Department of Gastrointestinal Surgery
Helsinki University Hospital

Faculty of Medicine
University of Helsinki, Finland

SURGICAL TREATMENT OF CROHN'S DISEASE

Gisele Aaltonen

ACADEMIC DISSERTATION

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Supervisor:

Adjunct Professor Anna Lepistö, M.D., Ph.D.
Department of Gastrointestinal Surgery
Helsinki University Hospital
University of Helsinki
Helsinki, Finland

Reviewers:

Adjunct Professor Heikki Huhtinen, M.D., Ph.D.
Department of Digestive Surgery
Turku University Hospital
University of Turku
Turku, Finland

Airi Jussila, M.D., Ph.D.
Department of Gastroenterology and Alimentary Tract Surgery
Tampere University Hospital
University of Tampere
Tampere, Finland

Opponent:

Adjunct Professor Tero Rautio, M.D., Ph.D.
Department of Surgery
Oulu University Hospital
University of Oulu
Oulu, Finland

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To my family

"Follow your dreams, believe in yourself
and don't give up."
-Rachel Corrie

CONTENTS

ABSTRACT

Background: Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract. It most commonly affects the terminal ileum and causes transmural inflammation of the bowel wall resulting in stenosis, fistula or abscess formation. Medication is the treatment of choice for CD, although most patients will require surgery at some point as a result of the disease. Changes in the approach to CD have occurred in the recent years including the increased use of magnetic resonance enterography (MRE) in diagnostics, the acceptance of laparoscopic surgery for CD and the development of new biological medications for CD treatment.

Aims: We compared preoperative MRE findings with surgical findings and evaluated how useful MRE is in the surgical planning. We also assessed whether the presence of inflammatory activity at the bowel resection margin affected postoperative anastomotic complications in CD patients. Our study evaluated the risk factors for anastomotic recurrence after primary ileocaecal resection and compared surgical recurrence after different types of bowel resection in CD patients.

Patients and methods: Our patient sample comprised of 249 consecutive CD patients undergoing surgery at the Helsinki University Hospital during 2006 and 2016. We applied a series of inclusion criteria to each study. Study I consisted of 55 patients who underwent preoperative MRE within the four months preceding surgery between 2011 and 2015. Study II consisted of 70 patients with available bowel resection margins operated on between 2011 and 2015. Study III consisted of 101 patients submitted to primary ileocaecal resection. Study IV consisted of all CD patients undergoing bowel resection with available postoperative follow-up information, yielding 218 patients. Data were retrospectively collected and analyzed.

Results: Preoperative MRE sensitivity compared to surgical findings was 100%, 77.8% and 80.0% while the specificity was 77.8%, 83.8% and 90.0%, respectively, for stenosis, fistula and abscess and calculated per patient. Among 55 patients, the operative plan was modified for 7 patients due to an erroneous preoperative MRE diagnosis of lesions compared to surgical findings. The MRE diagnosis did not agree with the surgical findings for 36 lesions. Furthermore, adhesions were responsible for 44.4% of the incorrect MRE diagnoses.

From a total of 70 patients, 46 patients (65.7%) had inflammatory activity in the bowel resection margin, of whom 34 (48.6%) had moderate or severe inflammatory activity. Postoperative complications were detected in 14

patients (20%), among whom 3 (4.3%) experienced anastomotic complications. The presence of inflammatory activity in the bowel resection margin did not significantly influence the occurrence of anastomotic complications.

Among 101 patients undergoing primary ileocaecal resection in our unit, 9 patients were excluded from analysis due to a follow-up of < 1 year. An end-to-end hand-sewn anastomosis was performed on 96.7% of the patients. Anastomotic recurrence occurred in 12 patients (13%), among whom 4 (4.3%) were treated with endoscopic dilatation and 8 (8.7%) needed repeat ileocolic resection. In the univariate analysis urgent surgery, stapled anastomosis and the need for postoperative steroids emerged as risk factors for anastomotic recurrence, while only stapled anastomosis remained as an independent risk factor in the multivariate analysis.

A total of 218 patients undergoing bowel resection for CD were followed-up for a median of 4.7 years. The frequency of surgical recurrence according to the type of the primary operation performed was as follows: 14 patients (10.1%) after an ileocolic resection, 6 patients (25.0%) after a small bowel resection, 7 patients (41.2%) after a segmental colon resection with colocolic anastomosis or left colon resection, 3 patients (75.0%) after a colectomy with ileorectal anastomosis and 12 patients (34.3%) after an end stoma operation. The CD location at the reoperation correlated with the location of the primary operation.

Conclusions: MRE represents a useful preoperative diagnostic tool for CD, although the presence of intra-abdominal adhesions may cause incorrect diagnosis using MRE. Inflammatory activity at the resection margins did not significantly influence the development of postoperative anastomotic complications, encouraging the use of bowel-sparing surgical techniques for CD. After primary ileocaecal resection, we found a 1.1% anastomotic recurrence rate at 1 year. Hand-sewn anastomosis with an opening of the bowel antimesenteric border appears to be a safe choice after ileocolic resection. In addition, ileocolic resection carries a lower risk of surgical recurrence than other types of bowel resections for CD.

TIIVISTELMÄ

Tausta: Crohnin tauti on tulehduksellinen suolistosairaus, joka voi esiintyä missä tahansa kohtaa ruoansulatuskanavaa suusta peräaukkoon. Tavallisin sijainti on ohutsuolen loppuosa. Crohnin taudissa tulehdus kattaa suolen seinämän kaikki kerrokset. Tulehdus voi aiheuttaa suolen ahtaumaa. Tulehdus voi myös syövyttää suolen seinämään aukon. Tämän seurauksena voi kehittyä märkäpesäkkeitä vatsaonteloon tai syntyä poikkeavia yhdyskäytäviä eli fisteleitä viereiseen suolen mutkaan tai viereisiin elimiin kuten emättimeen ja virtsarakkoon. Crohnin tautia hoidetaan ensisijaisesti lääkkeillä, mutta suurin osa potilaista tarvitsee jossain vaiheessa leikkaushoitoa tautiin liittyvien ongelmien vuoksi. Viime vuosina on tapahtunut kehitystä Crohnin taudin toteamisessa ja hoidoissa: ohutsuolen magneettikuvauksen (MRE) käyttö Crohnin tautiin liittyvien suolistomuutosten arvioimisessa ennen leikkaushoitoa on lisääntynyt, uusia biologisia lääkkeitä on otettu käyttöön ja tähystyskirurgian käyttö on yleistynyt.

Tavoitteet: Ensimmäisessä osatyössä selvitettiin ennen leikkausta tehdyn MRE-kuvauksen kykyä löytää leikkauksessa todetut ahtaumat, fistelit ja märkäpesäkkeet. Näin arvioitiin MRE-kuvauksen merkitystä leikkauksen suunnittelussa. Toisessa osatyössä tutkittiin suolen osapoiston yhteydessä jäljelle jääneen leikkauspinnan mikroskooppisen tulehduksen yhteyttä leikkauksen jälkeisiin suolisaumassa ilmaantuviin komplikaatioihin. Kolmannessa osatyössä selvitettiin riskitekijöitä Crohnin taudin muutosten uusiutumiselle suolisaumassa ohutsuolen loppupään typistyksen (ns. ileokekaalinen suolentypistys) jälkeen. Neljännessä osatyössä vertailtiin riskiä joutua uusintaleikkaukseen Crohnin taudin uusimisen vuoksi erilaisten suolentypistysten jälkeen.

Potilaat ja menetelmät: Aineiston perustan muodosti Helsingin yliopistollisessa sairaalassa vuosina 2006-2016 Crohnin taudin vuoksi leikatut peräkkäiset 249 potilasta. Ensimmäisessä osatyössä analysoitiin ennalta suunniteltuun leikkaukseen vuosina 2011-2015 tulevat 55 potilasta, joille oli tehty MRE-kuvaus neljän kuukauden sisällä ennen leikkausta. Toisessa osatyössä tutkittiin 70 leikattua potilasta vuosilta 2011-2015, joilta suolen leikkauspinnan näyte oli saatavilla. Leikkauspinnat arvioitiin yhtenäisin kriteerein uudelleen patologin avulla. Kolmanteen osatyöhön otettiin mukaan kaikki Crohnin taudin vuoksi ensimmäiseen ileokekaalisen suolentypistykseen joutuneet potilaat ajalta 2006-2016. Neljäs osatyö sisälsi aineistosta ne suolentypistyksen vaatineet 218 potilasta, joilta leikkauksenjälkeistä seurantatietoa oli saatavilla.

Tulokset: Ennen leikkausta suoritetun MRE-kuvauksen sensitiivisyys oli 100%, 77.8% ja 80.0% ja spesifisyys oli 77.8%, 83.8% ja 90.0% ahtaumille, fistelille ja märkäpesäkkeille. MRE-löydös ei vastannut leikkauslöydöstä 36 muutoksessa, mikä aiheutti seitsemällä potilaalla leikkauksen muuttumisen alun perin suunnitellusta. Kiinnikkeet selittivät 44.4% virheellisistä MRE-löydöksistä.

46 potilaalla (65.7%) havaittiin tulehdusta suolen leikkauspinnalla ja 34 potilaalla (48.6%) oli keskivaikeaa tai vaikeaa tulehdusta suolen leikkauspinnalla. 14 potilaalle (20.0%) ilmaantui leikkauksen jälkeisiä komplikaatioita, näistä kolmessa (4.6%) oli kyseessä suolisauman komplikaatio. Suolen leikkauspintaan jääneellä tulehduksella ei tilastollisesti ollut merkittävää yhteyttä leikkauksen jälkeisiin suolisauman komplikaatioihin.

101 potilaalle tehtiin ensimmäinen ileokekaalinen suolentypistys tutkimuksen ajanjaksolla, mutta 9 tapausta suljettiin pois analyysistä lyhyen seuranta-ajan vuoksi. Pää-päätä vasten käsin ommeltu suolisauma tehtiin 96.7%:lle potilaista. Taudin uusinta suolisaumassa todettiin 12 potilaalla (13.0%). Neljä (4.3%) uusintaa hoidettiin paksusuolentähystyksen yhteydessä tehdyllä pallolaajennuksella ja kahdeksan (8.7%) hoidettiin uudella suolentypistyksellä. Koneellisesti tehty suolisauma, päivystysleikkaus ja kortisonilääkityksen tarve leikkauksen jälkeen olivat merkittäviä riskitekijöitä taudin uusiutumiselle suolisaumassa.

Suolentypistyksen jälkeen todettiin uusintaleikkaustarve Crohnin taudin uusimisen vuoksi yhteensä 42 potilaalla (19.3%). Aineistossa seuranta-ajan mediaani oli 4.7 vuotta. Uusintaleikkaukseen oli joutunut 14 (10.1%) potilasta ileokoolisen suolentypistyksen jälkeen, 6 (25.0%) potilasta ohutsuolentypistyksen jälkeen, 7 (41.2%) potilasta paksusuolentypistyksen jälkeen, 3 (75%) potilasta peräsuolen säästävän paksusuolenpoiston jälkeen ja 12 (34.3%) potilasta pääteavanneleikkauksen jälkeen. Crohnin taudin uusimisen sijainti suolessa korreloi ensimmäisen suolentypistyksen sijaintiin.

Johtopäätökset: MRE on hyödyllinen Crohnin tautia sairastavien leikkauksen suunnittelussa, mutta kiinnikkeet voivat aiheuttaa virheellisiä MRE-löydöksiä. Mikroskooppinen tulehdus suolen leikkauspinnassa ei vaikuta merkittävästi leikkauksen jälkeiseen suolisauman komplikaatioon, joten tutkimuksen tulos puoltaa suolen pituutta säästävää leikkaushoitoa. Vuoden kohdalla ensimmäisen ileokekaalisen suolentypistyksen jälkeen taudin uusiutumisen riski suolisaumassa on vain 1.1%. Pää-päätä vasten käsin ommeltu suolisauma vaikuttaa olevan turvallinen vaihtoehto Crohnin taudissa. Uusintaleikkausriski on pienin ileokoolisen suolentypistyksen jälkeen.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals (I-IV):

I Aaltonen G, Keränen I, Carpelan-Holmström M, Savolainen R, Lindén R, Lepistö A. Intra-abdominal adhesions alter the interpretation of magnetic resonance enterography in Crohn's disease. Dig Surg. 2017; 34(1):30-35. Epub 2016 Jul 7.

II Aaltonen G, Ristimäki A, Keränen I, Carpelan-Holmström M, Lepistö A. Does a histologically inflamed resection margin increase postoperative complications in patients with Crohn's disease? Scand J Gastroenterol. 2018; 53(3):279-283. Epub 2018 Feb 12.

III Aaltonen G, Keränen I, Carpelan-Holmström M, Lepistö A. Risk factors for anastomotic recurrence after primary ileocaecal resection in Crohn's disease. Eur J Gastroenterol Hepatol. 2018; 30(10):1143-1147. Epub 2018 Jul 18.

IV Aaltonen G, Carpelan-Holmström M, Keränen I, Lepistö A. Surgical recurrence in Crohn's disease: a comparison between different types of bowel resections. Int J Colorectal Dis. 2018; 33(4):473-477. Epub 2018 Feb 28.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
CARD	Caspase-activating recruitment domain
CECDAI	Capsule endoscopy Crohn's disease activity index
CEUS	Contrast-enhanced ultrasonography
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDEIS	Crohn's disease endoscopic index of severity
CRP	C-reactive protein
CT	Computed tomography
CTE	Computed tomography enterography
ESR	Erythrocyte sedimentation rate
GHAS	Global histological activity score
GI	Gastrointestinal
HBI	Harvey-Bradshaw index
IASC	Intra-abdominal septic complication
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
IC	Indeterminate colitis
IL	Interleukin
LIFT	Ligation of the intersphincteric fistula tract
MR	Magnetic resonance
MRE	Magnetic resonance enterography
NOD	Nucleotide oligomerization domain
PA	Posteroanterior
SES-CD	Simple endoscopic score for Crohn's disease
SSIS	Side-to-side isoperistaltic stricturoplasty
TNF	Tumor necrosis factor
UC	Ulcerative colitis
US	Ultrasonography

INTRODUCTION

In addition to Crohn's disease (CD), inflammatory bowel disease (IBD) includes ulcerative colitis (UC), unclassified inflammatory bowel disease (IBDU) and indeterminate colitis (IC) (Silverberg et al. 2005). CD is a transmural inflammation with skip lesions that can affect any part of the gastrointestinal (GI) tract while UC is a mucosal inflammation limited to the colon. The term IBDU is applied when clinical features and endoscopic biopsies cannot distinguish between UC and CD. An indeterminate colitis diagnosis is used when colectomy specimens have overlapping features of both CD and UC (Silverberg et al. 2005). It remains unclear if IC is a distinct disease or merely a temporary diagnosis such as IBDU (Magro et al. 2013).

Although CD can affect any part of the gut from the mouth to the anus, the terminal ileum is the most affected segment. CD location is classified as the terminal ileum, ileocolonic, colonic or upper GI (Satsangi et al. 2006). Upper GI tract localization usually appears simultaneously to more distal disease. Based on behavior, CD is referred to as inflammatory, penetrating or fibrostenotic (Satsangi et al. 2006). The disease location tends to remain relatively stable over time, although the disease behavior may change rapidly (Louis et al. 2001).

Investigation of the entire bowel is important, especially when surgery is planned. Ileocolonoscopy is considered the gold standard examination for preoperative evaluation and follow-up of CD patients, but it is restricted to the colon and the terminal ileum. Since ileocolonoscopy cannot show a rather large part of the small bowel nor show transmural intestinal manifestations, imaging examinations are widely used for the complementary evaluation of CD patients (Leyendecker et al. 2009). Magnetic resonance enterography (MRE) has emerged as an important diagnostic tool in CD and its role in the preoperative planning has been previously investigated (Pous-Serrano et al. 2017, Seastedt et al. 2014, Spinelli et al. 2014).

CD is a chronic disease where asymptomatic periods can alternate with periods of deterioration. CD treatment is primarily medical, although surgery is required in about 70% of the patients as an additional treatment (Bernell et al. 2000b, Riss et al. 2014). Recurrence often follows surgery, and postoperative follow-up and medical treatment are essential. The identification of risk factors for postoperative recurrence could influence the surgical and postoperative approach in order to decrease CD recurrence. Smoking has been described as a risk factor for postoperative recurrence and CD patients should be encouraged to stop smoking (Onali et al. 2009).

Surgery for CD should be limited to the resection of the most affected bowel segments, since the resection length appears not to affect CD outcome (Fazio et al. 1996). Since bowel-sparing techniques are recommended, anastomosis might be performed in bowels with residual

inflammation. Recently, one study found that positive resection margins increase postoperative anastomotic complications (Shental et al. 2012), while another found that those margins increase postoperative recurrence (de Buck van Overstraeten et al. 2017). These results differ from previous studies (Fazio et al. 1996, Kotanagi et al. 1991, Pennington et al. 1980, Post et al. 1991) and should be interpreted with caution.

Contradictory results have been reported concerning risk factors for postoperative complications in CD (Alves et al. 2007, El-Hussuna et al. 2012, El-Hussuna et al. 2014, Iesalnieks et al. 2008, Tzivanakis et al. 2012). It remains unclear if preoperative corticosteroid or biological medication use and the presence of an abscess or fistula intraoperatively results in increased postoperative complications in CD patients. It is important to determine factors that may increase postoperative complications in order to optimize preoperative preparation and to improve postoperative outcomes.

