Surgery and medical therapy in Crohn’s disease
improving treatment strategies

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Rising prevalence and burden of disease of inflammatory bowel disease in a population-based cohort in The Netherlands


Abstract

Background
Reported epidemiology and phenotype distributions vary widely and disease burden of inflammatory bowel disease (IBD) is poorly described. Our aim was to establish these features in a population-based cohort covering 319,976 inhabitants. Furthermore, differences between tertiary referral and peripheral hospital patients were quantified.

Methods
IBD patients in the adherence area of three peripheral hospitals (2004–2012) were included. Medical and surgical treatment data were obtained. Quality of life and disease activity were evaluated. An outpatient cohort from a tertiary referral centre was accrued.

Results
A total of 1461 patients were included: 761 (52.1%) with ulcerative colitis (UC), 579 (39.5%) with Crohn’s disease (CD) and 121 (8.3%) with IBD-unspecified. Point prevalence of IBD was 432.1 per 100,000 inhabitants in 2010, which increased significantly over time, P-value of less than 0.0001. The mean annual incidence was 17.2 for UC, 10.5 for CD and 2.2 for IBD-unspecified. Tertiary referral Crohn's patients used thiopurines and biological therapy and underwent surgery significantly more often than patients in peripheral hospitals (P<0.0001). Disease activity correlated negatively with quality of life (P<0.0001) in UC and CD.

Conclusion
The prevalence of IBD is still increasing. Burden of disease was significantly more severe, mainly in Crohn's patients, in the referral centre, highlighting the importance of population-based studies to accurately describe phenotype distribution and disease burden.
Chapter 2

Laparoscopic ileocecal resection versus infliximab treatment of distal ileitis in Crohn's disease: a randomised multicenter trial (LIR!C-trial)
Submitted.

Abstract

Introduction
Treatment of patients with ileocecal Crohn's disease failing conventional therapy is commonly upscaled to biologics. However, surgery can offer excellent short- and long-term results. We aimed to compare laparoscopic ileocecal resection with infliximab in their ability to improve health-related quality-of-life.

Methods
In this multicenter, randomized controlled trial, adult patients with non-stricturing, ileocecal Crohn's disease, failing conventional therapy were randomized to laparoscopic ileocecal resection or infliximab therapy. Patients with diseased terminal ileum >40 cm, or abdominal abscesses were excluded. Primary outcome was disease-specific quality-of-life on the Inflammatory Bowel Disease Questionnaire (IBDQ) at 12 months.

Results
Seventy-three patients were allocated to resection and 70 to infliximab. Corrected for baseline difference, the mean IBDQ score at 12 months was 178.1 in the resection versus 172.0 in the infliximab group, a mean difference (MD) of 6.1 points (95%CI: -4.2-16.4; p=0.25). The generic quality-of-life Short Form-36 physical component summary score was significantly higher in the resection group from 6 months onwards (12 months: MD 3.1, 95%CI: 4.2-6.0; p=0.04). Scheduled and unscheduled readmissions
were similar. Intervention related Clavien Dindo IIIa complications occurred in 4 patients in the resection group. Treatment related serious adverse events occurred in 2 patients receiving infliximab. During a median follow-up of 4 years, 26 (37%) patients in the infliximab group underwent resection, while 12 (15%) patients in the resection group received anti-TNF.

Conclusion
With regard to restoring quality of life, laparoscopic resection in patients with limited, non-stricturing, ileocecal Crohn’s disease failing conventional therapy is at least as good as therapy with infliximab.

(Dutch Trial Registry, number NTR1150; EudraCT number 2007-005042-20)
Chapter 3

Abdominal abscess in Crohn’s disease: multidisciplinary management
E.J. de Groof, C.F. Carbonnel, C.J. Buskens, W.A. Bemelman


Abstract

Crohn’s disease (CD) is characterised by full-thickness inflammation of the bowel. For this reason, perforating complications such as intra-abdominal abscesses or fistulas are common. A concomitant intra-abdominal abscess with active CD of the small bowel is a challenging dilemma for gastroenterologists and surgeons. Since there is active and severe disease, this should be treated with immunosuppressive drugs. However, in the presence of an intra-abdominal abscess, immunosuppression can be dangerous. There are several treatment options for intra-abdominal abscesses in CD. Nowadays, the first-line treatment is antibiotic therapy with or without percutaneous drainage. Historically, patients were treated with surgical drainage. With the development of percutaneous drainage, treatment shifted to a more nonsurgical approach. Success rates for percutaneous drainage in the literature vary from 74 to 100%, and it is considered to be a relatively safe procedure. It has been reported that surgery can be avoided after successful percutaneous drainage in a variable number of patients (14-85%). If sepsis is controlled, CD medication should be started to prevent recurrence. It is important to monitor the effect upon CD lesions to avoid further perforating complications. Finally, an undrainable or small abscess can be treated with antibiotics alone, although high recurrence rates have been described with this approach. Patients with a concomitant stenosis, an enterocutaneous fistula or refractory active disease are likely to require surgery. Percutaneous drainage in combination with delayed surgery is useful to improve the patient’s condition prior to surgery and is associated with less morbidity, a lower stoma rate and more limited resection. In conclusion, when feasible, percutaneous drainage and antibiotics should be the treatment of choice in patients with an intra-abdominal abscess in CD. If surgery is inevitable, this must be delayed to reduce postoperative septic complications and high stoma rates.
Chapter 4

