reported incidence is between 3 and 17% (Lolohea et al., 2005). A systematic review of this matter concluded that the more common low fistulas can be treated by perineal approaches while high fistulas are best treated with an abdominal approach. The favourable perineal approaches include transvaginal repair or transanal mucosal flap repair or in case of stapled anastomosis advance the pouch down to the dentate line. (Maslekar et al., 2012.)

Cuffitis is an inflammatory condition of the residual rectal cuff. This is usually related to the stapled anastomosis being placed in the rectum rather than at the top of the anal canal (Sagar & Pemberton, 2012). In a study of 217 DS IPAA patients 14.7% had symptomatic cuffitis (Lavery et al., 1995). Topical mesalamine has been shown to be effective in the treatment of cuffitis (Shen et al., 2004).

2.2.4.3 *Pouch function*

“Normal” pouch function is usually defined as a 24h stool frequency of four to eight motions per day and one nocturnal motion, and the ability to defer pouch evacuation until convenient and nearly perfect continence (Michelassi et al., 2003).

The same kind of function was found in a large meta-analysis of 43 studies: mean defecation frequency was 5.2 per 24h with a mean night-time frequency of 1.0. Mean mild incontinence during the day was 17% and severe incontinence 3.7% (Hueting et al., 2005). A more frequent meta-analysis of 96 observational studies had very similar results: mean defecation frequency was 5.9 per 24h with mean night-time frequency of 1.5 with mild and severe daytime incontinence 14.3% and 6.1% respectively (de Zeeuw et al., 2012).

The reports on pouch function mainly report good and stable results (Michelassi et al., 2003; Wheeler et al., 2005; Tulchinsky et al., 2010) whereas others have found a slight deterioration in number of bowel movements and continence over time (Hahnloser et al., 2004; Kiely et al., 2012). Although continence deteriorated slightly, it had little or no influence on patient satisfaction (Delaney et al., 2003; Hahnloser et al., 2004). A Swedish study by Karlbom showed that age over 50 years ($p < 0.01$), presence of extra intestinal manifestations ($p < 0.05$) late complications, such as anastomotic stricture ($p < 0.05$), pouchitis ($p = < 0.01$) and anal pain ($p = < 0.05$), were related to a less favourable outcome (Karlbom et al., 2000).

2.2.4.4 Fertility and childbirth

Many of the patients in need of surgery for UC are young of reproductive age. For female patients' fertility, pregnancy and mode of delivery are of crucial importance. Studies have shown infertility rates of UC patients to be comparable to those in general population (Lamah & Scott, 2002). IPAA has been associated with impaired fertility (Cornish et al., 2007; Tulchinsky et al., 2013). A meta-analysis showed that relative risk of infertility was 3.17 (95% CI: 2.41–4.81) (Waljee et al., 2006). The decrease in fertility is thought to be caused by tubal occlusion due to adhesions. As laparoscopic surgery is associated with fewer adhesions, it has yielded better results for maintaining female fertility (Bartels et al., 2012; Beyer-Berjot et al., 2013). In a recent large study of 890 patients comparing open and laparoscopic IPAA postoperative infertility was increased. No difference was detected in postoperative fertility but patients in laparoscopic group were able to conceive dramatically faster (Gorgun et al., 2019).

A Danish nationwide cohort study showed that in vitro fertilisation (IVF) is used much more often with UC patients after IPAA than before it. The percentage of children born as a result of IVF is significantly higher in UC female patients after IPAA than before it. (Pachler et al., 2019.)

In pelvic surgery injury to the parasympathetic or sympathetic plexus supplying the pelvic organs is known to constitute a risk of causing sexual dysfunction. Dyspareunia is increased after IPAA, but this does not impair the overall sexual function, which may be a result of improved overall health (Cornish et al., 2007; Bharadwaj et al., 2014).

There is no consensus on the optimal method of delivery for women after IPAA. Caesarian section is more common among females after IPAA (Lepistö et al., 2007; Cornish et al., 2007). Vaginal delivery entails potential risks to the anal sphincter and therefore to continence but no significant deterioration in pouch function has been reported. (Lepistö et al., 2007; Cornish et al., 2007; Bharadwaj et al., 2014.) Young women should be counselled preoperatively about the impact of pouch surgery on fertility and advised that vaginal delivery is possible but that the mode of delivery should be considered by the obstetrician.

2.2.4.5 *Health-related quality of life*

The concept of quality of life describes the general well-being of an individual. The World Health Organization has defined HRQoL as an individual's perception of their position in life in the context of the culture and value systems in which they live, in relation to their goals, expectations, standards and concerns. It is a wide-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationships to salient features in the environment (Camilleri-Brennan & Steele, 1999).

The need to evaluate HRQoL to meet the objectives of therapy to improve the patient's general well-being has arisen. Survival or curing the disease alone is regarded as an insufficient method of disease management. Only treatment which improves HRQoL is regarded as an effective intervention (Sajid et al., 2008). HRQoL measurement can be used on a population level monitoring population health and changes therein to evaluate the effects of health and social policies and in allocating resources. On an individual level measurement evaluates the effects of therapy, describes the nature of the disease and assesses prognosis (Ebrahim, 1995).

Today many quality of life instruments reflect the multidimensionality of quality of life. There are two basic types of instrument, disease specific and generic. Disease specific instruments have been developed for a certain disease or a narrow range of diseases. Generic instruments are intended to be applicable to a wide range of health problems (Fitzpatrick et al., 1992). The most important function of generic instruments is to enable comparisons between populations with different diseases and also comparison with general population. Disease-specific instruments measure HRQoL in patients who suffer from a particular disease. A questionnaire commonly consists of several items, which can be grouped into dimensions. The three main domains of HRoL are physical, social and psychological. (Camilleri-Brennan & Steele, 1999.) Some questionnaires afford the opportunity to calculate a single score. The questionnaire is usually self-administered. Several different questionnaires have been used in studying HRQoL in UC patients, which complicates the comparison of different studies (Heikens & Laarhoven, 2012b). The most used general instrument is the SF-36 and the disease-specific inflammatory bowel disease questionnaire (IBDQ) (Lichtenstein et al., 2006).

The burden of UC on quality of life was measured with a systematic review and it showed that patients with active disease had poorer QoL in almost all measured aspects of functioning and well-being and that among those with UC in remission quality of life was comparable to that of healthy controls or general population samples in almost all domains (Yarlas et al., 2018). In the earlier years of IPAA a comparison of HRQoL for conventional proctocolectomy and ileostomy, Kock continent pouch and IPAA was conducted and revealed that quality of life was best among IPAA patients (Kohler et al., 1991). Table 5 summarizes the main points of the selected HRQoL studies published of IPAA patients.

Patients considered for surgery usually suffer from active disease except for the small percentage operated on due to cancer or risk of cancer. Therefore HRQoL results have been shown to improve after IPAA and in many studies to reach the level of general population (Thirlby et al., 1998; Fazio et al., 1999; Heikens & Laarhoven, 2012b). Poor functional results are connected to poorer HRQoL, however (Carmon et al., 2003; Berndtsson et al., 2007). Also, when comparing the HRQoL results for UC and FAP it is not surprising that UC patients' level of quality of life mainly improved while that of FAP patients deteriorated due to having been asymptomatic preoperatively.

Table 5. Quality of life after IPAA in selected studies

Author	Study design	Questionnaire	Years / patients (n)	Main findings
Fazio et al., 1999	Prospective	Cleveland Global Quality of Life score	1986–1997 922 IPAA (stapled)	QoL was shown to improve after the first 2 years after surgery, and there was no deterioration thereafter
Heikens et al., 2012a	Prospective, two-centre	WHO-QOL100	2003–2008, 30 IPAA	QoL improved after IPAA and reached levels comparable with those of the healthy reference population in a majority of domains.
Berndtsson et al., 2007	Retrospective	SF-36	1082–1995 370 IPAA 39 failures	HRQL on par with that of their counterparts in general population Poor pouch function affects health-related quality of life negatively. Patients with failure demonstrated an impaired HRQL.
Andersson et al., 2011	Retrospective	SF-36	1984–2003, 156 IPAA	Patients with IPAA reported slightly lower HRQoL rates than the general population
Carmon et al., 2003	Retrospective	SF-36	1990–2001 99 IPAA	Well-functioning pouches have a HRQoL that is comparable with the general population Functional outcome and QOL scores correlated strongly in all dimensions. Older age was associated with lower scores of QOL.
Kiely et al., 2012	Retrospective	Cleveland Global Quality of Life score	1983–2008, 3234 IPAA 200 (6.2%) pelvic sepsis	Pelvic sepsis after IPAA leads to worse functional outcomes and quality of life.
Thirlby et al., 1998	Prospective	Health Status Questionnaire	1994–1997 27 IPAA	HRQoL improved after IPAA and reached the level of general population
Polle et al., 2007	Prospective	SF-36 and Gastrointestinal Quality of Life Index (GIQLI)	2000–2003 60 IPAA	The QoL improved after IPAA surgery
McLeod et al., 1991	Prospective	time trade-off technique (TTOT) and direct questioning of objectives (DQO)	1987–1988 37 IPAA	Surgery is usually successful in improving HRQoL

Delaney et al., 2003	Prospective	SF-36 and CGQL	1983–1999 1285 IPAA	Although functional outcome after IPAA is not as good in older patients, appropriate case selection achieves acceptable quality of life for patients of all ages.
Muir et al., 2001	Prospective	SF-36, Time trade-off (TTO), The Rating Form of IBD (RFIPC)	– 20 IPAA	QoL improved after IPAA
Martin et al., 1998	Retrospective	An instrument developed by the group	– 29 IPAA	QoL comparable to that of UC patients in remission or mild disease
Richards et al., 2001	Retrospective	SF-36 EUROQoL	1986–1997 56 IPAA	HRQoL comparable to that of general population
Robb et al., 2002	Retrospective	SF-36, the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC)	1978–2002 138 IPAA	IPAA improves QoL significantly and approximates that found in general population
Scarpa et al., 2004	Retrospective	HRQL questionnaire for inflammatory bowel disease	1984–1999 36 IPAA	RPC patients, after a long-term follow-up, had an HRoL similar to that of the remission/mild UC patients. HRoL is influenced by drugs, stool frequency, pouchitis, postoperative pelvic complications, and age at diagnosis.
Tiainen & Matikainen, 1999b	Retrospective	RAND SF-36	1985–1995 68 IPAA	HRQoL comparable to that of general population
Hahnloser et al., 2007	Retrospective	Own form	1981–2000 1885	QoL is preserved after IPAA
Dafnis, 2019	Prospective	SF-36	1993-2008 90 IPAA	The HRQoL scores were high. The patients scored significantly higher than did the general Swedish population adjusted by age-group and sex on 6 out of 7 SF-36 subscales

2.2.4.6 *Salvage surgery*

For some, an end stoma can be a disaster. Perineal procedures to improve the function are chosen according to the cause of dysfunction, dilatation for stricture and fistula surgery being the most common operations. In some cases transabdominal revisional surgery may be an option. The procedures are often complex and difficult and very few centres gain a proper amount of experience due to the rarity of the procedure.

Indications for pouch reconstruction can be divided into mechanical and infectious/inflammatory. Identification of the precise cause of pouch dysfunction permits a surgical strategy to be formulated. Preservation of the original pouch is recommended if possible and the greatest success after redo pouch surgery is seen in patients with mechanical complications. (Sagar & Pemberton, 2012.)

Proper salvage surgery studies come from big pouch centres or meta-analyses. In a large Cleveland clinic study (n=502) on transabdominal salvage surgery the most common reason for surgery was leakage/fistula 52%, a new pouch was created in 41% and was J-pouch 87% and HS anastomoses in 82% of the cases. The functional results and QoL were found to be good postoperatively (Remzi et al., 2015).

A meta-analysis pooled the data on salvage surgery and successful healing was reported in procedures overall in 73.5%, in redo surgery 82.2%, revisional surgery 79.6% and in local/perineal procedures 68.5%. Postoperative morbidity was 41.4% for the overall procedures and functional success was achieved in a total of 71.9%, redo surgery in 83.9%, revisional surgery in 75.8% and local/perineal procedures in 71%. An eventual 18% pouch excision rate after re-do pouch surgery was reported. (Theodoropoulos et al., 2015.)

2.2.4.7 *Pouch failure*

Despite the evolved details of the operation and centralization of surgery to centres with the number of operations on an acceptable level, pouch-related complications and poor functional results may necessitate the excision of the pouch or the building of a permanent stoma. The long-term failure rate for IPAA is reported to be 5–17% (Sagar et al., 1996; Meagher et al., 1998; Lepistö et al., 2002; Tulchinsky et al., 2003; Tekkis et al., 2010). A large meta-analyses showed a reduction of 2.5% in the pouch failure rate in studies published before and after the year 2000 (de Zeeuw et al., 2012). Cumulative incidences of pouch failure have been reported in a Danish national study on 1992 patients reaching a 5-year risk of 9.1% (95% CI 7.9–10.4), a 10-year risk of 12.1% (10.7–13.7) and a 20-year risk of 18.2 (16.1–20.4), median follow-up time being 11.4 years. (Mark-Christensen et al., 2018.) The biggest centre performing IPAA surgery in Finland reported a 1-year risk of 1%, 5-year risk of 5% and 10-year risk of 7% (Lepistö et al., 2002). The most common indications for pouch failure are inflammatory complications such as leakage or fistula, chronic pouchitis, CD and poor pouch function (Korsgen & Keighley, 1997; Tulchinsky et al., 2003; Tekkis et al.,

2010). The frequencies, indications and possible risk or protective factors of selected failure studies reporting these parameters are shown in Table 7.

Many studies have examined the risk factors for pouch failure in individual patients. Higher age (Wibmer et al., 2010) and excessive weight gain (Wu et al., 2013) have been associated with an increased risk for pouch failure. Also, in a Danish national study of pouch failure the risk of failure was higher for women HR 1.39, 95% CI 1.10–1.75, primary non-diversion HR 1.63, 95% CI 1.11–2.41 and a low hospital volume HR 2.30, 95% CI 1.26–4.20 (Mark-Christensen et al., 2018). A large study from Cleveland clinic predicted survival of the pouch to be worse for two-stage procedure (HR, 1.44; 95% CI 1.08–1.93), CD (HR, 2.37; 95% CI 1.48–3.79), hand-sewn anastomosis (HR, 1.72; 95% CI, 1.23–2.42) and diabetes (HR, 2.31; 95% CI, 1.25–4.24) (Manilich et al., 2012).

There is one score, The Cleveland Clinic Foundation ileal pouch failure (IPF) score which was formed from the risk factors recognized in a large multivariate analysis (Fazio et al., 2003). These factors and the calculation of the index are presented in Table 6.

Table 6. The Cleveland Clinic Foundation IPF score (according to Fazio et al., 2003). The score is interpreted based on the years passed post pouch formation and pouch failure risk is calculable (<http://www.riskprediction.org.uk/index-ccfipf.php>)

Risk Factor	Points
Diagnosis	
FAP	0
UC on intermediate colitis	1
Crohn's disease	1.5
Patient comorbidity	
No comorbid conditions	0
1 comorbid condition	0.5
2 comorbid conditions	1.0
Prior anal pathology	
No prior anal pathology	0
Prior anal pathology	1
Anal sphincter manometry	
Normal manometry	0
Abnormal manometry (SP<100, RP<49)	1
Anastomotic separation	
No anastomotic separation	0
Anastomotic separation	1
Anastomotic stricture	
No stricture or asymptomatic stricture	0
Symptomatic stricture	1
Pelvic sepsis	
No sepsis	0
One episode of pelvic sepsis	1
Two or more episodes of pelvic sepsis	2
Fistula formation	
No fistula	0
Pouch-perineal fistula	1
Pouch-vaginal fistula	2
TOTAL score =	

Pouch failure is defined as the need for permanent ileostomy with or without a pouch excision operation. In previous reports the percentage of pouch excision in failure patients has varied: in the study by Foley 44% (Foley et al., 1995), Meagher and Tulchinsky 60% (Meagher et al., 1998; Tulchinsky et al., 2003), 84% in a study by McRae et al. (McRae et al., 1997) and in a study from Finland's biggest IBD surgery centre all 52 failed pouches were excised and none diverted (Lepistö et al., 2002).