1 REVIEW OF THE LITERATURE

1.1 HISTORICAL BACKGROUND OF CROHN'S DISEASE

Crohn's disease (CD) is named after the gastroenterologist Burrill Bernard Crohn from Mount Sinai Hospital in New York. Crohn and colleagues first wrote about the disease in 1932 identifying it as a regional ileitis (Crohn et al. 1952). As early as the 1800s, pathologists reported on granulomatous inflammatory masses of the terminal ileum different from tuberculosis and which at times mimicked tumors. The British surgeon Wells first used the term "Crohn's disease of the colon" in 1952, but this was widely accepted only after Lockhart-Mummery and Morson reported CD of the large bowel as a different disease from ulcerative colitis in 1960 (Lockhart-Mummery et al. 1960, Wells 1952).

The surgical treatment of CD was initially either bypass or resection of the affected bowel segment (Alexander-Williams et al. 1972, Colp 1938, Ferguson 1957, Garlock et al. 1951, Homan et al. 1978). Bypass was gradually completely replaced by bowel resection. Radical bowel resection, however, leads to short bowel syndrome, resulting in considerable morbidity. In 1982, Lee and Papaionnou described stricturoplasty, which was performed similarly to pyloroplasty instead of a bowel resection in CD short-segment strictures (Lee et al. 1982). Subsequently, bowel length-sparing resections gained popularity with the publication of a randomized trial carried out by Fazio and colleagues in 1996 showing that the presence of microscopic disease at the resection margins did not affect postoperative outcomes (Fazio et al. 1996). The appearance of biological medications in the 1990s and their popularization in the treatment of CD in the 2000s have also revolutionized the medical treatment of CD.

1.2 EPIDEMIOLOGY OF CROHN'S DISEASE

In North America and Europe, more than 1.5 million and 2 million people, respectively, suffer from inflammatory bowel disease (IBD). The highest CD prevalence in Europe is in Germany, standing at 322 per 100,000, but the incidence of CD is highest in North America, Scandinavia, Australia and New Zealand. In the last ten years, the incidence of IBD in adults has stabilized in North America and in many countries of Europe, but on the other hand has grown in Africa, Asia and South America (Ng et al. 2017). During the same period, a study concerning the pediatric population concluded that IBD is increasing worldwide, particularly CD (Benchimol et al. 2011). Approximately 25% to 30% of CD patients become ill before the age of 20,

although peak incidence occurs between the ages of 20 to 30 years (Lapidus et al. 1997).

In a national register study in Finland between 2000 and 2007 CD incidence has only slightly increased in the 2000s, and was estimated as 9.2 per 100,000 person year. CD incidence rates did not differ significantly between men and women in Finland. Furthermore, ulcerative colitis (UC) incidence was almost three times higher than CD incidence in Finland (Jussila et al. 2012).

1.3 ETIOLOGY AND PATHOGENESIS OF CROHN'S DISEASE

The pathogenesis of CD is not yet completely understood. It is believed that genetic predisposition, immune response, intestinal microflora and environmental factors together play a role in the development of the disease.

Approximately 10% to 14% of CD patients have an affected first-degree relative (Freeman 2002). The first described CD-associated gene located on chromosome 16 was nucleotide oligomerization domain 2 (NOD2), also known as caspase-activating recruitment domain 15 (CARD15) (Hugot et al. 2001). Today, over 200 genes related to IBD have been identified, of which 37 are specific for CD (Liu et al. 2015). The majority of the discovered genes play a role in the immunoregulation including the intestinal epithelial barrier and its capacity to recognize different bacteria and activate inflammatory pathways (Jostins et al. 2012). NOD2/CARD15 is expressed in intestinal epithelial cells, named Paneth cells, as well as in monocytes and dendritic cells, and represents a nucleotide-binding domain involved in the recognition of proteins along the wall of the bacterial cells (Butler et al. 2007, Inohara et al. 2003).

The intestinal microbiota seems to be associated with the development and maintenance of IBD (Kostic et al. 2014). Microbial diversity is substantially diminished in patients with IBD compared with healthy individuals. It is not an infectious agent such as a single bacterial species that causes CD. Yet, a disbalance in the intestinal flora may activate the host immune system. The intestinal microbiota seems also to play a role in the postoperative recurrence of CD, since one study showed absence of anastomotic recurrence in cases with a proximal diversion (D'Haens et al. 1998). However, most attempts to manipulate the intestinal microbiota with probiotics or antibiotics have been unsuccessful in modifying the natural history of CD (Torres et al. 2017).

The role of environmental factors in the onset of IBD was previously studied, yielding conflicting results. Researches assume that exposure to high doses of vitamin D may prevent CD due to its anti-inflammatory properties. This might explain why the highest incidence of CD is found in northern countries (Khalili et al. 2012). A high hygiene level was also associated with

an increased CD risk (Klement et al. 2008) and could also explain the high CD incidence in Scandinavia and North America. Furthermore, epidemiological studies have also speculated about the role of antibiotics, non-steroidal anti-inflammatory drugs and oral contraceptives in the etiology of CD (Ananthakrishnan et al. 2012, Garcia Rodriguez et al. 2005, Khalili et al. 2013, Virta et al. 2012). Smoking is the only environmental factor widely accepted as increasing the risk for CD, although its biological mechanism is not yet fully understood (Birrenbach et al. 2004, Parkes et al. 2014).

1.4 CLASSIFICATIONS OF CROHN'S DISEASE BY PHENOTYPE AND DISEASE ACTIVITY

CD has a quite heterogeneous clinical presentation, explaining the need for the implementation of classifications that group similar patients together. Classifications have been improved over the years, better reflecting disease prognosis and guiding clinical management. Currently, the Montreal classification is widely used in CD research (Silverberg et al. 2005). The Paris classification is an improved version of the Montreal classification for use among pediatric patients (Levine et al. 2011) (Table 1).

Aiming to evaluate CD outcomes as a whole, including all disease subtypes, disease activity indices were implemented and are widely used in clinical trials. However, disease activity indices refer to the assessment of the disease only at a specific time point. The Crohn's disease activity index (CDAI) is the gold standard for disease activity classification (Best et al. 1976) (Table 2). A simplified version of the CDAI, the Harvey-Bradshaw index (HBI), without laboratory variables and only recalling symptoms from the last 24 hours has also been proven useful (Harvey et al. 1980) (Table 3). Recently, a new classification, the Lémann score, which takes into consideration the cumulative bowel damage caused by CD was developed and validated for use in clinical trials (Table 4). While the Lémann score calculation is complex, an Excel file is available upon request making it relatively straightforward to use (Pariente et al. 2011, Pariente et al. 2015).

1.4.1 VIENNA, MONTREAL AND PARIS CLASSIFICATIONS

Table 1. Clinical classifications of Crohn's disease

Vienna (Gasche et al. 2000)		Montreal (Silverberg et al. 2005)		Paris (Levine et al. 2011; pediatric)	
Age at diagnosis		***Age at diagnosis***		***Age at diagnosis***	
A1	below 40 years	**A1**	< 16 years	**A1a**	0 ≤ 10 years
A2	above 40 years	**A2**	16 ≤ 40 years	**A1b**	10 ≤ 17 years
		A3	> 40 years	**A2**	17 - 40 years
				A3	> 40 years
Location		***Location***		***Location***	
L1	ileal	**L1**	ileal	**L1**	distal 1/3 ileum +/- limited caecal
L2	colonic	**L2**	colonic	**L2**	colonic
L3	ileocolonic	**L3**	ileocolonic	**L3**	ileocolonic
L4	upper	**L4**	isolated upper disease	**L4a**	upper disease proximal to the ligament of Treitz
				L4b	upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum
Behavior		***Behavior***		***Behavior***	
B1	non-stricturing, non-penetrating	**B1**	non-stricturing, non-penetrating	**B1**	non-stricturing, non-penetrating
B2	stricturing	**B2**	stricturing	**B2**	stricturing
B3	penetrating	**B3**	penetrating	**B3**	penetrating
		p	perianal disease modifier	**B2B3**	both penetrating and stricturing disease
				p	perianal disease modifier
				Growth	
				G0	no evidence of child growth delay
				G1	child growth delay

1.4.2 CROHN'S DISEASE ACTIVITY INDEX (CDAI)

Table 2. Crohn's disease activity index (CDAI; Best et al. 1976)

Variable	Description	Multiplied by
Number of liquid stools	Sum of numbers per 7 days	2
Abdominal pain during 7 days	0 = none, 1 = mild, 2 = moderate, 3 = severe	5
General well-being during 7 days	0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible	7
Extraintestinal complications	Number of complications: arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, fever > 37.8°C	20
Antidiarrheal drugs during 7 days	0= no, 1 = yes	30
Abdominal mass	0= no, 2 = dubious, 5 = present	10
Hematocrit	Expected (male = 47, female = 42) - observed	6
Body weight	[1-(ideal/observed)]x100	1

Score interpretation:

Remission (less than 150 points)

Response (greater than 70 points or more recently greater than 100 points)

Mild disease (150-220 points)

Moderate disease (220-450 points)

Severe disease (greater than 450 points)

1.4.3 HARVEY-BRADSHAW INDEX (HBI)

Table 3. Harvey-Bradshaw simple index (HBI; Harvey et al. 1980)

Variable	Scoring
General well-being	0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible
Abdominal pain	0 = none, 1 = mild, 2 = moderate, 3 = severe
Number of liquid stools daily	1 per occurrence
Abdominal mass	0 = none, 1 = dubious, 2 = present, 3 = present with tenderness
Complications	1 per each: arthralgia, uveitis, erythema nodosum, aphthous ulcer, pyoderma gangrenosum, anal fissure, new fistula, abscess

Total score interpretation:

Remission < 5

Mild disease 5-7

Moderate disease 8-16

Severe disease > 16

1.4.4 LÉMANN SCORE

Table 4. Parameters used for the calculation of the Lémann index (Pariente et al. 2015)

Organ	Segment	Number of segments	Investigation method	Grade 1	Grade 2	Grade 3
Surgical intervention						
Upper tract	Esophagus Stomach Duodenum	3		N/A	Bypass diversion or stricturoplasty	Resection
Small bowel	Each 20-cm segment	20		N/A	Bypass diversion or stricturoplasty	Resection
Colon/Rectum	Each segment[a]	6		N/A	Stoma, bypass diversion or stricturoplasty	Resection
Anus	Anus	1		Reconstruction procedure, flap, coring out fistula track or laying open of fistula	Major surgery leading to substantial sphincter damage Temporary diversion	Definitive diversion Proctectomy
Stricturing lesions						
Upper tract	Esophagus Stomach Duodenum	3	Endoscopy	N/A	Lumen narrowing, passable	Stricture, nonpassable
Upper tract	Esophagus Stomach Duodenum	2	MRI or CT	Wall thickening < 3 mm or segmental enhancement without prestenotic dilatation	Wall thickening ≥ 3 mm or mural stratification without prestenotic dilatation	Stricture with prestenotic dilatation
Small bowel	Each 20-cm segment	20	MRI or CT	Wall thickening < 3 mm or segmental enhancement without prestenotic dilatation	Wall thickening ≥ 3 mm or mural stratification without prestenotic dilatation	Stricture with prestenotic dilatation
Colon/Rectum	Each segment[a]	6	Colonoscopy	N/A	Lumen narrowing, passable	Stricture, nonpassable
Colon/Rectum	Each segment[a]	6	MRI or CT	Wall thickening < 3 mm or segmental enhancement without prestenotic dilatation	Wall thickening ≥ 3 mm or mural stratification without prestenotic dilatation or < 50% of the lumen	Stricture with prestenotic dilatation or > 50% of the lumen
Anus	Anus	1	Clinical examination	Mild stricture	Frank stricture, passable	Frank stricture, non-passable
Penetrating lesions						
Upper tract	Esophagus Stomach Duodenum	3	Endoscopy	Superficial ulceration	Deep ulceration	Fistula
Upper tract	Esophagus Stomach Duodenum	2	MRI or CT	N/A	Deep transmural ulceration	Phlegmon or any type of fistula
Small bowel	Each 20-cm segment	20	MRI or CT	N/A	Deep transmural ulceration	Phlegmon or any type of fistula
Colon/Rectum	Each segment[a]	6	Colonoscopy	Superficial ulceration	Deep ulceration	Fistula
Colon/Rectum	Each segment[a]	6	MRI or CT		Deep transmural ulceration	Phlegmon or any type of fistula
Anus	Anus	1	Clinical examination	Anal ulceration	Multiple fistulas	Multiple fistulas with extensive anal and perianal tissue destruction
Anus	Anus	1	MRI or CT[b]	Simple fistula	Branching fistula, multiple fistulas or any type of abscess > 1 cm	Extensive anal and perianal suppuration, horseshoe abscess or fistula(s) involving or extending above the levator plate

[a] *Cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum*

[b] *Only in the case of an abnormal clinical examination*

1.5 DIAGNOSIS, CLINICAL FEATURES AND NATURAL COURSE OF CROHN'S DISEASE

The diagnosis of CD requires a multidisciplinary approach. The combination of the patient's medical history, clinical evaluation, laboratory results, typical endoscopy and histopathological and radiological findings should be used to establish a CD diagnosis.

1.5.1 CLINICAL PRESENTATION

1.5.1.1 Disease location

Crohn's disease is a chronic progressive IBD that can affect any part of the gastrointestinal (GI) tract from the mouth to the anus. The terminal ileum is the most common location of the disease.

The involvement of the intestinal tract proximal to the ligamentum of Treitz has been reported in 1% to 5% of cases, yet in clinical practice gastroscopy is recommended only in CD patients with upper GI tract symptoms. Upper GI CD typically manifests together with more distal disease. The involvement of the esophagus is rare, occurring in less than 2% of patients, but may include inflammatory lesions or stenosis (D'Haens et al. 1994). In routine gastroscopy studies, mild upper GI tract lesions have been found in 16% to 32% of CD patients (Annunziata et al. 2012, Halme et al. 1996). Helicobacter pylori negative focal gastritis is a characteristic related to CD (Halme et al. 1996).

More than 60% of CD patients have colonic involvement and 20% of CD patients may have isolated colitis although ileocolonic involvement is more common (Mills et al. 2007). Crohn's colitis is usually segmental, whereby around 40% of patients will have a disease-free rectum (Mills et al. 2007). In such cases, the differential diagnosis of UC is easier. Colonic CD can also present as pancolitis involving the entire colon.

The risk of perianal disease development in CD patients is around 40% and is more common in patients with Crohn's colitis (Eglinton et al. 2012). Perianal disease can present as skin lesion, anal canal fissure, ulcer, stenosis and anorectal abscess or fistula. The latter one represents the most common perianal manifestation of CD. Perianal fistulas can be complex and extend to the adjacent organs causing rectovaginal fistulas or involving the labia and the scrotum.

1.5.1.2 Symptoms

The symptoms depend on the disease location, behavior, clinical activity and the presence or absence of extraintestinal manifestations. The most typical

symptoms are abdominal pain and diarrhea. Pain is usually localized in the lower right abdominal quadrant. Diarrhea is usually intermittent but not grossly bloody. Patients with Crohn's colitis may have more diffuse abdominal pain and diarrhea with mucus and blood (Hedrick et al. 2013). Systemic symptoms include anorexia, weight loss, fever, anemia and delayed growth in pediatric patients. Colonic CD can less frequently also manifest as fulminant colitis (Hedrick et al. 2013). Patients with disease limited to the small bowel have a more insidious onset of disease since many years of subclinical bowel inflammation may precede the progress to fibrotic stenosis resulting in occlusive intestinal symptoms. Physical examination may reveal fullness or a tender mass in the lower right abdominal quadrant in patients with terminal ileum disease. Patients with more acute disease onset in this region may be misdiagnosed as experiencing appendicitis.

1.5.1.3 Natural history and complications

CD manifests through periods of remission and periods of aggravation or "flare-ups". Persistent subclinical inflammation that occurs during clinical remission is thought to lead to complications such as stenosis, fistulas and abscesses resulting in progressive bowel damage (Torres et al. 2017). The CD behavior may vary substantially during the disease course, typically changing from inflammatory behavior to stricturing or penetrating. Factors associated with the development of CD complications are perianal disease and ileal involvement (Thia et al. 2010).

Complications from CD normally require surgical treatment. The most common complication from CD is stenosis, which can develop in any segment of the GI tract, but most frequently occurs in the small intestine. Stenosis may cause intestinal obstruction gradually with weight loss, anemia and other nutritional deficiencies or less commonly may manifest as acute bowel obstruction with acute abdominal pain, anorexia and vomiting. Perforation proximal to the obstructed bowel segment with peritonitis is rare, but is also a possible manifestation of CD. Bowel perforations in CD are primarily caused by the inflammatory process involving all layers of the bowel and usually manifest as abdominal abscesses or fistulas involving adjacent organs such as another bowel segment, the bladder or the vagina. Abdominal or pelvic abscesses present with a low fever and mild abdominal pain.

CD is related to an increased risk of GI cancer. The risk of colonic dysplasia and colorectal cancer in CD patients appears similar to the risk in UC patients; surveillance colonoscopy is recommended every one or two years at eight years following a CD diagnosis (Friedman et al. 2001, Itzkowitz et al. 2005). A cumulative risk of 25% of developing dysplasia or cancer in Crohn's colitis patients even after a primary negative screening colonoscopy was previously determined (Friedman et al. 2008). The cumulative risk of colorectal cancer is around 3% at 10 years following a CD diagnosis (Canavan

et al. 2006). In addition, CD is also associated with an increased risk of small bowel cancer that occurs in < 1% of CD patients, although the risk is higher in patients with small bowel CD and the prognosis is poor due to the advanced stage at diagnosis (Elriz et al. 2013). A national register-based study in Finland described an increased anal cancer risk in CD patients potentially explained by problems with differential diagnosis associated with chronic perianal fistulas. The same study also found an increased risk for small bowel and biliary tract cancer in CD patients (Jussila et al. 2013).