The association between intensified medical treatment, time to surgery and ileocolic specimen length in Crohn’s disease

E.J. de Groof, T.J. Gardenbroek, C.J. Buskens, P.J. Tanis, C.IJ. Ponsioen, G.R.A.M. D'Haens, W.A. Bemelman

"Colorectal Disease. November 2016."

Abstract

Background

During the last decade, treatment protocols have changed for patients with ileocolic Crohn’s disease. Anti-TNF has become part of standard medical treatment, usually in a step-up approach. The aim was to analyse if improved medical treatment has resulted in more limited ileocolic resections and a longer interval between diagnosis and surgery.

Methods

Patients undergoing ileocolic resection for Crohn’s disease were included (1999-2014). Patient characteristics were compared to the results of a population-based study (between 2004-2010) previously performed in the catchment area of the present tertiary referral centre. Time trends were analysed using Cochrane Armitage trend, Spearman’s correlation coefficient and linear regression.

Results

In total, 195 patients undergoing ileocolic resection were included. Patient characteristics were not significantly different from the background cohort, confirming a representative study group. 63 patients were male (32.3%, median age at surgery 30.0 years interquartile range 23.0-40.0). Anti-TNF and immunomodulator use prior to surgery increased significantly during the study period ($\chi^2=49.1, p<0.001$). Over the years, a significant increase in time from diagnosis to operation was found (median 39.0 months (interquartile range 12.0-86.0); rho 0.175, $p=0.014$). The length of resected ileum did not change significantly (median 20.0cm, interquartile range 12.0-30.0, rho -0.107, $p=0.143$). The number of fistulas or postoperative complications that needed re-intervention were not significantly different between the groups with or without anti-TNF.

Conclusion
This study demonstrated that over time patients with ileocolic Crohn's disease who eventually underwent ileocolic resection have been treated more intensively medically, however this did not result in reduced specimen size.
Chapter 5

**Single port laparoscopic ileocecal resection for Crohn's disease: a multicentre comparison with multi-port laparoscopy**


*Submitted.*

**Abstract**

**Background and aims:** The feasibility of single port (SP) ileocecal resection (ICR) in Crohn’s disease (CD) has previously been reported. However, large studies comparing SP and multi-port (MP) laparoscopic surgery are not available. The aim of our study was to compare short-term postoperative outcomes of SP and MP laparoscopic ICR for CD particularly with respect to postoperative pain scores and analgesia requirement.

**Methods:** Consecutive patients undergoing SP or MP ICR for CD were retrospectively selected from prospectively maintained databases in three tertiary referral centres (February 1999-October 2014). Baseline characteristics (age, sex, body mass index and indication for surgery) were collected and compared between the two groups (SP and MP). Primary endpoints were postoperative pain scores, analgesia requirements and short-term postoperative outcomes.

**Results:** SP ICR (n=101) and MP ICR (n=156) patients were included in the study. VAS scores were significantly lower after SP ICR on postoperative day (POD) 1 and 2 (p=0.016 and p=0.040, respectively). Analgesia requirement was significantly reduced on POD 2 in the SP group compared to the MP group (p=0.007). Duration of surgery, conversion to open surgery and stoma rates were comparable between the two groups. No significant differences were observed in postoperative complication rates, postoperative food intake, length of stay and readmissions.

**Conclusions:** SP ileocolic resection for CD is associated with less pain and analgesia requirements compared to MP ICR.
Chapter 6

The role of single port surgery in Crohn’s disease: a review of current evidence
E.J. de Groof, C.J. Buskens, W.A. Bemelman


Abstract

The majority of patients with Crohn’s disease (CD) and up to 35% of patients with ulcerative colitis (UC) will ultimately require surgery during the course of their disease. Over the past few years surgical techniques and experience in minimal invasive surgery have evolved resulting in single incision laparoscopic surgery. The aim of this approach is to diminish the surgical trauma by reducing the number of incision sites.

This review discusses the benefits and disadvantages of single port surgery in various procedures in patients with inflammatory bowel disease (IBD). Short-term postoperative results, functional outcome and costs available in the literature will be discussed.

