Optimizing strategies in gastrointestinal surgery
Vlug, M.S.

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UITNODIGING

Voor het bijwonen van de openbare verdediging van het proefschrift

OPTIMIZING STRATEGIES IN GASTROINTESTINAL SURGERY

door Malaika Vlug

Op vrijdag 19 november om 14.00 uur in de Agnietenkapel van de Universiteit van Amsterdam.

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Optimizing strategies in gastrointestinal surgery

Malaika S.Vlug
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The CCCA is one of eight Comprehensive Cancer Centers in the Netherlands. Its area is the north-west part of the Netherlands and involves 2,800,000 inhabitants, 16 general hospitals, two university hospitals and the Netherlands Cancer Institute. The comprehensive cancer centers (CCC’s) in the Netherlands have founded to provide comprehensive and high-quality cancer care close to home for all cancer patients. The CCCA provides and coordinates a collaboration of all health care professionals and institutions involved in cancer and palliative care. The CCCA functions as centre of knowledge and quality care that helps to improve cancer treatment, patient care and clinical research as well as prevention of cancer and decrease of cancer mortality.

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Optimizing strategies in gastrointestinal surgery

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ten overstaan van een door het college voor promoties
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Faculteit der Geneeskunde
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General introduction

Surgery for Ulcerative Colitis and Familial Adenomatous Polyposis (part I)

Ulcerative Colitis
Ulcerative colitis (UC) is a chronic inflammatory bowel disease of the colon and rectum, and is characterized by episodes of remission and relapses. In Europe incidence ranges from 1.5 to 20.3 cases per 100,000 person years. The incidence of UC has been increasing, but appears to be stabilizing nowadays. At this moment, around 30,000 people are diagnosed with UC in the Netherlands. Yearly, approximately 500 patients are newly diagnosed. Average age of onset is between 15 and 40 years of age, and slightly more men are affected by this disease.

Initially UC is treated with medications; during an exacerbation patients need remission-induction therapy, once regained, prophylactic therapy is given. The recommended method of treatment is the ‘step-up approach’. However, some patients are refractory to all medications and need surgical treatment. If surgery can be done in an elective setting, a proctocolectomy with ileal pouch anal anastomosis (IPAA) will be performed with or without temporary defunctioning loop ileostomy. This is decided by the surgeon depending on the perceived risks for an anastomotic leakage, like use of steroids and nutritional status. If surgery has to be done in an acute setting, a subtotal colectomy with an end ileostomy will be performed. In a later phase, a completion proctectomy with IPAA will be performed. The number of patients that require an operation because of refractory UC vary from 7.5% after 5 years of onset of the disease to 24% after 10 years of onset.

Colorectal dysplasia and colorectal cancer are, besides refractory colitis, other indications for a proctocolectomy with IPAA. Longstanding UC increases the risk of developing colorectal dysplasia and cancer. Eaden et al. even showed cumulative risks of 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease. Therefore, UC patients are advised to undergo colonic surveillance to detect dysplasia or colorectal cancer at a surgical curable stage.

Familial Adenomatous Polyposis
Familial adenomatous polyposis (FAP) is a rare autosomal dominant disease. Incidence is 1 case per approximately 100,000 individuals. This syndrome is characterized by the development of hundreds to thousands colorectal adenomas and is diagnosed between the age of 10 and 40 years. In the end more than thousands of adenomas will be present in the colon and rectum. The adenomas develop via the ‘adenoma-carcinoma pathway’ into a carcinoma. An untreated FAP will result in colorectal carcinoma in nearly 100% of the patients. FAP patients also have an increased risk of extracolonic manifestations.

Endoscopic surveillance is advised twice per year but, once multiple polyps have developed, endoscopic surveillance is unreliable. In those cases a patient is advised to undergo surgery; a proctocolectomy with IPAA will be performed.
Proctocolectomy with ileal pouch anal anastomosis

During the 1970s this procedure has been developed by Parks and Nicholls. They described an ileal pouch reservoir using a S configuration following distal rectal mucosectomy. This technique, however, was associated with impaired pouch emptying, and in 1980 Utsunomiya developed the J pouch. At present, most surgeons favour this type of reservoir.

The operation can be performed both open and laparoscopically. The first laparoscopic assisted proctocolectomy with IPAA has been described in 1992. A recently published meta-analysis showed that the laparoscopic approach is safe and feasible. An additional advantage of laparoscopy, especially in this relatively young patient group, is better cosmesis.

The operation consists of three parts: colectomy, rectal extirpation and formation of the IPAA. The construction of the pouch can be performed by a double-stapling technique, which is done in most cases, or by a mucosectomy, in order to prevent recurrence. Stapling devices have simplified the procedure. Nevertheless, it is still a very complex operation with potential morbidity. Stool frequency and continence are the two main factors that will determine optimal pouch function; average stool frequency at day time is about 6-7 times, at night time 1-2 times.

Enhanced Recovery After Surgery (part II)

Colorectal cancer

Worldwide, colorectal cancer is the second most common cancer. Its incidence is expected to rise with the increasing longevity and obesity of the Western population. In 2009, 11 450 people were newly diagnosed with colorectal cancer in the Netherlands. Yearly, about 4 500 patients die from this disease, which makes colorectal cancer, after lung cancer (9 414) the second highest cancer-related death. Overall 5-year survival is 60%, but differs dramatically between patients that have been diagnosed at an early stage (5-year survival 93%) or those that have been diagnosed with metastasis to other organs (5-year survival 9%).

Screening programs for colorectal cancer are implemented and will probably further increase the number of patients requiring treatment. The first line strategy to treat colorectal cancer is surgery.

Laparoscopy and fast track perioperative care

Over the past twenty years there have been two important developments in elective major abdominal surgery; the introduction of laparoscopic surgery and the implementation of an Enhanced Recovery After Surgery program, also referred to as ‘fast track’ perioperative care, both focusing on accelerated recovery resulting in shorter hospital stay.

Laparoscopic resection of bowel cancer was first described in 1991. Randomized clinical trials have shown that this technique is safe and effective for malignant disease, results in a hospital stay shorter by about 1-4 days, and less morbidity and postoperative pain than open colorectal surgery.

During the mid-nineties fast track perioperative care was pioneered by Henrik Kehlet.
Fast track programs consist of a multidisciplinary approach, involving dieticians, nurses, surgeons and anesthesiologists and are aimed at reducing surgical stress response, organ dysfunction and morbidity, thereby promoting a faster recovery after surgery.\textsuperscript{33-37} Fast track perioperative care comprises extensive preoperative counseling, no bowel preparation, no sedative premedication, carbohydrate-loaded liquids up to two hours before surgery, effective multimodal pain management, short acting anesthetics, adequate perioperative fluid management, small incisions, and no routine use of drains and nasogastric tubes. Postoperative care includes early oral feeding, enforced mobilization, early removal of urinary catheter and standard laxation.

Similar or even faster rates of recovery have been reported for fast track and open colectomy on comparison with laparoscopic colectomy in a standard perioperative care setting.\textsuperscript{38-41} Due to the implementation of fast track programs, the leading trials\textsuperscript{28-30}, comparing laparoscopic with open surgery with respect to recovery, are presently outdated as in these trials standard perioperative care was given. There are no trials to be found in literature addressing the four combinations of standard or fast track care with laparoscopic or open surgery.

It is hypothesized that fast track and/or laparoscopy are associated with less attenuation of the patient’s condition after surgery, resulting in a shorter postoperative stay and faster recovery to full activity. A faster postoperative recovery, i.e. shorter hospital stay, might have enormous consequences for hospital resources and costs of healthcare.

At present, it is still a matter of debate whether to apply either laparoscopy, fast track or a combination of both. So, now these new developments have proved their feasibility and safety and, as colorectal resections are one of the most common operations in the Netherlands, time has come to evaluate its use in colorectal surgery.\textsuperscript{42}

\textbf{Implementation and costs}

The introduction of fast track care and laparoscopy in daily practice is not simple. Both programs are costly and require extensive expertise. In order to make the fast track program work, the medical and nursing staff needs additional training how to implement the fast track elements. Up to now, full implementation seems troublesome, which is most likely explained by the need to break with longstanding traditions.\textsuperscript{34,43,44} Laparoscopic surgery is costly due to expensive disposables, additional operating time, and a considerable learning curve must be mastered.

The higher costs for laparoscopy and fast track care, might be counterbalanced by shorter hospital stay. In addition, the reduced hospital stay will increase hospital bed utilisation, thereby increasing the capacity to treat colorectal cancer patients resulting in shorter waiting lists. If waiting lists for malign colorectal surgery can be shortened, the patient deteriorates less, subsequently resulting in; less preoperative complications like acute colectomy due to an obstruction; less postoperative complications due to better preoperative condition, and; less tumour progression. Obviously, all this will lead to fewer costs.
Aim of the thesis
In this thesis several aspects of abdominal surgery for benign and malignt diseases are highlighted. The aim of part I is to evaluate the clinical and functional outcome of surgery in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). In part II, the aim is to critically appraise the effects of the two new major developments in elective abdominal surgery, i.e. laparoscopy and fast track.

Outline of the thesis
Surgery for Ulcerative Colitis and Familial Adenomatous Polyposis (part I)
The standard treatment for patients with UC and FAP is a proctocolectomy with IPAA via an open or laparoscopic approach. In laparoscopic surgery mostly a medial to lateral approach is applied, instead of the more commonly used lateral to medial approach in open surgery. In laparoscopic colectomy devascularisation can be started on the left side at the inferior mesenteric artery or at the right side at the ileocolic artery. The aim of chapter 1 is to determine whether the type of approach, open or laparoscopic, and the order of devascularisation in laparoscopic colectomy, affects intestinal barrier function, local inflammatory response and clinical outcome.

After a proctocolectomy with IPAA, UC patients with dysplasia or cancer in the resection specimen are still at risk for developing dysplasia or cancer in their IPAA. Since there is a considerable discrepancy in prevalence of dysplasia in the pouch, there is no surveillance guideline. In chapter 2 the prevalence of dysplasia in the IPAA is assessed in patients with UC who have undergone IPAA and demonstrated dysplasia in their resection specimen.

One of the complications seen after open and laparoscopic IPAA is sexual dysfunction. Up to date, little is known about sexual dysfunction after IPAA and the contribution of damage to the pelvic autonomic nerves. Aim of chapter 3 is to assess whether IPAA is associated with autonomic pelvic nerve damage and changes in subjective indices of sexual function in women.

Another complication after pouch surgery is the lower fertility rate in women. Fortunately many patients do become pregnant. However, there is no consensus about the optimal mode of delivery. The effect of vaginal delivery and its potential complications both before and after proctocolectomy on the function of the pouch is evaluated in chapter 4.

Enhanced Recovery After Surgery (part II)
There is accumulating evidence that short-term outcomes of laparoscopic surgery are better compared to open surgery. Up to date it is unclear whether this can be extrapolated to quality of life. In chapter 5, a systematic review of studies comparing quality of life in patients that underwent open or laparoscopic colorectal surgery is presented.

After the introduction of fast track care the question raised, whether or not laparoscopic surgery was still of added benefit. In chapter 6 all studies comparing laparoscopic surgery with open surgery within a fast track program are evaluated. In addition, we aimed to deter-
mine in a multicenter randomized trial, which form of perioperative treatment, laparoscopic or open surgery combined with fast track or standard care (LAFA-study), was the most optimal combination for patients undergoing segmental resection for colon cancer. The results are described in chapter 7.

The major determinant of recovery after colorectal surgery is a postoperative ileus characterized by delayed gastrointestinal transit. A side study of the LAFA-study is presented in chapter 8, in which it is evaluated whether fast track care and laparoscopic surgery lead to faster recovery of the gut after colonic surgery.

A major factor in the development of morbidity is the surgical stress response with subsequent increased demand on the patient’s reserves and immune competence. In chapter 9 the effect of laparoscopic or open colectomy with fast track or standard perioperative care on a patient’s immune status and stress response after surgery is evaluated.

Implementation of fast track care appears to be difficult. It remains questioned whether all separate fast track elements are actually essential for the enhanced postoperative recovery. The aim of chapter 10 is to determine which baseline characteristics or fast track elements are independent predictors of faster postoperative recovery in patients undergoing a colonic resection for colon cancer.