Pouch excision is a demanding procedure because of the need for reoperation deep in the pelvis and often after a chronic pelvic sepsis setting. In one study 57% of the pouch excision patients experienced short-term morbidity and 37% long-term morbidity and 11% needed short-term (<30d) reoperation and 13% needed long-term (>30d) reoperation (Lightner et al., 2017). A large multicentre study of 381 pouch excision patients reported a 30-day

major morbidity of 27.7% and reoperation required by 5.5% of the patients (Lachance et al., 2018). The major cause of postoperative morbidity after pouch excision is due to surgical site infection, especially for perineal wound (Karoui et al., 2004; Prudhomme et al., 2006). Kiran et al. compared short and long-term morbidity after pouch excision and pouch left in situ among ileostomy patients and found no difference between the groups. Quality of life was found to be significantly better in the pouch excision group than in the group with the pouch left in situ. (Kiran et al., 2012).

Bengtsson et al. analysed their diverted pouch failure patients who did not undergo excision and found no dysplasia or cancer in histopathology in pouch biopsies. None of the patients requested further surgery and the majority had satisfactory ileostomy function (Bengtsson et al., 2007). Altogether, dysplastic transformation in the ileal pouch has been estimated to be rare (Hulten et al., 2002; Borjesson et al., 2004).

Table 7. The frequencies, indications and possible risk or protective factors of selected failure studies

Author	Follow-up time (yrs., median or mean and range)	Number of patients	Pouch failure		Main reason for pouch failure	Risk or protective factors for pouch failure HR (95% CI), or p-value
			n	%		
Mark-Christensen et al., 2018	11.4	1991	295	14,8	-	Female sex 1.39 (1.10–1.75) Age <59y 1.35 (0.57–3.21) Use of stoma 0.61 (0.41–0.90) Very low volume hospital 2.30 (1.26–4.20)
Tekkis et al., 2010	4.5 (1month–28.9y)	1847	192	7.7	septic complications 35.1%, poor function 30.8% pouchitis 9.6% Crohn's disease 5.3%	Very high failure after salvage surgery, 40% at 10years.
Tulchinsky et al., 2003	7.1 ± 4.8	634	61	9.7	Pelvic sepsis (included fistulas and Crohn's) 52% Poor function 30% Pouchitis 11%	Crohn's disease failure rate 46% Females 12.2%, males 7.4% No stoma 15%, stoma 8%
Körsgen et al., 1997	at least 2 years	180	31	17.2	Sepsis/ fistula 35.5% Poor function 16.1% Ischaemia 19.3% Stricture 16.1% Crohn's disease 12.9%	Pelvic sepsis p < 0.0001 Fistulae p < 0.02
Meagher et al., 1998	6.5 (2–15)	1310	134	10	Chronic sepsis 30% Poor function 19.4% Ischaemia 2.2%	-

McRae et al., 1997	min 30 months	551	58	10.5	Leakage 36% Poor function 22% Pouchitis 7% Pouch leakage 12%	Hand-sewn anastomoses higher failure %, p<0.001 Crohn disease, 55% failure
Wasmuth et al., 2009	10 (1–22)	304	20	11	Fistula 35% Incontinence 20% Anastomotic dehiscence 15% Stenosis 10%	Late anastomotic complications 7.63 (CI 2.9–19.4)
Lepistö et al., 2002	9 (2–16)	486	26	5.3	Fistula 26.9% Crohn's disease 15.3% Incontinence 19.2% Persistent pouchitis 11.5%	Fistula development was associated with ultimate failure

3 Aims of the Study

The aim of this thesis was to analyse the operative outcome of UC patients operated on with RPC + IPAA in Tampere University Hospital.

The detailed aims were as follows:

1. To evaluate the long-term changes in operative treatment and early and late complications related to IPAA.
2. To explore health-related quality of life after IPAA in those with poor or good pouch function and to compare that to patients with active or inactive UC and to general population.
3. To evaluate the long-term functional outcome after IPAA.
4. To examine the pouch failure percentage of the IPAA patients and analyse the reasons for pouch removal and life cycle of the pouch in this patient population.

4 Patients and Methods

4.1 Study populations

All patients over 18 years of age with UC who underwent RPC + IPAA at Tampere University Hospital in the period 1985–2016 were identified in the hospital records using all ICD-9 and ICD-10 codes for UC and NOMESCO Classification for Surgical Procedures (NCSP) codes for the operations performed. The use of wide spectrum of codes was in order to find all the cases. This also made it possible to exclude probably incorrectly recorded operation codes. A database was collected from patient files including details on patient history, surgical technique, postoperative morbidity, and follow-up. In Studies I, II and III clinical data for the period 1985–2009 and in Study IV for the period 1985–2016 were retrieved from this registry.

In study IV 75 patients had moved elsewhere in Finland and therefore we did not have reliable information on follow-up and whether they had their pouch in use or not. Data on possible pouch excisions on these patients were retrieved from the register in the National Institute for Health and Welfare (NIHW). The patients were identified by the NCSP procedure codes ICD-9 for the period 1985–1996 and ICD-10 from 1996 onwards.

Study I included altogether 352 patients. In studies, II and III of these 352 patients 282 were alive with functional pouch and could be located. In study IV we had registry information from a longer period and had 491 patients in the IPAA registry. The median follow-up time in study I was five years (range 1 month to 24 years, and in Study IV is was 11 years (range 1 day to 33 years). Altogether 50 of the IPAA patients had had pouch failure and comprised the study population in study IV.

The control group in study II comprised 408 age and gender matched UC patients from the local IBD registry. It is a prospective register for all adult patients with diagnosed IBD. The examination of the generic 15D scores used a general population sample obtained from the National Health 2011 Survey.

To study the effect of time from surgery to HRQoL (Study II) the RPC patients were divided into subgroups of ≤ 10 years, 10.1–20 years and > 20 years from surgery. To study the effect of age at the time of surgery on functional outcome (Study III) the RPC patients were divided into subgroups of ≤ 35 , 36–62, ≥ 63 years of age.

4.2 Methods

4.2.1 Study I

Early complications were defined as occurring within 30 days of the operation and late complications thereafter. SBO was considered a complication when hospital stay exceeded the median 10 days. Anastomotic stricture was considered a complication if it caused functional difficulties and dilation was needed. Four groups of BMI were created (< 22 , 22–24, > 24 –27, and > 27) to examine the effect of BMI. Indications were regarded as 1) acute colitis in need of emergency colectomy, 2) chronic colitis with inadequate response to medical treatment and 3) cancer of risk of cancer, typically dysplasia or pseudopolyposis.

4.2.2 Questionnaires (Studies II and III)

The questionnaires were sent by post and one reminder was sent to non-respondents. Two different instruments were used to measure HRQoL; the generic (15D) 15-item questionnaire and one disease-specific 32-item IBDQ, which addresses four different aspects of life: digestive symptoms, social functioning, emotional status and systemic symptoms. Total IBDQ score ranges from 32 to 224, a higher score indicating better quality of life. The IBDQ was used under licence from McMaster University, Hamilton, Canada. Pouch function was assessed by Öresland score with the permission of the developer. The questionnaire includes items on day-time and night-time bowel movements, incontinence, pad usage, urgency, diet, medication and social handicap. The ratings are summarized into a single score (range 0–15; 15 being the worst possible). UC disease activity in the control group was examined by simple clinical colitis activity index (SCCAI). The 15D is a Finnish questionnaire and the rest of the questionnaires were translated from English and backtranslated to confirm linguistic accuracy. The Finnish versions of the 15D, SCCAI and Öresland score are to be found in the appendix. The IBDQ cannot be published due to licence agreement.

Of the study population of 352 IPAA patients 282 were eligible for inclusion in this study as their pouch was in place and they were alive and accessible. Altogether 187 (66.3%) returned the questionnaires; 87 (67%, of the women and 100, 66% of the men). Characteristics of the respondents are presented in Table 8. The 95 patients who did not respond had the same gender distribution, but they were on average three and a half years

younger. There were no differences in the most important complications concerning pouch function; leakage or pelvic sepsis.

In this questionnaire study non-operated UC patients were used as control group. Of the 408 UC patients 153 (37.5%) returned the questionnaires; 71 (46%) women and 82 (54%) men. The basic characteristics of these patients are presented in Table 8.

Table 8. Characteristics of the respondents of the IPAA patient and UC control group

	Number of patients	Female N (%)	Age at survey, yrs., median (range)	Time from surgery or diagnosis, yrs., median (range)
IPAA patients	187	87 (47)	53 (23–81)	13 (4–28)
UC patients	153	71 (46)	55 (24–81)	20 (6–48)

4.2.3 Study IV

The Charlson Comorbidity Index (CCI) was used to categorize pouch failure patients comorbidities. BMI was considered high at $>30\text{kg/m}^2$. Clavien-Dindo (C-D) classification was applied to classify complications. CD was diagnosed in endoscopy, histology, clinical picture and capsule imaging or MRI (magnetic resonance imaging) when necessary. Early complications were again defined as occurring within 30 days of the operation.

4.2.4 Statistics

Statistical analysis was performed with IBM SPSS Statistics 25.0. For categorical variables, the results are given as frequencies and percentages, for continuous variables as means and standard deviations, or as medians with range. Chi-Square or Fisher's exact test was used to assess differences in categorical variables. In studies I, III and IV binary logistic regression analysis was used to identify independent risk factors related to leakage, functional results and pouch failure. Results are shown as odds ratios (ORs) with their 95% confidence intervals (CIs). Statistical significance was set at $p \leq 0.05$. In Study II the power calculations were made using PS Power and Sample Size Calculations program, the difference for 15D being 0.03, power 80% and statistical difference 0.05.

4.2.5 Ethical aspects

All studies were carried out in accordance with the Helsinki Declaration and the guidelines for good clinical practice. Studies I and IV were retrospective and observational and therefore, no ethical approval of the committee was required. The medical director of the study hospital granted approval. The Ethics committee of Pirkanmaa Hospital District (code R12100) approved protocol for Studies II and III. All participants gave written consent to participate. In Study IV data on the pouch excision of the patients who had moved away from Pirkanmaa were retrieved from the register of the NIHW, with their permission THL/1965/5.05.00/2018.

5 Results

5.1 Surgery (I)

The IPAA patient baseline characteristics are presented in Table 9. The patients were young and healthy with minor co-morbidities and predominantly normal BMI. The characteristics have not changed from those of the population in studies I (1985–2009) and IV (1985–2016).

Table 9. Demographic data on patients undergoing proctocolectomy 1985–2016

Sex	n	%	median	range
men	282	57		
women	209	43		
Age at time of surgery			38	18–72
BMI at surgery			24	16–42
Co-morbidity index				
0	443			
1	35			
2	11			
3	2			
Duration of disease before surgery (yrs.)			5	0–45
Indication for surgery				
Acute	213	43		
Chronic	246	49		
Cancer or risk of cancer	32	6.5		
Hospital stay (d)			9	(2–48)

The first IPAAAs were all HS anastomoses, but around the year 2005 the practice in our hospital changed to the routine use of stapled anastomoses as can be seen in Figure 4. Today hand-sewn anastomoses are performed only in cases where rectal dysplasia is observed preoperatively.

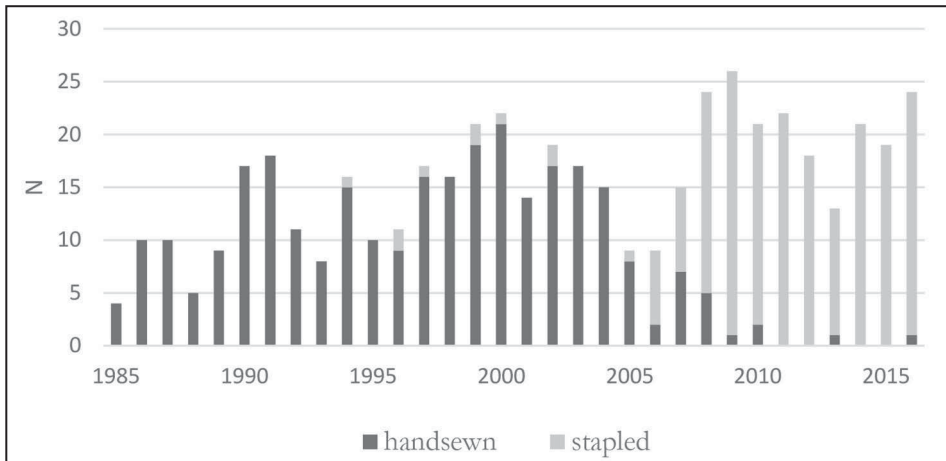


Figure 4. Types of anastomoses performed 1985–2016

The very first operations were performed with covering ileostomy and after that there was a quite long period when covering ileostomy was not routinely used, and was performed only when considered necessary. Figure 5 shows how the use of covering ileostomy has changed in our hospital. From approximately 2005 onwards, covering ileostomy has been used as a routine procedure.

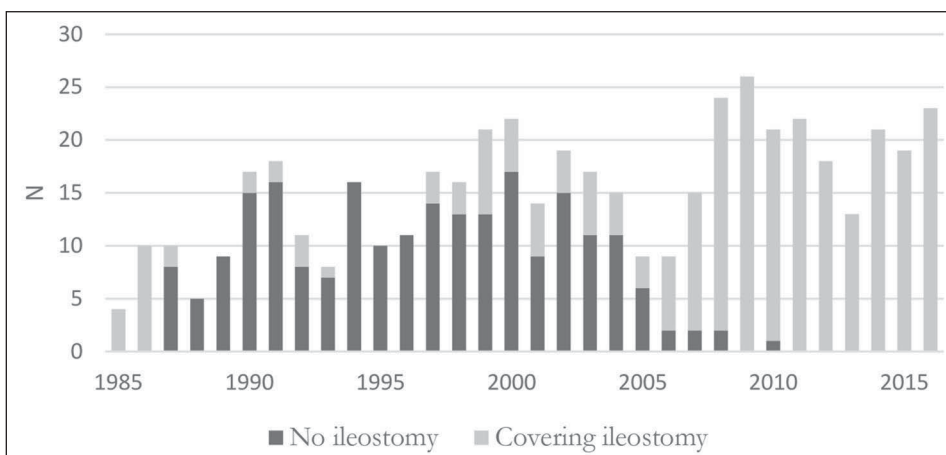


Figure 5. Use of covering ileostomy 1985–2016

5.2 Morbidity (I)

5.2.1 Early morbidity

One patient died the next day after IPAA giving a mortality rate of 0.3%. The most important early pouch related complications are listed in Figure 6. Eighty-one (23%) patients were readmitted in the early postoperative phase. Reasons for readmission to hospital in the early postoperative phase are presented in Figure 7. Thirty-two (9.1%) patients required re-operation in the early postoperative phase because of complications. Reasons for re-operations were leakage in 25, haemorrhage in two, SBO in four and perforation in one. Omission of covering stoma and high BMI were independent risk factors for leakage; ORs of 3.68 (95% CI 1.61–8.42) and 1.11 (CI 1.01–1.21) respectively. There were significantly more leakages and early re-operations when covering ileostomy was not performed than when it was done, 16.4% vs. 6.0% ($p=0.004$) and 11.9% vs. 4.5% ($p=0.02$) respectively, see original article I Figure 1. Dehydration was the only early complication occurring more frequently in patients with covering stoma 6.8% vs. 0.0%, $p=0.017$. Morbidity related to closure of the ileostomies is presented in Table 10.