Single port surgery in IBD has several benefits when compared to multi-port laparoscopic surgery. By using fewer incisions a potential reduction of postoperative pain with less morphine use can be accomplished. In addition, accelerated postoperative recovery can result in a shorter hospital stay. Furthermore, a superior cosmesis can be reached with placement of the port at the future ostomy site or at the umbilicus.

Literature on single port surgery in IBD consists mainly of case series and a few matched case series. These studies demonstrated that single port surgery seems to be a safe and feasible approach for the surgical treatment of IBD patients.
Chapter 7

Is the conventional randomised controlled trial still the holy grail? Lessons learned from the LIRIC trial
E.J. de Groof, C.J. Buskens, C.Y. Ponsioen, W.A. Bemelman
Submitted.

Abstract

Crohn’s disease (CD) is a chronic disease often located in the terminal ileum usually affecting patients at a young age. The traditional pyramid step up approach has not been changed for years, with surgery generally being considered as last resort when all medical options failed.

Throughout the years both medical treatment protocols and surgical techniques have improved. New approaches have preferably been analysed in RCTs, as this design is considered the gold standard for generating the highest level of evidence. Anti-TNF and laparoscopic surgery have been integrated in current guidelines after superiority was demonstrated in large RCTs. Almost a decade ago, designing the first trial directly comparing medical to surgical treatment for terminal ileitis, there was no doubt about the most optimal design. Recently, the LIRIC trial (Laparoscopic ileoceleal resection versus Infliximab for recurrent Crohn’s disease of the terminal ileum, with primary outcome parameter quality of life as measured with the Inflammatory Bowel Disease Questionnaire) has been finished after 7.5 years. Looking back on performing this monumental trial, there are several issues to be discussed. Surgery and medical treatment are difficult to compare, as both treatment modalities are associated with significantly different morbidities. Many patients have a distinct preference, which can lead to bias and limited external generalizability. Patient (and physician) preferences especially influence trials comparing quality of life. Currently, there is some suggestion that the RCT design might not be the most ideal design to compare complex interventions.

Here, we describe lessons learned from the LIRIC study. The patient group refusing randomisation will be compared to the patients included in the study to analyse how patient’s preferences might have influenced external trial validity. Finally, we will discuss the pitfalls encountered, and explore some interesting alternatives (e.g. the patient preference RCT design), to optimize future comparable trials.
Chapter 8

Complex fistulas and advanced soft tissue techniques
E.J. de Groof, C.J. Buskens, W.A. Bemelman


Abstract

Perianal fistulas are categorized as “complex” under the following conditions: a high tract passing the upper two third of the external sphincter, presence of multiple fistula tracts, rectovaginal fistulas, previous local irradiation and association with the presence of an anorectal stricture or Crohn’s disease. Treatment of complex fistulas can be challenging and carries a high risk of poor wound healing, recurrences and incontinence. Therefore a detailed understanding of perianal anatomy, knowledge of the extent of the disease and its relation to the various structures is required for proper management.

This chapter describes the technical approach of various advanced soft tissue techniques for complex fistula repair (i.e. the endorectal mucosal advancement flap, the anocutaneous advancement flap and the Martius flap) and discusses its indications, advantages and associated complications.

The reported success rates of endorectal advancement flaps in the literature is variable, but generally better for cryptoglandular (24-100%) compared to Crohn’s (33-92%) fistulas. The success rate in patients with Crohn’s disease appears to be slightly better under anti-TNF therapy. Sphincteroplasty following complete fistulotomy (episioproctotomy) can be an appropriate approach in a selected patient group.

In conclusion, treatment of complex perianal fistulas is challenging, and the advanced soft tissue techniques are an important option within the armamentarium of techniques that can be applied to treat this condition in a patient-tailored treatment approach.
Chapter 9

Treatment of perianal fistulas in Crohn’s disease: a systematic review and meta-analysis comparing seton drainage and anti-TNF treatment

Abstract

Aim
The introduction of anti-tumour necrosis factor (anti-TNF; infliximab and adalimumab) has changed the management of Crohn’s perianal fistula from almost exclusively surgical treatment to one with a much larger emphasis on medical therapy. The aim of this systematic review was to provide an overview of the success rates of setons and anti-TNF for Crohn’s perianal fistula.

Method
Studies evaluating the effect of setons and anti-TNF on Crohn’s perianal fistula were included. Studies assessing perianal fistula in children, rectovaginal and rectourinary fistulae were excluded. The primary end-point was the fistula closure rate. Partial closure and recurrence rates were secondary endpoints.