1.5.1.4 Extraintestinal manifestations

Table 5. Extraintestinal manifestations of Crohn's disease

Extraintestinal manifestations	Incidence	Relation to CD activity
Spondyloarthropathy		
Sacroilitis or ankylosing spondylitis	5-10%	No
Peripheral arthritis	10-20%	
Oligoarticular arthritis (type I)		Yes
Chronic polyarthritis (type II)		No
Ocular		
Iritis	0.5-3.5%	No
Scleritis or episcleritis	2-4%	Yes
Dermatological		
Pyoderma gangrenosum	1-6%	Yes/No
Erythema nodosum	2-6%	Yes
Psoriasis	10%	No
Aphthous stomatitis	20-30%	Yes
Hepatobiliary		
Primary sclerosing cholangitis	1.2-3.4%	No
Gallbladder stones	11-34%	No
Neurological		
Peripheral neuropathy	8.3-13.4%	No

CD: Crohn's disease

Compiled from Ardizzone et al. 2008, Ephgrave 2007, Harbord et al. 2016

1.5.2 LABORATORY TESTS

Laboratory tests can help with CD diagnosis, determine disease activity and monitor clinical course.

A stool culture and Clostridium difficile toxin are useful in the differential diagnosis. The white blood cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), known inflammatory markers, correlate with disease activity, although they are quite unspecific (Vermeire et al. 2004). Fecal lactoferrin and calprotectin are markers of intestinal inflammation, have a better correlation with CD activity and can predict disease relapse (Kolho et al. 2006, Sipponen et al. 2008a, Sipponen et al. 2008b, Tibble et al. 2000). Unfortunately, calprotectin also increases in

colorectal neoplasia and intestinal infections, limiting its use for diagnostical purposes.

1.5.3 ENDOSCOPY

Colonoscopy with intubation and evaluation of the terminal ileum is very important for CD diagnosis. In fact, endoscopy is the gold standard for CD diagnosis and follow-up. Endoscopy allows for the visualization of the bowel lumen and the collection of samples for histopathological examination. At least two biopsies from at least five different segments of the bowel, including the rectum and the terminal ileum should be taken, except in fulminant colitis (Magro et al. 2013). Biopsies should be stored in separate containers, since the localization of the sample provides important information for diagnosis. Biopsies should be taken from both lesions and normal mucosa. Endoscopic findings in CD depend on the disease activity and extension. In up to 50% of the patients with colonic CD the rectum is spared.

Endoscopic scores have been developed to standardize the quantification of CD extension and severity. Due to its complexity, a Crohn's disease endoscopic index of severity (CDEIS) (Mary et al. 1989) is not valuable for clinical use; the Simple endoscopic score for Crohn's disease (SES-CD), (Daperno et al. 2004) a simplified endoscopic classification, is preferred (Table 6). The Rutgeerts' score (Rutgeerts et al. 1990) is commonly used to quantify the postoperative recurrent CD (Table 7).

Endoscopy can also be used with therapeutic intention. Anastomotic strictures and short strictures <2 cm in the small bowel can be safely treated endoscopically with balloon dilatation instead of surgical resection (Saunders et al. 2004). A recent meta-analysis described balloon dilatation of strictures <4 cm as associated with a significantly lower risk of surgery (Navaneethan et al. 2016). Another important role for endoscopy lies in cancer surveillance, since CD is related to an increased intestinal cancer risk.

Small bowel CD has been reported in 10% to 30% of the patients with CD, so the evaluation of the entire small bowel is important. Enteroscopy allows for the visualization and biopsy collection of portions of the small bowel that would otherwise remain unreachable. Double-balloon enteroscopy, introduced in 2001 (Yamamoto et al. 2001), or, more recently, single-balloon enteroscopy and spiral enteroscopy permit the advancement of the scope into the small bowel, which can be performed using an anterograde or retrograde approach. Enteroscopy is typically indicated after an initial imaging examination of the small bowel through MRE or capsule endoscopy.

Although the small bowel and the colon represent the most commonly affected areas of the GI tract in CD, it can affect any portion of the gut. Thus, esophagogastroduodenoscopy is useful in ruling out CD involvement in the upper GI tract. In clinical practice, gastroscopy is recommended only in CD patients with upper GI tract symptoms.

1.5.3.1 Simple endoscopic score for Crohn's disease (SES-CD)

Table 6. Criteria for the calculation of the Simple endoscopic score for Crohn's disease

Variable	SES-CD* Score = 0	Score = 1	Score = 2	Score = 3
Size of ulcers	None	Aphthous ulcers (diameter 0.1 to 0.5 cm)	Large ulcers (diameter 0.5 to 2 cm)	Very large ulcers (diameter >2 cm)
Extent of ulcerated surface	None	<10%	10-30%	>30%
Extent of affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

**The total score is calculated by the sum of the results for each segment: ileum, right colon, transverse colon, left colon and rectum*

Daperno et al. 2004

1.5.3.2 Rutgeerts' score

Table 7. Description of the Rutgeerts' score

Rutgeerts' Score	Endoscopic findings
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with larger ulcers, nodules and/or narrowing

Rutgeerts et al. 1990

1.5.4 HISTOPATHOLOGY

Histological examination remains crucial for CD diagnosis. However, due to the frequent absence of pathognomonic histological signs, additional clinical information and endoscopic findings are sometimes essential to confirm the final diagnosis.

CD is characterized by the transmural inflammation of the bowel, causing strictures with a thickened bowel wall particularly in the terminal ileum, but can appear anywhere along the GI tract. CD can present as a cobblestoning mucosa, islands of surviving mucosa raised by edema and surrounded by ulcerated mucosa. It can form fissures, long serpiginous or linear ulcers that extensively and deeply involve the bowel wall leading to the formation of sinuses, fistulas or abscesses. Fistulas can occur between different bowel segments, adjacent organs or the abdominal skin. In the resected small bowel fat wrapping often occurs. Fat wrapping appears due to the extension of the

inflammation process to the subserosa and mesenteric fat which becomes hyperplastic and expands towards the antimesenteric bowel surface (Magro et al. 2013).

Typical microscopic features of CD include transmural chronic inflammation with subserosal lymphoid aggregates, focal deep mucosal ulceration, focal crypt architectural abnormalities and the presence of non-necrotizing granulomas which are collections of epithelioid macrophages or monocytes (Magro et al. 2013). Pyloric gland metaplasia, representing areas of epithelial regeneration after mucosal ulceration, typically appear in CD ileal biopsies and is useful for the differential diagnosis of UC. Biopsies from both inflamed and non-inflamed segments are important to reveal the segmental nature of the disease. The transmural characteristic of CD inflammation is usually recognized only in surgical specimens.

The microscopic and macroscopic features of CD are described in Table 8.

Table 8. Histopathological features in the differential diagnosis of Crohn's disease and ulcerative colitis

Histopathological features	Crohn's disease	Ulcerative colitis
Macroscopic		
Localization in the GI-tract	Entire GI-tract	Colon and rectum
Ileum	Often involved	Not involved, except in back-wash ileitis
Colon	Right > left	Left > right
Rectum	Typically spared	Commonly involved
Distribution	Segmental	Continuous
Ulcers	Deep ulcers, linear ulcers	Superficial ulcers
Cobblestone-pattern	Present	Absent
Fistulas	Present	Absent
Strictures	Present	Uncommon
Wall thickness	Increased	Normal
Fat wrapping	Present	Absent
Microscopic		
Localization	Transmural	Superficial, transmucosal, sometimes submucosal
Inflammation	Focal	Diffuse
Crypt irregularity	Focal	Diffuse
Crypt abscess	Common	Uncommon
Lymphoid aggregates	Commonly transmural	Frequently in mucosa and submucosa
Granulomas	Present	Absent, except with ruptured crypts
Pyloric gland metaplasia	Present	Rare
Paneth cell metaplasia	Uncommon	Present

Modified from Magro et al. 2013

In clinical trials evaluating the therapeutic outcomes, different clinical, endoscopic and radiological scores have been validated to determine the disease activity (Best et al. 1976, Daperno et al. 2004). Pathology reports should also include some information on the level of activity in the biopsies to assess the effect of therapy and the risk of relapse. Currently, none of the existing histological scores to evaluate CD activity have been completely validated. Many of the existing scores like the one we used to evaluate CD activity at the resection margins, represent modifications of the Global

histological activity score (GHAS) (D'Haens et al. 1998, Novak et al. 2017). Our score is in clinical use in our unit and has been compared to various clinical and endoscopic activity scores in medical trials evaluating the activity parameters for CD (Molander et al. 2015, Puolanne et al. 2016, 2017) (Table 9).

Table 9. Crohn's disease histological activity scale used for the evaluation of bowel resection margins

Category	Criteria
No inflammation	No residual microscopic disease
Inactive inflammation	Chronic inflammation without neutrophils
Mild activity	Infiltration of polymorphonuclear cells in the lamina propria or surface epithelium
	Cryptitis
Moderate activity	Polymorphonuclear cells in the epithelium
	Crypt abscess
Strong activity	Presence of erosion and/or ulcer

1.5.5 DIFFERENTIAL DIAGNOSES

The differential diagnoses of CD consist of coeliac disease, infections (such as Yersinia enterocolitica, Salmonella sp., Campylobacter sp. and tuberculosis), UC, Clostridium difficile-associated colitis, ischaemia, vasculitis, microscopic colitis and segmental colitis associated with diverticulosis. In the colonic CD, the differential diagnosis of UC can at times be difficult, resulting in an IBDU diagnosis. The IC definition should be reserved to cases where diagnosis is uncertain after colectomy despite complete histological analysis (Magro et al. 2013).

1.5.6 MAGNETIC RESONANCE ENTEROGRAPHY (MRE) AND COMPUTED TOMOGRAPHY ENTEROGRAPHY (CTE)

The small bowel is frequently affected in CD. However, the small bowel is the least accessible intestinal segment using endoscopy. Thus, imaging is quite important in the diagnosis and follow-up of CD. Furthermore, CD, with its transmural inflammatory characteristic, may result in abscesses and fistulas, which can only be diagnosed by imaging. Traditionally, the small bowel of CD patients was examined using barium follow-through radiography which is incapable of detecting the extramural findings of CD (Leyendecker et al. 2009). Yet, computed tomography (CT) provides detailed information about the intestinal wall and the extramural findings, although it does not provide much detail of the intestinal mucosa. This problem was overcome by combining contrast follow-through radiography technique with CT using CTE (Rollandi et al. 1999). Exposure of mostly young CD patients, however, to repeat ionizing radiation for diagnostic and follow-up examinations is a

concern. While CTE and MRE have both proved useful for CD imaging investigations, the latter is preferred due to the lack of radiation exposure (Horsthuis et al. 2008, Puylaert et al. 2015). However, the availability may be an issue concerning MRE.

The most common diagnostic findings in CD using MRE appear in Table 10. Table 11 summarizes the results from different studies determining the specificity and sensitivity of MRE for finding CD lesions compared to surgical findings.

Table 10. MRE findings in Crohn's disease

MRE finding	Explanation	Differential diagnosis
Cobblestone appearance	Irregular enhancement of the mucosa representing multiple continuous bowel wall ulcerations	
Stratification of the bowel wall	Heterogeneous enhancement of the layers of the abdominal wall with a hyperintense appearance of the mucosa and the serosa representing acute bowel wall inflammation	
Comb-sign	High-signal intensity parallel lines in the mesentery, perpendicular to the bowel wall representing mesenteric vascular engorgement typical of active disease	
Fat wrapping	Hypertrophic fat, proliferation of mesentery	
Mesenteric lymphadenopathy	Enlargement, hyperenhancement and edema of the lymph nodes pathognomonic for active CD	Non-enhancing lymphadenopathy may imply malignancy, chronic inflammation or tuberculosis
Stenosis	Aperistaltic bowel segments with fixed mural thickening and luminal narrowing	Peritoneal adhesions appear as acutely angled or tethered bowel loops with an abrupt transition in the luminal diameter and the absence of mural thickening
Intra-abdominal fistula, star-sign	Fistulas or sinuses appear as linear hyperenhancing tracts. The star-sign represents a conglomerate of inflamed bowel loops interconnected by multiple fistulous tracts	Adhesions are fibrotic and tend to be thinner and enhance later than fistulas
Intra-abdominal abscess	Fluid collections encapsulated by an enhanced wall which may contain air	

MRE: magnetic resonance enterography; CD: Crohn's disease; compiled from Amitai et al. 2013, Leyendecker et al. 2009

Table 11. Sensitivity and specificity of preoperative MRE for detecting intraoperative surgical findings in Crohn's disease

Study	Patients (N)	MRE finding					
		Stenosis		Fistula		Abscess	
		Sensitivity	*Specificity*	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*
Sinha et al. 2013	49	56 (41-63)	98 (93-99)	76 (61-77)	100 (95-100)	77 (48-79)	100 (97-100)
Fallis et al. 2013	51	97	95	83	95	89	98
Spinelli et al. 2014	75	96 (88-99)	67 (9-99)	71 (49-87)	96 (87-100)	40 (5-85)	99 (93-100)
Seastedt et al. 2014	76	68	100	60	100	87	87
Pous-Serrano et al. 2017	38	97 (85-100)	80 (38-96)	60 (36-80)	98 (90-100)	100 (34-100)	99 (92-100)

MRE: magnetic resonance enterography; values for the sensitivity and specificity are percentages; values in parentheses are 95% confidence intervals

1.5.6.1 MRE enteroclysis or enterography

The benefits of using enteric contrast material to achieve bowel distension in imaging for CD are undeniable. Examinations performed when the contrast agent is administered through duodenal intubation are termed enteroclysis while those when the contrast is administered orally are termed enterography. MRE enterography is preferred by patients and radiologists, since it does not require nasojejunal intubation (Negaard et al. 2008). Furthermore, MRE enterography does not require ionizing radiation, which is often necessary for localizing the nasojejunal tube tip that should be positioned close to the ligament of Treitz before administering the contrast agent in the enteroclysis technique. It has been shown that the radiation dose related to this procedure is equivalent to 10 posteroanterior (PA) chest x-rays (Puustinen et al. 2012). A study among 21 patients with CD demonstrated an equal accuracy for both MRE methods (Schreyer et al. 2004). However, one case-control study concluded that MRE enteroclysis better visualizes superficial mucosal abnormalities in the small bowel for CD patients, although both methods perform equally in finding mural stenosis and fistulas. That study suggests that MRE enteroclysis should be used for the initial evaluation of CD patients, while MRE enterography should be used during follow-up (Masselli et al. 2008).

1.5.7 CAPSULE ENDOSCOPY

Traditionally used to investigate GI bleeding, capsule endoscopy represents an important diagnostic tool for small bowel CD. It can evaluate the extent of the disease, disease severity, postoperative recurrence and mucosal healing and may be used instead of MRE. The Lewis score (Gralnek et al. 2008) and the Capsule endoscopy Crohn's disease activity index (CECDAI) (Gal et al. 2008) have been validated for the evaluation of CD activity in small bowel capsule endoscopy investigations (Cotter et al. 2015, Gal et al. 2008). Studies comparing MRE and capsule endoscopy demonstrated a good agreement for both methods in the detection and localization of IBD (Casciani et al. 2011, Tillack et al. 2008). Capsule endoscopy is contraindicated in cases of stenosis; but, in fact, the risk of capsule retention is rare in CD patients, reaching only around 2% according to a Swedish study (Nemeth et al. 2017). Unlike MRE, capsule endoscopy cannot detect extramural manifestations of CD.

1.5.8 OTHER IMAGING TECHNIQUES

Although ultrasonography (US) is not commonly used in Finland for the diagnosis and follow-up of IBD in adults, its use has increased globally. US is readily available, painless, non-invasive and radiation-free. Intestinal US allows for the visualization of the thickening, narrowing or loss of normal

stratification and motility in pathological bowel segments. It can also detect mesenteric thickening, inflamed lymph nodes and intra-abdominal fluid collections. US sensitivity and specificity in the detection of CD in the ileum reach 95.7% and 75.0% respectively, but may not identify abnormalities in the duodenum, proximal jejunum and rectum (Parente et al. 2003). However, a clear disadvantage of US is that it is operator dependent. Achieving a high accuracy in CD diagnosis using US requires expertise radiologists with extensive IBD experience. The concomitant use of oral contrast in US, contrast-enhanced ultrasonography (CEUS), assists in the evaluation of CD activity (De Franco et al. 2012).

1.6 MEDICAL TREATMENT OF CROHN'S DISEASE

Medical therapy stands as treatment of choice for CD, while surgery is reserved for treating disease complications. The pharmacodynamics, indications and side effects from medications used to treat CD are summarized in Table 12.

Any treatment plan should take into consideration the disease activity, disease location and behavior (Gomollon et al. 2017). Choosing the appropriate medication requires a balance between drug efficacy and its side effects. Medical therapy should aim to induce remission, maintain steroid-free remission, regulate disease activity and to prevent irreversible bowel damage. The response to therapy should be followed using clinical, endoscopic, laboratory and radiological findings.