Finally, in chapter 11 the ultimate level of fast track care, day-care surgery, is evaluated. In this study the feasibility and desirability of a 360° laparoscopic Nissen fundoplication in day-care is compared to laparoscopic cholecystectomy in day-care.
**References**

24. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW et al. Ileal pouch-anal anastomoses com-
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General introduction and outline of the thesis

PART 1
Surgery for Ulcerative Colitis and Familial Adenomatous Polyposis
CHAPTER 1

Intestinal barrier function in patients undergoing (sub)total colectomy

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Accepted for publication in Colorectal Dis.
Abstract

Aim
Aim of this pilot study was to determine whether the type of approach, open or laparoscopic, and the order of devascularisation in laparoscopic colectomy, affects intestinal barrier function, local inflammatory response and clinical outcome.

Method
Elective colectomy patients were included from April 2006 to July 2008. After informed consent, 22 patients scheduled for laparoscopic colectomy were randomized to start with inferior mesenteric artery or ileocolic artery devascularisation. Eighteen patients scheduled for open surgery served as a prospective control group. To assess the intestinal barrier function release of intestinal fatty acid binding protein (I-FABP; marker of mucosal injury and ischemia) was measured pre- and postoperatively. Mesenteric lymph nodes were harvested to assess expression of inflammatory mediator-related genes using Multiplex Ligation Probe Amplification. The study was registered under NTR1025.

Results
Laparoscopic devascularisation started at the ileocolic artery resulted in a significantly increased excretion of I-FABP over time (P=0.002). In this group I-FABP levels were significantly increased on postoperative days 1 and 3 compared to pre-operative values (P=0.011 and P=0.001, respectively). There were no differences in expression of inflammatory mediator-related genes or postoperative morbidity among the groups.

Conclusions
In this pilot study it was demonstrated that devascularisation started at the ileocolic artery during laparoscopic colectomy was associated with prolonged intestinal mucosal ischemia.
Chapter 1

Introduction

The lumen of the large bowel contains around $10^{12}$ bacteria per mL of faeces.\textsuperscript{1} Under normal circumstances, the gastrointestinal tract has the ability to separate these potentially pathogenic bacteria and other products from the extraluminal environment. This is the so called ‘intestinal barrier function’ and its function can be compromised by infectious and inflammatory conditions, cytotoxic drugs, radiation therapy, thermal injury, stress and ischemia.\textsuperscript{2} Failure of the intestinal barrier function enhances intestinal permeability and can lead to Bacterial Translocation (BT). BT is the passage of bacteria across the intestinal epithelium to sterile extraintestinal sites, such as mesenteric lymph nodes (MLNs) and other organs and forms the basis of the ‘gut origin of sepsis’ hypothesis.\textsuperscript{3-5} There is no consensus about the clinical and pathophysiological significance of BT.\textsuperscript{6} However, a recent study including 927 patients over 13 years showed that BT was associated with increased postoperative septic morbidity in surgical patients.\textsuperscript{7}

The most reliable method to evaluate BT is by sampling and culturing MLNs, in which a positive culture indicates BT.\textsuperscript{8} BT can lead to reaction in the mesenteric immune system resulting in up- or down regulation of inflammation-related genes. Multiplex Ligation robe Amplification (MLPA) can detect changes in RNA expression of genes encoding for inflammatory mediators.\textsuperscript{9}

As stated before, the ‘intestinal barrier function’ can be compromised by ischemia. Nowadays, there are several serological markers available for the early diagnosis of intestinal ischemia, for example D-lactate, glutathione S-transferase, and intestinal fatty acid binding protein (I-FABP). In this study intestinal ischemia was assessed by measuring I-FABP excretion in the urine. I-FABPs are small and abundant proteins within the cytoplasm of mature enterocytes located at the villus tip, the area most vulnerable to ischemia. A higher excretion of I-FABP correlates positively with intestinal ischemia.\textsuperscript{10;11} A recently published systematic review has pooled the results of 3 studies to calculate diagnostic accuracy. They stated a sensitivity of 72% (51%-88%) and a
specificity of 73% (62%-83%).

In laparoscopic surgery mostly a medial to lateral approach is applied, particularly in colorectal cancer, instead of the more commonly used lateral to medial approach in open surgery. In the medial to lateral approach vessel ligation is the first step in the procedure while in the lateral to medial approach vessel ligation is one of the last steps in the procedure. The medial to lateral approach results in ischemia in the beginning of the procedure, since parts of the colon will be devascularised at an earlier stage than in the open procedure. It can be hypothesized that this situation leads to more BT.

In laparoscopic colectomy devascularisation can be started on the left side at the inferior mesenteric artery (IMA) or at the right side at the ileocolic artery (ICA). When devascularisation is started at IMA, large bowel ischemia might be less pronounced because of the presence of collateral flow from ileocolic vessels and the superior rectal artery. Devascularisation started at ICA results in more rapid progression of colonic ischemia as there is no collateral flow from the terminal ileum. Apart from the difference in approach and order of devascularisation the operating time for a laparoscopic colectomy is longer. This prolonged operating time as well as the time of bowel ischemia may lead to progressive BT.

The aim of this pilot study was to determine whether the type of approach, open or laparoscopic, and the order of devascularisation in laparoscopic colectomy, affects intestinal barrier function, local inflammatory response and clinical outcome.

Materials and methods

Patients undergoing laparoscopic or open proctocolectomy with ileal pouch-anal anastomosis or laparoscopic or open (sub)total colectomy with ileal rectal anastomosis for inflammatory bowel disease, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer or colorectal malignancy were eligible for this study. Exclusion criteria were: patients under 18 years, no informed consent or antibiotics within a week prior to surgery. This study was approved by the Medical Ethics Committee of the Academic Medical Center (Amsterdam, The Netherlands) and registered under NTR1025.

Patients were preoperatively assigned to an open or laparoscopic procedure on a case by case basis by the operating surgeon. Patients planned for a laparoscopic resection were randomly assigned to start at the IMA or ICA with devascularisation using sealed nontransparent envelopes. Patients who underwent an open procedure served as prospective control group.

Primary endpoints were: excretion of intestinal fatty acid binding protein (I-FABP) in urine preoperatively and at postoperative days 1, 3, and 7, and expression of in
Chapter 1

Inflammatory mediator-related genes in mesenteric lymph nodes (MLNs). Secondary endpoints were: overall morbidity, number of reoperations, readmission rate, primary and total hospital stay and mortality rate. Morbidity was defined as any complication requiring unplanned medical or surgical intervention within 30 days surgery. Total hospital stay was defined as primary hospital stay plus the hospitalization period of patients who were readmitted within 30 days after surgery. **Surgical technique**

In an open colectomy right and left flexures were completely mobilized before ligating arteries and veins. In the left-sided laparoscopic approach, the IMA was ligated first, followed by the left and right branch of the medial colic artery and finally the ICA. The left hemicolon is not completely devascularised until the pelvic phase of the operation due to collateral flow from the rectum and terminal ileum. In the right sided approach, ICA was ligated first followed by the branches of the middle colic artery, resulting in a completely devascularised right hemicolon. In a later phase, the IMA and inferior mesenteric vein were ligated. **Intestinal fatty acid binding protein (I-FABP) in urine**

I-FABP is a marker of mucosal injury and ischemia, and excretion in the urine increases if intestinal ischemia occurs.\(^{11,12,14,15}\) I-FABP was assayed in urine collected for 12 hours at the day before operation and at postoperative days 1, 3, and 7. At day 7, urine was only sampled if the patient was still in the hospital. Two mL of the homogenized urine was stored at -20 °C until analysis. Determination of I-FABP concentration was performed by enzyme-linked immunosorbent assay. A commercially available kit (Hycult Biotechnology b.v. Uden, The Netherlands) was used, and the assay performed in accordance with the manufacturer’s instructions. The detection limit was 20 pg/mL. The concentration of I-FABP excretion measured in the 2 mL of the homogenized urine was multiplied by the 12-hour urine volume. This was done to calculate the total amount of I-FABP excreted in 12 hours.

**Multiplex Ligation Probe Amplification (MLPA) in mesenterial lymph nodes (MLNs)**

MLNs were sampled to assess expression of inflammatory mediator-related genes using MLPA. At the end of the operation, after specimen retrieval, a lymph node from the distal ileum mesentery was sampled and cut into two parts in a sterile area with sterile surgical instruments, put into sterile numbered tubes and stored at -80 °C. To isolate RNA, frozen lymph nodes were homogenized in liquid nitrogen using a mortar and pestle and a commercial RNA extraction kit (Nucleospin® RNA II, Macherey-Nagel GmbH & Co., KG Düren, Germany). After completion of the protocol total RNA was dissolved in 60 µL RNase-free water and stored at -80 °C until further analysis. Changes in RNA expression of interleukins and cytokines (IL15-R01, IL18, IL18b,
IL1RN, IL2, IL6, IL10, ScyA2, ScyA3, ScyA4, ScyA8) enzyme and enzyme inhibitors (CDKN1a, PARN, PDE4B, GSTP1, PTPN1, PTP4A2, SerpinB9) transcription factors and oncogenes (BMI1, MYC, NFkB2, NFkBIA, NFkB1) and other cellular factors (THBS1, LTA, Tnfrsf1a, MIF, PDGFb, TF, TNF) in the MLNs were assayed using MLPA human inflammation kits (R009, MRC-Holland, Amsterdam, The Netherlands) and expressed relative to the household gene Beta-2-Microglobulin (B2M). The assays were performed according to the manufacturer’s instructions.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0.1. All data for this pilot study were presented as median (inter-quartile range). For dichotomous endpoints, treatment groups were compared by using Chi-square test where appropriate. Mann Whitney U test and Kruskal Wallis test were used for quantitative endpoints when comparing two or more groups. The distribution of data over time between groups was analyzed using repeated measures with non-parametric ANOVA. The distribution of data per group per day was analyzed using non-parametric ANOVA. All values were rank transformed and to adjust for confounding effects IBD was introduced as a covariate. Significance was set at P<0.05, with appropriate Bonferroni corrections for multiple comparisons being employed in post hoc tests.

Results

Between April 2006 and July 2008, 84 patients were eligible of whom 40 (48%) gave informed consent. Of the included patients 18 underwent an open and 22 patients a laparoscopic operation. Of the laparoscopic group, 11 patients were randomized to start devascularisation at IMA and 11 to start at ICA. Apart from age distribution and operation time, there were no significant differences in patient characteristics (Table 1).
Measurement of mucosal injury and ischemia: I-FABP excretion in urine

I-FABP excretion was similar when compared on a day by day basis. When analyzing I-FABP excretion over time; a right-sided (ICA) start of devascularisation resulted in significantly increased excretion of I-FABP over time (P=0.002; Figure 1). I-FABP levels were significantly increased on postoperative days 1 and 3 compared to preoperative values (P=0.011 and P=0.001, respectively; Figure 1). After an open colectomy or a left-sided (IMA) start there was no significant effect on the excretion of I-FABP over time (P=0.111 and P=0.531, respectively).
Patients with colonic inflammatory bowel disease were compared to the non-inflammatory diseases needing surgery. There was no significant difference in I-FABP excretion in urine on any of the postoperative days between patients operated for inflammatory bowel disease (n=22) compared to those operated for non-inflammatory bowel disease indication (n=18). Moreover, there was no significant difference in I-FABP excretion in urine on any of the postoperative days between patients with or without morbidity.

*Measurement of inflammatory mediator-related genes: MLPA*

MLPA showed, after post hoc correction for multiple testing (P<0.0017), no statistical differences in RNA expression for inflammatory mediator-related genes between an open or laparoscopic IMA or ICA approach. Neither for patients operated for inflammatory bowel disease (n=22) or operated for non-inflammatory bowel disease
indication (n=18).

**Postoperative results**
None of the laparoscopic procedures were converted. There were no differences between the groups in secondary endpoints (Table 2).

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<thead>
<tr>
<th>Table 2 Postoperative results</th>
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<tbody>
<tr>
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<tr>
<td>Open (sub)total colectomy</td>
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<tr>
<td>IMA start laparoscopic (sub)total colectomy</td>
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<tr>
<td>ICA start laparoscopic (sub)total colectomy</td>
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<td>N</td>
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<tr>
<td>No. of patients with morbidity within 30 days</td>
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<td>Reoperation</td>
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<td>Readmission within 30 days</td>
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<td>Primary hospital stay (days)</td>
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<td>Total hospital stay (days)</td>
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<td>Mortality within 30 days</td>
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Values are median (inter-quartile range) / IMA = inferior mesenteric artery / ICA = ileocolic artery / †Chi-square test / †Kruskal-Wallis test

**Discussion**
The present pilot study indicated that devascularisation started at the ICA during laparoscopic colectomy was associated with prolonged intestinal mucosal ischemia. However, neither the type of approach, open or laparoscopic, nor the order of devascularisation in laparoscopic colectomy, affected the local inflammatory response and clinical outcome. The fear of some laparoscopic surgeons that this would be a disadvantage of the medial to lateral approach is therefore not justified.