Results
Ten studies on seton drainage were included (n = 305). Complete closure varied from 13.6% to 100% and recurrence from 0% to 83.3%. In 34 anti-TNF studies (n = 1449), complete closure varied from 16.7% and 93% (partial closure 8.0–91.2%) and recurrence from 8.0% to 40.9%. Four randomized controlled trials (n = 1028) comparing anti-TNF with placebo showed no significant difference in complete or partial closure in meta-analysis (risk difference 0.12, 95% CI –0.06 to 0.30 and 0.09, 95% CI –0.23 to 0.41, respectively). Subgroup analysis (n = 241) showed a significant advantage for complete fistula closure with anti-TNF in two trials with follow-up > 4 weeks (46% vs 13%, P = 0.003 and 30% vs 13%, P = 0.03). Of four included cohort studies, two revealed a significant difference in response in favour of combined treatment (P = 0.001 and P = 0.014).

Conclusion
Closure and recurrence rates after seton drainage as well as anti-TNF vary widely. Despite a large number of studies, no conclusions can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, immunomodulators and anti-TNF may be beneficial in achieving perianal fistula closure.
Chapter 10

Systematic review of evidence and consensus on perianal fistulas; an analysis of national and international guidelines
E.J. de Groof, V.N. Cabral, C.J. Buskens, D.G. Morton, D. Hahnloser, W.A. Bemelman

Abstract

Aim
Treatment of perianal fistula has evolved with the introduction of new techniques and biologicals in Crohn's disease (CD). Several guidelines are available worldwide, but many recommendations are controversial or lack high-quality evidence. The aim of this work was to provide an overview of the current available national and international guidelines for perianal fistula and to analyse areas of consensus and areas of conflicting recommendations, thereby identifying topics and questions for future research.

Method
MEDLINE, EMBASE and PubMed were systematically searched for guidelines on perianal fistula. Inclusion was limited to papers in English less than 10 years old. The included topics were classified as having consensus (unanimous recommendations in at least two-thirds of the guidelines) or controversy (fewer than three guidelines commenting on the topic or no consensus) between guidelines. The highest level of evidence was scored as sufficient (level 3a or higher of the Oxford Centre for Evidence-based Medicine Levels of Evidence 2009), or insufficient.

Results
Twelve guidelines were included and topics with recommendations were compared. Overall, consensus was present in 15 topics, whereas six topics were rated as controversial. Evidence levels varied from strong to lack of evidence.

Conclusion
Evidence on the diagnosis and treatment of perianal fistulae (cryptoglandular or related to CD) ranged from nonexistent to strong, regardless of consensus. The most relevant research questions were identified and proposed as topics for future research.
Multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA): study protocol of a randomised controlled trial


Trials. August 2015.

Abstract

Background

Currently there is no guideline for the treatment of patients with Crohn's disease and high perianal fistulas. Most patients receive anti-TNF medication, but no long-term results of this expensive medication have been described, nor has its efficiency been compared to surgical strategies. With this study, we hope to provide treatment consensus for daily clinical practice with reduction in costs.

Methods/Design

This is a multicentre, randomised controlled trial. Patients with Crohn's disease who are over 18 years of age, with newly diagnosed or recurrent active high perianal fistulas, with one internal opening and no anti-TNF usage in the past three months will be considered. Patients with proctitis, recto-vaginal fistulas or anal stenosis will be excluded. Prior to randomisation, an MRI and ileocolonoscopy are required. All treatment will start with seton placement and a course of antibiotics. Patients will then be randomised to: (1) chronic seton drainage (with oral 6-mercaptopurine (6MP)) for one year, (2) anti-TNF medication (with 6MP) for one year (seton removal after six weeks) or (3) advancement plasty after eight weeks of seton drainage (under four months anti-TNF and 6MP for one year). The primary outcome parameter is the number of patients needing fistula-related re-intervention(s). Secondary outcomes are the number of patients with closed fistulas (based on an evaluated MRI score) after 18 months, disease activity, quality of life and costs.
Discussion

The PISA trial is a multicentre, randomised controlled trial of patients with Crohn’s disease and high perianal fistulas. With the comparison of three generally accepted treatment strategies, we will be able to comment on the efficiency of the various treatment strategies, with respect to several long-term outcome parameters.

Trial registration

Nederlands Trial Register identifier: NTR4137 (registered on 23 August 2013).
Chapter 12

The role of mesorectal macrophages in complications after rectal resection in inflammatory bowel disease
E.J. de Groof, M.E. Wildenberg, O. van Ruler, J.R. de Bruyn, P.J. Tanis, G.R.A.M. D’Haens, G.R. van den Brink, W.A. Bemelman, C.J. Buskens

Submitted.

ABSTRACT

Objective
Aim was to compare postoperative outcome of close rectal dissection and total mesorectal excision in ulcerative colitis (UC) and Crohn’s disease (CD) patients. Since it has been suggested that mesenteric adipose tissue is involved in CD, immune cell populations in mesorectal tissue samples were analysed.