Table 10. Morbidity related to closure of covering ileostomies

	n or median	% or range
Overall morbidity	42	31.6
SBO	25	16.8
Leakage	4	3.0
Hospital stay	7	3–46

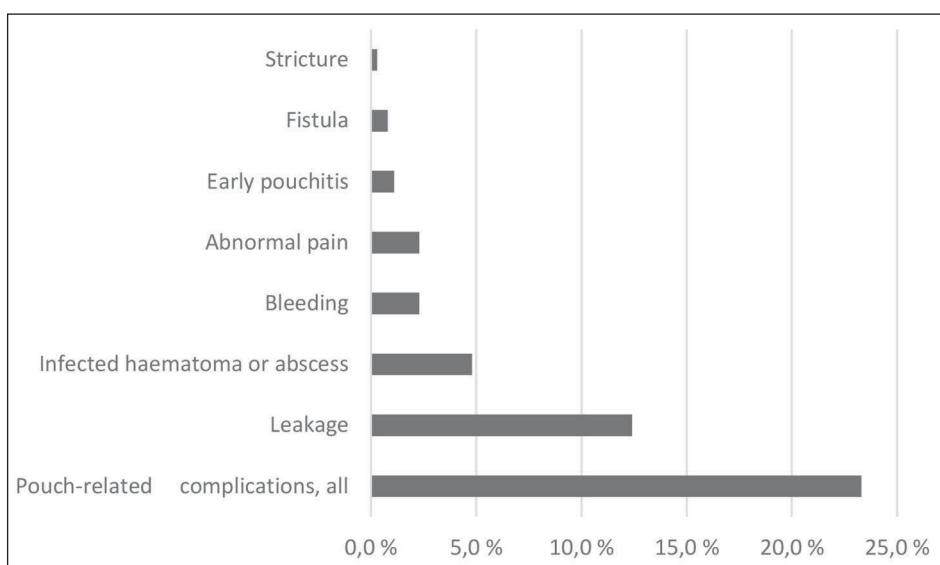


Figure 6. Pouch related complications of the IPAA patients operated in 1985–2009

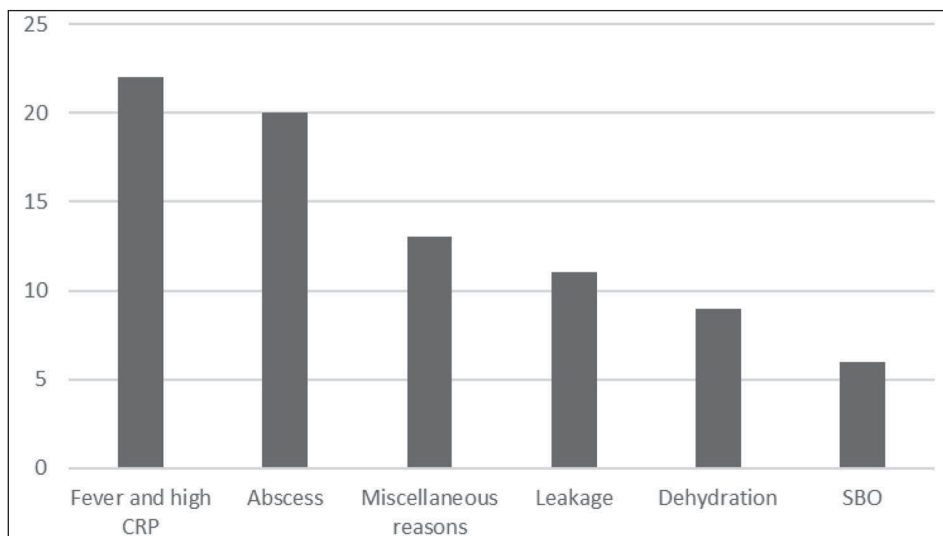


Figure 7. Reasons for readmission in IPAA patients operated on 1985–2009 (n= 81 out of 352, 23%)

5.2.2 Long-term morbidity

The long-term complications are presented in Figure 8; pouchitis 134 (39.3%) being the most common. The median follow-up time was five years (range: 1 month–24 years).

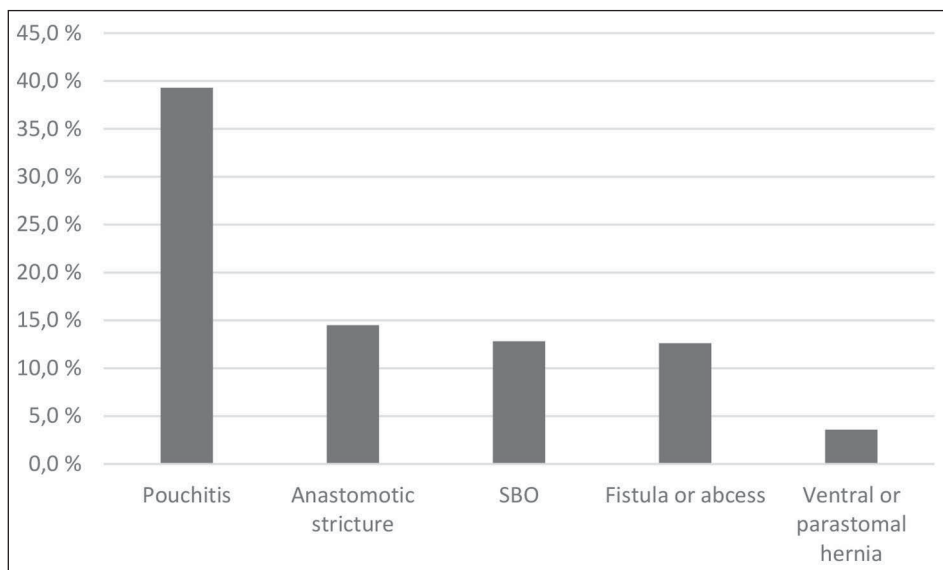


Figure 8. Percentages of late complications in IPAA patients operated on 1985–2009

5.3 Health-related quality of life (II)

IPAA patients scored significantly lower on eight of the 15 dimensions compared to age and gender matched general population, Figure 9. When the IPAA patients with good pouch function were compared to general population the only significantly lower score was seen on the excretion dimension.

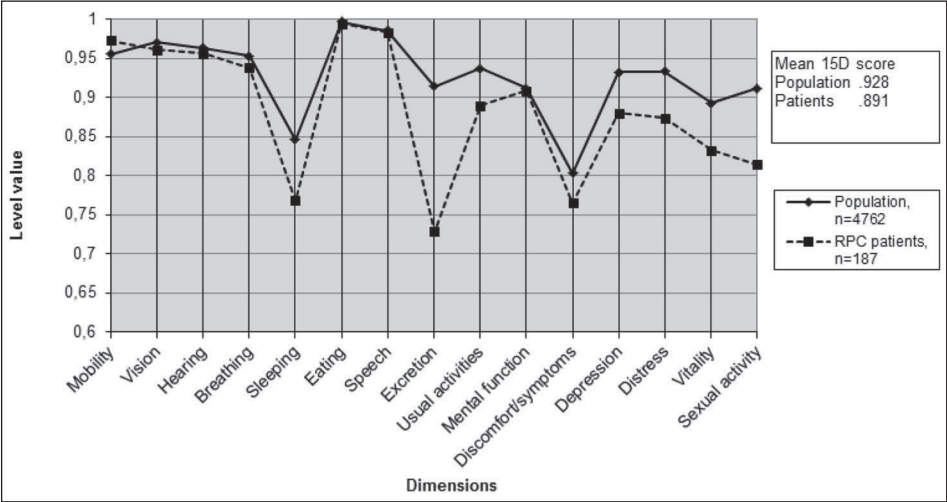


Figure 9. 15D scores of all IPAA patients with ileal pouch (n=187) compared to general population n=4762 (Helavirta et al. 2018)

HRQoL measured by the disease specific IBDQ questionnaire showed that IPAA patients with good pouch function had scores similar to those of UC patients in remission or mild disease activity. Those with poor pouch function had IBDQ scores similar to those with active disease Figure 10. No difference was seen in HRQoL after surgery comparing different indications or time from operation. The scores were lower for RPC patients with any indication for surgery or time from operation than for UC patients in remission but higher than for UC patients with active disease. The main finding of the subscores of the IBDQ was that patients with good pouch function showed better results on all subscores (bowel disorder, emotional disorder, systemic symptoms and social function) than did those with active colitis ($p < 0.001$), see Table 2 in original Study II.

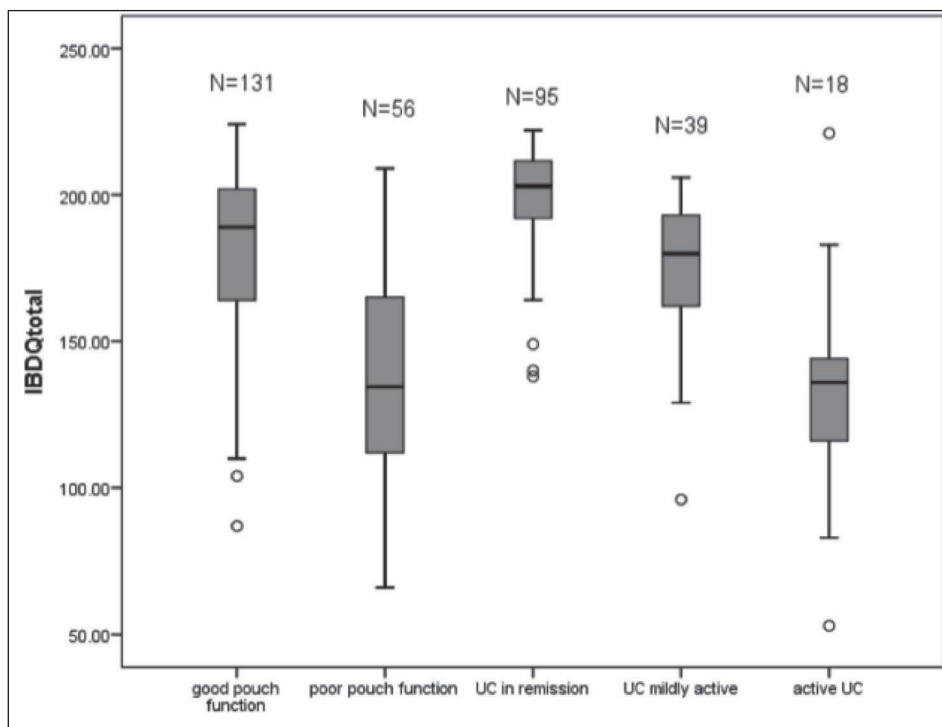


Figure 10. IBDQ total scores in different subgroups of patients with IPAA or UC (Helavirta et al. 2018)

5.4 Pouch function (III)

The majority of 131 (70%) of the patients reported having good pouch function (Öresland score <8). The median functional Öresland score was 5.0 for females and 5.5 for males.

More than half (55%) had daytime defecation frequency ≤ 5 and night time frequency 0 or ≤ 1 /week. Dietary restrictions were experienced by 49%, use of antidiarrheal medication was reported by 29% and a social handicap was experienced by 25%. When the postoperative results after IPAA between well-functioning pouches and poor functioning pouches were compared no significant difference of leakage or pelvic sepsis was recorded nor fistula, abscess or stricture. However, anastomotic stricture was twice as common in poorly functioning pouches as in well-functioning pouches, 7.9% vs. 13.2%, ($p=0.199$). Time elapsing since IPAA had no effect on pouch function. Seepage was experienced by 20% in daytime and by 42% occasionally at night time. Daytime seepage and use of protective pads were more common among older patients aged ≥ 63 years. Men suffered more from night-time incontinence than did women, 51% and 33% respectively, $p=0.015$, this being the only difference found between sexes.

A multiple logistic regression analysis of nine variables (sex, age at time of surgery, body mass index at time of surgery, type of anastomosis, use of covering stoma, complications including leakage, fistula or abscess, stricture and pouchitis) showed that only age at the time of surgery OR 1.03 (95% CI 1.00–1.06) $p=0.07$ and the development of pouchitis OR 4.21 (95% CI 1.94–9.10) $p<0.001$ were independently related to a poor functional outcome.

5.5 Pouch failure (IV)

Altogether 53 (10.8%) pouch failures were recorded: 10 (4.7%) out of 209 women and 43 (15.2%) out of 282 men OR 3.58 (95% CI 1.75–7.37). The characteristics of patients and IPAA surgery of the pouch failure patients and patients still with pouch are presented in Table 11. Half of the pouch failures occurred within the first five years and 70% within seven years of IPAA surgery. The cumulative risk for pouch excision at five years was 5.6%, at 10 years 9.4% and at 20 years 15.5%.

Table 11. Demographic, surgery related and IPAA information of the J-pouch and pouch failure cohorts
(Helavirta et al. submitted)

	Pouch failure n=53		Pouch in place n=438		p-value
	n or median	% or range	n or median	% or range	
Men	43	81	239	55	0.000
BMI at time of IPAA, mean, (SD)	25	(4.7)	25	(3.4)	
Age at time of IPAA (yrs.) median (range)	36	(18–71)	37	(18–72)	
Anastomoses					
Hand-sewn	45	85	243	56	0.000
Stapled	8	15	195	45	
Covering stoma	19	36	250	57	0.003
Hospital stay (days), median (range)	9	(4–42)	11	(2–48)	

The reasons for pouch failure were multiple. The different reasons recorded are shown in Figure 11. Several reasons were often recorded for a single patient. Poor function was most often recorded as a reason, but there was usually some septic event such as leakage, fistula and pouchitis or CD leading to poor function.

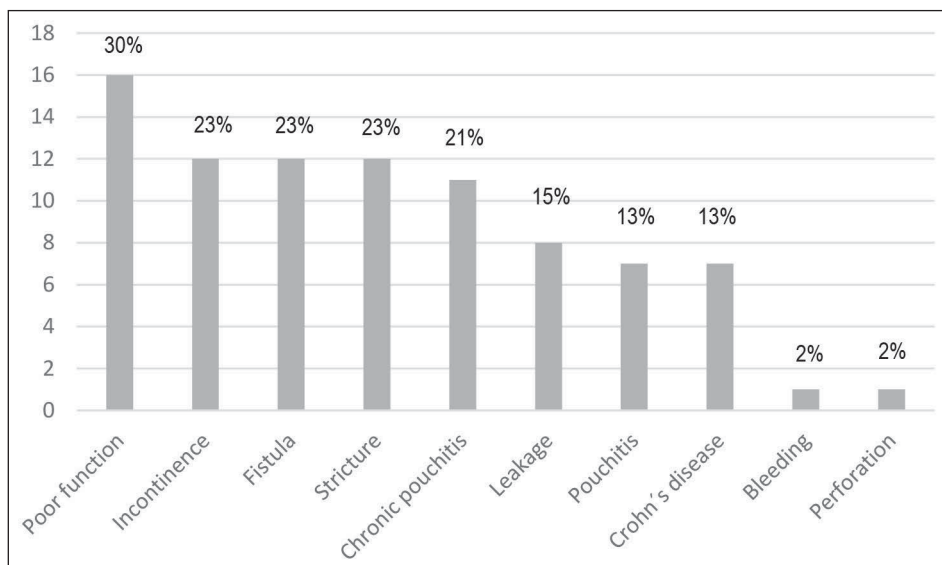


Figure 11. Reasons recorded for pouch failure (n=53 patients)

Twenty-eight (52.8%) had undergone surgery prior to pouch excision in order to maintain the pouch. The salvage operations were anastomotic dilatation 12 (22.6%), loop- or end ileostomy 14 (26.4%), fistula operation 6 (11.3%), abscess drainage 3 (5.7%), anastomotic repair 2 (3.8%) and new anastomosis in 1 (1.9%). The one new HS anastomosis performed was done transabdominally due to pouchvaginal fistula and was HS in the primary IPAA operation.