In this study patients that underwent open surgery were significantly older. Nevertheless, we do not think that this compromised the comparability between the groups with respect to primary endpoints. There was also some disparity in number of patients that underwent IRA between the open and laparoscopic groups. The difference between IRA and IPAA is that with an IRA the rectum does not need to be extirpated. As during the rectal extirpation phase of the operation, the devascularised colon has already been removed, this is not of influence on the outcome.
The high complication rate is remarkable in the open group, this can be explained by the fact that all complications, both intra- and extramural, were scored prospectively.

Apart from the order of devascularisation, difference in operating time between the three groups might have influenced the results. Obviously, operating time of an open approach was significantly shorter than of a laparoscopic approach. The colectomy part in the laparoscopic approach, i.e. the time the devascularised bowel was still in connection with the circulation, was 2-2.5 hours, while total operating time was more than 4 hour. Devascularisation time of the colectomy may have been too short to produce significant clinical inflammatory response.

Unfortunately, this study did not show any statistical clinical differences. There are several explanations for the discrepancy between the significant increase in I-FABP and the similar clinical outcomes. First of all, we did not perform a power calculation and therefore this was an underpowered study. Secondly, all laparoscopic operations have been performed by a fellow surgeon supervised by a senior surgeon (W.A.B.), and had normal operation times. Thirdly, patients were electively operated. This indicates that patients were not very ill. In our opinion, clinical relevance might show, if duration of the colectomy is prolonged, for example when in the hands of a surgeon still in its learning curve or when the operation is more complex or in an acute setting. Therefore, when long operating times are to be expected, devascularisation starting at IMA during laparoscopic colectomy may be preferred.

The inflammatory response caused by BT was assessed in sampled MLNs using MLPA. MLPA is a new method to detect changes in RNA expression of inflammation-related genes. In the present study, there were no significant changes in RNA expression of inflammatory mediator-related genes. It may well be that antibiotics prophylaxis given at the start of the operation affected the extent of this response. Although it is not likely that one dose of antibiotics changed luminal contents that much, but this cannot be ruled out. For example, pseudomembranous colitis has been described after operative antibiotics prophylaxis.\textsuperscript{16}

Limitations of our study were the small sample size, the heterogeneity of the illness of the patient, the and non-randomized study design of the open group.

In conclusion, the present study indicated no differences in outcome measures, except that devascularisation started at the ICA during laparoscopic colectomy was associated with prolonged intestinal mucosal ischemia.
References
Endoscopic surveillance of the ileoanal pouch following restorative proctocolectomy for colitis-associated dysplasia

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Abstract

Introduction
Patients with ulcerative colitis (UC) who have undergone a restorative proctocolectomy (RPC) with an ileo pouch anal anastomosis (IPAA) may still be at risk of developing dysplasia in their IPAA. A recent systematic review suggested that dysplasia identified before or at operation is a significant predictor of the development of dysplasia in the IPAA. The aim of this prospective study was to assess the prevalence of dysplasia in the IPAA of patients with UC who have undergone RPC and demonstrated dysplasia in their resection specimen.

Methods
Eligible patients were invited for surveillance endoscopy of their IPAA. The afferent and blind ileal loop, ileoanal pouch and rectal cuff were examined by standard endoscopy plus methylene blue dye-spraying. Mucosal abnormalities were sampled and random biopsies were taken from the afferent and blind ileal loop, pouch and rectal cuff each.

Results
44 patients (25 male, mean 49 yrs) underwent pouch-endoscopy. The mean time between RPC and pouch surveillance was 8.6 years. Dysplasia was detected through standard endoscopy in two patients (4.5%). In one patient low-grade dysplasia was detected in the rectal cuff. In a second patient low-grade dysplasia was detected in random biopsies in the pouch and blind ileal loop.

Conclusion
This prospective pouch-endoscopy study detected low-grade dysplasia in 2 out of 44 patients (4.5%). Chromoendoscopy appeared to have no added value in pouch surveillance. Until the significance of low-grade dysplasia in the pouch is proven, the benefit of routine surveillance for dysplasia in the pouch is uncertain.
Introduction

Long-standing ulcerative colitis (UC) increases the risk of developing colorectal dysplasia and cancer.\(^1\) When multifocal dysplasia or cancer in the colitic colon is found, restorative proctocolectomy (RPC) with ileal pouch anal anastomosis (IPAA) is the preferred treatment. After surgery, patients may still be at risk of developing dysplasia. Although several cases of dysplasia and adenocarcinoma arising in the pouch and rectal cuff have been reported, it remains unclear to what extent patients are at risk of developing dysplasia in their pouch or rectal cuff.\(^2\)-\(^7\) Incidence rates in studies vary from 0.6% in a diverse group of patients with an IPAA to 71% in a small group of selected patients.\(^4\);\(^8\) This discrepancy in prevalence may reflect differences in sample size or clinical diagnostic criteria. As a result, there is no pouch surveillance guideline and suggested initiation of surveillance differs greatly in time.\(^9\);\(^12\)

In order to allow identification of a subgroup of patients with an IPAA who might require surveillance, risk factors need to be identified that account for the development of dysplasia in the pouch. Several risk factors are thought to increase the risk of developing dysplasia in the pouch or rectal cuff: long-standing pouchitis, dysplasia or carcinoma in the resection specimen and primary sclerosing cholangitis.\(^5\);\(^7\);\(^12\);\(^13\) A recent systematic review demonstrated that dysplasia or carcinoma in the resection specimen was the only significant predictor for the development of dysplasia in the pouch and advocated a surveillance programme that takes this risk factor into account.\(^14\)

Most studies examining patients with an IPAA use standard white light endoscopy. To our knowledge, there have only been two studies using chromoendoscopy in pouch surveillance, both in patients with familial adenomatous polyposis.\(^15\);\(^16\) In the study by Friederich et al. the combined use of conventional and chromoendoscopy led to a higher detection of adenomas compared to using conventional endoscopy alone.\(^15\) Chromoendoscopy has also shown to increase the detection of dysplasia in patients with inflammatory bowel disease (IBD) in several studies, but has never been subjected to research in pouch surveillance of patients with IBD.\(^17\);\(^20\)

The aim of the current study was to assess the prevalence of dysplasia in the IPAA of
patients with UC who demonstrated dysplasia or carcinoma in their resection specimen as shown to be the only significant predictor for dysplasia in the pouch in a recent systematic review. Furthermore, we evaluated the added value of chromoendoscopy in the detection of dysplasia in the pouch.

**Methods**

All patients with UC who underwent RPC at the Academic Medical Centre at the University of Amsterdam between 1988 and 2008 were invited to participate when histopathology of their resection specimen displayed indefinite for dysplasia, dysplasia or carcinoma. Exclusion criteria were: non-correctable coagulopathy that precludes taking biopsies (international normalized ratio >2, or platelet count <90*10^9), age ≤ 18 years or an inability to obtain informed consent.

Data concerning age, sex, concurrent primary sclerosing cholangitis, previous episodes of pouchitis, indication of proctocolectomy, type of anastomosis, the type of dysplasia in the resection specimen, age at onset and duration of UC before proctocolectomy were recorded. Pouchitis was defined as an episode of symptoms (e.g. increased bowel movements) with endoscopic and histopathological evidence, for which antibiotics were prescribed.

All patients were prepared by 1L macrogol solution (Moviprep) on the morning of surveillance endoscopy of the IPAA. Just before the procedure, patients received an additional enema. With a standard video endoscope (GIF-Q160 or CF-Q160, Olympus Medical Systems Europe, Hamburg, Germany) all segments (the afferent ileal loop, the blind loop, the pouch and rectal cuff) were investigated with white light endoscopy. Hereafter, the mucosa of all segments was sprayed with methylene blue (0.1%) using a spray catheter and the mucosa was inspected for a second time. After targeted biopsies of every mucosal abnormality, 4 additional random biopsies were taken from each segment.

Histopathology was assessed by an expert gastrointestinal pathologist (SvE) according to the revised Vienna criteria, ranging from no intraepithelial neoplasia to invasive neoplasia. In case of (indefinite) dysplasia a second expert gastrointestinal pathologist assessed histopathology to confirm the diagnosis. The histological diagnosis of all biopsies was used as the reference standard diagnosis in each patient.

**Statistical analysis**

Descriptive statistics were used to characterize the study population. SPSS for Windows software (Chicago, IL, USA) version 15.0.1 was used for analysis.

**Results**

**Patient characteristics**

Between 1988 and 2008, 290 patients with IBD underwent RPC in the Academic Medical Centre in Amsterdam. Sixty-four of these patients had (indefinite for) dysplasia or carcinoma in their resection specimen and were eligible for inclusion. These patients were invited for
pouch surveillance endoscopy. Fourty-four patients participated. Of the 20 non-participants, 6 patients had deceased, 4 patients had undergone pouch excision, 5 patients were lost to follow-up, 3 patients had emigrated and 2 patients refused participation. Characteristics of non-participants are described in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Characteristics non-participants (n=20)</th>
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<tbody>
<tr>
<td>Irretrievable, n=5</td>
</tr>
<tr>
<td>Deceased, n=6</td>
</tr>
<tr>
<td>Irradically resected rectumcarcinoma</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Kahler’s disease</td>
</tr>
<tr>
<td>Pancreas carcinoma</td>
</tr>
<tr>
<td>Pulmonary carcinoma</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis secondary to coloncancer</td>
</tr>
<tr>
<td>Pouch excision, n=4</td>
</tr>
<tr>
<td>Irradically resected rectumcarcinoma</td>
</tr>
<tr>
<td>Recurrent abscess</td>
</tr>
<tr>
<td>Recurrent pouchitis</td>
</tr>
<tr>
<td>Recurrent ileus secondary to adhesions</td>
</tr>
<tr>
<td>after conversion to Crohn’s disease</td>
</tr>
<tr>
<td>Refusal, n=2</td>
</tr>
<tr>
<td>Emigration, n=3</td>
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</table>

Between January 2008 and July 2009 all 44 included patients underwent pouchoscopy. The mean age (25 male, 57%) was 49.3 years (SD 11.1). Characteristics of all included patients are described in Table 2.
Two experienced colonoscopists performed 32 procedures. The remaining 12 procedures were performed by 8 other experienced colonoscopists. A dedicated research-fellow was present during all procedures during which no adverse events occurred.

**Endoscopic findings**

During standard endoscopy 25 lesions were detected in 12 patients; 12 in the afferent loop, 8 in the blind loop and 5 in the rectal cuff. One of the 25 biopsies showed low-grade dysplasia and was taken from an adenoma-like lesion in the rectal cuff.

During chromoendoscopy, 14 additional lesions were detected in 9 patients; 8 in the afferent loop, 2 in the blind loop, 3 in the pouch and 1 in the rectal cuff. None of the biopsies showed dysplasia.

In all patients 4 random biopsies were taken from each segment (the afferent loop, the blind ileal loop, the pouch and rectal cuff). In total, 672 random biopsies were taken. Due to

<table>
<thead>
<tr>
<th>Table 2 Characteristics included patients (n=44)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
</tr>
<tr>
<td><strong>Primary Sclerosing Cholangitis</strong></td>
</tr>
<tr>
<td><strong>≥ 1 episode(s) of pouchitis</strong></td>
</tr>
<tr>
<td><strong>Anastomosis</strong></td>
</tr>
<tr>
<td>- Handsewn</td>
</tr>
<tr>
<td>- Stapled</td>
</tr>
<tr>
<td><strong>Indication of IPAA</strong></td>
</tr>
<tr>
<td>- Inflammation</td>
</tr>
<tr>
<td>- Dysplasia</td>
</tr>
<tr>
<td>- Carcinoma</td>
</tr>
<tr>
<td><strong>Histopathology resection specimen</strong></td>
</tr>
<tr>
<td>- IFD</td>
</tr>
<tr>
<td>- LGD</td>
</tr>
<tr>
<td>- HGD</td>
</tr>
<tr>
<td>- Carcinoma</td>
</tr>
<tr>
<td><em><em>Disease duration</em> (yr)</em>*</td>
</tr>
<tr>
<td><strong>Pouch duration (yr)</strong></td>
</tr>
</tbody>
</table>

IPAA = proctocolectomy and ileal pouch anal anastomosis / IFD = indefinite for dysplasia / LGD = low-grade dysplasia / HGD = high-grade dysplasia / *From time of diagnosis until pouch surgery
severe inflammation, no random biopsies were taken in 8 segments of 6 patients. Three out of 672 random biopsies demonstrated low-grade dysplasia (0.45%). Two biopsies (1 in the blind loop and 1 in the pouch) were from the same patient, the third random biopsy (rectal cuff) was from the patient who also demonstrated low-grade dysplasia in an adenoma-like lesion in his rectal cuff.