Summary background data
In nonrestorative proctectomy for inflammatory bowel disease, close rectal dissection with preservation of mesorectum might result in lower risks of infectious complications related to reduced dead space compared to total mesorectal excision.

Design
Perineal complications and healing were assessed in 62 consecutive patients. Rectal mesentery of 11 patients was cultured and walk-out cells were analysed. Wound healing macrophages were phenotyped by regulatory markers (CD14, CD206). Immunofluorescent double staining was performed.

Results
In UC (n=17), less perineal complications (17.6% versus 51.1%; p=0.022) and higher healing rates (88.2% versus 60.0%; p=0.038) were observed compared to CD, without significant differences between techniques. In CD (n=45), perineal complications were more frequently seen after close rectal dissection compared to total mesorectal excision (57.1% versus 20.0%; p=0.035), with lower healing rates (51.4% versus 90.0%; p=0.034). Analysis of rectal mesentery showed enhanced
infiltration of myeloid CD14+ cells in CD. These cells showed significantly less wound healing associated marker CD206 expression.

**Conclusion**

Highest perineal complication and lowest healing rates were observed after close rectal dissection in CD, compared to total mesorectal excision for CD or UC independent of surgical technique. This was associated with increased pro-inflammatory macrophages in mesorectum in CD. Therefore, total mesorectal excision seems to be the preferred technique in CD.
Salvage surgery for pelvic septic complications following colorectal surgery most often dictates radical removal of pelvic bowel structures with a definitive ostomy. Patients undergoing redo surgery are prone for developing recurrent pelvic infectious complications. Contaminated pelvic dead space after salvage surgery may progress into a sinus with persistent abscesses and the risk of secondary complications. Previous research suggests that obliterating the pelvic space with an omental plasty after abdominoperineal resection for rectal cancer results in enhanced perineal wound healing and a decrease in sinus formation due to angiogenesis and enhancement of inflammatory response. In the absence of omentum, and considering the morbidity related to autologous tissue flaps, obliteration of pelvic dead space with viable mesentery of a bowel segment that has to be removed as part of salvage procedures seems to be a valuable alternative. Although one patient had a persistent pelvic abscess, complete pelvic sinus healing was accomplished in all four patients.

More research is necessary to understand the physiologic immune responses of mesentery, which may be of additional value to control infectious complications besides anatomical filling itself. Availability of mesenteric tissue of adequate length and volume has to be assessed in every single patient, but might be preferred over myocutaneous flap reconstructions.
THESIS SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Part I - Epidemiology

In chapter 1, we reported the current population-based epidemiology in a cohort of 1,461 patients. An increase in prevalence of inflammatory bowel disease (IBD) within the 6-year study period was observed while the incidence rates remained stable. This could not be explained by decreasing mortality in the IBD cohort during the study period or shifts in the age distribution of the population due to moving of individuals. Hence, the most likely explanation is a steady incidence and negligible mortality from the disease itself and in general in IBD patients because of the age distribution. Compared to previous epidemiological data from The Netherlands, current incidence rates of ulcerative colitis (UC) and Crohn’s disease (CD) are considerably higher than the observed incidence rates in the past decades. It is generally assumed that tertiary referral patients will have a more severe phenotype and burden of disease as compared to patients in teaching hospitals. CD patients treated in the tertiary referral centre were significantly more often treated with thiopurines and anti-TNF and underwent perianal surgery more frequently when compared to patients treated in a teaching hospital. This also applied to proctocolectomies in UC patients.

Part II – Ileocecal Crohn’s disease

Chapter 2 consists of the The LIRIC trial comparing laparoscopic ileocecal resection with infliximab treatment for terminal ileitis in CD. This study showed that at 12 months laparoscopic ileocecal resection was at least as effective as infliximab in improving QoL. Although superiority of the surgical strategy in terms of IBDQ could not be demonstrated (MD 6.1, 95% confidence interval -4.2 to 16.4, p=0.245), resection is not inferior to infliximab treatment with regard to regaining QoL, given the lower bound of the confidence interval of -4.2 for the difference in IBDQ at 12 months. Additionally, the physical subscale of the more generic SF-36 was significantly better in the resection compared to the infliximab group at 6 and 9 months. Although disease specific quality of life is generally considered to be the best instrument to document specific changes in disease associated symptoms, the majority of patients was in remission at the end of this study. Hence, in patients with ileocecal CD failing conventional therapy resection should be offered as a good alternative to starting infliximab.

Chapter 3 reviewed treatment options for perforating complications as intra abdominal abscesses or fistulas in CD patients. Percutaneous drainage and antibiotics should be the treatment of choice in patients with a (‘drainable’) intra abdominal abscess in CD. If sepsis is controlled medication should be started with monitoring of the effect. Today, there is a role for surgery in these patients in case of failure of percutaneous drainage and antibiotics. In addition, surgery is indicated if there is a stenosis,
fistula or refractory active disease. Nevertheless, if possible, surgery should rather be delayed until
local sepsis is resolved.