Altogether 15 CD diagnoses were made in the IPAA cohort after the initial diagnosis of UC in five of these the diagnosis was set after pouch failure; pouch failure occurred in seven (47%).

More early leakage 15 (28.3%) vs. 32 (7.3%) $p < 0.001$, and early relaparotomy after IPAA 11 (20.8%) vs. 31 (7.1%) $p = 0.003$ occurred in failure patients than in those with functioning pouch. The only parameters significant in the multivariate analyses were leakage OR 3.65 (95% CI 1.21–11.83) $p = 0.022$ and male gender OR 3.83 (95% CI 1.80–8.12) $p \leq 0.001$.

6 Discussion

6.1 Controversial issues of technical details in IPAA surgery

The IPAA operation has evolved in the decades during which it has been used. One of the main changes has been the shift from HS to DS anastomosis. When deciding which anastomosis to employ one must consider three aspects: first the surgical outcomes regarding pouch complications or pouch failure, secondly the functional result and HRQoL, and the risk of malignancy in the mucosa left in place for DS.

It is still debatable whether to use a covering ileostomy or not. The most important consideration is the effect of the stoma in preventing septic complications and the morbidity connected to stoma closure.

6.1.1 Anastomosis

In the patient cohort of this study HS was mainly used during the earlier years 1985–2005 and DS thereafter. In study I no differences were found in early pouch related complications for the type of anastomoses used. Among late complications anastomotic stricture was significantly more common for HS than DS, 17.6% and 0%, respectively. Study III showed that there was no difference in the type of anastomosis used in the long-term functional results as studied using the Öresland score. For pouch failure a difference was seen in univariate analysis which disappeared when the use of covering stoma and time elapsing since IPAA operation was taken into account. The present results that DS is preferable to HS are corroborated in the literature. A large meta-analysis (n=4,183 patients) concluded that patients with HS had more night-time incontinence (Lovegrove et al., 2006). In a prospective study (n=3109) postoperative septic complications, anastomotic stricture, SBO and pouch failure occurred more frequently in HS and incontinence was also more

common in HS (Kirat et al., 2009). By contrast, a meta-analysis by (Schluender et al., 2006) found no difference regarding the type of anastomoses used for functional results but the number of subjects was relatively small (n=86 vs. 98).

In the present study, the malignancy rate after IPAA was 0.4%, comprising two patients, both with HS anastomoses. For comparison, in a large review aiming to identify the risk of neoplasia after RPC the pooled prevalence of confirmed dysplasia in the pouch, ATZ or rectal cuff was 1.13% (range 0–18.75). The prevalence of high-grade dysplasia was likewise equally frequent for these anatomical parts (Scarpa et al., 2007). It has been shown that mucosectomy is not always complete (O’Connell et al., 1988; Lovegrove et al., 2006; Vento et al., 2011). DS is technically easier to perform and evidence suggests that it achieves better functional results and the risk of dysplasia or malignancy is low. Dysplasia or invasive cancer diagnosed before RPC or found in the operation specimen have been reported to be a significant risk factor for the further development of neoplastic change in the pouch or in the rectal cuff and ATZ (Scarpa et al., 2007). In HS it is possible to remove all the rectal mucosa. We thus agree with the ECCO guideline and perform HS only when dysplasia is found in the rectum preoperatively (Öresland et al., 2015).

6.1.2 Covering ileostomy

Study I showed that there were significantly fewer leakages and early reoperations when covering ileostomy was used than when it was not used (6.0% vs. 16.4%, $p=0.004$ and 4.5% vs. 11.9%, $p=0.02$ respectively). The morbidity connected to ileostomy closure was quite common, 31.6% (n=42). The most common complication was SBO (16.8%), which kept the patients in hospital longer. The most serious complication was leakage, which was luckily uncommon, occurring in 3.0%. All four patients needed early reoperation. The only randomized controlled study reported that risk of pelvic sepsis was not increased by omitting ileostomy (Grobler et al., 1992). Other studies are observational in nature and may suffer from selection. Some authors have concluded that use of covering ileostomy reduces the morbidity of anastomotic leakage and pelvic sepsis (Tjandra et al., 1993; Williamson et al., 1997; Mennigen et al., 2011). By contrast, some state that the one-stage procedure is superior (Heuschen et al., 2001; Sahami et al., 2016) while others conclude that ileostomy can be omitted for selected patients (Widmar et al., 2019). The studies suggesting the selective use of ileostomy are more recent and there seems to be a trend towards this (Lovegrove, et al., 2011; Worley et al., 2018a). It is somewhat controversial whether ileostomy closure is associated with considerable morbidity (Wong et al., 2005; Mennigen et al., 2014; Rottoli et al., 2018; Karjalainen et al., 2019). The findings of this study support the use of ileostomy, accepting the increased though slight morbidity.

6.2 Complications

Complications after IPA A can be categorized by timing and aetiology. Usually early (<30d after operation) and late complications are reported. Infectious complications include pelvic sepsis and anastomotic leakage resulting in abscess and fistulae. Inflammatory complications include pouchitis and cuffitis. Mechanical complications consist of obstruction and pouch dysfunction in various forms: stricture, pouch prolapse, low volume pouch or pouch volvulus (Leinicke, 2019).

6.2.1 Early complications

The mortality in the present study included only one patient and this was because the patient declined blood transfusions, had a serious bleeding complication and the reoperation the next day could not save his life. According to the literature mortality is also low, less than 1% (Gorgun & Remzi, 2004). One obvious reason is that the patients are mainly young and have few, if any, comorbidities. Thus, this and other studies indicate that the operation is safe in this respect.

The most important early complications are pouch related and of these leakage or pelvic sepsis occur in 6–15% of patients (de Zeeuw et al., 2012; Sagar & Pemberton, 2012). In the present study the leakage rate was comparable, 12.5%. The leakage did not seem to have a negative effect on the functional results comparing poorly and well- functioning pouches (study III) but the pouch failure group had significantly more early leakages than did those with pouch in place (study IV). Infection complications were also among the main reasons for early reoperations (81%) and readmissions to hospital (65%) (study I).

It is wise always to suspect leakage and then one is able to diagnose and start treatment promptly, which may save effects on long-term function. Traditionally the treatment has been diversion and drainage but new data show that better results may be achieved with endosponge assisted early closure (Wasmann et al., 2019). In preventing leakage the technical accuracy of performing anastomoses with good blood supply, without tension is of the utmost importance. It is important to recognise the patient-associated risk factors (high corticoid dosage or other preoperative medications, high BMI, aging) and to plan the surgery accordingly: timing of surgery and whether to perform two- or three-stage surgery.

6.2.2 Late complications

In the present study, the most common late complication was pouchitis, occurring in 39%. By comparison, in the literature percentages of up to 46% have been reported (Dalal et al., 2018). Antibiotic treatment with metronidazole or ciprofloxacin is the first-line therapy and the majority of patients respond to it (Shen et al., 2001).

IPAA patients are at high risk of SBO because of extensive abdominal and pelvic dissection and the possible need for several operations. In study I early SBO was recorded for 5.6% and late SBO with a median follow-up time of five years occurred in 13.2% of patients and 20% of early and 37.8% of late SBOs required surgery. The use of covering ileostomy did not result in more SBOs altogether 14.6% vs. 12.4%, $p=0.6$. A large study reported late SBOs in 25.3%, of which 27.6% needed surgery (Fazio et al., 1995) and similar results have also been reported from Sweden: 3.2% early and 25.5% late SBOs, of which 34% needed surgery (Åberg et al., 2007). In another large study ($n=1,178$), the cumulative percentage of SBOs was 9% at 30 days, 18% at on year, 27% at five years and 31% at ten years. SBO was managed conservatively in the majority of cases, as operative treatment was required in 1% within 30 days, in 3% at one year, in 7% at five years, and 8% at ten years (MacLean et al., 2002). Laparoscopy has been shown to result in fewer adhesions and also in fewer SBOs (Hull et al., 2012). We plan to explore this in our series in the future.

There were significantly more strictures for HS than DS in study I, 14.6% vs. 0%, $p=0.001$. Comparable percentages have been reported earlier: 12% vs. 4%, $p=0.003$ (Prudhomme et al., 2003). Stricture leading to functional problems and multiple dilatations or other surgical interventions and pouch failure was not rare, 23% in Study IV, which again speaks for the use of DS anastomoses.

6.2.3 Pouch failure

Pouch failure is defined as new permanent ileostomy with or without pouch excision. In study IV pouch failure occurred in 53 (10.8%) out of 491 IPAA patients. The cumulative risk for pouch excision at five years was 5.6%, and threefold at 20 years, 15.5%. The long-term failure rate for RPC has been variable, 5.8–17% in the literature (Lepistö et al., 2002; Tulchinsky et al., 2003; Wasmuth et al., 2010; Mark-Christensen et al., 2018). The main reasons for pouch failure were poor function 30%, incontinence 23%, fistula 23%, stricture 23%, chronic pouchitis 21%, leakage 15% and CD 13%. The same reasons appear in several studies with long-term follow up (Lepistö et al., 2002; Tulchinsky et al., 2003; Tekkis et al., 2010). Many IPAA studies have included FAP patients. In a meta-analysis ($n=9,317$) the indications for IPAA were UC 87.5%, IC 2%, FAP 8.9%, CD 0.8% and other 0.7%. The complication and pouch failure rates were reportedly lower for FAP. (Hueting et al., 2005.) The present study focused on UC surgery only and this should be considered when comparing the results of the studies.

In the present study 15.2% of men and 4.7% of women suffered from pouch failure. By contrast, in a Danish population based study with 295 failures, there was a higher risk for female patients to experience pouch failure, HR 1.39, 95% CI 1.10–1.75 (Mark-Christensen et al., 2018). No significant gender difference has been reported earlier (Fazio et al., 2003; Manilich et al., 2012; Worley et al., 2018b). The results are thus variable and maybe dependent on patient series.

Regarding whether the failed pouch should be excised or left in situ, the comparison of morbidity and risk of malignancy should be considered. In study IV one mucinous cancer was found in the operation specimen giving a malignancy rate of 0.2%. Thus, this seems not to be a significant problem. An early complication was recorded in 23 (44%) of the patients after surgery but 16 (70%) of these were C–D grade I–II and the CCI was grade 0 for 89% of the patients. The most common early complications were SBO in 17% and perineal wound infection in 6%. Readmission to hospital was recorded for 13 (25%) of the pouch excision patients. A limited number of studies exploring the postoperative complications of pouch excision link the operation to significant morbidity. The studies on this subject report 25–57% short-term morbidity and 5.5–19% of short-term reoperation, long-term complication rates of 28–40% and readmission rates of 19–38% (Karoui et al., 2004; Lightner et al., 2017; Lachance et al., 2018). The most important and most common complications and reason for readmission is surgical site infection at the perineal wound (Karoui et al., 2004; Prudhomme et al., 2006). Interestingly, the morbidity does not differ when pouch excision and pouch left in situ are compared. Moreover, quality of life was found to be better for excision patients (Kiran et al., 2012). In the present study in all but one pouch failure patient pouch excision was performed. The indication for failure is commonly a septic event leading to incontinence, and although a diversion is performed, the morbidity of the incontinent pouch or fistula still persists. The patients with pouch excision had usually few comorbidities and the complications were mostly mild. Therefore, excision has been the main choice in our unit.

6.3 Health-related quality of life and functional results

There are two things that relate to the achievement of a good quality of life for IPAA patients operated on for UC: the removal of the disease symptoms and of fear of malignancy and the avoidance of a permanent stoma. In study II HRQoL among patients with well-functioning pouch was similar to that of general population and to that of non-operated UC patients in remission. Patients with well-functioning pouches also showed better results in all sub scores (bowel disorder, emotional disorder, systemic symptoms and social function) of IBDQ than those with active colitis. This observation verifies findings reported earlier where pouch function was connected to level of HRQoL (Carmon et al., 2003; Scarpa et al., 2004; Berndtsson et al., 2007; Kiely et al., 2012), IPAA improves HRQoL in symptomatic UC patients (Thirlby et al., 1998; Fazio et al., 1999; Muir et al., 2001; Polle et al., 2007; Heikens et al., 2012a) and HRQoL reaches the level of general population or slightly under (Thirlby et al., 1998; Richards et al., 2001; Robb et al., 2002; Carmon et al., 2003; Berndtsson et al., 2007; Andersson et al., 2011; Heikens et al., 2012a). In the present study there was no difference between groups divided by indications for surgery. When we operate with an indication of dysplasia on a patient whose UC is in

remission we can expect HRQoL to deteriorate, as was also seen in this study. For these patients the removal of risk of malignancy plays a bigger role.

In study III the pouch function results for a long median follow-up of 13 years (range 4–28) were good and stable among the majority of patients at 70% (Öresland score <8). The number of daily bowel movements was ≤ 5 in 55% of patients. These are close to what is considered good and “normal” frequency (4–8 day, 1 night) and almost perfect continence (Michelassi et al., 2003). Eighty per cent were continent during the day and 64% at night. Similar continence result have been reported by others (Berndtsson et al., 2007; de Buck van Overstraeten et al., 2014). In the present study men suffered from nocturnal incontinence more than women, 51% and 33% respectively, $p=0.015$. This finding has also been observed by others (Meagher et al., 1998; Farouk et al., 2000; Berndtsson et al., 2007) the reason for this difference remains unknown. Even if the majority experienced good functional results, dietary restrictions were experienced by 49% and use of bowel regulating medications was reported by 29%. A study from Belgium reported 50% using antidiarrheals and about half reporting dietary restrictions (de Buck van Overstraeten et al., 2014).

In the present study the poorly functioning group had significantly more pouchitis than the well-functioning group, 51.0% and 25.6 ($p=0.001$). Stricture was almost twice as common in the poorly functioning group as among those with well-functioning pouches, 13.2%, vs. 7.9% but the difference was not statistically significant, $p=0.27$. Patient's ≥ 63 years of age reported more daytime incontinence than younger ones. Other studies have similarly concluded that continence deteriorates in the oldest age groups, but still has a minor influence on patient satisfaction (Delaney et al., 2003; Hahnloser et al., 2004). Pelvic sepsis or leakage showed no association with poor function in this study although there was a clear difference for the pouch failure vs. the pouch in place groups 15 (28.3%) vs. 32 (7.3%) $p<0.001$, 15 (28.3%) vs. 60 (13.7%) $p=0.005$ respectively. We did not explore the salvage operations more closely for patients with pouch still in use but 52.8% of pouch failure patients had had some kind of salvage operations performed before pouch excision.

RPC with IPAA may be connected to different kinds of morbidity, and 10% failed in the long run. Nevertheless, most IPAA patients are doing well, and HRQoL does not differ from that in the population. The present findings help to inform patients of the IPAA operation when indication for surgery emerges. It should still be noted that the complication risks increase with age. Pouch malignancy seemed not to be a major problem. The centralization of IPAA surgery concerns not only the surgery itself but also co-operation with gastroenterologists, prompt diagnosis and treatment of postoperative complications and the knowledge to deal with different kinds of late onset pouch problems. The team must constantly evaluate their results and keep up to date with new treatment strategies. Using these guidelines we can offer the majority of surgically treated patients the lowest possible morbidity and high quality of life that lasts.

6.4 Limitations of the study

The limitations of this thesis were the retrospective nature (studies I and IV) and lack of annual follow-up data. The long time period and the changed routines in patient care may to some extent challenge the comparisons. The limitations of studies II and III were the large number of patients who did not return the questionnaires. In the analysis of the non-respondent groups of patients there were no obvious major differences between responders and non-responders.