Remission in moderate to severe disease can be achieved through combination therapy such as anti-tumor necrosis factor (TNF) alpha combined with thiopurines (Colombel et al. 2010). In mild or moderate disease monotherapy with a thiopurine can be used initially. Methotrexate can be used instead if thiopurine is not tolerated. Steroids are useful for the rapid induction of remission or the rapid control of disease exacerbation. Budesonide is the preferred steroid in mild or moderate ileal disease but plays no role in distal colonic disease where prednisolone or intravenous steroids should be chosen (Gomollon et al. 2017). The treatment of relapses should take into account previously successful therapies.

Traditionally, CD treatment follows the step-up therapy while biological medication was used only when other medications had failed. This approach has been challenged and top-down therapy using biological drugs or even combination therapy right from the beginning is now preferred in patients with severe disease or even in patients with moderate disease if they have poor prognostic features such as young age of onset, smoking habits, perianal disease or extensive small bowel disease. After achieving deep remission, treatment can be simplified, since the prolonged use of combination therapy increases the risk of side effects. Top-down therapy aims to reduce the development of bowel damage, such as stenosis or fistula, although this

remains unproven yet. Perianal disease, a young age of onset and the need for initial steroids have been described as independent risk factors for severe disease (Beaugerie et al. 2006).

Table 12. Medications used in the treatment of Crohn's disease

Medications	Mechanism	Indications	Collateral effects
Corticosteroids *Summers et al. 1979* *Malchow et al. 1984*	Inhibit the expression of inflammatory genes and migration of inflammatory cells to tissues	Effective for short term control of symptoms. Bridge to maintenance therapy	Psychiatric disturbances, insomnia, high blood pressure, hyperglycemia, acne, osteoporosis, obesity, infections
Mesalamine and sulfasalazine *Summers et al. 1979* *Malchow et al. 1984*	Unknown, some anti-inflammatory effect	Indication in UC but not in CD. May have a small improvement in Crohn's colitis compared to placebo	Mesalamine: pancreatitis, nausea, diarrhea, nephrotoxicity Sulfasalazine: hepatitis, pancreatitis, pneumonitis, lupus-like reaction, rash, aplastic anemia, agranulocytosis
Antibiotics *Bernstein et al. 1980* *Thia et al. 2009*	Treat infections. Alter the intestinal microbiota	Perianal and abdominal abscesses. Perianal fistulizing disease. May reduce CD symptoms. Metronidazole and ciprofloxacin are the most used antibiotics	Metronidazole: nausea and peripheral neuropathy Ciprofloxacin: diarrhea, tendinitis evolving to tendon rupture
Thiopurines: Azathioprine and 6-mercaptopurin *Present et al. 1980* *Candy et al. 1995* *Peyrin-Biroulet et al. 2009*	6-thioguanine is the active metabolite that inhibits the proliferation of lymphocytes and stimulates T-cell apoptosis	Maintains remission and increases steroid-free period. May reduce the risk of major abdominal surgery and perianal disease	Nausea, liver and bone marrow toxicity, pancreatitis, rash, headache and arthralgias. Increases non-Hodgkin's lymphoma and non-melanoma skin cancer risk. If azathioprine is not tolerated, 6-mercaptopurin can still be tried
Methotrexate *Oren et al. 1997* *Feagan et al. 2000*	Inhibits folic acid and is effective in many autoimmune diseases	Reduces disease activity compared to placebo. Used mostly in cases of thiopurine contra-indication or failure. Combined use with anti-TNF alpha medication to improve remission maintenance	Nausea, liver function test abnormalities, diarrhea, headache, infections, bone marrow depression, pneumonitis. Teratogenic. Requires folic acid supplementation
Anti-TNF alpha: Infliximab, adalimumab and certolizumab (not available in Finland) *Hanauer et al. 2002* *Hanauer et al. 2006* *Colombel et al. 2007*	Inhibits the pro-inflammatory cytokine TNF alpha	Sustained clinical remission, increases the steroid free period. Induce and maintain closure of abdominal or perianal fistulas. After initial response, patients may develop response loss due to antibody formation. Combined therapy with thiopurines or methotrexate may prevent antibody development. In the case of a loss of response, switch to another anti-TNF alpha medication is recommended	Demyelinating disease, hepatotoxicity, serious infections, congestive heart failure, rash, psoriatic dermatitis
Anti-integrin: Vedolizumab *Sandborn et al. 2013* *Sands et al. 2014*	Selectively inhibits recruitment of leucocytes to the gut. Integrins are glycoproteins expressed on the surface of circulating leukocytes	Indicated in patients with prior anti-TNF failure	Nasopharyngitis
Anti-IL12/23: Ustekinumab *Sandborn et al. 2012* *Feagan et al. 2016*	Selectively inhibits IL12 and IL23 binding to their common p40 subunit. Both IL12 and IL23 are pro-inflammatory cytokines	Patients resistant to anti-TNF alpha therapy. In a more recent trial, also indication for anti-TNF alpha naive patients with moderate to severe CD	Nasopharyngitis, nausea, headache, arthralgia other infections

UC: ulcerative colitis; CD: Crohn's disease; TNF: tumor necrosis factor; IL: interleukin

Important clinical trials concerning CD biological medications are described in Table 13.

Table 13. Anti-TNF alpha medical trials

Author	Trial	Patients	Conclusions
Hanauer et al. 2002	ACCENT I	573 CD patients with moderate disease (CDAI ≥ 220) received either placebo or infliximab after a single dose of infliximab	CD patients who responded to an initial dose of infliximab tends to achieve and maintain long-term remission if infliximab is continued every eight weeks
Sands et al. 2004	ACCENT II	282 CD patients with fistulizing CD were randomized to receive placebo or infliximab after three doses of infliximab	Infliximab was effective for the treatment of fistulizing CD and continued therapy maintained significantly longer fistula closure than placebo
Hanauer et al. 2006	CLASSIC I	299 patients with moderate to severe CD naive to biologicals were randomized to receive adalimumab in three different doses or placebo	Adalimumab was better than placebo to induce remission and the highest dose had a better response at week 4 and did not increase side effects
Sandborn et al. 2007	CLASSIC II	276 patients from CLASSIC I trial were included. Patients in remission after the first trial were randomized to placebo or continuation of adalimumab, while patients not in remission received open label adalimumab	Adalimumab achieved and maintained remission up to 56 weeks in patients with moderate to severe CD naive to biologicals
Colombel et al. 2007	CHARM	778 patients with moderate to severe CD with or without previous biological medication were randomized to receive placebo or adalimumab every week or every other week after two doses of adalimumab	Adalimumab was well tolerated and more effective than placebo to induce and maintain remission up to 56 weeks in patients naive to biologicals and also to patients who had previously received infliximab. However, better results were achieved in patients naive to biologicals
Colombel et al. 2010	SONIC	508 patients with moderate to severe CD randomized to receive infliximab, azathioprine or both	Infliximab or combined therapy were more effective for achieving remission than azathioprine alone in moderate to severe CD

TNF: tumor necrosis factor; CD: Crohn's disease; CDAI: Crohn's disease activity index (Best et al. 1976)

1.7 SURGICAL TREATMENT OF CROHN'S DISEASE

Despite recent innovations in the medical treatment of CD through the emergence of new and more powerful medications, the majority of CD patients (70-80%) will still require one or more surgeries during their lifetime (de Buck van Overstraeten et al. 2012).

1.7.1 INDICATIONS FOR SURGERY

Surgery is indicated in symptomatic CD patients who do not tolerate, do not respond to or are not compliant with medical treatment. The clinical course of CD results in cumulative structural damage to the bowel. Initial inflammatory behavior progresses over time to fibrostenotic or penetrating behavior or both, all of which will typically require surgical treatment (Louis et al. 2001). Around 15% to 25% of CD patients, excluding those with perianal disease, already have stenotic or penetrating complications at the time of the diagnosis (Louis 2012, Thia et al. 2010). Ileocolonic and small bowel involvement relates more often to fibrostenotic behavior than colonic

disease (Bernell et al. 2000a). Stenosis represents the most common indication for surgery in CD of the terminal ileum (Bernell et al. 2000b). Surgery is not curative and around 30% of the CD patients will require repeat surgery by 10 years following the primary operation (Michelassi et al. 1991, Toh et al. 2018). The treatment of symptomatic stenotic lesions normally consists of resection of the affected bowel segment, but stricturoplasty and endoscopic balloon dilatation represent alternative treatment options in selected cases. Asymptomatic entero-enteric fistulas may not require treatment at all, but symptomatic fistulas or more complex fistulas may require resection of the primary diseased bowel segment with repair of the secondarily involved bowel segment or bladder. Intra-abdominal abscesses can be drained percutaneously or treated surgically. In the presence of concomitant obstructive disease, surgery including bowel resection and abscess drainage stands as the treatment of choice. Penetrating anorectal disease will also often require surgery to control local sepsis. Although less common than in UC, patients with fulminant CD colitis (4-6% of CD patients) not responding to conservative treatment will need operative intervention (Berg et al. 2002). Other more rare indications for surgery in CD are unstable intestinal hemorrhage (2-3 % of CD patients) usually from the small bowel, and perforation with acute peritonitis (1-3% of CD patients; Berg et al. 2002). Surgery is also needed for CD-related intestinal cancer or dysplasia.

1.7.2 TECHNICAL ASPECTS OF THE SURGICAL TREATMENT

1.7.2.1 Laparoscopic or open surgery

As early as the 1990s, initial descriptions of the advantages of laparoscopic surgery in patients with CD were published (Milsom et al. 1993, Reissman et al. 1996).

A meta-analysis comparing laparoscopic surgery to open surgery for CD concluded that laparoscopic surgery was more time consuming, but resulted in shorter hospital stays and shorter postoperative ileus (Rosman et al. 2005). Sixteen studies were included in this meta-analysis and the conversion rate ranged from 0% to 29%. The majority (11/16) of the studies in this meta-analysis included only ileocolic resection. Laparoscopic surgery correlated with lower postoperative complication rates and lower surgical recurrence rates, although the authors assumed a selection bias for the severity of disease due to the low conversion rates and the fact that none of the studies were truly randomized.

A Cochrane review including only two randomized trials compared open versus laparoscopic ileocolic resections in CD patients finding no significant difference in the postoperative outcome between the two techniques (Dasari et al. 2011). One of the two trials included in that review randomized the

patients only after a diagnostic laparoscopy to determine if laparoscopic surgery was feasible. Thus, patients were not truly randomized.

One recent retrospective study compared 250 CD patients undergoing laparoscopic bowel resection to 750 CD patients undergoing open surgery, concluding that incisional hernia can be significantly decreased or completely eliminated through the use of intra-abdominal anastomosis and minimal transverse extraction incisions (Heimann et al. 2017). This study showed similar incisional hernia rates for open and laparoscopic CD surgery with the highest incisional hernia rate in patients requiring conversion (16%) and with no incisional hernia in patients submitted to intracorporeal anastomosis.

A recent meta-analysis including seven studies comparing laparoscopic surgery for primary versus recurrent surgery in CD patients concluded that recurrent surgery had a higher conversion rate, but did not show an increased risk for postoperative complications (Shigeta et al. 2016). Adhesions were the primary reason for conversion.

Laparoscopic surgery appears safe in CD patients and can be used in primary or recurrent surgery, but not in all patients. Furthermore, in certain cases it may demand a high level of laparoscopic experience. Currently, there are no selection criteria for choosing CD patients suitable for laparoscopy. Preoperative imaging findings and previous surgery reports may contribute to the decision. Laparoscopic surgery is, however, the recommended surgical approach for ileocaecal resection in uncomplicated CD (Tavernier et al. 2013).

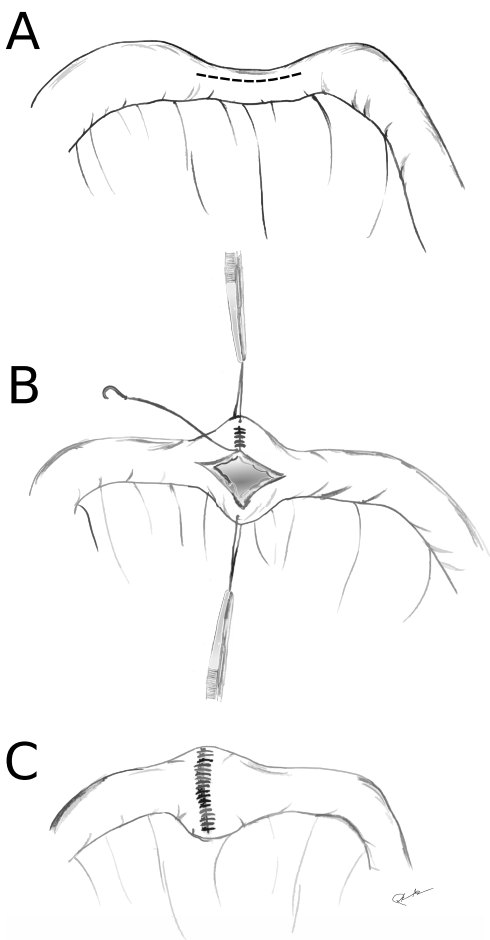

Figure 1 Heineke-Mikulicz stricturoplasty. Drawn based on Fazio et al.1989.

1.7.2.2 Stricturoplasty or resection

Stricturoplasty is indicated in patients with stenosis of the small bowel. The use of stricturoplasty is of extreme importance in patients submitted to previous bowel resections more than 100-cm long and to patients already diagnosed with short bowel syndrome (Campbell et al. 2012). Stricturoplasty should not be performed in cases of dysplasia or cancer suspicion.

The Heineke-Mikulicz and the Finney stricturoplasties represent the most-used techniques and are known as conventional stricturoplasties. Choosing the appropriate technique is based on the number, length and location of the stenoses.

Heineke-Mikulicz is recommended for short stenosis (<7 cm) (Fazio et al. 1989). It requires a longitudinal incision along the antimesenteric border of the bowel, extending 2 cm proximally and distally to the stenosis with a transversal closure of the enterotomy (Figure 1). Double Heineke-Mikulicz stricturoplasty can be used for two successive stenoses within a short distance from each other (Campbell et al. 2012, Sasaki et al. 1996). A single longitudinal incision is made over both stenoses including the normal bowel segment in between. A transversal closure for each stenosis is then performed separately and also the segment left in between is closed transversely.

Finney stricturoplasty is used for 7- to 15-cm long stenoses (Fazio et al. 1989, Hurst et al. 1998). A U-shaped incision is made between the mesenteric and antimesenteric borders of the bowel segment so that the two ends of the enterotomy face each other. The enterotomy is then closed using a running continuous suture resulting in a large lateral diverticulum (Figure 2).

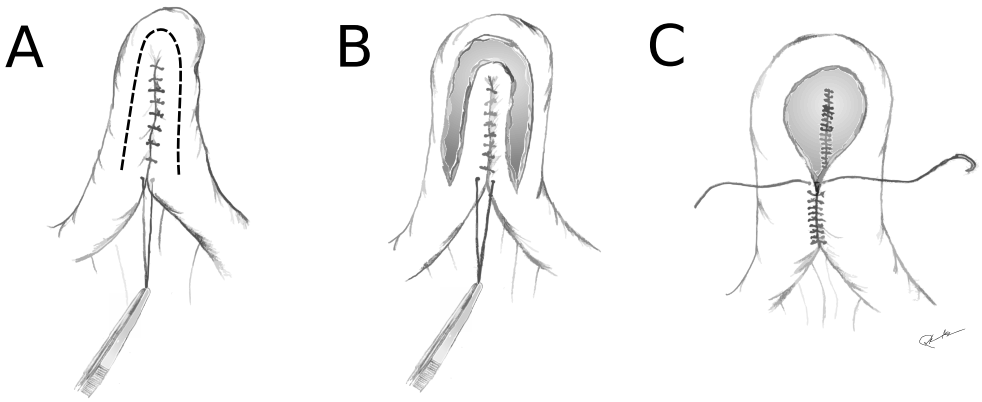

Figure 2 Finney stricturoplasty. Drawn based on Hurst et al. 1998.

Michelassi side-to-side isoperistaltic stricturoplasty is indicated for long segments of bowel with multiple successive short stenoses (segments as long as 100 cm) (Michelassi 1996). This stricturoplasty first requires division of the bowel and the mesentery at the midpoint of the affected bowel. Then, the proximal bowel loop is placed over the distal loop and the two loops are sutured using interrupted stitches in a side-to-side manner. Subsequently, a longitudinal enterotomy is performed in both loops and the suture line is formed with an internal row of running sutures which is continued anteriorly as a running suture as well. Finally, the outer anterior line is also reinforced

with interrupted stitches (Figure 3). The thickened inflamed mesentery may limit movement of the proximal bowel segment over the distal segment for lengths more than 50 cm. Resection at the middle part of the affected bowel may allow this technique to be performed for even longer bowel segments. A modification of the Michelassi stricturoplasty including additional Heineke-Mikulicz stricturoplasties at both ends of the side-to-side isoperistaltic anastomosis appears to prevent recurrence at the ends (Sasaki et al. 2004). The most important studies reporting results of the Michelassi stricturoplasty or of its modifications are summarized in Table 14. A comparison between conventional and non-conventional stricturoplasties showed that non-conventional techniques had similar outcome (Campbell et al. 2012).