During the last decades treatment protocols have changed for patients with ileocolic Crohn's disease.
Anti-TNF has become part of standard medical treatment, usually in a step-up approach. In chapter 4
we demonstrated that over time patients were treated more intensively with different types of drug
combinations since the introduction of anti-TNF. As a result, the time interval from initial diagnosis to
surgery increased. The optimization of medical treatment protocols did not result in more limited
resections throughout the years as is sometimes argued as one of the benefits of extensive
treatment.

The feasibility of single port ileocecal resection in CD has previously been reported. However, large
studies comparing SP and multi port laparoscopic surgery are not available. In chapter 5 we showed
in an international multicentre study that visual analog scale scores were significantly lower after
single port ileocecal resection on postoperative day 1 and 2. Additionally, analgesia requirement was
significantly reduced on postoperative day 2 in the single port group compared to the multi port
group. Duration of surgery, conversion to open surgery and stoma rates were comparable between
the two groups and no significant differences were observed in postoperative complication rates,
postoperative food intake, length of stay and readmissions.

Operative techniques have evolved rapidly over the past decades. There is still limited literature on
single port laparoscopic surgery in IBD. However several (matched) case series demonstrated that
single port laparoscopic surgery is a feasible and safe approach in IBD. These studies are reviewed in
chapter 6. There are several beneficial aspects with single port laparoscopy with respect to
postoperative pain, morphine use, length of hospital stay and (functional) long term outcomes, when
compared to conventional multi-port laparoscopic surgery. Promising indications are ileocolic
resections, (subtotal or procto) colectomy if the specimen is not too bulky. The transanal minimally
invasive surgery (TAMIS) completion proctectomy in Crohn's or completion proctectomy with an
ileoanal pouch are likewise promising developments that need to be studied further.

In Chapter 7 we described lessons learned from the LIRIC study. During the last decades, treatment
protocols have changed for patients with ileocecal CD. New medical therapies were introduced and
surgical techniques improved. Discussing the most optimal treatment approach for terminal ileitis,
the LIRIC trial was designed almost a decade ago. After 7.5 years, the results will be published soon.
Although this RCT will probably change current guidelines, there are also several drawbacks in terms
of external validity to any trial taking this long to complete accrual. An interesting alternative to the conventional RCT could be the patient’s preference RCT design, where both randomised and non-randomised patients participate, which benefits the external validity of the study results.

Part III – Perianal Crohn’s disease

Chapter 8 reviews advanced soft tissue techniques for complex fistulas. Treatment of complex fistulas is challenging and carries a high risk of poor wound healing and continence impairment due to iatrogenic injury of the sphincter complex. Proper management requires a detailed understanding of perianal anatomy, knowledge of the extent of the disease and its relation to the various structures.

In all sphincter-sparing advanced soft tissue flap techniques, controlling local sepsis before any attempt at definitive repair is essential. Therefore, seton drainage prior to advancement flap repair is of significant importance. Furthermore, the creation of a broad based, well vascularised, tension free flap, de-epithelialization of the fistula tract and excision of the internal opening of the tract are essential steps in these type of procedures.

Sphincteroplasty can be an appropriate approach in some cases, especially when preoperative incontinence is present. However patient selection should be prudent, and careful description and detailed informed consent in these advanced techniques is critical.

Chapter 9 consists of a systematic review and meta-analysis on the effect of seton drainage and/or anti-TNF on perianal fistula partial and complete closure and recurrence. Based on the results of this systematic literature review it can be concluded that closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely. Despite a large number of studies analysing the results of both treatment options, no conclusion can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, an immunomodulator and anti-TNF may be beneficial in achieving perianal fistula closure.

Treatment of perianal fistula has evolved with the introduction of new techniques and biologicals in CD. Worldwide several guidelines are available, but many recommendations are controversial or lack high quality evidence. In chapter 10 we provided an overview of the current available national and international guidelines for perianal fistula and analysed areas of consensus and areas of conflicting recommendations, thereby identifying topics and questions for future research. The included topics were classified as having consensus (unanimous recommendations in at least two thirds of the guidelines) or controversy (less than three guidelines commenting on topic or no consensus) between guidelines. The highest level of evidence was scored as sufficient (Oxford level of Evidence
2009 3a or higher) or insufficient. Twelve guidelines were included and topics with recommendations were compared. Overall, consensus was present in 15 topics, whereas six topics were rated as controversy. Evidence levels varied from strong to lack of evidence. Therefore, evidence on the diagnosis and treatment of perianal fistulas (cryptoglandular or related to CD) ranged from nonexistent to strong, regardless of consensus.