Thus, in 2 out of 44 patients (4.5%) biopsies revealed low-grade dysplasia. The characteristics of these two patients are shown in Table 3.

### Table 3 Characteristics of patients demonstrating dysplasia in their IPAA

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
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</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong>&lt;br&gt;resection specimen</td>
<td>IFD</td>
<td>Diffuse LGD and focal HGD</td>
</tr>
<tr>
<td>Disease duration* (yr)</td>
<td>18.2</td>
<td>15.7</td>
</tr>
<tr>
<td>Primary Sclerosing Cholangitis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>≥ 1 episode(s) of pouchitis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pouch duration (yr)</td>
<td>4.7</td>
<td>17.3</td>
</tr>
<tr>
<td>Stapled vs. handsewn</td>
<td>Stapled</td>
<td>Stapled</td>
</tr>
<tr>
<td>Histopathology pouch</td>
<td>LGD</td>
<td>LGD</td>
</tr>
<tr>
<td>Location</td>
<td>Rectal cuff</td>
<td>Blind loop and pouch</td>
</tr>
<tr>
<td>Random vs. targeted</td>
<td>Targeted and random</td>
<td>Random</td>
</tr>
</tbody>
</table>

*From time of diagnosis until pouch surgery / IPAA = proctocolectomy and ileal pouch anal anastomosis / IFD = indefinite for dysplasia / LGD = low-grade dysplasia / HGD = high-grade dysplasia

**Discussion**

Patients with UC who have undergone RPC with an IPAA could be at risk of developing dysplasia in their IPAA. The exact risk of developing dysplasia remains unknown despite several studies.3-5;12;14;22-24

In the current study we evaluated patients with UC who underwent RPC with an IPAA and who demonstrated dysplasia or carcinoma in their resection specimen. Dysplasia was detected in both the pouch and rectal cuff, through 1 targeted and 3 random biopsies in 2 patients. The yield of endoscopic surveillance for the detection of low-grade dysplasia in the IPAA was 4.5%. Chromoendoscopy did not increase the yield of detection of dysplasia.
In the first patient demonstrating low-grade dysplasia several lesions were detected in the rectal cuff which were biopsied, one biopsy demonstrating low-grade dysplasia. One random biopsy in the rectal cuff also demonstrated low-grade dysplasia. He was planned for follow-up 3 months later for resection of 3 lesions in the rectal cuff that initially remained in situ. All three lesions were adenomas with low-grade dysplasia. Follow-up 3 months after therapy did not show dysplasia. The second patient demonstrated low-grade dysplasia in random biopsies of the mucosa of the blind loop and in the pouch which was detected again upon follow-up at 6 months. Biopsies taken at follow-up at 12 months showed indefinite for dysplasia in the pouch and afferent loop. This patient is kept under close surveillance and pouch resection will be considered in the event of detecting high-grade dysplasia.

The study by Thompson-Fawcett et al., in which the percentage of included patients with dysplasia in the resection specimen was only 10%, demonstrated a low dysplasia prevalence in the pouch of 1%, which seems in concordance with the concept that dysplasia in the resection specimen is a risk factor for developing dysplasia in the pouch. However, in a population of patients with an IPAA that underwent proctocolectomy for chronic relapsing or long-standing colitis the prevalence of dysplasia was similar to our study (4.4%).

When dysplasia in the pouch is found, its predictive value remains unknown and recommended surveillance intervals differ greatly between centres. A recent study conducted amongst 931 UC patients with an IPAA concluded the risk for dysplasia and carcinoma is small but real and recommended intensified surveillance in a subgroup of patients. In contrast, Thompson-Fawcett et al. concluded that surveillance of pouches for dysplasia is not indicated because the risk of dysplasia progressing to cancer is thought to be extremely small. Some authors have also concluded that the risk of malignant transformation of dysplastic mucosa seems to be small and that even high-grade dysplasia can revert to normality with time. Similar conversions have been described in the cervix with some cases reverting to normal histology. This conversion might be a result of the poor agreement shown in inter-observer studies of pathologists regarding dysplasia in IBD.

Other authors argue initial diagnosis of dysplasia is occasionally an overdiagnosis, which could also explain why cases with dysplasia occasionally revert to normal histology. Therefore, the natural history of dysplasia in patients with IBD, particularly low-grade, remains uncertain and there is little agreement on the optimal strategy. For patients who demonstrate low-grade dysplasia in the pouch, the optimal treatment also remains unknown. Mucolectomy with pouch advancement seems to be the recommended treatment upon consecutive findings of low-grade dysplasia or progression to high-grade dysplasia.

In the current study, one of the two patients demonstrating low-grade dysplasia reverted to normal histology after 6 months while the other reverted to indefinite for dysplasia after one year. Although both gastrointestinal histopathologists agreed on the biopsies showing dysplasia, this reversion could be explained by the fact that both patients had a concurrent pouchitis at initial diagnosis of their dysplasia, complicating histopathological assessment.

The majority of patients in the current study (93%) underwent a stapled procedure, in-
cluding both patients who demonstrated low-grade dysplasia. A possible disadvantage of the double-stapled anastomosis is the remaining rectal cuff where dysplasia can arise, which was the case in 1 of the 2 patients. However, even with a handsewn ileoanal anastomosis, complete eradication of mucosa cannot reliably be achieved and remnants of residual mucosa can occur in up to 20 percent of cases after mucosectomy. Furthermore, the systematic review by Scarpa et al. showed no difference in the prevalence of dysplasia in the ileal pouch and the rectal cuff, suggesting that both handsewn and double-stapled anastomosis carry a similar risk.

Both patients in our study demonstrating low-grade dysplasia had one or more episodes of pouchitis. Previous studies have shown that long-standing pouchitis is a potential risk for neoplastic transformation in the pouch, although this was not confirmed in the systematic review by Scarpa et al. In order to establish the diagnosis of long-standing pouchitis, regular biopsies are needed during the first three years of the pouch. However, episodes of pouchitis in our patient population were defined as episodes of symptoms (e.g. increased bowel movements) with endoscopic and histopathological evidence, for which antibiotics were prescribed. Therefore, the contribution of long-standing pouchitis to the development of dysplasia in the current study is unknown, as it was not well recorded.

To evaluate a possible added value of chromoendoscopy to standard white light endoscopy, we performed a second inspection of the pouch with chromoendoscopy, resulting in 14 additional detected lesions. Although this was a considerable number of additional lesions, none of these showed dysplasia. Contrary to dysplasia surveillance in the colon of patients with UC, the added value of chromoendoscopy in the pouch of patients with UC appears limited.

In conclusion, there is a risk of developing dysplasia in the pouch and rectal cuff in patients with IBD and dysplasia in their resection specimen. Our study suggests this risk is limited. In this study, chromoendoscopy appeared not to have an added value in pouch surveillance. Until the significance of low-grade dysplasia in the pouch is clear, the benefit of routine surveillance is unproven. More data from larger cohorts are needed for risk assessment based on several risk factors which could more precisely predict the chance of developing dysplasia in the pouch.
Chapter 2

References


CHAPTER 3

Genital and subjective sexual response in women after restorative proctocolectomy with ileal pouch anal anastomosis
– A prospective clinical trial –

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Paul J. van Koperen
Sebastiaan W. Polle
Willem A. Bemelman

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Abstract

Introduction
Sexual dysfunction after ileo pouch anal anastomosis (IPAA) is common. The most systematic physical reaction to sexual stimulation is an increase in vaginal vasocongestion. Genital response can be assessed by vaginal pulse amplitude (VPA) using vaginal photoplethysmography.

Aim
To assess whether restorative proctocolectomy with IPAA is associated with autonomic pelvic nerve damage and changes in subjective indices of sexual function in women.

Methods
Female patients undergoing IPAA between April 2004 and January 2006 were included. During sexual stimulation (visual and vibrotactile) changes in vaginal vasocongestion were measured by vaginal photoplethysmography. Concurrently, quality of life (SF-36) and sexual functioning (FSFI, FSDS) were assessed using validated questionnaires.

Main Outcome Measures
Primary endpoint was difference in VPA pre- and postoperatively. Secondary endpoints were differences in feelings of sexual arousal and estimated lubrication pre- and postoperatively and difference in psychological and sexual functioning pre- and postoperatively.

Results
Eleven patients were included. For 8 patients (median age 37 [22-49 yrs]) pre- and postoperative data were collected. VPA analysis showed a significant reduction in vaginal vasocongestion during sexual stimulation postoperatively, P=0.012. Subjective sexual arousal and estimated lubrication during the experiment, reported psychological and sexual functioning pre- and postoperative were not different.

Conclusions
Vaginal vasocongestion after IPAA was significantly reduced in this small study; indicating that IPAA in women might possibly be associated with autonomic pelvic nerve damage or partial devascularization of the vagina. Subjectively reported sexual arousal, estimated lubrication, psychological and sexual functioning were not diminished. Future research should focus on the possible advantage of a full close rectal dissection in these patients.
Introduction

The standard treatment for patients with refractory ulcerative colitis (UC) and familial adenomatous polyposis (FAP) is restorative proctocolectomy with ileo pouch anal anastomosis (IPAA) via an open or laparoscopic approach. At present, the laparoscopic approach is the preferred procedure, because it proved to be safe and feasible with clear cosmetic advantages in this relatively young and sexually active patient group. One of the complications seen after open and laparoscopic IPAA is sexual dysfunction. This complication may have a large impact as most of the patients are sexually active.

In some studies up to 27% of the female patients have reported dyspareunia and vaginal dryness after IPAA. Other studies reported an improved or preserved sexual function after IPAA.

The most systematic physical reaction to sexual stimulation in women is an increase in vaginal vasocongestion. A direct result of this increased vasocongestion is lubrication, as pressure in the small vessels of the vaginal wall increases and plasma transudate passively flows through the epithelium. Damage to the autonomic nerves disrupt this process. However, this is not the only cause of sexual dysfunction, anatomical changes, pouch related problems, psychological functioning, quality of life, and body image play a role as well.

The currently most sensitive, specific and reliable instrument for measuring vaginal vasocongestion is vaginal photoplethysmography. Vaginal pulse amplitude (VPA) fluctuations reflect phasic changes in the blood content of the illuminated capillary bed of the vaginal wall at each heart beat, with greater amplitudes indicating increased vasoengorgement. Subjective sexual arousal and sexual functioning can be assessed by validated questionnaires.

To this day, published studies only assessed pre- and postoperative sexual function using subjective, validated or even non-validated, questionnaires. Mostly, sexual function is only evaluated after surgery. Only 2 studies assessed prospectively preoperative sexual function all well. All other studies compared preoperative sexual function to postoperative sexual function retrospectively. There are no studies that assessed genital response after IPAA, notwithstanding the fact that this measure has frequently been used in other studies, in which, for example, premenopausal women with and without sexual problems were compared.

Two studies have assessed vaginal blood flow after hysterectomy. Maas et al. found radical
hysterectomy to be associated with a reduced VPA during sexual arousal compared to women who underwent simple hysterectomies and a control group. In a preliminary report from the same study group, Pieterse et al. have shown that patients who underwent a radical hysterectomy with a nerve-sparing technique had higher VPA response during sexual stimulation than comparable patients who had had conventional surgery. These studies suggest that radical pelvic surgery is associated with pelvic autonomic nerve damage causing increased denervation of the vagina.

Sexual dysfunction after IPAA is common, but little is known about the contribution of damage to the pelvic autonomic nerves. Aim of this prospective study was to assess whether IPAA is associated with autonomic pelvic nerve damage and changes in subjective indices of sexual function in women.

**Methods**

**Recruitment**

All female patients undergoing an elective laparoscopic IPAA with or without defunctioning ileostomy for UC or FAP between April 2004 and January 2006 were eligible for this study. Exclusion criteria were being under 18 years of age, no informed consent, prior operation on genitals, diabetes mellitus, a history of sexual abuse or preexistent sexual dysfunction, use of medication with a possible effect on sexual response (antihypertensives, psychopharmaceutical drugs) and presence of a depressive disorder. This comparative prospective study was approved by the Medical Ethics Committee.