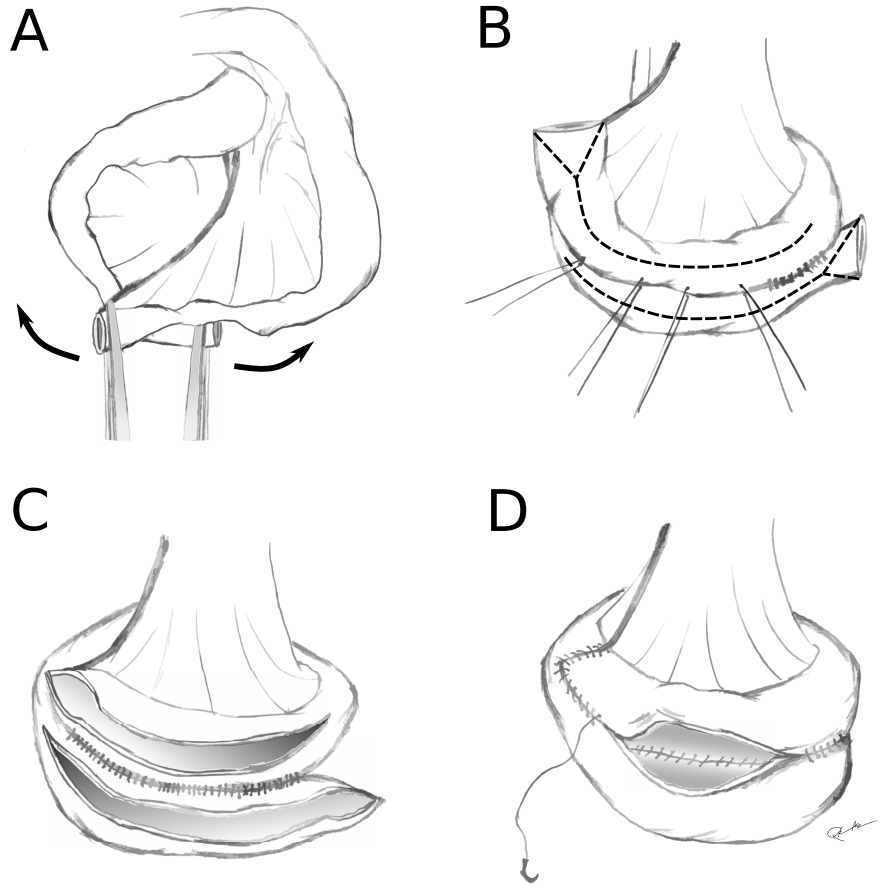

Figure 3 Michelassi side-to-side isoperistaltic stricturoplasty. Drawn based on Maggiori et al. 2012.

Two meta-analyses on studies comparing outcomes between stricturoplasty and bowel resection for small bowel CD could not find significant difference related to postoperative complication or surgical

recurrence rates (Reese et al. 2007, Yamamoto et al. 2007). However, stricturoplasty was primarily performed in short fibrotic strictures, while the resection group consisted of more complicated disease including perforation, fistula, abscess and long stenosis. None of the studies included in these meta-analyses were randomized controlled trials, since such trials have not been performed.

Table 14. Summary of studies concerning Michelassi side-to-side isoperistaltic stricturoplasty and its modifications

Study	Patients	Median follow-up (months)	Complications	Recurrence
Michelassi et al. 2000	21 patients submitted to SSIS, mean bowel length for anastomosis construction 22.5 cm (10-75 cm)	45	One postoperative gastrointestinal hemorrhage, probably along the suture line	No surgical site recurrence
Tonelli et al. 2004	31 patients submitted to SSIS	28	No anastomotic complications	One surgical recurrence at the SSIS
Michelassi et al. 2007	184 patients submitted to SSIS (in part the same patients were included in other publications), mean bowel length for anastomosis construction 32.4 cm (7-110 cm)	NA	7 anastomotic leaks, 4 gastrointestinal hemorrhages, 3 bowel obstructions	14 surgical recurrences at the SSIS, 41 surgical recurrences in total
de Buck van Overstraeten et al. 2016	29 patients submitted to modified SSIS over the ileocaecal valve or ileocolic anastomosis	21	Two anastomotic leaks	One surgical recurrence at SSIS
Fazi et al. 2016	91 patients submitted to SSIS (84 patients remained in the follow-up, in part the same patients were studied by Tonelli et al), median bowel length for anastomosis construction 55 cm (10-140 cm)	86	4 anastomotic complications, one of which was leak at the SSIS	15 surgical recurrences at the SSIS (affecting the SSIS body in 8 cases, inlet in 4 cases and outlet in 3 cases)

SSIS: Michelassi side-to-side isoperistaltic stricturoplasty; NA: not available

1.7.2.3 Resection length

After bowel resection overtook bypass as the main surgical procedure for CD, discussions regarding how much bowel should be resected began. Extensive bowel resections with wide margins of macroscopically normal bowel were recommended by some surgeons who believed that extensive surgery could decrease the recurrence rate (Bergman et al. 1977, Karesen et al. 1981, Krause et al. 1971, Wolff et al. 1983). Furthermore, some surgeons advocated using peroperative frozen sections to avoid leaving microscopic disease at the resection margin (Karesen et al. 1981, Wolff et al. 1983). However, many studies showed no difference in CD recurrence rate despite the microscopical state of the disease at the resection margins (Fazio et al. 1996, Hamilton et al.

1985, Heuman et al. 1983, Kotanagi et al. 1991, Pennington et al. 1980, Post et al. 1991). A trial among 152 patients randomized to a limited resection (with 2 cm of macroscopically uninvolved bowel) or an extended resection (with 12 cm of macroscopically uninvolved bowel) revealed no advantages for extensive resection in relation to CD recurrence (Fazio et al. 1996). Furthermore, the same trial found that microscopical involvement of the resection margin also did not increase the recurrence rate. This trial was decisive for the affirmation of bowel sparing surgery for CD which is currently widely accepted. Thus, only grossly affected bowel should be removed or stricturoplasty should be performed to preserve the bowel length.

The effect of microscopic positive resection margins on the rate of anastomotic leak was also evaluated in some studies. Anastomotic leak rate did not increase based on the microscopic positive resection margins according to previous studies (Heuman et al. 1983, Pennington et al. 1980, Post et al. 1991). However, recently, one study found that a microscopic positive margin increased the risk for anastomotic complications after ileocolic resection for CD (Shental et al. 2012) and another study concluded that a microscopic positive margin is a risk factor for clinical and surgical recurrence after primary ileocaecal resection for CD (de Buck van Overstraeten et al. 2017). Both studies should be interpreted with caution since they are retrospective and do not provide detailed descriptions of the criteria used for the evaluation of the resection margins.

1.7.2.4 Type of anastomosis

Anastomotic recurrence with re-stenosis is common following bowel resections for CD. Recently, the effect of intraoperative strategies, such as the type of anastomosis on the postoperative recurrence of CD has been studied. Figure 4 shows the main types of anastomotic configurations used after ileocolic resections.

A retrospective study of 138 CD patients found that surgical recurrence after side-to-side stapled anastomosis was lower than that following end-to-end hand-sewn anastomosis (Munoz-Juarez et al. 2001). That study suggests that a narrower lumen after end-to-end anastomosis may increase ischemia and cause re-stenosis.

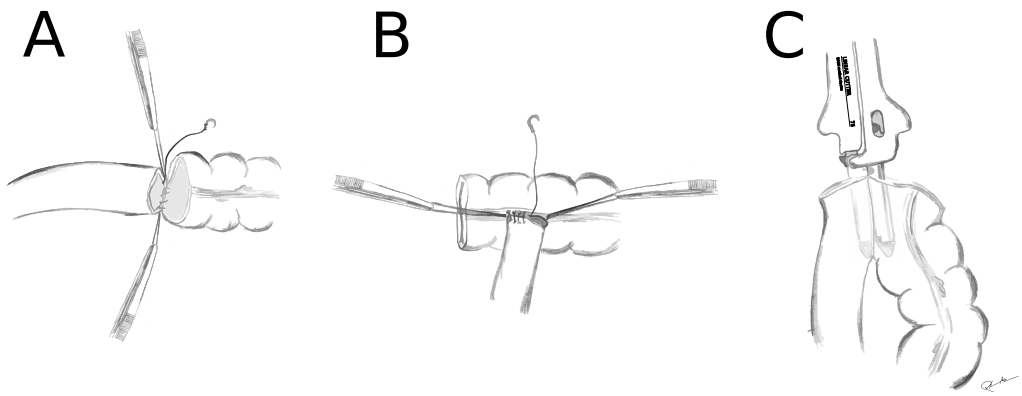

Figure 4 Main types of anastomotic configurations after ileocolic resection: **A** end-to-end anastomosis; **B** end-to-side anastomosis; **C** side-to-side anastomosis.

Another retrospective study including 84 surgical CD patients compared outcomes between stapled end-to-side, stapled side-to-side and hand-sewn side-to-side anastomosis (Scarpa et al. 2004). That study found no difference in relation to postoperative complications, but found a lower incidence of surgical recurrence in the stapled and hand-sewn side-to-side anastomosis compared to the stapled end-to-side technique. This study did not include hand-sewn end-to-end anastomosis.

A trial among 139 CD patients undergoing ileocolic resection randomized patients into side-to-side or end-to-end anastomosis groups, and found no difference in endoscopic recurrence rates (McLeod et al. 2009). However, surgical recurrence was not evaluated in that trial.

Another smaller randomized trial among 63 CD patients who underwent different types of bowel resection found significantly less surgical recurrence in the stapled anastomosis group. Configuration of the anastomosis was not reported in the hand-sewn group and included side-to-side and circular stapling in the stapled group.

One meta-analysis compared end-to-end hand-sewn anastomosis versus side-to-side stapled anastomosis after bowel resection in CD (Simillis et al. 2007). That meta-analysis concluded that perianastomotic clinical or surgical recurrence does not differ between groups. However, the anastomotic leak rate was lower in the side-to-side anastomosis group.

Another meta-analysis comparing side-to-side anastomosis to other types of anastomotic configurations after bowel resections for CD found no difference concerning the anastomotic leak, but detected lower endoscopic, symptomatic and surgical recurrence in the side-to-side group (Guo et al. 2013).

A new anastomosis technique, the Kono-S anastomosis, was described in 2011 for CD surgery involving small bowel or colon (Kono et al. 2011). This technique consists of a transection of the bowel segments with the linear

stapler positioned so that the mesentery is located at the center of the stump. The mesentery should be divided close to the bowel and not in a fan-shape, as performed in cancer surgery, to avoid devascularization or denervation. The two stapler lines are approximated using interrupted sutures to create a ”supporting column”. Longitudinal enterotomy is then performed along the antimesenteric side of both stumps starting from no more than 1 cm from the stapler line. The transverse lumen of the longitudinal enterotomy should be around 7-cm long. The enterotomy is closed transversely. The ”supporting column” remains behind the posterior wall of the anastomosis (Figure 5).

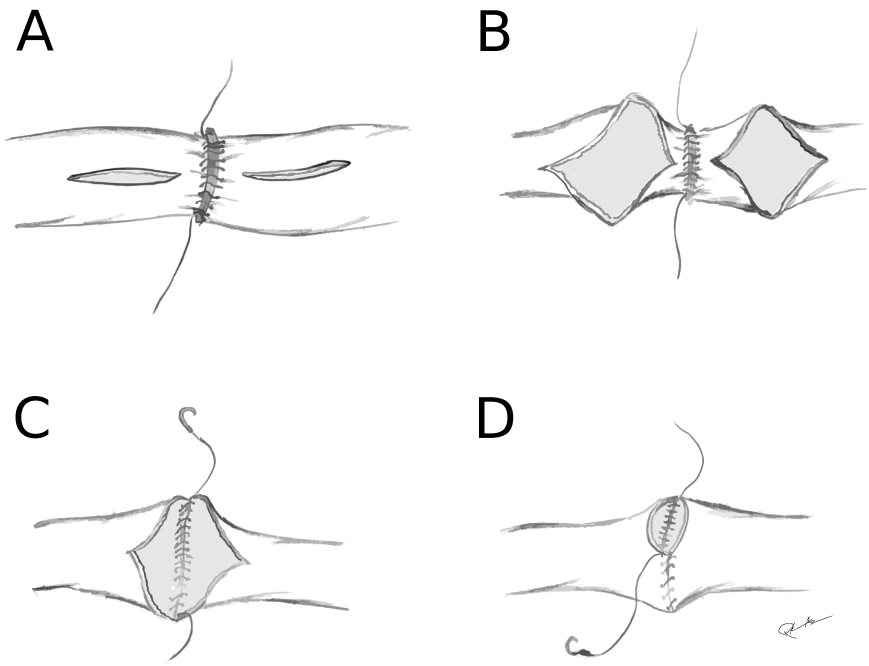

Figure 5 Kono-S anastomosis. Drawn based on Kono et al. 2011 and Fichera et al.2012.

The mesentery defect is typically so small that it does not require closure. Thus far, no contraindications to perform this anastomosis technique have been identified (Fichera et al. 2012, Kono et al. 2011). Differences in the intestinal caliber between the anastomosed bowel segments are not a problem (Fichera et al. 2012, Kono et al. 2011). This technique was introduced in Japan in 2003 and in the USA in 2010. A retrospective study consisting of 144 CD patients undergoing Kono-S anastomosis after bowel resection of either the small bowel or the colon reported a 10-year recurrence rate of only 1.4% (Kono et al. 2016). Prospective randomized trials comparing Kono-S anastomosis with traditional bowel anastomosis are ongoing and the results of those trials are eagerly expected.

To summarize, studies comparing anastomosis types in CD are heterogeneous since they include various types of bowel resections and

different anastomosis techniques. Most comparisons are retrospective with contradictory results. CD recurrence is evaluated in different ways, with some studies focusing on clinical, endoscopic or surgical findings to determine recurrence. Currently, there is insufficient evidence to favor one specific type of anastomosis technique over any other in CD.

1.7.3 UPPER GASTROINTESTINAL SURGERY

Gastroduodenal CD is rare and seldom requires operative treatment. Duodenal stenosis can be treated using balloon dilatation (Singh et al. 2017). Stricturoplasty techniques are usually performed in the jejunum and the ileum; however, these techniques have also been described in CD stenosis of the duodenum with results comparable to bypass surgery (Worsey et al. 1999). Heineke-Mikulicz stricturoplasty can be used in isolated stenosis of the first, second and third part of the duodenum. Finney stricturoplasty, however, might be a better option for stenosis of the fourth part of the duodenum, since it can be performed by including the first loop of the jejunum. One study comparing duodenal stricturoplasty to resection surgery in CD patients concluded that multiple stenoses in the first or fourth segment favor resection, while stricturoplasty should be performed for one or two stenoses in the second or third part of the duodenum (Tonelli et al. 2013). On the other hand, another retrospective study of duodenal CD described a high incidence of postoperative complications and recurrence following stricturoplasty (Yamamoto et al. 1999a). All previous studies have been retrospective and have included only a small number of patients (< 15 patients per study), so further research to clarify the role of stricturoplasty in the management of the duodenal CD is necessary. Bypass surgery remains the safest option for CD surgery of the upper GI tract.

1.7.4 SMALL BOWEL SURGERY

The primary aim of small bowel surgery for CD lies in restoring function while preserving the intestinal length. Limited bowel resection or stricturoplasty represent the typical operations performed on the small bowel in CD patients (Yamamoto et al. 2007). Stenosis is the most common indication for ileocaecal resection in CD and can lead to complete obstruction (Bernell et al. 2000b). Typically, the acute obstructive episode can be initially treated conservatively and elective surgery is considered later. Penetrating disease with the presence of fistulas or abscesses are also common either alone or concomitantly with stenotic lesions (Bernell et al. 2000b). For limited symptomatic ileocaecal disease (affected terminal ileum < 40 cm) resistant to traditional immunosuppressive medications, surgery may represent a reasonable alternative to infliximab treatment (Ponsioen et al. 2017).

At the beginning of the operation, an inspection of the entire bowel should be performed to evaluate the extent of the disease. Findings should be accurately described in the surgical report. If adhesions exist, the surgeon must weigh the benefits of a detailed intraoperative evaluation against the risk of potential injuries related to extensive adhesiolysis. Following exploration, a decision should be made between resection or stricturoplasty of the affected segments. Only the grossly affected bowel segments should be resected (Fazio et al. 1996). Minor aphthous ulcerations in the anastomotic line do not require further resection. Non-stenotic and non-penetrating disease encountered during surgery should be left intact. The length of the resected specimens and also the length of the remaining small bowel should be reported. Performing an anastomosis after resection is typical the rule in small bowel surgery for CD.

1.7.5 COLONIC SURGERY

Colitis unresponsive to medical treatment or steroid dependent, fulminant colitis, complications such as stenoses, fistulas or abscesses and dysplasia or cancer of the colon are indications for colonic surgery in CD (Mills et al. 2007).

In a population-based study including isolated Crohn's colitis patients, 40% had segmental colon involvement, 31 % had total colon involvement, 26% had left colon involvement and 3% had right colon involvement (Lapidus et al. 1998).

Traditionally, proctocolectomy with end ileostomy represented the treatment of choice for Crohn's colitis. This procedure remains necessary for patients with pancolitis accompanying severe perianal disease or anal incontinence (Hedrick et al. 2013). The disadvantages of this procedure include the requirement for a permanent stoma, the need for pelvic dissection and the need for a perineal wound with its healing difficulty (Hedrick et al. 2013, Yamamoto et al. 2014). Trying to minimize the problem of unhealed perineal wounds in CD patients, a study including 25 patients with severe anorectal CD advocated a low Hartmann's procedure leaving only 3 cm to 5 cm of rectum as an alternative to standard proctectomy (Sher et al. 1992). Authors described complete perineal wound healing in 15 patients (60%) while 10 patients underwent perineal proctectomy in a mean follow-up of 5.8 years. The overall perineal wound healing rate was 88% in this study. However, the advantages of a low Hartmann's procedure are controversial. The excluded rectal stump or the remaining anal canal can be a source of morbidity with continuing discharge and sepsis. When proctectomy is necessary, several technical factors such as intersphicteric dissection, careful hemostasis, avoidance of fecal contamination and appropriate closure of the pelvic floor may lower unhealed perineal wound rates in CD (Genua et al. 2007). Subtotal colectomy with ileostomy can be used in emergency surgery since patients with minimal

rectal disease may undergo ileorectal anastomosis afterwards. The rate of secondary proctectomy for a rectal stump after colectomy with end ileostomy is around 50% (Harling et al. 1991, Yamamoto et al. 1999c). Patients with a diseased rectal stump resistant to medical treatment should undergo proctectomy to avoid persistent fistulization and to minimize the risk of developing rectal cancer.