Currently there is no guideline for the treatment of Crohn’s patients with high perianal fistulas. Most patients receive anti-TNF medication, but no long-term results of this expensive medication have been described, nor has its efficiency been compared to surgical strategies. With this study we hope to provide treatment consensus for daily clinical practice with reduction in costs. The PISA-trial described in chapter 11 is a multicentre randomised controlled trial in patients with high perianal fistulas in CD. Patients will then be randomised to (I) chronic seton drainage (with 6MP) for one year, to (II) anti-TNF medication (with 6MP) for one year (seton removal after 6 weeks) or to (III) surgical closure via e.g. an advancement plasty after 8 weeks seton drainage (under 4 months anti-TNF and 6MP for one year). The primary outcome parameter is the number of patients needing fistula-related re-intervention(s). Secondary outcomes are the number of patients with closed fistulas (based on an evaluated MRI-score) after 18 months, disease activity, QoL and costs. With the comparison of three generally accepted treatment strategies we will be able to comment on the efficiency of the various treatment strategies with respect to several long-term outcome parameters.

Although, it could be hypothesised that close rectal dissection would reduce complications in IBD patients by leaving the rectal mesentery in situ, we showed the contrary in chapter 12. Perineal complications and impaired perineal wound healing occurred significantly more frequent in CD patients when compared to UC patients, especially after close rectal dissection. Perineal complications in CD patients were almost three fold after close rectal dissection when compared to total mesorectal excision. No differences between the two surgical techniques were observed in UC regarding perineal complication and healing rates.

More infectious complications after preserving the mesorectum in CD may be explained by the increased pro-inflammatory myeloid cell population with decreased wound healing macrophages, irrespective of the presence of a defunctioning stoma. Therefore, the pro-inflammatory phenotype seems not to be a mere reflection of the inflammatory status of the intestine. These findings suggest that excision of the mesorectum at time of proctectomy is of crucial importance in CD.
Salvage surgery for pelvic septic complications following colorectal surgery most often dictates radical removal of pelvic bowel structures with a definitive ostomy. Patients undergoing redo surgery are prone for developing recurrent pelvic infectious complications. Contaminated pelvic dead space after salvage surgery may progress into a sinus with persistent abscesses and the risk of secondary complications. Previous research suggests that obliterating the pelvic space with an omental plasty after abdominoperineal resection for rectal cancer results in enhanced perineal wound healing and a decrease in sinus formation due to angiogenesis and enhancement of inflammatory response. In chapter 13 a novel technique is described. In the absence of omentum, and considering the morbidity related to autologous tissue flaps, obliteration of pelvic dead space with viable mesentery of a bowel segment that has to be removed as part of salvage procedures seems to be a valuable alternative. Although one patient had a persistent pelvic abscess, complete pelvic sinus healing was accomplished in all four patients.

More research is necessary to understand the physiologic immune responses of mesentery, which may be of additional value to control infectious complications besides anatomical filling itself. Availability of mesenteric tissue of adequate length and volume has to be assessed in every single patient, but might be preferred over myocutaneous flap reconstructions.

FUTURE PERSPECTIVES

In this thesis we have focused on medical and surgical treatment strategies for Crohn’s disease (CD). We have demonstrated that the currently worldwide used step up medical protocol, with surgical resection considered as a last resort option, is not an universal truth. In contrast, the results of the LIRIC study showed that laparoscopic ileocecal resection was a cost-effective non-inferior alternative treatment option to infliximab, with respect to specific quality of life (QoL), and improved generic QoL in patients following resection several months after start of treatment. Since the primary endpoint of this study was set at one year, it is expected that long-term results will be even more promising, with more pronounced differences in QoL when comparing surgical results to chronic medical treatment.

These results will establish a new place for surgical resection in current guidelines of terminal ileitis treatment and it is time to extend this research to the newly diagnosed patients. Currently, the LIRIC II study is being set up for these patients, where we hypothesize that early surgery followed by tight follow up and early treatment of recurrent inflammation is the preferred strategy for limited newly diagnosed CD of the terminal ileum with respect to QoL. The design of this subsequent study will be optimized taking into account the largest drawback of LIRIC I, which was the slow accrual rate.
As it took 7.5 years to complete inclusions, it can be concluded that many patients were not randomized in this randomized controlled trial (RCT), resulting in reduced external validity. To ensure that all eligible patients will be included in LIRIC II, a multicentre, comprehensive cohort design (patient-preference or 'Brewin-Bradley design') has been chosen. The patient-preference design is suggested to be a more suitable approach for studies comparing significantly different strategies, with QoL as the primary outcome parameter. With this design, all Crohn's patients with newly diagnosed terminal ileitis can be included, resulting in a dynamic study with generally applicable results. Since the patient is allowed to make its own choice after extensive counselling, it can be expected that the willingness to participate will be high. The primary outcome parameter will again be QoL as measured with the Inflammatory Bowel Disease Questionnaire (IBDQ), as patient reported outcome parameters remain the most important indicator in chronic diseases.