After a brief telephone interview in which details of the study were provided, patients were mailed a detailed information sheet. Subsequently, the patient visited the department of Sexology for a detailed sexual history and to sign the informed consent. The second visit was a familiarization visit in which neutral and sexual videos were shown and VPA was recorded to get acquainted with the experimental procedures. In addition, validated questionnaires had to be filled out. During the third visit the preoperative test session was done. After at least 1 year of surgery and, in case of a defunctioning ileostomy, at least 3 months after bowel continuity was restored, patients were approached for the postoperative experiment. All patients received travelling expenses and a fee of €50 to compensate them for invested time.

**Endpoints**

Primary endpoint was difference in VPA pre- and postoperatively. Secondary endpoints were differences in feelings of sexual arousal and estimated lubrication pre- and postoperatively and difference in psychological and sexual functioning pre- and postoperatively.

**Surgical Technique**

The colon was resected applying a total laparoscopic approach. The rectum was laparoscopically dissected down to the pelvic floor and transected at midrectum. The colon and half of the rectum were removed through a Pfannenstiehl incision. In all the cases hypogastricus nerves were identified and spared. Further dissection of the rectum, pouch construction (J-pouch and double-stapled) and making of the ileo anal anastomosis were done via the Pfan-
nenstiehl open. Posteriorly, the rectum was dissected applying the total mesorectal excision
technique, anteriorly a close rectal dissection was done. All operations were performed or
supervised by a senior surgeon.

**Measures and materials**

*Vaginal Pulse Amplitude (VPA)*

VPA was continuously measured using vaginal photoplethysmography developed by the de-
partment of Technical Support (Department of Psychology) based on instruments initially
developed by Sintchak and Geer (Figure 1).

![Figure 1 Probe used for vaginal photoplethysmography](image)

This device, sized and shaped as a menstrual tampon, can easily be inserted by the patient
herself and contains a light source (3-mm light-emitting diode; Agilent Technologies HLMP-
NH04, Santa Clara, CA, USA, \( \lambda = 620 \text{nm} \)) and an optical sensor (Texas Instruments TSL250;
Dallas, TX, USA). The devices were produced in batches of 100 pieces, resulting in a set with
nearly identical electronic characteristics. A signal-conditioning amplifier (Technical Support)
separated the VPA from the direct current component using a 12-dB/octave, 0.7-Hz filter.
Additional filtering for VPA was a 24-dB/octave, 0.4-Hz high-pass filter. The signal was
digitalized at 100 Hz with a Keithley KPCI3107 A/D converter (Keithley Instruments, Cleve-
land, OH, USA) running on a Window 2000 system. Depth of the probe and orientation of
the light source were controlled by a device (a 9 x 2-cm US Food and Drug Administration
[FDA]-approved perspex plate; ODV Rubber en kunststoffen, Zaandam, the Netherlands)
attached to the cable within 5 cm of the optical sensor. Patients were instructed to insert the
probe such that the plate touched their labia. The probe and plate were sterilized in a solu-
tion of Cidex-activated glutaraldehyde (Cidex OPA; Johnson and Johnson, Amersfoort, the Netherlands).

**Sexual Arousal and Lubrication Estimate**

To assess sexual feelings and sexual affect during sexual stimulation patients were asked to fill out a 37-item questionnaire (Subjective Self-Assessment Questionnaire [SSAQ]), prior to and immediately after the erotic films. This questionnaire consisted of five scales: sexual arousal (sexually aroused, mentally sexually aroused, physically sexually aroused; Cronbach’s alpha = 0.87); genital sensations (any physical reaction, any genital feelings, feelings of warmth, genital pulsing or throbbing, warmth of genitals, genital wetness or lubrication; Cronbach’s alpha = 0.96); sensuality (sensuous, a desire to be close to someone, loving, uninhibited, relaxed; Cronbach’s alpha = 0.73); positive affect (pleasant, interested, attracted, aroused, sexually attractive; Cronbach’s alpha = 0.93); and negative affect (anxious, worried, angry, disgusted, embarrassed, guilty; Cronbach’s alpha = 0.65). Each question was preceded by “During the video, I felt:…” after which a positive, negative, physical, or sexual experience was described – for instance, pleasant, worried, genital pulsing or throbbing, and sexual aroused. All items were measured on a 1 (not at all) to 7 (intensely scale).

At the end of the procedure patients were asked to estimate their vaginal lubrication on a 10-point scale from 1 (no lubrication) to 10 (fully lubricated).

**Psychological, Relational and Sexual Functioning**

Pre- and postoperative psychological, relational and sexual functioning was assessed by validated questionnaires. To assess psychological and relational functioning patients were asked to fill out the Short Form-36 (SF-36), Beck Depression Inventory (BDI) and Maudsley Marital Questionnaire (MMQ).

The SF-36 consists of 36 items within eight dimensions: Psychological Functioning; Role Limitations due to physical problems; Pain; General Health Perceptions; Energy/Vitality; Social Functioning; Role Limitations due to emotional problems and Mental Health. Scores range from 0 to 100, with a higher score representing a better quality of life. BDI was used to determine if a depressive disorder was present. For each answer a value of 0-3 was assigned, the total score was compared to a key, in which 0-9 indicates no depression, 10-18 indicates mild-moderate depression, 19-29 indicates moderate-severe depression and 30-63 indicates severe depression. MMQ is an instrument used for assessment of relationship quality comprised of three scales: marital, sexual and general life, with higher scores representing greater dissatisfaction.

To assess sexual functioning two questionnaires were used: the Female Sexual Functioning Index (FSFI) and the Female Sexual Distress Scale (FSDS). FSFI assesses sexual functioning on the six domains of desire, arousal, lubrication, orgasm, satisfaction and pain. By adding individual domain scores, a total score was calculated. Higher scores indicate better sexual functioning (maximum score: 36). A total score of < 26.55 is considered indicative of sexual dysfunction. Sexuality related personal distress was measured by FSDS, in which a higher score (range 0 – 48) indicates more sexual distress.
Stimuli
In each test-session two different erotic stimuli were provided. The first stimulus was a 5-minute clip of an erotic film depicting manual caressing of genitals and cunnilingus. The second stimulus was an erotic film consisting of 5 minutes of intercourse, during this film clitoral vibration was given. Women-made, female-initiated and female-centered erotic film clips were used. Even though the postoperative test session was done at least one year after the preoperative test session, two different but comparable sets of erotic visual stimuli were used to avoid habituation resulting from repeated exposure to the same sexual stimulus.

The clitoral vibrator consisted of a rubber stopper of two centimeters in diameter. The vibrator was mounted on a flexible metal strap lined with washable lycra cloth. The patient was instructed to place the rubber stopper against the clitoris. The design of the vibrator did not compromise the VPA measurements. In two earlier studies, vibrotactile stimulation combined with visual stimulation generated significantly greater genital responses than visual stimulation alone.

Procedure
The experiment was carried out by a female experimenter. During the whole experiment the patient was alone in the laboratory with the experimenter in an adjacent room. Patients were instructed to insert the probe and take a seat in front of the monitor. When they felt comfortable, they were asked to let the experimenter know, through an intercom-system, that the session could start. From then on all instructions were provided by monitor, only by written text, and VPA was continuously registered.

First, baseline value was determined by showing a nonerotic documentary for 5 minutes, of wherein the last 2 minutes were used to determine baseline 1 (B1). After that the first erotic film was shown. After filling out the SSAQ, the nonerotic documentary was continued to allow genital response to return to baseline. If after 3 minutes, genital response had not returned to B1 level, patients were asked to count backwards until B1 was reached. Subsequently, a new baseline measurement was done for 2 minutes (B2) and the 2nd erotic film was shown with concurrent clitoral vibration. Finally, patients were asked to fill out the SSAQ and to estimate their vaginal lubrication. The entire experimental setup is shown in Figure 2. Patients were asked not to masturbate during the experiment.

Figure 2 Experiment set-up

<table>
<thead>
<tr>
<th>Placing probe</th>
<th>SSAQ</th>
<th>Nonerotic documentary 5 min, last 2 min determining baseline value</th>
<th>B1</th>
<th>Erotic film (manual caressing of genitals and cunnilingus) (5 min)</th>
<th>SSAQ</th>
<th>Nonerotic documentary (3 min)</th>
<th>SSAQ</th>
<th>Nonerotic documentary Determining baseline value (2 min)</th>
<th>B2</th>
<th>Erotic film (intercourse) &amp; Clitoral vibration (5 min)</th>
</tr>
</thead>
</table>
| SSAQ=Subjective Self-Assessment Questionnaire
Data Reduction and Statistical Analysis
VPA was registered during the entire experiment. Data were entered into a computer program developed at the department of Psychology. After artefact deletion peak-to-through amplitude was calculated for each remaining pulse, averaged over 30-second epochs and multiplied by 0.000477 to convert to mV. For all VPA analyses differences relative to preceding mean baseline were used. A mean VPA score (VPAmean) for erotic film and erotic film and clitoral vibration (each lasting 5 minutes) minus each participant’s mean baseline was calculated, as well as a maximum VPA consisting of the highest 30-second epoch minus baseline (VPAmmax). All dependent variables were submitted to a 2 (pre- or postoperative) x 2 (erotic film or erotic film and clitoral vibration) analysis of variance. To inspect possible differences in change in VPA response over time, the 30-second VPA epochs minus each participant’s mean baseline value were submitted to a 2 (pre- or postoperative) x 2 (erotic film or erotic film and clitoral vibration) x 10 (change in response over time) repeated measures analysis. Data were presented as mean (standard error of the mean, [SEM]) or median (range) were appropriate. Questionnaire endpoints were analyzed by Mann-Whitney U test. Statistical analysis was performed using SPSS for Windows version 15.0.1. Significance was set at P<0.05.

Results
Participants
Thirty-three women underwent an elective laparoscopic IPAA with or without primary protecting loop ileostomy for UC or FAP between April 2004 and January 2006, of those patients 30 were eligible. Eleven (37%) patients gave informed consent and were included in this study (Table 1) of whom three refused to undergo the postoperative session. Two patients refused because they felt undergoing another test session was too bothersome (one of them did fill out the questionnaires) and one patient refused because her husband had just had a cerebrovascular accident. For the final analysis, eight patients were available.

Median (range) age at the time of the preoperative test session was 36 (21-41) years and during the postoperative test session 38 (23-42) years. None of the patients was post-menopausal. Preoperative, five out of the eight patients were taking corticosteroids whether or not combined with mesalazine and/or azathioprine, four out of the eight patients were taking mesalazine combined with corticosteroids and/or azathioprine, and four out of eight were taking azathioprine whether or not combined with corticosteroids and/or azathioprine. One patient was not taking any medication.

None of the patients had an alcohol intake of more than two glasses per week. The postoperative test session was done after a median of 1.9 (range, 1.0–3.7) years and in case of a defunctioning ileostomy 1.4 (range, 1.4–2.0) years after bowel continuity was restored.

Sexual History
Preoperatively all patients had a monogamous heterosexual relationship. At the time of the postoperative test session one patient was divorced and she did not have a sexual relationship. Patients had a median (range) number of 3 (1–15) prior sex partners and 2 (1–3) long-term
**Table 1** Characteristics and postoperative results of eligible patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with informed consent</th>
<th>Patients without informed consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Age</td>
<td>37 (22-49)</td>
<td>33 (18-57)</td>
</tr>
<tr>
<td>ASA I : II</td>
<td>4 : 7</td>
<td>9 : 10</td>
</tr>
<tr>
<td>Operating time</td>
<td>300 (235-341)</td>
<td>277 (200-360)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ulcerative Colitis</td>
<td>10 (91%)</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>- Familial Adenomatous Polyposis</td>
<td>1 (9%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- IPAA</td>
<td>9 (82%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>- IPAA + defunctioning ileostomy</td>
<td>2 (18%)</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Number of patients with morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>within 30 days, n (%)</td>
<td>5 (45%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Major complications within 30 days, n (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anastomotic leakage</td>
<td>1 (9%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>- Reoperation because of suspicion</td>
<td>2 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>- Other complication requiring reoperation</td>
<td>0</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Minor complications within 30 days, n (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>1 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>- Urinary tract infection</td>
<td>1 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>- Other infection</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Reoperation within 30 days, n (%)</td>
<td>3 (27%)</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>Readmission within 30 days, n (%)</td>
<td>2 (18%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Primary hospital stay (days)</td>
<td>10 (7-16)</td>
<td>8 (5-41)</td>
</tr>
<tr>
<td>Total hospital stay (days)</td>
<td>10 (7-17)</td>
<td>8 (5-71)</td>
</tr>
</tbody>
</table>

Values are median (range) / ASA = American Society of Anaesthesiologists / BMI = Body Mass Index / IPAA = proctocolectomy with ileal pouch anal anastomosis
relationships. Two patients had never seen erotic materials prior to the study.