Given the recurrent nature of CD, surgery for CD has developed towards limited bowel resection in colonic disease as well (Andersson et al. 2009). Attempting to avoid permanent stoma also currently remains a goal of colonic surgery for CD (Andersson et al. 2009).

The diffuse involvement of the colon can be treated using colectomy with the preservation of the rectum and an ileorectal anastomosis (Cattan et al. 2002, O'Riordan et al. 2011). The rate of functional ileorectal anastomosis for Crohn's colitis at 10 years reaches roughly 70% to 80% (Cattan et al. 2002, O'Riordan et al. 2011, Yamamoto et al. 2000b). When the rectum is also severely involved, proctocolectomy and ileostomy should be performed. Ileoanal anastomosis is normally not recommended in CD (Braveman et al. 2004, Brown et al. 2005). Although some studies suggest an ileal pouch in selected patients with prolonged evidence of disease confined to the colon without small bowel or perianal involvement, such findings should be interpreted with caution, since they include a small number of patients, some of which had a UC diagnosis before surgery (Le et al. 2013, Melton et al. 2008). CD represented a significant risk for ileal pouch failure in a study of 3707 patients undergoing ileal pouch surgery (Fazio et al. 2013). That study included 150 patients with a CD diagnosis, finding 80% had a functional pouch 10 years following the ileal pouch operation (only 59 CD patients remained in the follow-up at 10 years) (Fazio et al. 2013).

Segmental colonic resection is the choice given limited colon involvement (Andersson et al. 2009, Andersson et al. 2002). A right hemicolectomy is performed for segmental involvement of the right colon. Sigmoidectomy or left hemicolectomy with colorectal anastomosis is recommended in cases with distal colonic CD when the rectum is spared. Even in patients undergoing proctectomy, a permanent colostomy instead of a proctocolectomy with ileostomy should be chosen for segmental distal CD to preserve the absorptive properties of the colon correlating with better functional results. However, some controversy surrounds the indication for proctectomy with colostomy in CD patients with severe perianal disease. One previous study consisting of only 10 patients reported a 90% recurrence rate in the proximal colon at a median time of 9.5 months despite the normal appearance of the proximal colon preoperatively (de Buck van Overstraeten et al. 2013). Another study reported an earlier and higher recurrence rate after segmental colonic resections compared to proctocolectomy (Fichera et al. 2005). By contrast, other studies reported a better functional outcome and the possibility of postponing the need for a permanent stoma following segmental colonic resections (Andersson et al. 2002, Longo et al. 1988).

Furthermore, many studies found no statistically significant difference in surgical recurrence rates after segmental colonic resection compared to subtotal or total colectomy for Crohn's colitis (Allan et al. 1989, Andersson et al. 2002, Handler et al. 2016, Kiran et al. 2011, Longo et al. 1988, Sanfey et al. 1984). When comparing proctocolectomy to colectomy and ileorectal anastomosis, the surgical recurrence is significantly lower following proctocolectomy (Bernell et al. 2001, Yamamoto et al. 1999d). However, the postoperative complication rate is higher following proctocolectomy, primarily resulting from perineal sepsis (Yamamoto et al. 1999d). The primary bowel resections performed in Crohn's colitis are shown in Figure 6.

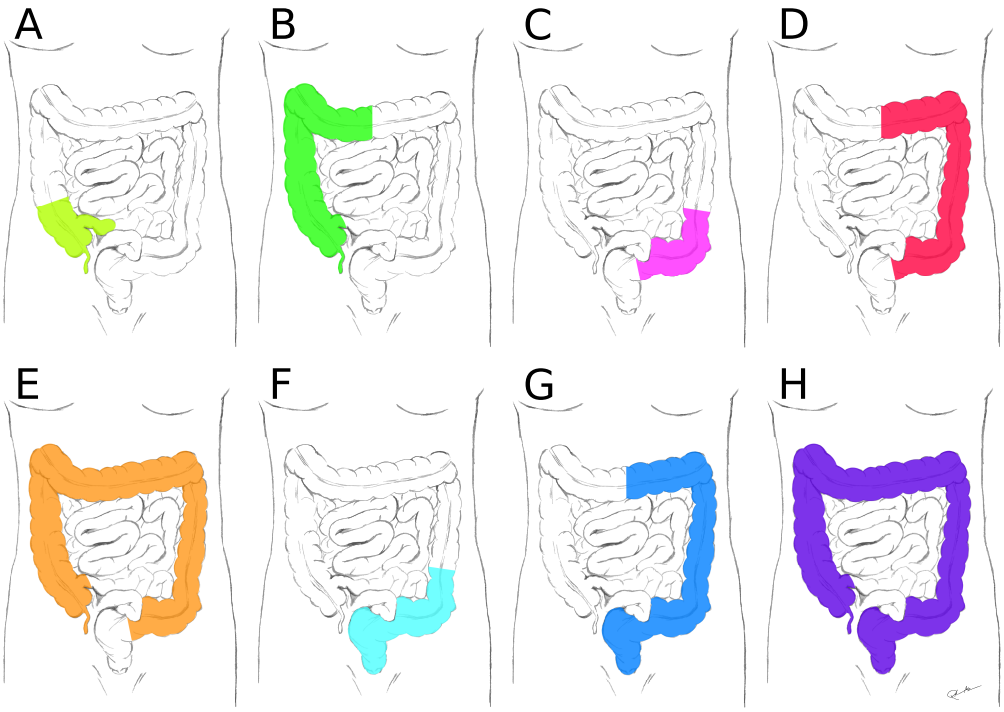

Figure 6 Main bowel resections in Crohn's colitis: **A** ileocaecal resection; **B** right hemicolectomy; **C** sigmoidectomy; **D** left hemicolectomy; **E** colectomy; **F** proctosigmoidectomy; **G** left hemicolectomy + proctectomy; **H** proctocolectomy.

1.7.6 PERIANAL SURGERY

Treating perianal CD involves medical and surgical therapy. Following the introduction of anti-TNF alpha medications, the treatment of fistulas in CD patients has changed to a more conservative approach.

Fistulas and anorectal abscesses represent the primary perianal CD manifestations. Abscesses should be surgically drained with care to avoid sphincter damage. Even so, the majority of the CD patients with a perianal abscess will develop an anal fistula during the course of the disease. The

treatment of perianal fistulas depends on the complexity of the fistula and on the degree of inflammation in the rectum. Surgical approaches for fistulas in CD patients do not differ much from the treatment of fistulas in the general population and may include the placement of a seton drain, fistulotomy, fibrin glue, a collagen fistula plug, an advancement flap or ligation of the intersphincteric fistula tract (LIFT) procedure (Marzo et al. 2015). Low fistulas can be treated using fistulotomy, while high fistulas can be treated by draining setons combined with anti-TNF alpha therapy (Marzo et al. 2015). An advancement flap should be used only in the absence of significant rectal mucosal inflammation (Sonoda et al. 2002). While CD patients with asymptomatic fistulas should not be treated surgically, patients with complex fistulas may need fecal diversion through the construction of a loop ileostomy or a transversostomy (Mueller et al. 2007). Recently, adipose-derived mesenchymal stem cells locally injected in perianal fistula tracts have emerged as a promising approach to treat refractory complex perianal fistulas in CD. A pilot study among 24 patients showed complete closure of complex perianal fistulas in 56% of CD patients treated using expanded adipose-derived stem cells (de la Portilla et al. 2013). Additionally, a randomized placebo-controlled multicenter study consisting of 212 patients has demonstrated the safety and efficacy of the adipose-derived stem cells treatment for CD patients with complex perianal fistulas (Panes et al. 2016). However, that study excluded patients with rectovaginal fistulas (Panes et al. 2016). The treatment of rectovaginal fistulas in patients with proctitis remains challenging and typically requires fecal diversion (Mueller et al. 2007). Skin tags and hemorrhoids should rarely be treated surgically in CD patients, since they may be associated with poor healing (Cracco et al. 2014, Lewis et al. 2010). In addition, anal stenosis can also be a manifestation of CD. The stenosis can be treated using anal dilatation, although cancer must be considered and biopsies are recommended (Brochard et al. 2014).

1.7.7 SURGICAL COMPLICATIONS

Postoperative complications are a concern following surgery for CD. It is assumed that the rate of postoperative complications is higher in CD patients compared to other patients undergoing colorectal surgery (Uchino et al. 2009). Based on a meta-analysis evaluating risk factors for postoperative intra-abdominal septic complications (IASCs) in CD patients, low albumin levels, preoperative steroid use, a preoperative abscess and the presence of previous surgery were factors associated with a higher rate of IASCs (Huang et al. 2015). On the other hand, no association was found between postoperative IASCs and the type of anastomosis, preoperative biological medication use, and preoperative immunosuppressive medication use other than steroids (Huang et al. 2015). The evidence used in this meta-analysis was rather low-quality, since it included only retrospective studies and the studies were rather heterogeneous (Huang et al. 2015).

A Swedish case-control study evaluating the influence of preoperative biological medication use within two months of surgery identified no association between biological medication use and any postoperative complications or anastomotic complications (Myrelid et al. 2014).

Across studies evaluating risk factors for postoperative complications following surgery for CD, different steroids, imunnosuppressive and biological medications have been used, in varying dosages and for varying durations. In addition, many patients use multiple CD medications preoperatively. The criteria for low albumin levels also vary between studies. Some studies include only patients undergoing ileocolic resection, while other studies also include other types of bowel resections and stricturoplasties. The most important studies evaluating risk factors for postoperative complications in CD patients are summarized in Table 15.

Table 15. Risk factors for postoperative complications following surgery for CD

Study	Description	Association with postoperative complications	
		Risk factor	**No association**
Heimann et al. 1985	130 patients undergoing surgery for CD with anastomosis or stoma. Analyzed postoperative complications in general	Low albumin, multiple previous operations, stoma need, extensive bowel resections	Preoperative abscess, preoperative fistula, disease duration, preoperative steroid use, positive resection margin
Post et al. 1991	429 operations for CD followed by anastomosis in 368 patients. Analyzed postoperative complications in general	Preoperative steroid use, intraoperative abscess	Disease duration, previous operation, nutritional status, emergency surgery, positive resection margin
Yamamoto et al. 2000a	566 operations for CD followed by anastomosis in 343 patients. Analyzed postoperative IASCs	Low albumin, preoperative steroid use, intraoperative abscess, intraoperative fistula	Previous operation, covering stoma, type of anastomosis
Alves et al. 2007	161 CD patients undergoing primary ileocaecal resection. Analyzed postoperative IASCs	Nutritional status, preoperative steroid use for more than 3 months, intraoperative abscess	Disease duration, smoking status, emergency surgery, type of anastomosis, ASA class, blood transfusion, operation time
Iesalnieks et al. 2008	331 operations for CD followed by anastomosis in 282 patients. Analyzed postoperative IASCs	Weight loss, articular disease manifestation, duration of symptoms	Intraoperative abscess, preoperative steroid use, previous surgery, covering stoma, smoking status
Tzivanakis et al. 2012	173 patients undergoing ileocolic resection for CD with anastomosis. Analyzed anastomotic complications	Preoperative steroid use, intraoperative abscess	Previous operation, intraoperative fistula, preoperative albumin level, emergency surgery, type of anastomosis, smoking status
El-Hussuna et al. 2012	417 CD patients undergoing bowel resection and/or stricturoplasty. Analyzed postoperative IASCs	Preoperative use of high dose prednisolone (>20 mg), operation time and colo-colic anastomosis	Previous operation, preoperative biological medication, emergency surgery, type of anastomosis
Shental et al. 2012	166 CD patients undergoing ileocolic resection with anastomosis. Analyzed postoperative IASCs	Disease duration, positive resection margin, additional sigmoidectomy	Intraoperative abscess, low albumin, type of anastomosis, smoking status, preoperative biological medication
de Buck van Overstraeten et al. 2017	538 CD patients undergoing primary ileocaecal resection. Analyzed anastomotic complications	ASA class III, preoperative biological medication, length of bowel resection	Disease duration, preoperative steroid use, positive resection margin, type of anastomosis

CD: Crohn's disease; IASC: intra-abdominal septic complications; ASA: American Society of Anesthesiologists

Although many studies have evaluated the risk factors for postoperative complications in CD, there is a lack of randomized controlled trials. Definitive conclusions and recommendations regarding the need to pause CD medications preoperatively cannot be drawn. Correcting severe hypoalbuminemia before elective CD surgery is recommended and, in the presence of multiple possible risk factors for IASCs preoperatively, the use of a protective stoma may be justified.

1.7.8 RECURRENCE AFTER SURGERY

CD recurrence following bowel resection is common. Recurrence is defined clinically, radiologically, endoscopically or surgically through different studies rendering comparisons difficult. Endoscopic recurrence is typically evaluated with the Rutgeerts' score (described above in section 1.5.3.2; Rutgeerts et al. 1990). In one study, clinical recurrence during the five-year follow-up period occurred in 11% of patients with a Rutgeerts' score of i0 or i1, 57% of patients with i2, 75% of patients with i3 and 100% of patients with i4 (Yamamoto et al. 2013a). In that study, endoscopic evaluation was carried out six months following surgery. Indeed, the Rutgeerts'score of i2 or more is considered as a significant recurrence in clinical trials.

A prospective multicenter cohort study of patients undergoing ileocolic resection concluded that a large proportion of endoscopic recurrence of CD occurred within six months from the ileocolic resection (Orlando et al. 2014). Table 16 summarizes the results from the principal studies analyzing risk factors for postoperative CD recurrence.

A meta-analysis evaluating the effect of smoking on postoperative surgical recurrence of CD concluded that smokers have a 2.5-fold increased risk of reoperation due to CD recurrence compared to non-smokers (Reese et al. 2008). Furthermore, the risk of surgical recurrence among former smokers did not significantly differed from non-smokers (Reese et al. 2008). Thus, encouraging smokers to quit remains quite important in order to minimize postoperative disease recurrence.

As mentioned above in section 1.7.2.4, a multicenter randomized controlled trial concluded that anastomotic type (side-to-side vs. end-to-end) did not affect the endoscopic or symptomatic recurrence rate following ileocolic resection (McLeod et al. 2009). This trial also concluded that previous bowel resection represented a risk factor for endoscopic or symptomatic recurrence, while compliance with postoperative maintenance therapy served as a protective factor (McLeod et al. 2009). In addition, a meta-analysis also found no significant difference in clinical or surgical recurrence between side-to-side and end-to-end anastomoses for CD (Simillis et al. 2007).

Table 16. Risk factors for postoperative Crohn's disease recurrence

Study	Description	Recurrence rate	Association with recurrence	
			Risk factor	No association
Bernell et al. 2000b	722 CD patients undergoing primary bowel resection. Risk factors for recurrence were analyzed in 476 patients	43% (307 of 722) of the patients had clinical recurrence with a median follow-up of 6.8 years	History of perianal disease and length of bowel resection were risk factors for recurrence	Sex, age at diagnosis, CD duration, type of bowel resection, presence of postoperative complication
Polle et al. 2005	91 CD patients undergoing segmental colonic resection for CD. Patients undergoing ileocolic resections were excluded	30 patients (33%) had surgical recurrence with a median follow-up of 8.3 years	Female sex and a history of perianal disease were risk factors for surgical recurrence	Smoking, family history of IBD, age at diagnosis, CD duration
Onali et al. 2009	183 CD patients undergoing bowel resection (145 undergoing ileocolic resections and 38 patients undergoing other bowel resection)	Clinical recurrence occurred in 16 patients (42%) after non-ileocolic resections with a median follow-up of 8 years and 128 patients (88.3%) after ileocolic resection with a median follow-up of 6 years	Smoking, previous appendectomy and a family history of IBD were risk factors for recurrence	
Riss et al. 2014	116 CD patients undergoing primary ileocaecal resection	Surgical recurrence rate was 12% at 10 years after the primary operation	Urgent surgery increased recurrence. Postoperative azathioprine or 6-mercaptopurine decreased recurrence	Smoking, postoperative biological medication, intraoperative fistula or abscess, need for additional bowel resection at primary operation
de Barcelos et al. 2017	127 CD patients undergoing ileocolic resection	43 patients (34%) had early endoscopic recurrence verified by colonoscopy at 6 to 12 months postoperatively	Preoperative steroid use was a risk for recurrence	Smoking, concomitant perianal CD, preoperative immunosuppressive or biological medication use, type of anastomosis, presence of postoperative complication
de Buck van Overstraeten et al. 2017	538 CD patients undergoing primary ileocaecal resection	Rates of clinical and surgical recurrence were 45.4% and 6.5% after 5 years and 55.0% and 19.1% at 10 years following the primary operation	Smoking, positive microscopic resection margin were risk factors for clinical recurrence	Sex, CD duration, length of bowel resection, type of anastomosis
Koriche et al. 2017	83 CD patients undergoing definitive stoma operation	35 patients (42%) had clinical recurrence with a median follow-up of 10 years	Anoperineal lesions and colostomy at the time of definitive stoma operation were risk factors for clinical recurrence	Age, sex, presence of extraintestinal manifestations, smoking

CD: Crohn's disease; IBD: inflammatory bowel disease

According to another meta-analysis, perforating CD associates with a higher rate of surgical recurrence (Simillis et al. 2008). However, the authors concluded that further studies are necessary to confirm this finding due to the high heterogeneity across the studies included (Simillis et al. 2008).