6.5 Future prospects

In the future we are planning to explore the effect of the laparoscopic surgery initiated as a standard procedure from 2017 onwards. The use of biological medication and its effects on surgical outcome is planned to be explored. We also intend to analyse the new reservoirscopy follow-up protocol in use. The new robot surgery should also be explored prospectively.

7 Conclusions

The main conclusions of the present thesis are:

- 1 Our surgical technique is justified. The data show that the most severe and important complications concerning pouch function remained on an acceptable level.
- 2 IPAA patients with a well-functioning pouch had HRQoL similar to that in general population and in UC patients with their disease in remission or mildly active.
- 3 The long-term functional outcome of IPAA patients was good in the majority (70%) of cases. Elderly patients need careful patient selection and consultation.
- 4 Pouch failure occurred in 10.8% patients. The cumulative risk for pouch excision at five years was 5.6%, at ten years 9.4% and at 20 years 15.5%. Prevention, diagnostics and early aggressive treatment of septic events are of great importance, because they lead to deterioration of pouch function and failure in most cases.

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10 Appendices

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Ohje: Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. Menetelkää näin kaikkien kysymysten 1–15 kohdalla. Kustakin kysymyksestä rastitetaan siis yksi vaihtoehto.

KYSYMYS 1. Liikuntakyky

- 1 () Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
- 2 () Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
- 3 () Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
- 4 () Pystyn kävelemään sisälläkin vain toisen avustamana.
- 5 () Olen täysin liikuntakyvytön ja vuoteenoma.

KYSYMYS 2. Näkö

- 1 () Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
- 2 () Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
- 3 () Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
- 4 () En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
- 5 () En näe kulkea oppaatta eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo

- 1 () Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
- 2 () Kuulen normaalia puheääntä pienin vaikeuksin.
- 3 () Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
- 4 () Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
- 5 () Olen täysin kuuro.

KYSYMYS 4. Hengitys

- 1 () Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
- 2 () Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
- 3 () Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
- 4 () Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
- 5 () Minulla on hengenahdistusta lähes koko ajan, myös levossa.

KYSYMYS 5. Nukkuminen

- 1 () Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
- 2 () Minulla on lieviä uniongelmiä, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
- 3 () Minulla on melkoisia uniongelmiä, esim. nukun levottomasti tai uni ei tunnu riittävältä.
- 4 () Minulla on suuria uniongelmiä, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
- 5 () Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

KYSYMYS 6. Syöminen

- 1 () Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
- 2 () Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
- 3 () Tarvitsen hieman toisen apua syömisessä.
- 4 () En pysty syömään itse lainkaan, vaan minua pitää syöttää.
- 5 () En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

KYSYMYS 7. Puhuminen

- 1 () Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
- 2 §() Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
- 3 () Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
- 4 () Muilla on vaikeuksia ymmärtää puhettani.
- 5 () Pystyn ilmaisemaan itseäni vain elein.

KYSYMYS 8. Eritystoiminta

- 1 () Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
- 2 () Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
- 3 () Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
- 4 () Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti ”vahinkoja” tai peräruiskeiden tai katetroinnin tarvetta.
- 5 () En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot

- 1 () Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
- 2 () Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
- 3 () Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
- 4 () Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
- 5 () En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

Kysymys 10. Henkinen toiminta

- 1 () Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
- 2 () Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti
- 3 () Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä
- 4 () Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä
- 5 () Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

KYSYMYS 11. Vaivat ja oireet

- 1 () Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- 2 () Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
- 3 () Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
- 4 () Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
- 5 () Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

KYSYMYS 12. Masentuneisuus

- 1 () En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
- 2 () Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
- 3 () Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
- 4 () Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
- 5 () Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

KYSYMYS 13. Ahdistuneisuus

- 1 () En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 2 () Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 3 () Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 4 () Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 5 () Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

KYSYMYS 14. Energisyys

- 1 () Tunnen itseni terveeksi ja elinvoimaiseksi.
- 2 () Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
- 3 () Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
- 4 () Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes ”loppuun palaneeksi”.
- 5 () Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin ”loppuun palaneeksi”.

KYSYMYS 15. Sukupuolielämä

- 1 () Terveystilani ei vaikeuta mitenkään sukupuolielämääni.
- 2 () Terveystilani vaikeuttaa hieman sukupuolielämääni.
- 3 () Terveystilani vaikeuttaa huomattavasti sukupuolielämääni.
- 4 () Terveystilani tekee sukupuolielämäni lähes mahdottomaksi.
- 5 () Terveystilani tekee sukupuolielämäni mahdottomaksi.

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J-pussin eli suolisäiliön toimintaan liittyvä kyselylomake, (Öresland score)

Lue ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitse rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä suolisäiliöleikkauksen jälkeistä suolen toimintaanne. Valitse kustakin kysymyksestä yksi, parhaiten tilannetta vastaava kohta.

Kokonaisuuden kannalta on tärkeää, että vastaisit kaikkiin kysymyksiin, vaikka muissa saamissasi kaavakkeissa on saman tyyppisiä kysymyksiä.

1. Kuinka monta kertaa suolenne on toiminut keskimäärin päiväaikaan viimeisen kahden viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- 4 kertaa tai vähemmän
- 5 kertaa
- 6 kertaa tai enemmän

2. Kuinka monta kertaa suolenne on toiminut keskimäärin öisin viimeisen kahden viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- ei kertaakaan
- kerran tai enemmän viikossa
- 2 kertaa tai enemmän yössä

3. Minulla on ollut kiire vessaan siten, etten ole pystynyt siirtämään ulostamista ulostamistarpeen tultua yli 30min.

- ei
- kyllä

4. Kärsin ulostamisvaikeudesta siten, että olen joutunut viettämään ulostamassa yli 15 min kerrallaan viimeisen kahden viikon aikana.

- ei
- kyllä

5. Minulla on ollut ulosteen pidätyskyvyttömyyttä tai alusvaatteiden tahatonta tahriintumista päiväaikaan viimeisen kahden viikon aikana?

- ei
- kerran tai useammin viikossa

6. Minulla on ulosteen pidätyskyvyttömyyttä tai alusvaatteiden tahatonta tahriintumista öisin

- ei
- kerran tai useammin viikossa

7. Minulla on ollut kipua tai arkuutta peräaukon seudussa viimeisen kahden viikon aikana.

- ei
- ajoittain
- jatkuvaa

8. Olen joutunut käyttämään suojasidettä päiväaikaan viimeisen kahden viikon aikana.

- ei
- kerran tai useammin viikossa

9. Olen joutunut käyttämään suojasidettä öisin viimeisen kahden viikon aikana.

- ei
- kerran tai useammin viikossa

10. Olen joutunut välttämään tiettyjä ruoka-aineita, jotka vaikuttavat J-pussin toimintaan, viimeisen kahden viikon aikana.

- ei
- kyllä

11. Olen joutunut käyttämään suolensisältöä muokkaavia lääkkeitä viimeisen kahden viikon aikana.

- ei
- kyllä

12. J-pussin toiminta on haitannut normaalissa päivätyössä käymistä tai muuta normaalia sosiaalista elämää viimeisen kahden viikon aikana.

- ei
- kyllä

Taudin aktiivisuuden liittyvä kyselylomake (SCCAI)

Tämä kyselykaavake on laadittu selvittämään paksusuolen tulehduksen aktiivisuutta Sinulla tällä hetkellä. Merkitse kussakin kysymyksessä rasti (x) sen vaihtoehdon kohdalle, joka parhaiten vastaa omaa tilannettasi viimeksi kuluneiden kahden viikon aikana.

1. Kuinka monta kertaa suolesi on toiminut keskimäärin päiväaikaan viimeisen kahden viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- 1–3 kertaa
- 4–6 kertaa
- 7–9 kertaa
- yli 9 kertaa

2. Kuinka monta kertaa suolesi on toiminut keskimäärin öisin kahden viimeisen viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- Ei kertaakaan
- 1–3 kertaa
- 4–6 kertaa

3. Onko ulostaminen on ollut pakonomaista siten, että on tullut kiire vessaan viimeisen kahden viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- ei kiirettä
- täytyy kiirehtiä
- täytyy päästä heti
- valuu housuihin

4. Onko ulosteissasi esiintynyt verta kahden viimeisen viikon aikana? Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- ei
- veriviiruja
- toisinaan kirkasta verta
- yleensä kirkasta verta

5. Yleistilani kahden viimeisen viikon aikana on ollut. Ole hyvä ja valitse seuraavista yksi, parhaiten sopiva vaihtoehto.

- erittäin hyvä
- hyvä
- huono
- erittäin huono
- sietämätön

6. Onko Sinulla esiintynyt jotain seuraavista suolen ulkopuolisista sairauden ilmentymistä? (Voi rastittaa useamman vaihtoehdon.)

- nivelsärky
- värikalvon tulehdus silmässä eli iriitti
- kyhmyruusu
- haavainen ihotulehdus eli pyoderma gangrenosum
- peräaukon haavauma
- peräaukon fisteli
- perianaalipaise
- suun aftat

Original Publications

PUBLICATION

I

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In 1985–2009

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RESTORATIVE PROCTOCOLECTOMY FOR ULCERATIVE COLITIS IN 1985–2009

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ABSTRACT

Background and Aims: Restorative proctocolectomy is the most common operation in patients with ulcerative colitis. The aim was to evaluate long-term changes in our operative treatment and early and late complications related to restorative proctocolectomy.

Material and Methods: The study comprised 352 (149 females) patients over 18 years of age with ulcerative colitis who underwent restorative proctocolectomy in 1985–2009 median follow-up time of 5 years.

Results: The indication for surgery was active chronic colitis in 168 (47.7%), acute colitis in 159 (45.2%), and cancer or dysplasia in 25 (7.1%) patients. Ileal pouch-anal anastomosis was performed using hand-sewn anastomosis with mucosectomy in 283 patients and stapled anastomosis in 69. A shift from hand-sewn to stapler ileal pouch-anal anastomosis took place in 2005. Covering ileostomy was carried out in 133 (37.8%) patients. There were 82 (23.3%) J-pouch-related complications. The operative mortality was 0.3%. There were significantly fewer leakages and early re-operations when covering ileostomy was used than when it was omitted: 6.0% versus 16.4% ($p=0.004$), 4.5% versus 11.9% ($p=0.02$), respectively. There were more strictures in hand-sewn than in stapled ileal pouch-anal anastomoses (17.6% vs. 0%, $p=0.001$). Pouchitis occurred at least once in 134 (38.1%) patients.

Conclusion: The ileal pouch-anal anastomosis technique used in restorative proctocolectomy had changed over the past years from hand-sewn to stapled anastomosis. Covering ileostomy seemed to protect against major complications. Pouchitis was the most common late complication.

Key words: Ulcerative colitis; ileal pouch-anal anastomosis; restorative proctocolectomy; complication

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TABLE 1
Types of operations for ileal pouch-anal anastomosis (IPAA).

	Number	%
Type of operation		
Proctocolectomy + IPAA	98	27.8
Proctocolectomy + IPAA + covering ileostomy	87	24.7
Proctectomy + IPAA after colectomy	121	34.4
Proctectomy + IPAA + ileostomy after colectomy	46	13.1
Type of anastomosis		
Hand-sewn	283	80.4
Stapled	69	19.6

TABLE 2
Number of pouch-related complications.

	Number	%	Hand-sewn/ stapler	Stoma/no stoma, n
Pouch-related complications	82	23.3		
Leakage	44	12.4	39/5	8/36*
Bleeding	8	2.3	8/0	0/8*
Abnormal pain	5	2.3	5/0	2/3
Fistula	3	0.8	3/0	1/2
Stricture	1	0.3	0/1*	1/0
Early pouchitis	4	1.1	4/0	1/3
Infected hematoma or abscess	17	4.8	13/4	9/8

INTRODUCTION

Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) is the treatment of choice when surgical treatment in ulcerative colitis (UC) is needed (1). The operation is associated with considerable morbidity; leakage and pelvic sepsis are the most serious complications, occurring in 6%–25% of patients (2, 3). Pouchitis is the most common of the late complications; at least one episode is experienced within 10 years after surgery in 25%–48% of patients (4–6); in 3%–17%, pouch failure requiring permanent ileostomy is inevitable (7–9).

The operative technique has gone through changes in recent decades. The use of covering ileostomy is recommended but not mandatory (10, 11). Stapled anastomosis has in many cases replaced hand-sewn anastomosis (12).

The aim of this study was to evaluate the results of RPC in 352 consecutive patients operated for UC in 1985–2009. Special focus was on the effects of the changed IPAA technique on early and late complications.

MATERIAL AND METHODS

All patients with UC who underwent RPC at Tampere University Hospital between March 1985 and December 2009 were identified in the hospital records; the total number of subjects was 352 (149 women, 42.3%), median age of 36 years, range of 18–72. A database was collected from patient files including details on patient history, operation technique, postoperative morbidity, and follow-up.

Indications for surgery were categorized into three groups: acute colitis resistant to conventional medical management, chronic colitis and the development of dysplasia, cancer or estimated high risk of progression to malignancy. Acute colitis was determined when urgent colectomy had to be performed. Chronic colitis included failure of medical treatment, corticosteroid dependent or resistant disease or active disease despite any treatment.

Early complications were defined as occurring within 30 days of the operation. Pelvic sepsis was present when there was a leakage, pelvic abscess, or pelvic infected hematoma. Small bowel obstruction (SBO)

*Statistically significant.

was considered a complication when hospital stay exceeded the median 10 days in the whole series.

Late complications consisted of all problems recorded more than 30 days after the operation. The diagnosis of pouchitis was based on clinical signs and symptoms and occasionally on endoscopic and histological findings. Anastomotic stricture was considered a complication if it caused functional difficulties and the dilatation was needed. Pouch failure was defined as the need for a permanent ileostomy with or without pouch excision.

STATISTICAL ANALYSES

Grouped data are expressed as median and range. Chi-Square or Fisher's exact test was used to assess differences in categorical variables. Statistical significance was set at $p \leq 0.05$. Binary logistic regression analysis was used to determine the predictors of leakage. Results are shown as odds ratios (ORs) with their 95% confidence intervals (CIs).

RESULTS

SURGERY

Indications for surgery were acute colitis in 159 (45.2%), chronic colitis in 168 (47.7%), and cancer or risk of cancer in 25 (7.1%) patients. Colectomy was performed on 47.7% of patients prior to the IPAA procedure. During 1985–2005, nearly all IPAAs were hand-sewn with distal mucosectomy, and from 2005 onwards the main technique was a stapled IPAA with a covering ileostomy. Before this, a covering ileostomy was performed only when considered necessary. A J-shaped reservoir was used in all cases. The types of operations and anastomoses performed are shown in Table 1. Four experienced surgeons performed 91% of the operations.

EARLY MORBIDITY

Pouch-related complications were the most common, occurring in 82 (23.3%) (Table 2); of these, altogether 61 (17.3% of all) had pelvic sepsis, including 44 leakages.

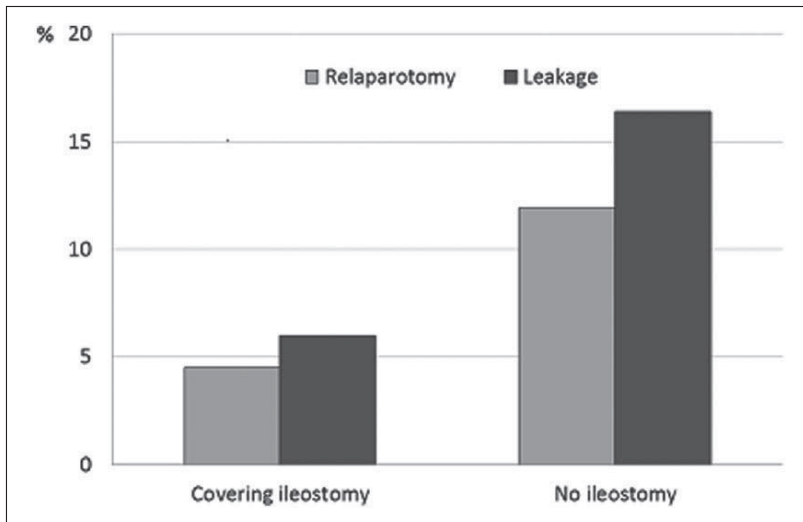


Fig. 1. Influence of covering ileostomy on leakages ($p=0.004$) and early re-operations ($p=0.02$).