**Vaginal Pulse Amplitude (VPA)**

Mean (±SEM) VPA baseline values (B1 and B2) were significantly lower postoperatively (2.14 mV ± 0.68 and 2.10 mV ± 0.55) than preoperatively (6.05 mV ± 0.85 and 7.16 mV ± 1.39), P<0.001. Pre- as well as postoperatively, B2 value returned to B1 value, P=0.51 and P=0.96, respectively.

There were no significant differences in mean (±SEM) preoperative VPA baseline values (B1 and B2) between patients taking corticosteroids or no corticosteroids, patients taking mesalazine or no mesalazine or patients taking azathioprine or no azathioprine. There was a significant negative effect of the operation (P=0.012) and a significant effect of stimulus (P=0.022), indicating that visual stimulation combined with clitoral vibration yields higher levels of VPA than visual stimulation alone. Also, the change in response over time was significant (P = 0.049), signifying an expected increase in VPA over time (Figure 3). The operation x change in response over time interaction was marginally significant (P=0.074). Postoperatively, VPA responses increased at a slower rate than preoperative VPA responses. In Figure 4, the significant effect of operation and significant effect of stimulus on VPAmean and VPAmax are represented.

Three patients were suspected for an anastomotic leakage (Table 1) of whom one refused to undergo the postoperative test session. These three patients were reoperated. Because a second procedure may have had a greater impact on VPA, a subanalysis of the VPA data was done without the reoperated patients. In this subanalysis, the negative effect of the operation remained (P=0.033 for VPAmean and P=0.030 for VPAmax). All other effects remained significant as well.

**Sexual Arousal and Lubrication Estimate**

There was no effect of the operation on sexual feelings and affect on any of the five scales as measured by SSAQ (Table 2). Both pre- and postoperatively there was an effect of stimulus however, patients reported significantly stronger feelings of sexual arousal, genital sensations and positive affect during the erotic film & clitoral vibration than during the erotic film alone (P=0.016, P=0.006, P=0.042, respectively). Preoperative estimated vaginal lubrication was not significantly different from postoperative estimation (5.6 ± 1.27 versus 5.9 ± 0.73, respectively).

**Psychological, Relational and Sexual Functioning**

There were no significant differences between pre- and postoperative reported psychological and relational functioning. Orgasmic functioning as measured with FSFI was significantly better postoperatively. The other postoperative scores on the different sexual functioning scales were not significantly different (Table 2).
Figure 3 Results of vaginal pulse amplitude (VPA) response during sexual stimulation

Values are mean / Significant effect of operation and stimulus, P = 0.012 and P = 0.022

Figure 4 Results of vaginal pulse amplitude (VPA) response during sexual stimulation

Values are mean (VPAmean) and maximum (VPAmax) increase in VPA (±SEM) relative to baseline / VPAmean: Significant effect of operation and stimulus, P = 0.012 and P = 0.020 / VPAmax: Significant effect of operation and stimulus, P = 0.009 and P = 0.023
## Table 2 Outcome of questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSAQ (all scales 1-7); erotic film</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual arousal</td>
<td>3.2±1.1</td>
<td>2.6±0.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Genital sensations</td>
<td>3.2±1.2</td>
<td>2.9±1.1</td>
<td>0.57</td>
</tr>
<tr>
<td>Sensuality</td>
<td>3.1±1.3</td>
<td>3.1±0.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive affect</td>
<td>2.6±1.3</td>
<td>2.3±0.5</td>
<td>0.50</td>
</tr>
<tr>
<td>Negative affect</td>
<td>1.1±0.1</td>
<td>1.1±0.2</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>SSAQ (all scales 1-7); erotic film &amp; clitoral vibration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual arousal</td>
<td>4.1±1.3</td>
<td>3.9±1.1</td>
<td>0.73</td>
</tr>
<tr>
<td>Genital sensations</td>
<td>4.4±1.3</td>
<td>4.1±0.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Sensuality</td>
<td>3.7±1.0</td>
<td>3.4±0.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Positive affect</td>
<td>3.4±1.4</td>
<td>3.1±1.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Negative affect</td>
<td>1.1±0.2</td>
<td>1.2±0.2</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>SF-36 (all scales 0-100)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>80 (45-95)</td>
<td>90 (35-100)</td>
<td>0.47</td>
</tr>
<tr>
<td>Role physical</td>
<td>25 (0-100)</td>
<td>25 (25-100)</td>
<td>0.34</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>73 (41-100)</td>
<td>74 (64-100)</td>
<td>0.51</td>
</tr>
<tr>
<td>General health perception</td>
<td>35 (25-97)</td>
<td>87 (25-100)</td>
<td>0.13</td>
</tr>
<tr>
<td>Vitality</td>
<td>45 (20-70)</td>
<td>60 (40-85)</td>
<td>0.08</td>
</tr>
<tr>
<td>Social functioning</td>
<td>63 (50-100)</td>
<td>100 (50-100)</td>
<td>0.29</td>
</tr>
<tr>
<td>Role emotional</td>
<td>100 (67-100)</td>
<td>100 (0-100)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mental health</td>
<td>72 (60-88)</td>
<td>92 (40-96)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>BDI†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (0-63)</td>
<td>9.5 (7-17)</td>
<td>8 (3-17)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>MMQ†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital satisfaction (0-80)</td>
<td>1.5 (0-28)</td>
<td>6.5 (1-14)</td>
<td>0.21</td>
</tr>
<tr>
<td>Sexual satisfaction (0-40)</td>
<td>5 (1-16)</td>
<td>6.5 (2-19)</td>
<td>0.72</td>
</tr>
<tr>
<td>General life (0-40)</td>
<td>11 (2-16)</td>
<td>9.5 (6-14)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>FSFI†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire (1.2-6)</td>
<td>3 (2.4-3.6)</td>
<td>3.6 (2.4-4.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Arousal (0-6)</td>
<td>4.5 (0-6)</td>
<td>5.1 (1.2-6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Lubrication (0-6)</td>
<td>5.7 (0-6)</td>
<td>5.9 (3.6-6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Orgasm (0-6)</td>
<td>4.4 (0-6)</td>
<td>5.6 (2.8-6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Satisfaction (0.8-6)</td>
<td>4.8 (1.6-6)</td>
<td>4.8 (3.6-5.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Pain (0-6)</td>
<td>6 (0-6)</td>
<td>6 (4-6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Total score (2-36)</td>
<td>28.2 (5-34)</td>
<td>31.8 (19-33)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>FSDS†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (0-48)</td>
<td>14.2 (0-25)</td>
<td>7.6 (0-26)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or median (range)

†Student’s t-test / †Mann-Whitney U test

SSAQ= Subjective Self-Assessment Questionnaire; score ranging from 1 (not at all) to 7 (intensely)
SF-36=Short-Form 36; higher score is better quality of life
BDI=Beck Depression Inventory; higher score is more depression
MMQ=Maudsley Marital Questionnaire; higher score is more dissatisfied
FSFI=Female Sexual Function Index; higher score is better sexual function
FSDS=Female Sexual Distress Scale; higher score is more sexual distress
Preoperatively patients scored significantly worse on three domains of the SF-36 (Role limitations due to physical problems, General health perceptions and Energy/vitality) when compared to a norm group of 135 healthy Dutch women aged 36 to 45 years. Postoperative scores did not increase significantly compared to preoperative values, but postoperative scores no longer differed from the same norm group (Table 2).

Preoperative MMQ and BDI scores did not differ significantly from postoperative MMQ and BDI scores. One patient had a score of 28 on the domain of marital satisfaction measured by MMQ preoperatively; she was divorced at the time of the postoperative test session and did not fill in the MMQ postoperatively as she was not in a relationship. Her preoperative ΔVPA mean values for S1 and S2 were 0.87 and 1.78 mV respectively; postoperative values were 0.37 and 0.65 mV. The other patients had MMQ scores that were not indicative of marital discord. No patient scored higher than 20 on the BDI, indicating that none of them was suffering from a depression.

Three patients had a preoperative FSFI score below 26.55, a score that is indicative of sexual dysfunction in one or more of the domains. All of these women reported distress about their sexual function (FSDS scores > 15), as did one other woman with a FSFI score of 28.30. Postoperatively one of these three women still scored below 26.55 on the FSFI, she complained of vaginal dryness and dyspareunia and reported distress (FSDS score of 19.1) about her sexual functioning. None of the women scoring within the functional range preoperatively had FSFI and FSDS scores within the dysfunctional range postoperatively.

Discussion
The present study is the first prospective clinical trial comparing preoperative genital response with postoperative genital response during sexual stimulation measured objectively by VPA in women who underwent a restorative proctocolectomy with IPAA.

Pelvic autonomic nerves regulate the blood flow in the vessels of the vaginal wall. This study demonstrated that vaginal blood flow after IPAA was significantly reduced, indicating some sort of damage to the pelvic autonomic nerves. As the lubrication response is also neurogenically controlled, reduced lubrication will result in vaginal dryness, which can lead to dyspareunia. Nevertheless, self-estimated vaginal lubrication, psychological and sexual functioning before and after surgery were comparable. Sexual feelings and sexual affect after an erotic stimulation were also assessed, these were equally strong pre- and postoperatively.

It was surprising that VPA was significantly lower after IPAA as the hypogastricus nerve was carefully identified and spared in all patients. As the hypogastric nerve trunk was preserved, and anteriorly a close rectal dissection was performed it is difficult to explain the cause of decreased VPA after surgery. Extirpation of nerve vibes in the mesorectum might play a role. Another explanation might be the disconnection between the posterior vaginal wall and the anterior part of the rectum, possibly affecting vaginal blood flow, but this is not likely as the vaginal blood flow originates from the side. The role of inflammation and its concomitant effect on vascularized tissues should be considered as a possible explanation as well. Seven out
of the eight analyzed patients were operated because of refractory ulcerative colitis. Ulcerative colitis is an inflammatory bowel disease. Inflammation can be classified into acute or chronic inflammation. Acute inflammation is characterized by a classic vascular response (dilatation of the small vessels resulting in tissue hyperaemia) while chronic inflammation is associated with a diminished vascular perfusion. All operations were performed in an elective setting. This suggests that most patients were suffering from chronic inflammation and not from acute inflammation, which implies that the significantly higher preoperative VPA values have not been caused by higher vascularisation in the genital system due to ulcerative colitis. Nevertheless, this assumption cannot be assured, as the colon of a refractory colitis patient, in an elective setting, can definitely be engorged and inflamed. So, it might be possible that the inflammatory response has been responsible for the elevated pre-operative baseline VPA values in this study.

As a reduced genital response was recorded after IPAA, it could be expected that postoperative sexual arousal, estimated vaginal lubrication and sexual functioning was diminished. This would have been in accordance with eight out of the ten studies published about sexual function after IPAA. However, sexual feelings, perception of lubrication and sexual functioning were similar pre- and postoperatively in our study group. This observation can be explained by the fact that correlations between genital arousal and subjective sexual arousal are generally low in women. In addition, the best predictors of good sexual functioning in women are emotional well-being and the emotional relationship with the partner, whereas physical aspects (including arousal, lubrication) are poor predictors. Another explanation might be that all patients in this study were operated for a benign disease and studies have shown that ulcerative colitis patients have a better quality of life after IPAA as removal of the diseased colon has reduced the need for hospital visits and the usage of medication. Lastly, sexual function is not only determined by the autonomic nerves. Anatomical changes, pouch related problems and psychological factors play a role as well.