To optimize data collection and ensure patient empowering, we will use the MyIBDcoach app. This is expected to have a positive effect on patient satisfaction and compliance as well. Patients will feel more engaged in the research project, and can be kept up-to-date by providing updates in the MyIBDcoach about the number of inclusions and participating centers, changes in the protocol, and the final results. Furthermore, strict monitoring of the disease warrants patient safety and makes it possible for the Crohn en Colitis Ulciosa Vereniging Nederland (CCUVN) to collect data from the system, which can be used for future studies.

Optimizing the surgical technique for CD patients, will also be part of future research plans to improve clinical outcome. It has been known for a long time that pathological changes within the enhanced mesenteric tissue (creeping fat) are associated with disease activity. So far this has been largely ignored and the general concept is to perform close bowel resections in this benign disease. However, we have demonstrated that in Crohn's mesentery the balance between CD3+ T-cells and CD14+ myeloid cells is skewed significantly towards the myeloid population, with an altered pro-inflammatory phenotype of macrophages irrespective of a defunctioning stoma. This suggests a mesentery specific rather than a reactive inflammation induced phenotype. As the affected mesentery is correlated to ongoing disease activity and disturbed perineal healing after proctectomy, it could also be hypothesized that leaving diseased mesentery in situ after ileocecal resection could result in increased recurrences. We are currently completing a proof of principle clinical study by performing surgical excision of the mesorectum in ten CD patients suffering from a persistent presacral abscess after proctectomy, thus providing the evidence required to drastically change the current surgical management. In another follow-up study, we will use the macrophage phenotype to determine the extent of mesenteric alterations. If a gradient does occur, with increasing proportions of regulatory macrophages towards the non-affected resection margin and central vasculature, the
next step will be to analyse if endoscopic and surgical recurrences of Crohn’s disease can be reduced by mesenteric-based surgical strategies. Further research should assess if there is indeed a cut-off point where more extensive mesenteric excision no longer outweighs the disadvantages of tissue damage.

Finally, treatment options for perianal fistulas should be optimized as well. There should be a surgical algorithm of the treatment options for the various types of fistulas. A current RCT compares existing treatment strategies, which will give us insight in the role of setons, anti-TNF and surgical closure, but with all currently available options, closure rates are disappointing, and QoL is still severely affected. Guidelines for treatment are preferably based on the highest level of evidence; level 1 evidence which is derived from a systematic review RCTs. For some clinical questions however, other sources of data and study designs can be (more) informative. Population based studies derived from national audits or other forms of registration can provide us with valuable information. Several years ago the Snapshot principle was introduced in the research field of colorectal surgery. With these successful cross-sectional multicentre studies we are able to gather large sample sizes in a short period of time from physicians (mainly residents) from many (inter)national hospitals giving insight in routine daily practice. Data can be used to explore differences in patients, techniques and management across the cohort in order to identify areas of practice variability that may result in apparent differences in outcome. In order to address research questions e.g. timing of seton removal in CD patients with perianal fistulas, closure rates after combining medical therapy with surgical strategies or when to stop anti-TNF, we are planning to set up a Snapshot study for fistula treatment.

Recently an innovative treatment option, the Super Seton, was designed by Medishield BV. The conventional knotted seton is relatively difficult to clean, and the knot has a tendency to rotate towards the external opening of the fistula tract and sometimes even migrates into the fistula tract. This can cause complaints of pain and discomfort. The Super Seton is a knotless smooth seton that aims at improving comfort and QoL for patients with perianal fistulising disease. We are currently assessing the feasibility of the Super Seton. The Snapshot study design could also be a suitable design for a follow-up study with this promising new treatment option.
About the author

Elisabeth Joline de Groof was born on the 21st of June 1987 in Haarlem. After graduating as a Medical Doctor from the University of Amsterdam in 2013, she started working as PhD fellow at the department of Surgery and the department of Gastroenterology & Hepatology under the supervision of prof. dr. W.A. Bemelman, prof. dr. G.R.A.M. D’Haens, dr. C.J. Buskens and dr. C.IJ. Ponsioen. Her thesis focusses mainly on the multidisciplinary treatment of Crohn’s disease.

During medical school and the 1st year of her PhD research she obtained a Master’s degree in Clinical Epidemiology at the University of Amsterdam. Joline is also interested in the organisational aspects of healthcare and followed some additional courses of the Healthcare Management Master at the Erasmus University in Rotterdam.

Joline currently works as a surgical resident at Tergooi in Hilversum and Blaricum.