A previous study has suggested that bacteria and intestinal contents play a role in postoperative recurrence in CD, while no recurrence along the anastomosis was observed in cases with a proximal diversion (D'Haens et al. 1998).

A Cochrane review evaluating the effect of postoperative medical therapy for preventing CD clinical recurrence concluded that metronidazol, mesalamine, azathioprine and 6-mercaptopurine were better than placebo in reducing the risk for CD clinical recurrence (Doherty et al. 2009). Only randomized controlled trials were included in this review.

Furthermore, a combination of metronidazol with azathioprine appears more effective than azathioprine alone in preventing postoperative endoscopic recurrence in CD (D'Haens et al. 2008).

More recently, multiple studies showed that the postoperative use of biological medications significantly reduced the endoscopic recurrence of CD compared to a placebo or mesalamine or azathioprine treatment (De Cruz et al. 2015, Papamichael et al. 2012, Regueiro et al. 2009, Savarino et al. 2013, Sorrentino et al. 2010, Yamamoto et al. 2009, Yoshida et al. 2012).

A review study of postoperative CD recurrence suggests initiation of azathioprine or 6-mercaptopurine medication postoperatively for patients with risk factors for recurrence (smoking, perforating disease, multiple previous resection) and endoscopic evaluation for all patients 6 months following surgery initiating biological therapy for patients with a Rutgeerts' score of i2 to i4 (Yamamoto et al. 2013b).

Another review study suggests more aggressive treatment initiating biological therapy following surgery for patients with more than one risk factor for recurrence (active smoking, perforating disease, previous surgery, perianal disease, bowel resection length >50 cm, myenteric plexitis at the resection margin) (Vuitton et al. 2013). According to the authors, postoperative medication should be initiated two weeks after surgery and ileocolonoscopy should be performed six months following surgery with step-up therapy for patients with a Rutgeerts' score of i1 to i4 (Vuitton et al. 2013).

2 AIMS OF THIS STUDY

The present study aims to analyze the surgical treatment of Crohn's disease in our colorectal unit during the era of MRE, biological medications and laparoscopic surgery. We emphasized on innovations and unresolved topics. The specific aims are listed below:

I. To evaluate the MRE accuracy in detecting preoperatively stenoses, fistulas or abscesses in CD and its utility in surgical planning.
II. To verify the influence of the degree of inflammatory activity at the bowel resection margin on anastomotic complications and to identify other possible risk factors for postoperative CD complications.
III. To describe the risk factors for anastomotic recurrence following primary ileocaecal resection in CD.
IV. To compare the surgical recurrence rate of different types of bowel resections in CD patients and to determine the CD location at reoperations.

3 PATIENTS AND METHODS

3.1 PATIENT CHARACTERISTICS

A total of 249 consecutive patients underwent surgery due to CD at the Helsinki University Hospital between 2006 and 2016. Data were retrospectively collected from these patients' clinical records according to the study plan and entered into the IBM SPSS software for statistical analyses. The study protocol was approved by the institutional ethics committee. Since this was a retrospective chart review study, the patient's informed consent was not required.

Study I
This study included 55 consecutive patients operated electively due to CD between January 2011 and May 2015, which underwent preoperative MRE in our hospital within the four months preceding surgery.

Study II
Data were collected from 70 patients with information available on the bowel resection margins. These patients underwent elective bowel resection followed by primary anastomosis due to CD between January 2011 and December 2015. Patients were followed-up for one month postoperatively to exclude the development of anastomotic complications.

Study III
The study population comprised of 101 patients submitting to primary ileocaecal resection with primary anastomosis between 2006 and 2016. Nine patients with a follow-up < 1 year were excluded from the analyses. Altogether 83 patients had an elective primary ileocaecal resection, while 9 patients were admitted through our emergency department due to acute CD symptoms requiring urgent surgery (surgery scheduled within 48 hours of the hospital admission). Patients who required endoscopic dilatation or re-resection of the ileocolic anastomosis during the postoperative follow-up were considered to have anastomotic recurrence in this study.

Study IV
This study included all patients undergoing bowel resection due to histologically confirmed CD between 2006 and 2016 with available postoperative follow-up information. Patients were divided into five groups according to the type of bowel resection performed: ileocolic resection, small bowel resection, segmental colon resection with colocolic or colorectal anastomosis, colectomy with ileorectal anastomosis and end stoma operation. The small bowel resection group included jejunal and ileal

resection subgroups. The end stoma operation group included end ileostomy and end colostomy subgroups.

3.2 PREOPERATIVE MRE (I)

Siemens Avanto fit (1.5T) or Siemens Verio (3T) machines were used to perform MREs. The MRE protocol included the prior administration of 1500 ml of mannitol orally or through nasojejunal intubation and the intravenous injection of 20 mg of hyoscine butylbromide or 1 mg of glucagon. A thick slab T2 haste fat saturated sequence was performed first to confirm achievement of an adequate bowel distension. T2 weighted and T1 fat-saturated gadolinium-enhanced images were performed for all patients in the axial and coronal planes. Diffuse weighted images and cine images were obtained for only a portion of the patients due to changes in the MRE protocol during the study period. All MRE reports were completed by specialist abdominal radiologists. Data concerning the number and location of stenoses, and the presence of abscesses and fistulas were collected retrospectively from MRE reports for comparison with operative findings. The data for all patients with discordance between the MRE and surgical findings were reviewed specifically focusing on remarks concerning adhesions.

3.3 RESECTION MARGIN (II)

A single gastropathologist unaware of the clinical findings reviewed and classified all slides for the resection margins utilizing the CD histological score (described above in section 1.5.4) used clinically in our hospital to evaluate inflammatory activity. According to this score the degree of inflammatory activity is graded as follows: no inflammation (no residual microscopic disease), inactive (the presence of chronic inflammation without neutrophils), mild (infiltration of polymorphonuclear cells in the lamina propria or surface epithelium and/or the presence of cryptitis), moderate (the presence of polymorphonuclear cells in the epithelium and/or an abscess) and strong inflammation (the presence of erosion and/or ulcers). Both proximal and distal resection margins were graded and the margin with a higher inflammatory activity was recorded for analyses. Firstly, we compared patients with no inflammation and inactive inflammation at the resection margins for patients with active inflammation (mild, moderate and strong). Secondly, we compared patients with no inflammation, inactive and mild inflammation at the resection margins to patients with moderate and strong inflammation.

3.4 STATISTICAL ANALYSIS

The preoperative MRE sensitivity, specificity and accuracy of detecting stenoses, abscesses and fistulas using the operative findings as the gold standard, were calculated and reported using the Clopper-Pearson 95% confidence interval (CI) (I). The Fisher's exact test was used to evaluate if the degree of inflammatory activity at the resection margins affected the postoperative anastomotic complication risk (II). In addition, the Fisher's exact test was also used for the subgroup analyses concerning surgical recurrence (IV). The possible risk factors for any postoperative complication were evaluated using the Mann-Whitney U-test for continuous data and the Pearson's chi-squared test or the Fisher's exact test for categorical data (II). The Kaplan-Meier curve was used to calculate the cumulative survival without anastomotic recurrence following a primary ileocaecal resection (III). We also used univariate and multivariate Cox regression analyses to calculate the risk factors for anastomotic recurrence following primary ileocaecal resection (III). Finally, we used binary univariate logistic regression analysis to compare the surgical recurrence rate between different types of bowel resection groups (IV). Univariate variables with $p < 0.05$ were included in the multivariate analysis (III). For all studies, p values < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software version 24 (I-IV).

4 RESULTS

4.1 EFFICIENCY OF PREOPERATIVE MRE (I)

In total, study I consisted of 55 patients undergoing surgery due to CD who also underwent preoperative MRE a median of two months before surgery (range 0-4 months). Briefly, 26 patients (47.3%) were men and the median age was 45 years (range 17-82). Ileocolic resection was performed on 43 patients (78.2%), of whom 2 (3.6%) had concomitant ileal resection. Furthermore, 4 patients (7.3%) underwent ileal resection alone, 6 patients (10.9%) colonic resection and 2 patients (3.6%) adhesiolysis alone. Laparoscopic surgery was successfully performed in 27 patients (49.1%), 1 patient (1.8%) required conversion due to abdominal adhesions and 27 patients (49.1%) underwent primary open surgery. Previous abdominal surgery had been performed on 32 patients (58.2%).

4.1.1 COMPARISON OF PREOPERATIVE MRE AND SURGICAL FINDINGS

MRE contrast was administered orally to 35 patients (63.6%) and through nasojejunal intubation to 20 patients (36.4%).

Using the surgical findings as the reference, MRE detected 72 of the 80 stenoses diagnosed at surgery. In addition, MRE detected 12 stenoses that could not be confirmed by surgery. Furthermore, 10 of these 12 false positive stenoses turned out to be only adhesions upon surgery. Concerning diagnoses of abscesses, MRE detected 4 of the 5 abscesses diagnosed during surgery, while 5 abscesses found using preoperative MRE were not present during surgery. The one false negative abscess upon MRE was described as multiple adhesions between bowel segments in the MRE report. However, intraoperatively both an ileosigmoid fistula and an abscess were detected. Finally, MRE diagnosed 14 of the 18 fistulas detected during surgery. Out of the 4 false-negative fistulas not identified using MRE, 3 were described as the presence of adhesions in the MRE report, while among 6 false-positive fistulas in MRE, 2 were diagnosed as adhesions during surgery.

Table 17 provides the preoperative MRE sensitivity, specificity and accuracy for detecting lesions calculated per patient. Altogether, 80 stenoses were detected during surgery in 46 patients. The sensitivity of MRE to detect the absolute number of stenosis compared to the surgical findings was 90.0% (95% CI 81.2-95.6), which can be partially explained by the fact that two consecutive short stenoses were usually interpreted as a single long stenosis by MRE.

The MRE diagnosis differed from the surgical findings in 36 lesions, 16 of which were due to erroneous differential diagnoses with adhesions.

Table 17. Magnetic resonance enterography (MRE)

Finding[a]	Number		Magnetic resonance enterography (MRE)		
	By surgery	By MRE	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)
Fistula	18	20	77.8 (52.4–93.6)	83.8 (68.0–93.8)	81.8 (69.1-90.9)
Abscess	5	9	80.0 (28.4–99.5)	90.0 (78.2–96.7)	89.1 (77.8-95.9)
Stenosis	46	48	100 (92.3-100.0)	77.8 (40.0-97.2)	96.4 (87.5-99.6)

CI: confidence interval

[a]*Calculated per patient*

4.1.2 MODIFICATION OF THE PREOPERATIVE PLAN

The operative plan was modified for 7 patients (12.7%) due to the discordance between preoperative MRE and the surgical findings. In 6 patients (10.9%), the modification in the surgical plan consisted of a more extensive bowel resection or an additional surgical procedure required due to false-negative lesions in preoperative MRE. In addition, 1 patient (1.8%) had 2 stenoses detected using MRE, although only adhesions were found during surgery, requiring adhesiolysis alone.

4.2 POSTOPERATIVE COMPLICATIONS (II)

Among the 70 CD patients included in this study, 51 patients (72.7%) underwent ileocolic resection, 6 patients (8.6%) small bowel resection, 3 patients (4.3%) ileocolic resection and small bowel resection, 3 patients (4.3%) sigmoidectomy with colorectal anastomosis, 1 patient (1.4%) subtotal colectomy with ileosigmoidal anastomosis and 6 patients (8.6%) colectomy with ileorectal anastomosis. Furthermore, 5 patients (7.1%) underwent proximal diversion. Table 18 presents the patient characteristics.

Table 18. Characteristics of the patients with available resection margins

Patient characteristic	n = 70
Median age in years (range)	41.5 (14-82)
Sex	
Male	37 (52.9%)
Female	33 (47.1%)
Previous surgery	34 (48.6%)
Presence of abscess	5 (7.1%)
Presence of fistula	23 (32.9%)
Immunosuppressive medications	27 (38.6%)
Steroids	12 (17.1%)
Anti-TNF alpha	13 (18.6%)
Median preoperative albumin, g/l (range)	36.8 (17.4-45.4)
Median faecal calprotectin, µg/g (range)	309 (6-1983)
Median C-reactive protein, mg/l (range)	7 (3-201)

TNF: tumor necrosis factor

4.2.1 POSITIVE RESECTION MARGIN INFLUENCE ON ANASTOMOTIC COMPLICATIONS

The resection margins in our patient sample were graded as follows: 8 patients (11.4%) had no inflammation, 16 patients (22.9%) had inactive inflammation, 12 patients (17.1%) had mild inflammatory activity, 5 patients (7.1%) had moderate inflammatory activity and 29 patients (41.4%) had severe inflammatory activity. Altogether 46 patients (65.7%) had inflammatory activity in the bowel resection margin, among whom 34 (48.6%) had moderate or severe inflammatory activity.

Anastomotic complications developed in 3 patients (4.3%), among whom 2 underwent laparoscopic ileocaecal resection and 1 had colectomy with ileorectal anastomosis.

The presence of inflammatory activity at the resection margin did not significantly influence the development of an anastomotic complication (p=0.55). Although all three anastomotic complications developed in patients with moderate or severe inflammatory activity at resection margin, this result did not reach statistical significance (p=0.11).

4.2.2 RISK FACTORS FOR POSTOPERATIVE COMPLICATIONS

Postoperative complications were detected in 14 patients (20.0%), among whom 3 (4.3%) were anastomotic complications. According to the Clavien-Dindo classification, complications were graded as follows: 2 patients (2.9%) grade I, 7 patients (10.0%) grade II and 5 patients (7.1%) grade IIIb. None of

the risk factors evaluated in our study were significantly associated with the development of postoperative complications in CD patients (Table 19).

Table 19. Univariate analysis of risk factors for postoperative complications

Risk factor	No postoperative complications n = 56	Any postoperative complication n = 14	P-value
Median age in years	40	47	0.48
Sex male:female	28:28	9:5	0.34
Previous surgery	28	6	0.63
Laparoscopic surgery	26	6	0.81
ASA class I:II:III:IV	3:41:10:2	1:10:3:0	0.92
Presence of abscess	5	0	0.58
Presence of fistula	18	5	0.80
Immunosuppressive medications	20	7	0.33
Steroids	8	4	0.21
Anti-TNF alpha	9	4	0.28
Low albumin[a]	21	6	0.75
Low haemoglobin[b]	20	5	1.00
Median faecal calprotectin, µg/g	311	238	0.95
Median C-reactive protein, mg/l	7	18	1.00

ASA: American Society of Anesthesiologists; TNF: tumor necrosis factor; chi-square test for categorical variables and the Mann-Whitney's U test for continuous variables

[a]Low albumin < 36 g/l ≤ 70 years or < 34 g/l > 70 years

[b]Low haemoglobin < 117 g/l female or < 134 g/l male

4.3 SURGICAL RECURRENCE (III, IV)

4.3.1 ANASTOMOTIC RECURRENCE AFTER PRIMARY ILEOCAECAL RESECTION (III)

In total, 101 CD patients underwent primary ileocaecal resection during the study period. Nine of these patients were excluded from analysis since the follow-up time was less than one year. Patient characteristics are described in Table 20.

The median follow-up time from the ileocaecal resection was 4.7 years (range 1.3-10.8). Anastomotic recurrence, defined as the need for endoscopic dilatation or a new ileocolic resection occurred in 12 patients (13.0%). The median time to recurrence was 2.9 years (range 1.0-9.5). The risk for anastomotic recurrence was 1.1% and 6.9%, respectively, 1 and 3 years following the primary ileocaecal resection using the Kaplan-Meier curve. Univariate analysis detected urgent surgery, stapled anastomosis and postoperative steroid treatment as significant risk factors for anastomotic recurrence after the primary ileocaecal resection, while only stapled anastomosis remained significant in the multivariate analysis (Table 21).

Table 20. ***Patient characteristics among those undergoing primary ileocaecal resection with a follow-up of ≥ 1 year***

Patient characteristic	n = 92
Median age in years (range)	30.5 (14.8-82.7)
Male sex	55 (59.8%)
Smoker[a]	44 (53%)
Median CD duration in years (range)	2.4 (0-25.6)
Previous surgery	14 (15.2%)
History of perianal CD	18 (19.6%)
Intraoperative fistula or abscess	33 (35.9%)
Urgent surgery	9 (9.8%)
Laparoscopic surgery	32 (34.8%)
Hand-sewn anastomosis	89 (96.7%)
Preoperative steroid medication	37 (40.2%)
Preoperative biological medication	11 (12.0%)
Postoperative steroid medication	11 (12.0%)
Postoperative biological medication	17 (18.5%)
Postoperative complication	7 (7.6%)

CD: Crohn's disease

[a]Data is missing for some patients

Table 21. ***Univariate and multivariate analyses of risk factors for anastomotic recurrence after primary ileocaecal resection***

Variable	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at primary operation	0.98 (0.94-1.03)	0.479	1.00 (0.95-1.06)	0.983
Male sex	0.98 (0.28-3.35)	0.970	2.07 (0.32-13.50)	0.446
Urgent surgery	4.98 (1.45-17.11)	0.011	2.47 (0.53-11.44)	0.248
Postoperative steroid	3.58 (1.03-12.40)	0.044	2.25 (0.60-8.43)	0.228
Stapled anastomosis	20.34 (5.06-81.77)	<0.001	19.21 (2.33-158.37)	0.006
Preoperative steroid	2.93 (0.86-10.02)	0.087	—	—
Smoking	3.27 (0.86-12.49)	0.083	—	—

HR: hazard ratio; CI: confidence interval

[a]Cox regression analysis adjusted for age and sex

4.3.2 COMPARISON BETWEEN DIFFERENT TYPES OF BOWEL RESECTION (IV)

In total, 218 patients were included and followed for a median of 4.7 years (range 0.3-10.5). Surgical recurrence occurred in 42 patients (19.3%). Patient data by operation type is showed in Table 22.