At the end of the procedure patients were asked to estimate their vaginal lubrication, which is obviously a subjective account. Another way to estimate vaginal lubrication is by measuring vaginal transudate using a weighed absorbent material (tampons, filter paper, gel) inserted into the vaginal lumen and left for a fixed time. On its removal it is weighed, heated to dryness and then reweighed. From these weighings the amount of fluid and solid absorbed onto the absorbent can be calculated. The method cannot follow rapid changes in lubrication and it is difficult to do serial measures as the tampons dry out the epithelium. Also, reliability of the method is questionable given that the squamous surface of the vaginal epithelium may not allow accurate assessment of transudate volume. It is therefore unknown whether measurement of vaginal transudate is more accurate then subjective patient accounts of vaginal lubrication. Very few studies matched subjective lubrication estimates with physiological data. One small pilot study reported on the relationship between subjective lubrication and vaginal vasocongestion using magnetic resonance imaging and vaginal photoplethysmography. The physiological measures did not correlate with subjective assessments of lubrication.
Another study found reasonable agreement between VPA and subjective lubrication scores.\textsuperscript{52} After a radical prostatectomy, erectile dysfunction is one of the major complications and considered a consequence of neuropraxia (cavernosal dysfunction). Literature has shown though, that recovery of erectile function occurs. Up to three years of recovery time has been reported.\textsuperscript{53-55} In this study the postoperative test session was done within two years after the operation. When considering the time needed for recovery in erectile function, a recovery in vaginal vasocongestion due to a recovery of the hypogastric nerve is not unimaginable. So, we might have performed the postoperative VPA measurement too early. It will be interesting to measure the same patients again.

The applied surgical technique has been a nerve saving total mesorectal excision approach towards the posterolateral rectum. Anteriorly, the dissection was done close rectal in order to avoid nerve damage anteriorly. It is unknown whether the nerve fibres within the mesorectum running to the pelvic floor play a role. A close rectal approach posteriorly might preserve these fibres. Whether this is clinically relevant must be determined by future research.

It proved to be very difficult to recruit patients for this study as it is an intimate experiment and may be experienced as invading on one’s privacy; the power of this study is therefore low. Only 11 of the 30 eligible patients wanted to participate in this study, but as patient characteristics of the nonparticipants and participants were comparable, these results are representative for the entire patient group. Nevertheless, the nature of this study has introduced a volunteer bias as it is known that patients willing to participate in a sexuality study have a more positive attitude towards sexuality and are more sexually active. This is true for all women participating in this type of research, regardless of their health-status.\textsuperscript{56} The small sample size should be taken into account when interpreting the results of the questionnaires. Although there were no significant differences found, all scores on the domains of the SF-36 and FSFI were similar or higher postoperatively, and higher scores are related to a better quality of life and better sexual function. Unfortunately, the small sample size precluded an originally planned multiple regression analysis investigating whether potential changes in vaginal vasocongestion postoperatively can be explained by psychological and relationship functioning. The descriptive information provided on these variables suggests that it is unlikely that the reduction in postoperative vaginal vasocongestion can be explained by changes in these variables.

Up to date, the role between anxiety and VPA is still unclear; some studies have shown an increase of VPA and some a decrease of VPA. In this study the VPA procedure did not result in negative affect and therefore it is unlikely that negative affect has been of influence on genital response.

Patients that were reoperated because of a suspected anastomotic leakage were excluded in a subanalysis as this could possibly be of bigger influence on the postoperative VPA data than the noncomplicated patients. Nevertheless, vaginal vasocongestion was still significantly reduced after the operation in the remaining six noncomplicated patients.

In conclusion, vaginal vasocongestion after IPAA was significantly reduced in this small study; indicating that IPAA in women might possibly be associated with autonomic pelvic
nerve damage or partial devascularization of the vagina. Subjective reported sexual arousal, estimated lubrication, psychological and sexual functioning were not diminished. Future research should include more patients and focus on the possible advantage of a full close rectal dissection.
References


CHAPTER 4

Effect of vaginal delivery on long-term pouch function

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Abstract

Background
The optimal method of childbirth for women with a restorative proctocolectomy (RP) has yet to be determined. Little is known about long-term ileal pouch function after vaginal delivery, especially when childbirth occurred before RP. The aim of this study was to evaluate the effect of vaginal delivery before or after RP on long-term pouch function.

Methods
All 267 women who underwent RP between January 1985 and November 2004 were invited to participate. Functional outcome was assessed by colorectal functional outcome questionnaire, and patients were asked about their pregnancies and risk factors for obstetric injury. Linear regression analysis was performed to study potential risk factors for poor pouch function.

Results
The response rate was 82.6%. Median follow-up after pouch surgery was 7.2 (range 1.0–19.7) years. One hundred patients had at least one delivery. Fifty-two (60%) of the 86 patients who attempted a vaginal delivery had an increased risk of obstetric injury according to predefined risk factors. In these patients ageing and longer follow-up were significant risk factors for impaired incontinence.

Conclusion
Women who had RP and vaginal delivery with a high risk of obstetric injury had impaired continence with ageing and longer follow-up. Patients with RP should be informed about the considerable risk of vaginal delivery on long-term ileal pouch function.
**Introduction**

Restorative proctocolectomy (RP) is the preferred surgical procedure in patients with refractory ulcerative colitis or familial adenomatous polyposis (FAP). Most women are in their reproductive years at the time of operation. Although there is evidence that fertility in women decreases after surgery\(^1,2\), many become pregnant after the operation. In general, pregnancy and vaginal delivery are considered safe but some authors prefer a caesarean section because of the potential for damage to the ileal pouch, pelvic floor, anal sphincters or pudendal nerves.\(^3\) At present, however, there is no consensus about the optimal mode of delivery in these women.\(^4,6\)

In a meta-analysis of 717 women from the normal population, anal sphincter defects were demonstrated by ultrasonography in 26.9 per cent after a first delivery and in an additional 8.5 per cent after a second vaginal delivery. Only one-third of these women were symptomatic after delivery\(^7\), but the maximum follow-up in the included studies was only 6 months after childbirth. It is likely that more patients with the demonstrated anal sphincter defects would become symptomatic with increasing follow-up. As the incidence of occult obstetric injury in the general population is much higher than commonly estimated, such injuries can also be expected in a substantial proportion of women with ulcerative colitis or FAP who have undergone RP. It is likely that damage to the anal sphincter, pelvic floor or pudendal nerves in these patients has more clinical impact at an earlier age. This is because stools are generally looser after RP.

The few studies that have described the effect of childbirth in women with RP have focused on deliveries that occurred after the pouch procedure. Most did not discriminate between an uncomplicated vaginal delivery and a delivery with increased risk of obstetric injury. Moreover, postoperative follow-up was generally too short to draw valid conclusions on the long-term impact of vaginal delivery.\(^5,6,8–10\) Because obstetric injury before RP can have a negative impact in the period after pouch construction, vaginal deliveries before pouch surgery should also be taken into account when evaluating long-term pouch function.

The aim of this study was to evaluate the effect of vaginal delivery and its potential complications both before and after RP on function of the ileal pouch.
Patients and methods
All women who underwent RP between January 1985 and November 2004 were recruited retrospectively from three academic medical centres in the Netherlands (Amsterdam Medical Centre, Vrije Universiteit Medical Centre Amsterdam and Leiden University Medical Centre).

Women eligible for RP routinely underwent physical examination of the anal sphincters and an obstetric history was taken. Anorectal physiology was investigated if there was any doubt about sphincter dysfunction. Only patients with clinically adequate sphincters were counselled for pouch surgery. A double-stapled anastomosis was normally constructed, but mucosectomy with a handsewn anastomosis was performed in a few patients with FAP and polyps extending to the dentate line.

All patients were mailed two questionnaires and invited to participate in the study. They were followed until January 2005, which was defined as the end of the study period. The colorectal functional outcome (COREFO) questionnaire, described in detail by Bakx et al., was used to evaluate pouch function. This validated questionnaire contains 27 questions that assess functional outcome after colorectal surgery, including RP. The questionnaire related to events during the 2 weeks before it was completed. A pregnancy questionnaire was developed after consultation with the department of gynaecology. Patients were asked about their number of pregnancies, complications during pregnancy, number of deliveries, type of delivery (spontaneous vaginal, instrumental vaginal or caesarean section) and complications during delivery. Patients who did not respond within a month were sent a reminder.

From responses to the COREFO questionnaire, scores on a scale from 0 to 100 were calculated for incontinence, social impact, defaecation frequency, bowel motion-related aspects and medication. A total score was also calculated. Low scores corresponded to better outcome on all scales. Defaecation frequency was defined as the number of times a patient had to defaecate during the day or night. A score of less than 5.6 points on the incontinence scale was defined as perfect continence. This score was based on the mean incontinence score of a cohort of patients without complaints of incontinence.

Patients who responded and had a minimum follow-up of 1 year were divided into three groups. Group 1 included patients who never gave birth. Group 2 included patients who had one or more uncomplicated vaginal deliveries (before or after pouch surgery). Group 3 included patients who had one or more vaginal deliveries, at least one of which had an increased risk of obstetric injury or resulted in an emergency caesarean section (before or after pouch surgery). Vaginal delivery with high risk of obstetric injury included forceps or vacuum delivery, delivery with episiotomy, delivery with vaginal tears requiring perineoplasty, delivery of a baby weighing more than 4000 g, delivery that resulted in an emergency caesarean section or delivery with a prolonged second stage of labour (more than 2 h).

Predictors of pouch function, including ageing, length of postoperative follow-up, age at time of operation and vaginal deliveries (with increased risk of obstetric injury), were analysed. Functional outcome of patients with a follow-up of less than 1 year was analysed separately.
Statistical analysis

To test for any differences between groups, the Mann-Whitney U test or Kruskal-Wallis test was performed for quantitative variables and $\chi^2$ or Fisher’s exact test for categorical variables. Multiple linear regression analysis was performed to analyse the effect of risk factors on incontinence scores. $P < 0.050$ was considered statistically significant for all tests. Statistical analysis was performed using the SPSS version 12.0 statistical package (SPSS, Chicago, Illinois, USA).

Results

Between January 1985 and November 2004, 267 consecutive women underwent RP, of whom more than 95% had a double-stapled anastomosis. Questionnaires were sent to 253 patients; the remaining 14 had died. Two hundred and nine patients returned the questionnaires and 44 did not respond, giving a response rate of 82.6%. Of the 209 patients who responded, ten were excluded from the analysis of functional outcome because they refused to participate (n=8) or did not complete the questionnaires fully (n=2). Another 27 patients were not included in the analysis because the pouch was excised (n=13), they had a temporary stoma (n=3) or postoperative follow-up was less than 1 year (n=11) (Figure 1).

Figure 1 Study flow chart
The postoperative pathological diagnosis in the 267 patients was ulcerative colitis in 174 (65.2%), FAP or hereditary non-polyposis colorectal carcinoma in 43 (16.1%), Crohn’s disease in 14 (5.2%), indeterminate colitis in 12 (4.5%) and ‘other’ or unknown in 24 women (9.0%).

The 172 patients included in the analysis had a median age of 42.0 (mean 42.1, range 19.1–73.7) years at the time of completing the questionnaires. Median age at the time of RP was 34.7 (mean 34.4, range 9.5–66.0) years. The median interval between RP and completion of questionnaires was 7.2 (mean 7.7, range 1.0–19.7) years.

Of the 172 women, 72 never gave birth (group 1) and 100 delivered at least once. The mean number of deliveries for the parous women was 1.9. Of these, 83 delivered at least once vaginally and 14 patients by elective caesarean section only. Three patients had an emergency caesarean section. Of the 83 patients who delivered at least once vaginally, 78 had their first delivery before RP. In 34 (40%) of 86 women who attempted a vaginal delivery, deliveries were always uncomplicated (group 2) and in 52 (60%) at least one delivery was associated with an increased risk of obstetric injury according to the predefined risk factors (group 3).

Patients in group 1 were significantly younger than patients in both other groups, both at the time of operation and at the time of assessment (P<0.001) (Table 1). The median time from delivery of the first child until the end of the study period was 18.0 (mean 19.6, range 0.1–39.5) years.

Of the 17 patients who delivered by caesarean section, four gave birth before and 13 after RP. Indications for caesarean section before RP were purely obstetric in three patients and a result of surgical advice in one patient. After RP the decision to perform a caesarean section was made on obstetric grounds in two patients, for surgical reasons in five patients, and as a result of mutual agreement between the patient, gynaecologist and surgeon in six. The indication for emergency caesarean section in three women was obstetric.

Thirteen (6.5%) of the 199 patients who fully completed the questionnaires underwent pouch excision. Three of these women previously had a vaginal delivery and all three had a delivery with increased risk of obstetric injury.

**Functional outcome**

Long-term functional outcome in the 172 patients was assessed using the COREFO questionnaire (Table 1). Most patients had a daily defaecation frequency of seven or less and a nightly defaecation frequency of two or less. Perfect continence was reported in 32.6% of the patients and this did not differ significantly between the three groups (P=0.164). Some 21.0% reported soiling during the day at least once a week. During the night, this was 27.3%. A total of 10.1% of the women reported no defaecation during the night.