One patient (0.3%) died of postoperative bleeding; he was re-operated on to achieve hemostasis on the first postoperative day, but declined blood transfusions for religious reasons.

A total of 32 (9.1%) of the patients required re-operation due to complications. The indications were leakage in 25, hemorrhage in 2, SBO in 4, and perforation in 1. In all, 23 loop ileostomies were made in these re-operations, of which all but 2 were closed later; 1 permanent end-ileostomy was made due to a leakage.

A total of 81 (23%) patients were re-admitted to hospital within the postoperative period. The reasons were fever in 22, abscess in 20, leakage in 11, dehydration in 9, SBO in 6, and miscellaneous reasons in 13.

There were significantly fewer leakages and early re-operations when covering ileostomy was used than when it was not used, 6.0% versus 16.4% ($p=0.004$) and 4.5% versus 11.9% ($p=0.02$), respectively (Fig. 1). In the logistic regression analysis, no single factor constituted an independent risk for pelvic sepsis. Omission of covering stoma and high body mass index (BMI) were independent risk factors for leakage, ORs of 3.68 (95% CI: 1.61–8.42) ($p=0.002$) and 1.11 (1.01–1.21) ($p=0.03$), respectively. When the patients without covering stoma were divided by BMI into four groups (<22, 22–24, >24–27, and >27), the most obese group were found to be at clearly higher risk of leakage, 6.5% versus 25.0% ($p=0.017$).

Of the early complications, dehydration was the only which occurred significantly more frequently in the patients with covering stoma than in those without stoma, 6.8% versus 0.0% ($p<0.001$), respectively. The rate of early SBOs did not differ between these two groups, occurring in 6.0% and 5.9%.

Five of the covering ileostomies made were closed in another hospital. The median time from IPAA to ileostomy closing operation was 113 days

(range: 30–912). Of the 125 cases closed in our unit, the median hospital stay was 7 days. The overall morbidity related to closing of covering stomas was 31.6% ($n=42$), the most common being SBO in 16.8% patients ($n=25$); SBO was considered a complication when it led to longer hospital stay than median or re-admission. A total of 17 (11.4%) patients had an infection complication after ileostomy closure, 4 of whom (3.0%) experienced leakage; all patients with leakage needed re-operation. Three of the covering ileostomies were never closed before pouch excision.

LONG-TERM COMPLICATIONS

The median follow-up time was 5 years (range: 1 month–24 years). Late complications are presented in Table 3. The most common of these was pouchitis, occurring in 134 (39.3%) patients. Of these 106 (76.3%) experienced more than one episode. A total of 45 (13.2%) patients had at least one episode of SBO; 17 (37.8%) of them underwent a laparotomy and adhesiolysis due to obstruction. The use of covering ileostomy and subsequent closing operation did not result in more late SBOs than omitting the temporary ileostomy, occurring in 14.6% versus 12.4% ($p=0.6$), respectively. SBO occurred in 15.9% when IPAA was constructed later after colectomy, and in 10.7% when it was done at the same time ($p=0.16$).

Patients with hand-sewn anastomosis had significantly more anastomotic strictures than those with stapled anastomosis (17.6% vs. 0%, $p=0.001$).

A total of 41 (12.2%) patients underwent pouch excision, and 1 patient was satisfied with the diverting ileostomy constructed due to peritonitis. One of the patients had the pouch removed due to chronic pouchitis 20 years after the primary operation, and histologic sample revealed mucinotic rectal cancer, of which the

TABLE 3
Late complications in the series.

	Number	%	Hand-sewn/ stapler	Stoma/ no stoma
Small bowel obstruction	45	12.8	41/4	18/27
Fistula or abscess	42	12.6	37/5	12/30
Anastomotic stricture	49	14.5	49/0*	16/33
Ventral or parastomal hernia	12	3.6	7/5*	4/8
Pouchitis	134	39.3	117/17*	41/93

*Statistically significant.

patient died 2 years later; in this case, the anastomosis was performed by hand-sewn mucosectomy.

DISCUSSION

The IPAA operation used should offer low postoperative mortality and an acceptable rate of complications. Loop ileostomy is not an ideal form of stoma for the patient to cope with, and it is sometimes associated with considerable morbidity. The only significant difference in early complications between covering stoma and omitting it in our study was dehydration; and the number of patients ($n=9$, 6.8%) was low. However, some complications extended the hospital stay. On the other hand, most patients with SBO were treated conservatively after the closing operation, and the most serious complication, leakage, was rare (3%). The morbidity of closing operations in our hospital was at acceptable level when compared to the literature (13).

Some studies recommend ileostomy only in selected cases, since there were no differences in the morbidity rate or pouch-related complications when ileostomy was used or not (10, 14). A meta-analysis of this concluded that the omission of covering ileostomy might be justified in patients defined as low risk, but low risk was not well defined (15). The study by Kiran et al. (16) aimed to identify factors which predict septic complications, and making or omitting stoma had no influence.

Altogether, 18.5% of our patients had experienced pelvic sepsis and leakage occurred in 12.5%. In the literature, the pelvic sepsis figures range from 3% to 25% (2, 3, 5, 7, 17–19) depending on the definition. About one-third (6) of the patients with pelvic sepsis were re-operated on and the others were treated conservatively. Our finding advocates the use of loop ileostomy, as patients with covering ileostomy had significantly fewer leakages and early relaparotomies. This is in line with the recent European Crohn's and Colitis Organisation (ECCO) recommendation, where the use of loop ileostomy is advocated except in highly selected cases (20). The study by Mennigen et al. (11) supports our finding: they likewise showed that loop ileostomy reduced pouch-related septic complications and the need for early relaparotomies.

SBO is the late complication of IPAA which leads most often to laparotomy. It is thought to be caused especially by pelvic adhesions. In our series, the frequency of early

SBO was 5.6% and of late SBO 13.2%. The corresponding figures in the literature are 7.5% and 25% (17). In our series, 20% of early and 35.6% of late SBOs required relaparotomy; the respective percentages in the literature being 3.2%–8.7% and 22.9%–31.4% (17, 21, 22). The incidence of SBO has been reported to increase with time after operation, and has been shown to be more frequent when covering ileostomy is used (22). Our data do not support this.

Stapled technique in anastomosis for IPAA has been shown to result in better nocturnal continence than hand-sewn anastomosis and is also easier to perform (12). According to some studies, stapled technique results in fewer septic complications than hand-sewn technique (23, 24). A systematic review of dysplasia after IPAA in 2040 patients showed a pooled prevalence of dysplasia of 1.13% in the pouch, the anal transitional zone, and the rectal cuff. The only identified risk factor for subsequent dysplasia in the rectal cuff with IPAA was the finding of dysplasia in the surgical specimen (25). It is noteworthy that even hand-sewn mucosectomy is not complete in excising the mucosa of the transition zone (12). Because of the accumulating data in favor of stapler anastomosis as mentioned above, we shifted from making hand-sewn anastomoses to mainly stapler anastomoses around the year 2005.

We still perform hand-sewn anastomosis with mucosectomy, when the patient is operated on for cancer or when there is dysplasia in the rectum. The known risk factors for colorectal cancer in patients with inflammatory bowel disease are family history, extensive colitis with active endoscopic or histologic prolonged inflammation, primary sclerosing cholangitis, and pseudopolyposis (26); in these cases, hand-sewn anastomosis might be recommended, but the issue requires further research.

In this study, one cancer was found after IPAA, and the anastomosis was hand-sewn. Hand-sewn anastomoses resulted in significantly more late strictures than did stapled anastomoses. The same has also been shown in a study comprising 3109 patients (23).

Pouchitis was clearly the most common late complication, 134 (39.3%); 23% had experienced only one episode. These figures are in concordance with other studies reporting pouchitis in 23.5%–48% (3, 5–7, 17).

The main limitations of this study were its retrospective character and the lack of annual follow-up data. The postoperative protocols changed in our hospital during the study period, rendering it challenging to compare the different groups. Also, the different follow-up periods of the two groups of patients with different types of anastomoses made it impossible to compare the long-term outcome between these groups.

In conclusion, serious acute complications in RPC were comparable with previous studies. We favor the routine use of covering ileostomy to avoid the most critical complications considering the functional outcome and long-term success rate, pelvic sepsis, and leakage. The stapled anastomosis technique is favored over the hand-sewn technique, except in selected cases with high risk of dysplasia or cancer. Pouch-related complications are most common in the long-run.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

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Health-Related Quality of Life after Restorative Proctocolectomy: A Cross-Sectional Study

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HEALTH-RELATED QUALITY OF LIFE AFTER RESTORATIVE PROCTOCOLECTOMY: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background and Aims: Patients undergoing restorative proctocolectomy have often suffered from active ulcerative colitis which should be remembered when assessing quality of life after operation. The aim of this study was to explore health-related quality of life after restorative proctocolectomy in those with poor or good pouch function and to compare that to patients with active or inactive ulcerative colitis and to the general population.

Material and Methods: Altogether, 282 restorative proctocolectomy patients were investigated. The control group comprised 408 ulcerative colitis patients from the local register. Generic 15D and disease-specific inflammatory bowel disease questionnaire health-related quality of life instruments were used. Population-based data were available for 15D. Pouch function was evaluated with Öresland score and colitis activity with simple clinical colitis activity index.

Results: 15D results showed that patients with good pouch function had health-related quality of life similar to that of the general population. Health-related quality of life with inflammatory bowel disease questionnaire was equally good in patients with good pouch function (n = 131; 70%) and inactive colitis (n = 95; 63%), and equally impaired in patients with poor pouch function (n = 56; 30%) and active colitis (n = 18; 12%).

Conclusion: The majority of patients had health-related quality of life comparable to that in general population. Most patients with active ulcerative colitis are likely to improve their health-related quality of life after successful surgery. These findings are important when informing colitis patients about life after surgery.

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Key words: Quality of life; restorative proctocolectomy; IPAA; ulcerative colitis; 15D instrument; inflammatory bowel disease questionnaire

INTRODUCTION

Restorative proctocolectomy (RPC) is the standard operation for patients with active ulcerative colitis (UC) (1). With successful surgery, patients can avoid a permanent stoma and are able to live a normal life. Health-related quality of life (HRQoL) is essential in evaluating the long-term results of the operation, since RPC may be associated with complications and functional failures (2, 3).

Many studies have shown that HRQoL in RPC patients has been comparable to that in general population (4–6). On the other hand, poor functional results are associated with impaired quality of life (7–9), which again may influence these patients' daily lives. It must be noted that patients undergoing RPC usually suffer from active colitis and HRQoL after the operation is important in this group.

Here, we compared results separately to non-operated colitis patients with active or inactive disease and similarly in RPC patients with good or poor functional result. This information about functional outcome and quality of life is valuable when the physician is discussing surgical treatment with the patient.

MATERIAL AND METHODS

PATIENT SELECTION

This cross-sectional study included all consecutive 352 patients with UC who underwent RPC at the Tampere University Hospital between 1985 and 2009; the subjects were identified in the hospital records using the International Classification of Diseases, 9th Revision (ICD-9) and International Classification of Diseases, 10th Revision (ICD-10) codes for UC and official codes for the operations performed. A database to form an RPC registry was collected from patient files including details on patient history, operation technique, postoperative morbidity, and follow-up. Of these, 282 had their pouch in function and could be located and they were sent questionnaires. Data were collected between October 2012 and May 2013. The control group consisted of 408 age- and sex-matched UC patients from the local inflammatory bowel disease (IBD) register. It is a prospective register for all adult patients with IBD. Cases were collected retrospectively before 1986 and after that prospectively. The age and gender distributions of the study group and the control group were similar. See the selection path for the groups in Fig. 1. The clinical data of the study patients are retrieved from these registries mentioned above.

QUESTIONNAIRES

The questionnaires were sent by mail, and one reminder was sent to the non-respondents. Two different instruments were used to measure HRQoL; one generic (15D) and one disease specific (inflammatory bowel disease questionnaire (IBDQ)). Pouch function was assessed by Öresland score (10) and disease activity in non-operated

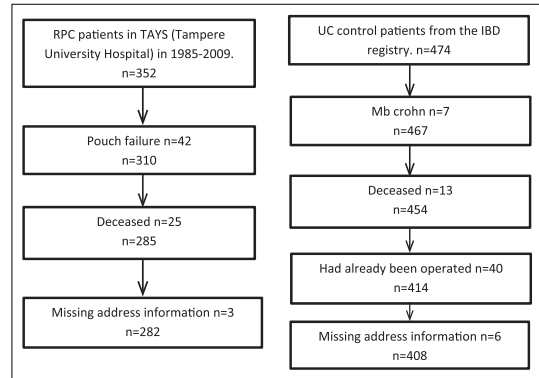


Fig. 1. Flow chart of the formation of the study and the control group.

subjects with UC by simple clinical colitis activity index (SCCAI) (11). The 15D instrument is Finnish, and the other questionnaires were translated from English into Finnish by official translators and a back-translation into English was done to confirm the linguistic accuracy of the translation.

The 15D is a generic self-administered measure of HRQoL. The instrument can be used both as a profile and as a single score measure. The questionnaire includes 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, respondents choose one of the five ordinal levels best describing their current state of health. The valuation system is based on an application of multi-attribute utility theory. The single-index score (15D score), reflecting overall HRQoL on a 0–1 scale (1 = full health, 0 = being dead) and similarly, the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension = 1 and to being dead = 0, were calculated from the questionnaire using a set of population-based preference or utility weights. Mean dimension level values were used to draw 15D profiles. A difference of ≥ 0.03 in 15D score was considered clinically important in the sense that a person can, on average, feel the difference (18). The 15D has been used with IBD patients before (12). The 15D data for general population came from the National Health 2011 Survey representing Finnish population aged 18 and above. This sample ($n = 4763$) was weighted to reflect the age and gender distribution of the patients (13).

A disease-specific IBDQ is a widely used standardized 32-item questionnaire, which addresses four different aspects of life: digestive symptoms, social functioning, emotional status, and systemic symptoms. The questionnaire has been validated in patients undergoing RPC for UC (14). It has been translated into Finnish and used in

TABLE 1
Characteristics of RPC and the control UC patients and also the non-respondents.

	Number of patients	Female, n (%)	Age at survey, years, median (range)	Time from diagnosis, years, median (range)	SCCAI, n (%)		
					≤2	3–4	≥5
Non-operated patients	153	71 (46)	55 (24–81)	20 (6–48)	95 (62)	39 (25)	18 (12)
Non-respondents	255	112 (44)	49 (25–79)	21 (6–48)			
					Öresland score, n (%)		
					Time from operation		
					<8	≥8	
RPC patients	187	87 (47)	53 (23–81)	13 (4–28)	131 (70)	56 (30)	
Non-respondents	95	43 (45)	48 (24–89)	12 (3–27)			

SCCAI: simple clinical colitis activity index; RPC: restorative proctocolectomy.

IBD (15). Total IBDQ score ranges from 32 to 224, a higher score indicating better quality of life.

Pouch function was assessed by Öresland score (10). It includes items about the number of daytime and night-time bowel movements, incontinence for liquid or solid stools, pad usage, urgency, diet, medication, and social handicap; these ratings are summarized into a single score (range, 0–15; 15 being worst). The questionnaire was translated into Finnish and was used with the permission of the developer (10). This questionnaire has been tailored for RPC and used in previous studies to elicit pouch function and HRQoL in UC. In the study by Berndtsson et al., poor Öresland scores correlated negatively with HRQoL results (7). The authors classified the score indicating very good 0–4, good 5–7, or poor pouch function 8–15. We decided to combine the groups with very good and good pouch function and hence the limit was set at a score of 8.