The ileocolic resection group underwent recurrence-related surgery less frequently than the other types of bowel resections (Table 23). The reoperation rate due to CD recurrence was not significantly different (p=0.33) between jejunal resection (37.5%; 3 of 8 patients) and ileal resection (21.1%; 4 of 19 patients). Similarly, no significant difference

(p=0.60) in the surgical recurrence was found between end ileostomy (33.3%; 5 of 15 patients) and end colostomy (35.0%; 7 of 20 patients).

The location of CD at reoperations correlated with the CD location during the primary operation in most of the cases (Table 24).

Table 22. Patient data according to the primary operation type

Total n = 218	Ileocolic resection n = 138	Small bowel resection n = 24	Segmental colon resection with colocolic or colorectal anastomosis n = 17	Colectomy with ileorectal anastomosis n = 4	End-stoma operation n = 35
Median age in years (range)	39.3 (14.8-82.7)	35.4 (18.6-70.1)	33.1 (18.1-54.1)	25.6 (17.7-74.1)	44.3 (22.9-71.3)
Female	56 (40.6%)	11 (45.8%)	7 (41.2%)	2 (50.0%)	24 (68.6%)
Smoker[a]	67 (54.0%)	12 (60.0%)	6 (46.2%)	1 (50.0%)	13 (44.8%)
Previous surgery	47 (34.1%)	8 (33.3%)	4 (23.5%)	2 (50.0%)	26 (74.4%)
Laparoscopic approach	38 (27.5%)	5 (20.8%)	2 (11.8%)	1 (25.0%)	1 (2.9%)
Preoperative fistula or abscess	50 (36.2%)	6 (25.0%)	1 (5.9%)	0	17 (48.6%)
History of perianal CD	28 (20.3%)	3 (12.5%)	9 (52.9%)	2 (50.0%)	22 (62.9%)
Postoperative thiopurine or methotrexate	90 (65.2%)	18 (75.0%)	11 (64.7%)	1 (25.0%)	14 (40.0%)
Postoperative biological medication	31 (22.5%)	9 (37.5%)	6 (35.3%)	1 (25.0%)	3 (8.6%)
Median follow-up in years (range)	4.3 (0.3-10.8)	6.4 (0.7-10.5)	5.3 (1.2-10.7)	6.3 (3.5-10.4)	4.2 (0.4-10.5)

CD: Crohn's disease

[a]Data is missing for some patients

Table 23. Binary logistic regression comparing surgical recurrence between groups

Operation type	Surgical recurrence	OR (95% CI)[a]	P-value
Ileocolic resection	14 (10.1%)	—	—
Small bowel resection	6 (25.0%)	2.95 (1.01-8.66)	0.049
Segmental colon resection with colocolic or colorectal anastomosis	7 (41.2%)	6.20 (2.04-18.87)	0.001
Colectomy with ileorectal anastomosis	3 (75.0%)	26.57 (2.59-273.01)	0.006
End-stoma operation	12 (34.3%)	4.62 (1.90-11.26)	0.001

OR: odds ratio; CI: confidence interval

[a]Ileocolic resection is the reference group in the statistical analysis

Table 24. Location of surgical recurrence by primary operation type

Primary operation type	Location of recurrence		
	Small bowel	Ileocolic	Colon and/or rectum
Ileocolic resection	1 (7.2%)	10 (71.4%)	3 (21.4%)
Small bowel resection	5 (83.3%)	1 (16.7%)	0
Segmental colon resection with colocolic or colorectal anastomosis	0	1 (14.3%)	6 (85.7%)
Colectomy with ileorectal anastomosis	0	—	3 (100%)
End ileostomy	4 (80.0%)	—	1 (20.0%)
End colostomy	1 (14.3%)	0	6 (85.7%)

5 DISCUSSION

5.1 PREOPERATIVE MRE (I)

MRE has been increasingly used for the preoperative evaluation of CD patients since it can detect bowel stenosis and extraintestinal lesions such as abscess and fistula (Leyendecker et al. 2009). Another advantage of MRE over other imaging techniques is the lack of exposure to radiation (Malgras et al. 2012).

Our study found an MRE sensitivity of 100.0% for detecting stenosis calculated for each patient, although the sensitivity decreased to 90.0% when we considered the absolute number of stenoses. Consecutive short stenoses found during surgery were interpreted as a single long stenosis during MRE, explaining most of the false-negative stenoses through MRE. It is possible that due to preoperative CD medication inflamed bowel sections recovered and only fibrotic segments remained during surgery.

MRE performed better for excluding abscesses with a specificity of 90.0% than for detecting abscesses with a sensitivity of 80.0%. This finding agrees with previous studies (Fallis et al. 2013, Sinha et al. 2013, Spinelli et al. 2014). One reason for the false-positive identification of abscesses upon MRE might be that some patients received preoperative antibiotic treatment which healed the abscesses before surgery.

Adhesions were responsible for 44.4% of erroneous MRE diagnoses compared to surgical findings. Adhesions represented a confusing factor for false-positive or false-negative diagnoses of fistulas as well as for false-positive diagnoses of stenosis during MRE. Adhesions might pose a problem particularly in patients submitted to multiple operations. However, due to our small patient sample size, we could not perform further statistical analyses between previously operated and non-operated patients. In conclusion, interpreting adhesions as stenoses using MRE may lead to unnecessary surgeries in CD patients with mild obstructive symptoms.

In our study, MRE predicted the operative plan in 87.3% of the patients. A previous study found a similar figure, whereby 90.7% of the patients underwent the surgical plan predicted based on their preoperative MRE (Spinelli et al. 2014). According to our findings, no patient needed conversion to open surgery or the placement of an unplanned stoma due to erroneous preoperative MRE diagnoses. The most serious incorrect diagnoses through MRE in our study were two false-positive stenoses identified in one patient who only had adhesions found during surgery.

5.2 RESECTION MARGINS AND OTHER POSSIBLE RISK FACTORS FOR POSTOPERATIVE COMPLICATIONS (II)

In our study, inflammatory activity at the bowel resection margins was rather common following CD surgery. This may be explained by our practice of resecting only the most affected bowel segments and performing anastomosis not necessarily on grossly disease-free bowel. In total, we found histologically inflamed resection margin in 65.7% of patients, among whom 48.6% had moderate or severe inflammatory activity at the resection margin. Despite of this, we found only a 4.3% anastomotic complication rate following CD surgery. This is somewhat surprising, since CD surgery is believed to be related to higher postoperative complication rates compared with other colorectal surgeries (Uchino et al. 2009). By contrast, our low postoperative complication rate agrees with recent CD studies performed in other referral colorectal units (de Buck van Overstraeten et al. 2017, Lightner et al. 2018). It appears that outcomes following CD surgery have improved in recent years, reflecting the fact that surgery is performed at earlier stages of the disease and also that patients are better optimized preoperatively.

In addition, in our study, inflammatory activity at the bowel resection margin was not a significant risk factor for anastomotic complications, agreeing with previously reported findings (Heuman et al. 1983, Pennington et al. 1980, Post et al. 1991). By contrast, one study described positive resection margin as an independent risk factor for postoperative intra-abdominal complication after ileocolic resection for CD (Shental et al. 2012).

A total of 14 patients (20.0%) developed any postoperative complication in our study, among whom 3 patients (4.3%) had anastomotic complications. We attempted to determine the risk factors for any postoperative complications following CD surgery, but none of the factors we analyzed were significant in the univariate analysis. Our small study sample with a low postoperative complication rate weakened the statistical power of our analysis.

Previous studies reported conflicting results regarding the risk factors for postoperative complications after CD surgery. Preoperative steroid use was identified as a significant risk factor in five previous studies (Alves et al. 2007, El-Hussuna et al. 2012, Post et al. 1991, Tzivanakis et al. 2012, Yamamoto et al. 2000a). But, in agreement with our findings, preoperative steroid use did not associate with CD postoperative complications in three previous studies (de Buck van Overstraeten et al. 2017, Heimann et al. 1985, Iesalnieks et al. 2008). The preoperative use of biological medication increased the risk for anastomotic complications in one study (de Buck van Overstraeten et al. 2017), but similar to our findings did not associate with postoperative complications in two other earlier reports (El-Hussuna et al. 2012, Myrelid et al. 2014). In addition, a low albumin level was not a significant risk factor for surgical complications in two previous

studies (Shental et al. 2012, Tzivanakis et al. 2012), but was significant in two others (Heimann et al. 1985, Yamamoto et al. 2000a). We did not find an increased postoperative complication rate in patients with a low albumin level, although the nutritional status of our patients was quite good and only three patients had a preoperative albumin level below 25 g/l. We considered a low albumin level as any value below normal in our analysis. The presence of an intraoperative abscess represented a risk factor for surgical complications in four studies (Alves et al. 2007, Post et al. 1991, Tzivanakis et al. 2012, Yamamoto et al. 2000a), but was not associated with postoperative complications in three others (Heimann et al. 1985, Iesalnieks et al. 2008, Shental et al. 2012). Finally, an intraoperative fistula was identified as a risk factor in one previous study (Yamamoto et al. 2000a), but did not significantly affect complications in two others (Heimann et al. 1985, Tzivanakis et al. 2012). In our study, neither an abscess nor a fistula emerged as a significant risk factor for postoperative complications following CD surgery. In total, we detected 23 patients with an intraoperative fistula, but only 5 patients with an abscess.

5.3 SURGICAL RECURRENCE (III, IV)

Our study on anastomotic recurrence following primary ileocaecal resection for CD detected a 1.1% anastomotic recurrence rate at one year. Our finding agrees with another recent study that described a 0.6% repeat surgery rate following primary ileocaecal resection (de Buck van Overstraeten et al. 2017). Unlike our findings, the need for anastomotic dilatation was not considered as anastomotic recurrence in that study. Endoscopic dilatation should be the treatment of choice for short anastomotic stenoses in CD, reducing the need for repeat surgery (Navaneethan et al. 2016).

Urgent surgery, postoperative steroid need and stapled side-to-side anastomosis represented risk factors for anastomotic recurrence in our study. Only stapled side-to-side anastomosis remained significant in the multivariate analysis. This is a surprising finding, since previous studies described a lower rate of anastomotic recurrence following side-to-side stapled anastomosis for CD, explained by the fact that side-to-side anastomosis provides a wider anastomotic lumen (Hashemi et al. 1998, Munoz-Juarez et al. 2001, Yamamoto et al. 1999b). However, a meta-analysis comparing side-to-side stapled anastomosis with end-to-end hand-sewn anastomosis revealed no significant difference in surgical recurrence between both anastomotic types (Simillis et al. 2007). In our colorectal unit, end-to-end hand-sewn anastomosis is the treatment of choice with the widening of the small bowel antimesenteric border to guarantee that the anastomosis lumen remains large enough (Figure 7).

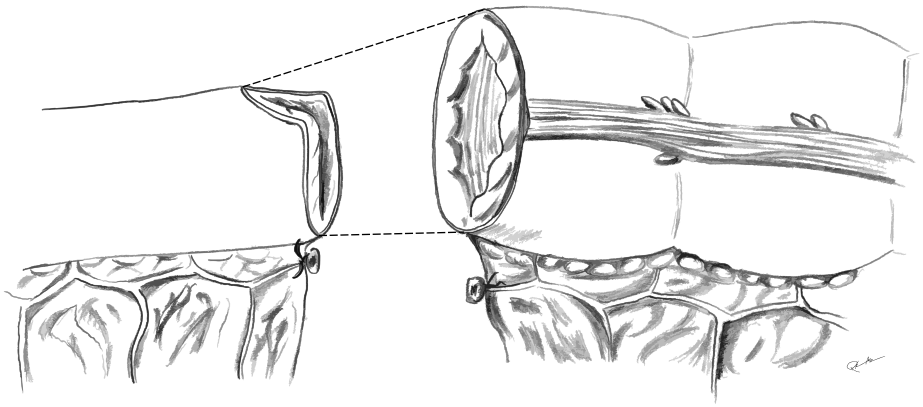

Figure 7 End-to-end hand-sewn ileocolic anastomosis.

Since our study included only three patients with stapled side-to-side anastomoses and our results differed from previous studies, we can only conclude that an end-to-end hand-sewn anastomosis with the widening of the small bowel antimesenteric border following primary ileocaecal resection is a safe choice.

Urgent surgery was previously described as a risk factor for anastomotic recurrence following primary ileocaecal resection (Riss et al. 2014). Postoperative corticosteroid need may already reflect the clinical recurrence of CD; as such, it is expected to relate to an increased rate of surgical anastomotic recurrence. Furthermore, in our study, also the preoperative use of steroid tended towards an increased anastomotic recurrence rate ($p=0.09$). Moreover, the need for steroids may be related to more aggressive CD.

Smoking almost emerged as a significant risk factor for anastomotic recurrence in our study ($p=0.08$). According to previous studies, smokers have a higher risk of postoperative recurrence and CD patients should be encouraged to quit smoking (Reese et al. 2008).

In our study comparing surgical recurrence frequency between different types of bowel resections in CD patients, surgical recurrence was lowest following ileocolic resection. By contrast, a previous study reported a higher recurrence rate following ileocolic resection (Onali et al. 2009). Different from us, that study diagnosed recurrence based on endoscopic and radiological examinations. In our study, only reoperations including a new bowel resection due to recurrent disease were considered as surgical recurrence. Perianal procedures were not included in the analysis.

We found 10.1% of surgical recurrence after ileocolic resection at a median follow-up of 4.3 years. This recurrence is comparable to a previous Austrian study reporting 15.8% of surgical recurrence at a median follow-up of 8.4 years (Riss et al. 2013). Following segmental colon resection with colocolic or colorectal anastomosis, our surgical recurrence was 41.2% at a

median follow-up of 5.3 years. This result also agrees with previous studies reporting surgical recurrence rates between 33% and 47% following segmental colon resection (Bernell et al. 2001, Polle et al. 2005). Moreover, our surgical recurrence after a definitive stoma operation was 34.3% at a median follow-up of 4.2 years, thus agreeing with a recent study describing 38.0% recurrence rate among end stoma patients suffering from CD at a median follow-up of 10 years (Koriche et al. 2017).

According to our findings, postoperative follow-up is important after all types of bowel resections; our results suggest the need for more aggressive postoperative medication following resections different from the ileocolic type. A previous study evaluating outcomes among CD patients with a definitive stoma operation indicates postoperative anti-TNF alpha treatment for all end stoma patients receiving a colostomy or with a history of anoperineal lesions, since both factors associate with surgical recurrence (Koriche et al. 2017).

In our study, the reoperation location for surgical recurrence correlated with the primary operation location. This is in line with previous studies demonstrating that the anatomic location of CD tends to remain stable during the course of the disease (Fichera et al. 2006, Louis et al. 2001). However, an interesting finding from our study suggests that even patients without a previous history of small bowel CD may develop recurrence in the small bowel following colectomy or proctocolectomy combined with end ileostomy.

5.4 LIMITATIONS OF THE STUDY

All the four studies included in this dissertation were retrospective. This particular approach carries several limitations, specifically a potential selection bias for patients, the unavailability of some data and a certain inherent imprecision involved in data acquisition regarding the fact that data are not systematically registered. The small patient sample size limits the strength of our findings, particularly in studies I and II. Another limitation of study I was the heterogeneity of protocols concerning the preoperative MRE. The low occurrence of anastomotic complications limits the statistical power of study II while the small number of patients undergoing stapled side-to-side ileocolic anastomosis represents a limitation of study III. In study IV, the small number of patients undergoing non-ileocolic resections restricted the possibility of subgroup analyses.

6 CONCLUSIONS

I
Our results demonstrate that preoperative MRE is useful for identifying lesions and predicting the surgical plan in the majority of CD patients. However, MRE differential diagnosis between intra-abdominal adhesions and Crohn's fistulas or short-segment stenosis remains challenging.

II
We conclude that bowel sparing surgery with resection of only the most affected bowel segments should be performed in CD patients since inflammatory activity at the bowel resection margins does not increase postoperative anastomotic complications. Furthermore, the use of preoperative CD medications and the presence of intraoperative fistula do not seem to be associated with increased postoperative complications following CD surgery.

III
In the present study, urgent surgery, postoperative steroid need and stapled side-to-side anastomoses were risk factors for anastomotic recurrence following primary ileocaecal resection. Hand-sewn anastomosis with the widening of the small bowel antimesenteric border represents a safe choice following ileocolic resection for CD.

IV
We conclude that surgical recurrence in CD patients is lower following ileocolic resections compared to other types of bowel resections. Surgical recurrence in CD typically maintains the disease location of the primary operation. After an end stoma operation, surgical recurrence in CD patients is still high, whereby one-third of patients receiving an end stoma will need a new bowel resection within five years.

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9 ORIGINAL PUBLICATIONS