Disease activity of UC was measured using the SCCAI (11). A score of ≤2 was defined as remission, 3–4 as mild or moderately active disease, and ≥5 as severely active disease (16, 17).

STATISTICS

The data were analyzed using SPSS (IBM Corp, released 2012. IBM SPSS Statistics for Windows, version 21.0; IBM Corp, Armonk, NY).

The 15D index was chosen to be the main parameter with which the power calculations were made in the planning phase. With 15D difference ≥0.03 can be detected by an individual (18). Power calculations have been made using PS program difference being 0.03, power 80%, and statistical difference 0.05. In this way, both groups need to include 142 patients.

For categorical variables, the results are given as frequencies and percentages and for continuous variables as means and standard deviation or as medians. Comparisons between different patient groups were tested with chi-square test and in IBDQ scores with Kruskal–Wallis test. Independent samples *t*-test was used to compare the mean 15D scores of the patients and the age- and gender-standardized sample of

general population. *P*-values ≤0.05 were considered statistically significant.

RESULTS

The gender distribution of the respondents was 47% of women in the study and 46% in the control group. The median age was 53 years in the study group and 55 years in the control group. The demographic data on both groups for responders and non-responders are shown in Table 1.

RPC PATIENTS

Of the 352 patients operated on between 1985 and 2009, pouch failure (pouch excision or permanent ileostomy without excision) had occurred in 42 and were excluded, 3 could not be reached and 25 had died (Fig. 1). Of the eligible 282 patients, 187 (66.3%) returned the questionnaires; 87 (67%, n=130) of the women and 100 (66%, n=152) of the men. The median age of the patients was 53 (range, 23–81) years, and the median follow-up time after RPC was 13 (range, 4–28) years.

The 95 RPC patients who did not return the questionnaire were on average three and a half years younger than those who did respond; there was no gender difference between respondents and non-respondents. When we compared the clinical data concerning the operation, we found that there was no significant difference in leakage or pelvic sepsis between the respondents and non-respondents.

Altogether, 131 (70%) of the patients had a well-functioning pouch with a score of <8, and 56 (30%) had a poor pouch function.

UC PATIENTS

In non-operated UC patients, 153 (37.5%) of 408 returned the questionnaire. Seventy-one (46%) of them were women and 82 (54%) men. The median age of the patients was 55 (range, 24–81) years. Of the non-operated UC patients 95 (62.1%) were in remission, 39 (25.5%) had mild to moderately active disease, and 18 (11.8%) severely active, as defined by SCCAI.

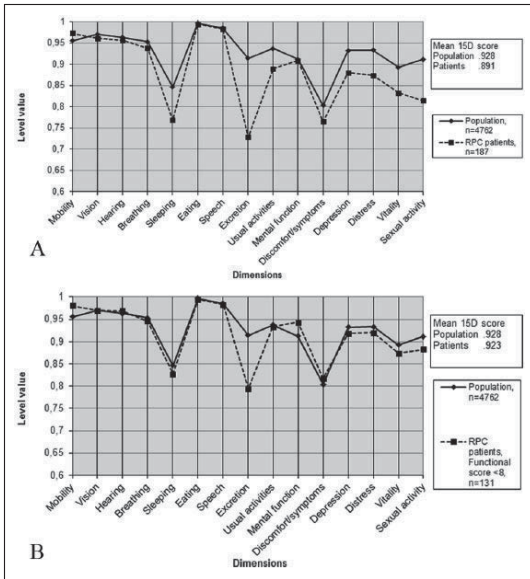


Fig. 2. (2A) 15D scores of all restorative proctocolectomy patients with ileal pouch (n = 187) compared to general population n = 4762 and (2B) scores for well-functioning pouches (n = 131) in comparison to the population.

15D SCORES

The mean 15D score of the RPC patients undergoing surgery was lower (0.891 (0.097)) than that of general population (0.928 (0.077); $p < 0.001$). The RPC patients scored statistically significantly lower on 8 of the 15 dimensions compared to the age- and gender-standardized sample of general population: sleeping, usual activities, excretion, discomfort and symptoms, depression, distress, vitality, and sexual activity (Fig. 2A). In RPC patients with well-functioning pouches, the only significantly decreased score was in excretion (Fig. 2B).

IBDQ SCORES

Fig. 2A shows that HRQoL was equally good in patients with good pouch function and inactive UC when measured by disease-specific IBDQ and also equally impaired in those with poor pouch function and active UC.

The IBDQ subscores for the different groups are presented in Table 2.

Patients with good pouch function showed better results in all subscores than those with active colitis ($p < 0.001$). There was no difference between groups when divided by the indication for surgery ($p = 0.135-0.850$).

The IBDQ scores for subgroups of different indications for patients undergoing surgery compared to UC of different disease activity are shown in Fig. 3B. Fig. 3C shows the IBDQ scores of operated patients with different time from operation.

There was no difference in HRQoL after surgery in different indications or time from operation. The scores were lower for RPC patients for any indication for surgery or time from operation than UC patients in remission but higher than UC patients with active disease.

DISCUSSION

This study investigated HRQoL using generic (15D) and disease-specific (IBDQ) questionnaires in a large cohort of patients operated on at a single institution within a period spanning over two decades. The main finding of this study was that RPC patients with a well-functioning pouch achieved HRQoL similar to that in general population and UC patients with their disease in remission or mild to moderate activity.

HRQoL has previously been reported to improve after RPC and reach the level of that in general population (4-6), although the results are inconsistent (19, 20). In a recent Finnish multicentre study HRQoL was impaired compared to the general population. This study also aimed to identify factors for poor outcome and found older age at time of operation and preoperative hypertension to be significant predictors (21). In this study, most ($n = 131, 70.1\%$) of the RPC patients had well-functioning pouch. Well-functioning pouch was associated with good HRQoL, and therefore, the majority of RPC patients were satisfied with their lives after surgery. Poor functional results of the pouch have been associated with low HRQoL (7-9, 22). This was also shown in this study. This is something about which we can inform the patients preoperatively even though we do not know the reliable risk factors to identify patients prone to poor pouch function or pouch failure before surgery (23, 24).

UC patients with only mildly active disease or the disease in remission reported quality of life equally as good as that of RPC patients with well-functioning pouch. The quality of life scores were equally poor in patients with poorly functioning pouch or severely active UC. An Italian study showed similar results: UC in remission showed an overall QoL similar to that of uncomplicated RPC patients, while the same two groups of patients with mild clinical activity had an overall QoL score similar to those of patients with complicated RPC (25). A recent study also showed that even though RPC patients reported higher bowel movement frequency than patients treated with anti-TNF (tumor necrosis factor), the RPC patients reported better outcomes for general HRQoL (26).

The patients who are considered for operative treatment are those with active acute severe colitis or medically refractory disease or those with dysplasia or cancer. There was no difference in HRQoL when comparing study patients divided by indication. But, as we can see in Fig. 3B, patients in remission undergoing surgery due to dysplasia or cancer were likely to experience deterioration in HRQoL, whereas patients operated on for active disease experience an improvement in HRQoL after successful surgery. For dysplasia patients, we should emphasize the fact that with surgical treatment potentially life-threatening disease

TABLE 2

IBDQ scores and subscores of patients undergoing surgery for different indications, pouch function groups, and control colitis patients for different disease activity groups.

Mean scores (MD)	Total score	Bowel disorder	Emotional function	Systemic symptoms	Social function
Patients undergoing surgery					
Indication					
Acute colitis (n=79)	170.3 (36.8)	5.3 (1.0)	5.4 (1.3)	5.1 (1.3)	5.7 (1.4)
Medically refractory (n=93)	165.9 (35.7)	5.0 (1.1)	5.3 (1.2)	4.6 (1.3)	5.9 (1.2)
Cancer or risk of cancer (n=15)	172.3 (33.3)	5.3 (0.7)	5.3 (1.4)	4.8 (1.1)	6.4 (0.7)
Pouch function					
Good, score <8 (n=131)	181.7 (27.1)	5.6 (0.7)	5.6 (1.0)	5.1 (1.1)	6.3 (0.9)
Poor, score ≥8 (n=56)	136.1(34.2)	4.2 (1.0)	4.2 (1.2)	3.8 (1.2)	4.9 (1.5)
Colitis patients not undergoing surgery					
UC in remission (n=95)	199.3 (16.8)	6.3 (0.6)	6.2 (0.6)	5.7 (0.8)	6.8 (0.4)
UC mildly active (n=39)	173.4 (25.0)	5.4 (0.8)	5.4 (1.0)	4.7 (1.1)	6.2 (0.8)
Active UC (n=18)	133.7 (38.3)	4.1 (1.3)	4.1 (1.2)	3.7 (1.3)	4.6 (1.6)

UC: ulcerative colitis.

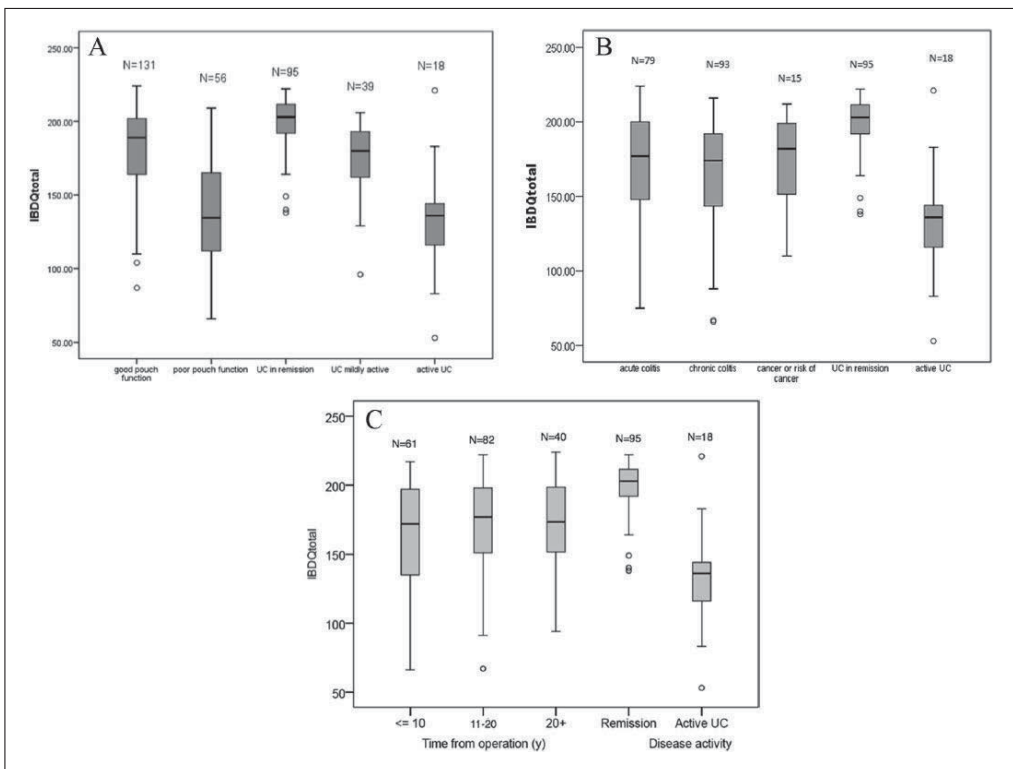


Fig. 3. IBDQ total scores in different subgroups of patients with ileal pouch or ulcerative colitis (UC) compared to non-operated patients for different disease activity groups. The score limits for each subgroup have been described in the Methods section; pouch function was measured by Öresland score and the activity of colitis by SCCAI score. (A) IBDQ total scores for good and poor functioning pouches. (B) IBDQ total scores in different subgroups of indication for surgery. (C) IBDQ total scores on subgroups on how much time had passed since operation.

will be treated, and yet, one can in most cases perform ileal pouch surgery with moderately good and stable HRQoL without permanent ileostomy.

The long-term results are important, since most of the patients undergoing surgery are young; the median follow-up time of 13 (range, 4–28) years in this study

gives a good perspective on this. Quality of life was not dependent on the time elapsing since the operation.

A limitation of this study was the large number of patients who did not return the questionnaires. Response rates have declined in Finland in recent decades both in men and women in all age groups, faster among men and in younger age groups (27). The non-response rate was high especially in non-operated UC. Nevertheless, it was possible to make comparisons between patients with active and inactive UC, as we had enough patients in each activity group. Furthermore, there was no gender difference between operated and non-operated colitis patients, and the median age was almost the same. For comparison, in the entire colitis register, 45% were women, that is, the same percentage as in this study. The non-responders in RPC group were 3 years younger than the responders. Although younger patients have had slightly better functional results, we assume that this small difference did not influence the results significantly. Pelvic inflammatory complications may impair the functional outcome (28, 29). The respondents and non-respondents did not differ in leakage or pelvic sepsis. Therefore, we assume that the functional result that we used on dividing the RPC groups was valid. We did not investigate RPC patients who had experienced pouch failure. It would have not been possible to study the HRQoL before and after the pouch failure, which we think would have given the full picture. We did not include the patients undergoing permanent ileostomy. The number of such patients was low, including mostly elderly patients with a poor sphincter function and do not have RPC as an option. We did not have individual information about pre- and postoperative HRQoL. However, the results of our study show the same trend as studies with preoperative HRQoL data of how HRQoL improves after surgery (4, 6).

In conclusion, this study showed that successful RPC surgery for UC affords the majority of patients good and stable functional results. This again enables good long-term HRQoL, being comparable to that in the general population and in UC patients in remission. In the case of poor pouch function, quality of life remains at the same level to that in active UC. On the other hand, the surgery removes the disease-carrying colon, eliminating several risks, such as bleeding or cancer development, and in most patients, burdensome and expensive medications can be discontinued. Nevertheless, our results are important when counseling the patients before the operation.

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DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The Research and Ethics Committee of Pirkanmaa Hospital District approved the study (R12100). All participants gave written informed consent.

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PUBLICATION
III

**Long-term functional outcome after restorative proctocolectomy: a
cross-sectional study**

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Long-term Functional Outcome after Restorative Proctocolectomy

A cross-sectional study

Short title: Restorative Proctocolectomy

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The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The Research and Ethics Committee of Pirkanmaa Hospital District approved the study (R12100). All participants gave written informed consent.

Abstract

Objective

Restorative proctocolectomy is the procedure of choice in the surgical treatment of ulcerative colitis. Functional outcome is the key result of surgery. The aim of this study was to evaluate the long term-functional outcome after the procedure.

Material and Methods

The study comprised 282 ulcerative colitis patients over 18 years of age who underwent restorative proctocolectomy between 1985 and 2009. The median follow-up time was 13 years (range 4-28). Functional outcome of the pouch was evaluated by the disease specific Öresland questionnaire with a score 0 to 15; 15 being the worst, and score <8 considered well-functioning.

Results

The mean functional score was 5.5 (men 5.6, women 5.0). Seventy per cent of the patients had a well-functioning pouch. Those with poor function had had significantly more pouchitis than the patients with well-functioning pouches, 51.0 vs. 25.6 % respectively ($p=0.001$). No association was found between functional score and the time since the operation. In multiple regression analysis only the occurrence of pouchitis were associated with poor functional results.

Conclusions

The functional results were good and remained stable in the majority of the patients. Pouchitis seemed to have a negative impact on the functional results. Elderly patients especially need careful planning and counselling before restorative proctocolectomy.

Keywords: Functional results, restorative proctocolectomy, ulcerative colitis, ileal-pouch-anal anastomoses, Öresland score

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Discloser of interest: The authors report no conflict of interest.

Data availability: Data is available upon request from the corresponding author

Introduction

Restorative proctocolectomy (RPC) is the standard operation for patients with active ulcerative colitis (UC) [1, 2]. With successful surgery people are expected to live a normal life, the cancer risk is no more concrete and a permanent stoma is avoided. However, RPC is associated with complications and functional failures [3, 4] likely to affect health related quality of life [5]. The majority of patients are young with a long life-expectancy. Therefore, long-term functional outcome is essential in evaluating the decision how to operate and the results of the operation.

Some studies have reported good and stable functional results [6-8] whereas others have found a slight deterioration in number of bowel movements and continence over time [9, 10]. This study aimed to assess the long-term functional results and determining factors over a period of two decades in a single centre.

Material and Methods

Patients

In this cross-sectional study, all consecutive 352 patients with UC who had undergone RPC at Tampere University Hospital between 1985 and 2009 were identified in the patient records using the ICD-9 and ICD-10 codes for UC and NCSP (Nordic Classification for Surgical Procedures) codes for the operations performed. A database to form an RPC registry was collected from patient files including details on patient history, surgical technique, postoperative morbidity and follow-up. The clinical data on the study patients were retrieved from this registry.

Pouch failure (excision or permanent ileostomy without excision) had occurred in 42 patients, three could not be reached and 25 had died. Only one died due to the complication off RPC. The patient had an early postoperative haemorrhage, and refused of red cell transfusion for religious reasons. One patient died of musinotic colorectal cancer found in the pouch after its removal due to fistula and functional problems. Of the remaining patients 282 (80.1%) could be identified and were included in this study. The questionnaire was sent by surface mail; one reminder was sent to the non-respondents. Data were collected between October 2012 and May 2013.

All pouches were of J-type and the anastomosis was either hand-sewn (80%) or stapled (20%). Covering ileostomy was applied in 76 (41%). The surgical technique has moved towards stapled anastomoses and the standard use of covering ileostomy in our hospital [11].

Assessment of Pouch Function

Pouch function was assessed by Öresland score [12]. This questionnaire has been tailored for RPC and has been used in many studies to elicit pouch function [5, 13, 14]. The questionnaire includes items about the number of day-time and night-time bowel movements, incontinence for liquid or solid stools, pad usage, urgency, diet, medication and social handicap; the ratings are summarized into a single score (range 0-15; 15 being the worst possible). The questionnaire was translated into Finnish and was used with the permission of the developer [12]. In the study by Berdtson et al. poor Öresland scores correlated negatively with health-related quality of life results; the authors classified the score indicating function to be very good (0-4), good (5-7) or poor (8-15) [5]. In the present study we decided to combine the very good and good pouch function groups and the cut-off between the groups was therefore set at a score of 8.

Statistics

The data were analysed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). For categorical variables the results were given as frequencies and percentages, for continuous variables as means and standard deviations, or as medians. Comparisons between different patient groups were tested with chi-square test. Multiple regression analysis was used to identify independent patient and operation characteristics related to functional results. P -values ≤ 0.05 were considered statistically significant.

Ethics

This study was conducted according to the principles of the Declaration of Helsinki. The Research and Ethics Committee of Pirkanmaa Hospital District approved the study (R12100). All participants gave written informed consent. The Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, Grant number 9P060, supported this study financially.

Results

Of the 282 patients, 187 (66.3%) (87 women, 100 men) returned the questionnaires. The median age of the responders was 53 years (range 23-81) and the median follow-up time after RPC was 13 years (range 4-28). The 95 RPC patients who did not return the questionnaire were three years younger on average than those who responded and median follow-up time of the non-responders was 11.7 years (range 4-28). There was no gender difference or significant difference in the occurrence of leakage or pelvic sepsis between the respondents and non-respondents.

Altogether 131 (70%) of the patients reported having a well-functioning pouch with a score of < 8 , and the remainder 56 (30%) poor function [Fig.1.]. The surgical details of the patients and most relevant complications for good and poor pouches are shown in [Table 1.]. The poor function group had had significantly more pouchitis than the well-functioning group, 25.6 and 51.0% respectively ($p=0.001$). The poor function group patients were slightly older at the time of surgery 41.0 vs. 36.9 ($p=0.044$) but the difference disappeared in the multiple regression analysis. There was no significant difference between these groups in pelvic sepsis, leakage or in whether the patient developed fistula, abscess or stricture. No association was found on how much time had elapsed since the operation. Anastomotic stricture was almost twice as common in the poor function group as in the well-functioning pouches, 7.9% vs. 13.2%, respectively, but the difference was not statistically significant (Table 3).

The median functional Öresland score was 5.5 for males and 5.0 for females. The various functional sub-scores are presented in [Table 2.]. Fifty-five per cent of the recipients had ≤ 5 bowel movements in daytime and 66% had 0 or ≤ 1 /week at night. Occasional seepage or incontinence was reported by 20% in daytime and by 42% at night. Forty-nine per cent had experienced dietary restrictions, 29% used antidiarrheals and 25% had experienced a social

handicap. The only significant difference between the genders was that males suffered more from nocturnal incontinence than females, 51% and 33% respectively, $p = 0.015$. When the patients were categorized into three age groups (≤ 35 , 36-62, ≥ 63 years of age), the older groups reported more daytime incontinence than younger ones, 0%, 21.2%, 27.3% respectively ($p=0.02$), but nocturnal incontinence was not age-dependent. The use of protective pads was significantly more frequent in subjects in the oldest group, ≥ 63 years of age than in the younger patients; both in daytime (in 4.0, 8.5, 27.3%, $p = 0.002$) and at night (12.0, 22.9, 40.9% respectively, $p = 0.016$).

A multiple regression analysis of nine variables (sex, age at time of surgery, body mass index at time of surgery, type of anastomosis, use of covering stoma, complications including leakage, fistula or abscess, stricture and pouchitis) showed that only age at the time of surgery and the development of pouchitis were independently related to a poor functional outcome [Table 3.].

Discussion

In this study the long-term functional outcome of RPC was found to be good and stable in the majority (70%) of patients. Pouch function was assessed by means of a questionnaire based on Öresland score questionnaire which has especially adapted for this purpose and has been employed in several studies [5, 13, 14].

Development of pouchitis seemed to have a negative impact on functional results. The number of bowel movements was ≤ 5 in 55% of patients. Eighty percent were continent during the day and 64% at night. These findings are similar to those of earlier reports with the median follow-up time [5, 6, 15, 16]. As in the present study, nocturnal seepage or incontinence in males has also been reported by others [5, 17, 18].

In this study patients ≥ 63 years of age reported more daytime incontinence than younger ones, whereas nocturnal incontinence was not age-dependent. In the multivariate analysis, age at time of surgery weakened the functional outcome. Similar results have also been reported in two studies with a large number of patients and an organized follow-up. Hanhloser et al. [9] reported in a study of 409 patients with follow-up at 1, 5, 10 and 15 years that bowel movement frequency remained the same within the follow-up period, but perfect continence dropped from 81% to 55%. Delaney et al. [19] reported functional results in 1,895 patients divided into age groups of ≤ 45 , 46-55, 56-65 and >65 years and follow-up data at 1, 3, 5 and 10 years after surgery. Stool frequencies remained constant but perfect continence was least common in the oldest group after 10 years 53%. Although results of continence deteriorated slightly, this had little or no influence on quality of life or on patient satisfaction [9, 19]. All these studies showed that the functional results were stable over time, and that patient selection in the oldest patient groups had to be carefully planned, especially concerning sphincter function, although age in itself is not a contraindication for RPC.

In our study pelvic sepsis or leakage had no association with poor pouch function. On the contrary, people with well-functioning pouches had experienced such complications more frequently; pelvic sepsis in 16.0 vs. 10.7% ($p=0.24$) and leakage in 10.7 vs. 7.1% ($p=0.32$). By contrast, Kiely et al. [10] reported in a large study ($n=3234$), that pelvic sepsis (6.2%) did weaken perfect continence; 77.8 vs. 69.5% ($p=0.03$) and daytime seepage 21.8 vs. 30.4% ($p=0.03$). An Italian study reported an association with septic pouch complications and poor functional results for stool frequency, pad usage and use of antidiarrhoeals, although all patients nevertheless reported good quality of life [20]. As in our study, two Swedish studies showed that leakage or fistulae had no impact on long-term functional results, but, as also in the present study, pouchitis did [21, 22]. In this study there was more strictures in the poor functioning group, although not statistically significantly. We have earlier reported before that patients with hand-sewn anastomosis had significantly more anastomotic strictures than those with stapled anastomosis (17.6% vs. 0%, $p=0.001$) [23]. Partly due to this we have performed handsewn anastomoses only for the patients with rectal dysplasia preoperatively since the year 2005 [23].

The limitation of this study was the large number of patients who did not return the questionnaires. Response rates have declined in Finland in recent decades both in men and women in all age groups, faster among men and in younger age groups [24]. Another limitation of our study was the cross-sectional design without organized follow-up at specific intervals. There are larger studies than ours, but the results are in line with those of larger studies, and this was a single-centre study including all patients undergoing RPC in our catchment area.

In conclusion, our results support the finding that RPC yields good and stable functional results for the majority of patients. Older patients considered for surgery require careful

individual planning and due to the continence problem we recommend assessment of sphincter function. Pouchitis is the most common long-term complication affecting the functional results and therefore research on the prevention of pouchitis is important.

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Table 1. Demographic, surgery related and complication information on patients operated on for restorative proctocolectomy (mean (range) or n (%))

	Total	Good pouch Score <8, n=131	Poor pouch score ≥8, n=56
Sex			
Male	99 (52.9)	65 (49.6)	34 (60.7)
Female	88 (47.1)	66 (50.4)	22 (39.3)
BMI at time of surgery	24.7 (16-36)	24.7 (18-36)	24.9 (16-34)
Age at time of surgery(yrs)	38 (18-67)	36.9 (18-65)	41.0 (19-67) p=0.044
Duration of the disease before surgery (yrs)	6.7 (0-41)	6.5 (0-34)	7.0 (0-41)
Indication for surgery			
Acute colitis	79 (42.2)	57 (43.5)	22 (39.3)
Medically refractory	93 (49.7)	63 (48.1)	30 (53.6)
Cancer or risk of cancer	15 (8.0)	11 (8.4)	4 (7.1)
Anastomosis			
Hand-sewn	140 (74.9)	98 (74.8)	42(75.0)
Stapled	47 (25.1)	33 (25.2)	14 (25.0)
Covering stoma			
yes	76 (40.6)	49 (37.4)	27 (48.2)
no	111 (59.4)	82 (62.6)	29 (51.8)
Pelvic sepsis	27 (14.4)	21 (16.0)	6 (10.7)
Leakage	18 (9.6)	14 (10.7)	4 (7.1)
Relaparotomy	10 (5.3)	9 (6.9)	1 (1.8)
Hospital stay (days)	11 (4-42)	11.3 (6-42)	11.3 (4-29)
Long-term complication			
Occlusion	23 (12.3)	15 (11.8)	8(15.1)
Fistula/abscess	13 (7.0)	10 (7.9)	3 (5.7)
Stricture	17 (9.1)	10 (7.9)	7 (13.2)
Pouchitis	58 (31.0)	32 (25.6)	26 (51.0) p=0.001
Chronic pouchitis	14 (8.0)	7 (5.6)	7 (13.7)

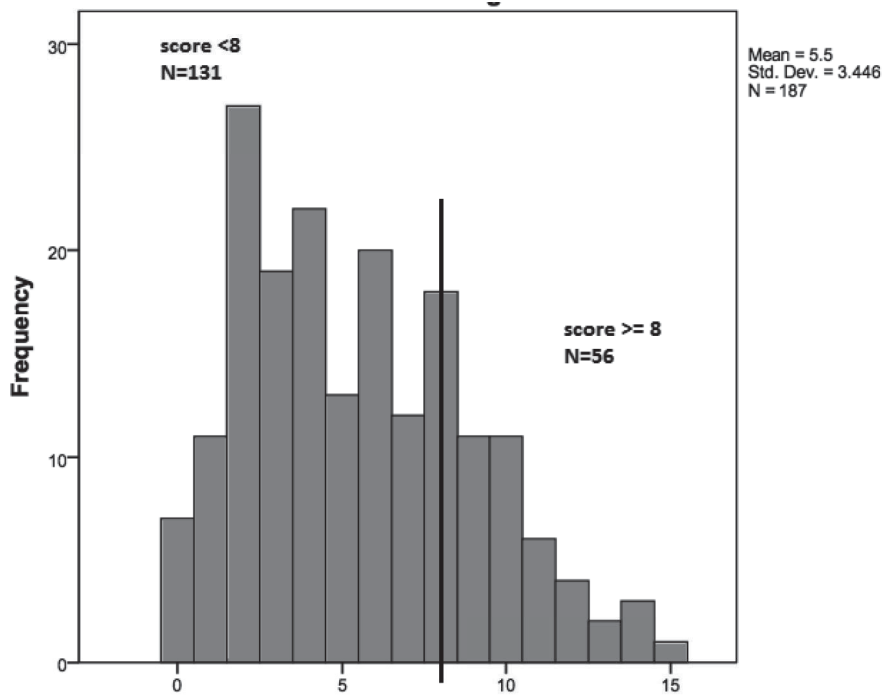
	<i>Rating</i>	<i>N</i>	<i>%</i>
Bowel movements			
<u>Daytime</u>			
≤ 4	0	43	23
5	1	60	32
≥6	2	84	45
<u>At night</u>			
0	0	21	11
≥1/week	1	99	53
≥2/night	2	67	36
Urgency	1	60	32
Evacuation difficulties	1	17	9
Soiling or seepage			
Daytime ≥ 1/week	1	37	20
At night ≥ 1/week	1	79	42
Perianal soreness			
Occasional	1	86	46
Permanent	2	16	9
Protective pad			
Daytime ≥ 1/ week	1	23	12
At night ≥ 1/ week	1	48	26
Dietary restrictions	1	91	49
Medication	1	55	29
Social handicap	1	44	24

Table 2. Functional results of Öresland score in 187 patients with ileal pouch
Urgency = inability to defer evacuation ≥ 30 minutes; evacuation difficulties = ≥ 15 minutes spent on toilet on any occasion during the week; medication = to modify stool consistency; social handicap = not able to resume fulltime occupation or to participate in social life.
Score: best 0; worst 15.

Table 3. Univariate and multivariate analysis of patients and operation characteristics in relation to poor pouch function defined by Öresland score (≥ 8).

	% or mean	Univariate		p-value	Multivariable		p-value
		OR	CI		OR	CI	
Sex							
Female	52.9	1.57	0.83-2.97	0.17	0.95	1.00-1.06	0.90
Male	47.1						
Age at surgery	36.9	1.03	1.00-1.05	0.04	1.03	1.00-1.06	0.07
BMI at surgery	24.7	1.01	0.94-1.10	0.74	0.99	0.89-1.09	0.78
Anastomosis							
Hand-sewn	70.1	1.01	0.49-2.08	0.98	1.33	0.48-3.68	0.58
Stapled	29.9						
Stoma	40.6	1.56	0.83-2.93	0.17	1.94	0.78-4.82	0.15
Leakage	9.6	1.56	0.50-4.95	0.46	1.23	0.35-4.36	0.75
Fistula/ abscess	7.0	1.43	0.38-5.40	0.60	1.54	0.37-6.46	0.56
Stricture	9.1	1.78	0.64-4.96	0.27	1.40	0.42-4.66	0.58
Pouchitis	63.1	3.02	1.53-5.97	0.00	4.21	1.94-9.10	0.00

Figure 1. Distribution of Öresland scores in the study population. A score of 8 was set as the limit between well-functioning pouches and poorly functioning pouches.



PUBLICATION IV

Pouch failures following restorative proctocolectomy in ulcerative colitis

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Submitted