There was no difference in mean scores on various scales from the COREFO questionnaire between the three groups (Table 1). However, when univariate linear regression analysis was performed to evaluate time effects, a significant increase in incontinence, social impact and total scores in group 3 was observed with increasing length of postoperative follow-up (R=0.402, P<0.001; R=0.084, P=0.037; and R=0.147, P=0.005, respectively) (Figure 2).
Scores for frequency, medication and bowel motion-related aspects did not correlate significantly with the duration of follow-up in group 3. In groups 1 and 2 there was no correlation between length of postoperative follow-up and subscale score or the total score for functional outcome.

<table>
<thead>
<tr>
<th>Table 1 Functional outcome of the three groups included in analysis</th>
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*Values are mean / values in parentheses are median / Group 1 = no childbirth / Group 2 = uncomplicated vaginal delivery / Group 3 = high risk of obstetric injury / †Kruskal-Wallis test / ‡χ²-test (group 1 versus group 2 versus group 3)
Ageing was found to correlate with higher incontinence scores in univariate linear regression analysis in group 3 (R=0.086, P=0.035) (Figure 3), but not with any of the other subscales or total score for functional outcome. In groups 1 and 2, there was no correlation between ageing and any of the subscales or the total score.

Multiple linear regression analysis was performed to determine whether the correlations in group 3 calculated by univariate linear regression, were significantly different from those in groups 1 and 2. The correlation between incontinence scores and duration of postoperative follow-up in group 3 was significantly different from that in both other groups (P=0.004). The correlation of incontinence scores with ageing in group 3 was different from that in group 2 (P=0.048) but not group 1. The correlations between social impact or total scores and length of postoperative follow-up in group 3 were not significantly different from those in both other groups (P=0.431 and P=0.265, respectively).

In an attempt to distinguish the effects of ageing and length of postoperative follow-up on continence, each of the three groups was divided into two subgroups with higher and lower than median age (34.7 years) at the time of operation. To test whether the correlation between
duration of postoperative follow-up and incontinence scores varied between the age groups, the predictors were included in a multiple linear regression model. In none of the three groups was there a significant difference between the two age subgroups after adjustment for length of postoperative follow-up (P=0.687, P=0.640, and P=0.703 for groups 1, 2, and 3, respectively).

Considering only patients with a postoperative follow-up of more than 10 years, the 13 women with an uncomplicated delivery had significantly lower incontinence scores than the 17 who had a delivery with an increased risk of obstetric injury (P=0.012) (Figure 4). Incontinence scores were significantly worse in women with follow-up of less than 1 year after RP than in those with longer follow-up (P=0.001) (Figure 5).

Discussion
This study shows that vaginal delivery does not necessarily impair faecal continence in women who have undergone RP. However, patients who had a vaginal delivery with a high risk of ob-
Figure 4 Incontinence scores in patients with an uncomplicated vaginal delivery or a high risk of obstetric injury who were followed up for more than 10 years

Kruskal Wallis test, P = 0.012

Figure 5 Incontinence scores in relation to length of follow-up
Obstetric injury had significantly higher incontinence scores with ageing and increasing length of postoperative follow-up than those who had an uncomplicated vaginal delivery.

The present study is one of the largest to assess long-term pouch function specifically in women. Although a response bias cannot be excluded, this was unlikely because the major reason for a lack of response to the questionnaires was an incorrect address.

No discrimination between deliveries that occurred before or after RP was made, because it can be expected that obstetric injury (damage to the pudendal nerves, pelvic floor or anal sphincters) before RP can have a negative impact on function of a pouch constructed at a later date. This is in contrast to other studies that evaluated the effects of childbirth on pouch function.\textsuperscript{8,9}

Patients in group 1 were significantly younger than those in the other groups. In the Netherlands, the mean age of a mother at the time of a first delivery is approximately 30 years.\textsuperscript{12} The median age of patients in group 1 was 38.6 years and it is likely that only a small proportion of these patients will have children in the future.

Overall functional outcome in terms of daily and nightly frequency were similar to published figures.\textsuperscript{13–15} The pouch was excised in 6.5% of the women, comparable with other large series with long-term follow-up.\textsuperscript{16,17} Although three of the 13 patients who had the pouch excised had a delivery with an increased risk of obstetric injury, it is not known whether obstetric injury was the cause of pouch excision.

No significant differences between the three groups were apparent when mean scores on the different subscales were compared using a non-parametric test. The fact that there were no differences in functional outcome scores is in accordance with the results of most other studies. Significant differences in incontinence scores were noted only between groups 2 and 3 in women with a minimum postoperative follow-up of 10 years. Linear regression analysis gave more insight into the time effects of ageing and duration of follow-up. Ageing and length of postoperative follow-up were significantly associated with higher incontinence scores in group 3 only, and both correlations in this group were significantly different from those in group 2. It is difficult to explain why there was no effect of ageing on incontinence scores in group 2. A few outliers with high incontinence scores among relatively young patients might partially explain the paradoxical effect of ageing in this group. Despite the correlation of both ageing and postoperative follow-up with social impact and total scores in group 3, these were not statistically different from correlations in group 1 and 2 in multiple linear regression.

Although it is difficult to discriminate between the effect of longer follow-up and ageing (patients become older with increasing follow-up), it seems that the effect of postoperative follow-up in group 3 was more strongly associated with higher incontinence scores than was ageing. Ramalingam et al.\textsuperscript{18} have already hypothesized that incontinence in middle age is probably the result of several ‘hits’, including ageing and obstetric injury. Anal sphincter defects might initially be masked by compensation of the puborectal muscle. However with ageing, especially after menopause, muscle strength is thought to decrease, eventually resulting in symptomatic incontinence.\textsuperscript{19} Faecal incontinence is estimated to occur in about 2% of
the adult general population and in about 7% of healthy independent adults over the age of 65 years. Patients in the present study were generally young (half were younger than 42.0 years). A considerable number of young patients had high incontinence scores. This might be related to the ileal pouch function itself and therefore be inevitable. However, most patients with higher incontinence scores had a delivery with an increased risk of obstetric injury. Although comparison with a control group of healthy women from the general population was not performed, it is conceivable that the present patients became less continent earlier in life. A recent study from the Cleveland Clinic, in which the effect of vaginal delivery on pouch function was assessed, concluded that vaginal delivery was associated with a higher incidence of anal sphincter injury than caesarean section. Although anal sphincter damage did not substantially influence pouch function in these patients on short-term follow-up, the authors concluded that long-term effects remain unknown.

In this study patients with a postoperative follow-up of less than 1 year after RP had higher incontinence scores than women with longer follow-up. This can be explained by the fact that it takes about 18 months for the pouch to reach its final volume, during which time function improves.

The defined risk factors for obstetric injury are well recognized. However, it can only be assumed that patients with a vaginal delivery in which one of these factors was present actually had an increased risk of obstetric injury. Objective measurements such as ultrasonography of the anal sphincter, anal manometry and assessment of pudendal nerve function were not performed to confirm the presence of such injury. The association between both ageing and length of postoperative follow-up with higher incontinence scores might be stronger if more objective measurements had been made to decrease the number of false positives (predefined risk factor for obstetric injury present without objective findings) and false negatives (absence of predefined risk factor for obstetric injury with positive objective findings). Therefore, the impact of obstetric injury as assessed in the present study might have been underestimated.

In this retrospective study, women who had a vaginal delivery with an increased risk of obstetric injury had significantly worse functional outcome in terms of continence in the long term. The most likely reason for this was occult sphincter or pelvic floor damage. Because incontinence and night-time stool frequency have been shown to be the most important determinants of quality of life after RP, preservation of the anal sphincter as a key factor in continence is of great importance. Patients with ulcerative colitis or FAP should be informed about the considerable risk of vaginal delivery on long-term pouch function, which can be avoided by an elective caesarean section.

**Acknowledgements**

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References


PART 2
Enhanced Recovery After Surgery
Quality of life after laparoscopic and open colorectal surgery: A systematic review

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Abstract

Aim
This study was a systematic review of the available evidence on quality of life in patients after laparoscopic or open colorectal surgery.

Methods
A systematic review was performed of all randomized clinical trials (RCTs) comparing laparoscopic with open colorectal surgery. Study selection, quality assessment and data extraction was independently done by two reviewers. Primary endpoint was quality of life after laparoscopic and open colorectal surgery, as assessed by validated questionnaires.

Results
The search resulted in nine RCTs that included 2263 patients. Short- and long-term results of these RCTs were described in 13 articles. Postoperative follow-up ranged from 2 days to 6.7 years. Due to clinical heterogeneity, no meta-analysis could be conducted. Four RCTs, did not show any difference in quality of life between laparoscopic or open colorectal surgery. The remaining five studies reported a better quality of life in favor of the laparoscopic group on a few quality of life scales at time points ranging from 1 week to 2 years after surgery.

Conclusion
Based on presently available high-level evidence, this systematic review showed no clinically relevant differences in postoperative quality of life between laparoscopic and open colorectal surgery.
Introduction

Since the introduction of laparoscopic surgery in the early 90s, several multicenter randomized clinical trials (RCTs) have established that laparoscopy is a safe and feasible approach in colorectal surgery. These studies have focused on benign diseases such as diverticulitis, ulcerative colitis (UC), pre-malignant diseases like familial adenomatous polyposis (FAP)\(^1\)\(^2\) and malignant diseases, mostly colorectal carcinoma.\(^3\)\(^5\) Advantages of laparoscopic surgery include shorter postoperative hospital stay, less perioperative blood loss, less postoperative pain and cosmetic advantages. Long-term follow-up will most probably show less incisional hernias and adhesions. However, no sufficient data are available yet. Morbidity and oncologic follow-up have been reported to be similar for open and laparoscopic colorectal surgery.\(^4\)\(^6\) Disadvantages are the prolonged operating time, the higher costs and the need for an experienced surgeon, since it takes at least 20 procedures to get through the learning curve.\(^7\)\(^8\)

After colorectal surgery for malignancy, many patients experience a combination of physical and emotional problems for a longer period of time. Symptoms such as fatigue, pain and disturbed bowel function, as well as problems in social and role functioning, inevitably affect the patients’ wellbeing. Assessment of self-reported quality of life is therefore increasingly important in clinical trials, and also when considering the higher costs for laparoscopy and its cost-effectiveness. In addition, in cancer trials, it has been shown that assessing quality of life could contribute to an improved treatment.\(^9\) In 2008, Dowson et al.\(^10\) performed a systematic review included studies published up to March 2007 on quality of life following laparoscopic and open surgery. The authors however concluded that there was a lack of data and a need for further research.\(^10\) Over the last three years, more trials on quality of life after open or laparoscopic colorectal surgery have been published, therefore, an update of this systematic review was required.

The aim of this systematic review was to examine the latest evidence of quality of life in patients after laparoscopic or open colorectal surgery.
Materials and methods

Search Strategy

A literature search of the following electronic databases was conducted: PubMed, Cochrane Central Register of Controlled Trials, and EMBASE (all from January 1980 to April 2010). The key words used were: (colon [MeSH] OR colon OR colonic OR colorectal OR rectal OR mesorectal OR rectoanal OR anorectal OR rectum [MeSH] OR rectum OR coectomy [MeSH] OR colectomy) AND (minimal* AND invasive OR laparoscopy [MeSH] OR laparoscop* OR laparotomy [MeSH] OR laparotom*) AND (quality of life [Mesh] OR quality of life).

No limits as to language were applied. Additionally, a hand-search was performed of the references of relevant studies. Two reviewers (SB and MV) independently selected studies on the basis of their titles and abstracts. Studies were included if they were a RCT that compared laparoscopic and open colorectal surgery for malignant or benign disease, and contained comparative data on quality of life, either as primary or secondary endpoints. If studies reported on similar patient data, the study with the largest sample size was included. Exclusion criteria were: clinical comparative studies, case series, case reports, reviews, letters, or abstracts. In case of disagreement between the two reviewers, a third reviewer (WB) was involved.

Data extraction

The results of each included trial were extracted onto a form that contained the following items: methodological aspects of the trial (i.e. randomization, concealment of allocation, blinding, follow-up, intention to treat, possible selective reporting, other possible bias), inclusion and exclusion criteria, patient characteristics, details on the surgical procedures, primary and secondary endpoints, instruments, timing, and results of the quality of life measurements. All quality of life results were extracted at any time interval, as well as preoperative baseline characteristics and short- and long-term postoperative follow-up data.

Assessment of methodological quality

The methodological quality of the RCTs was assessed using “The Cochrane Collaboration's Tool for Assessing Risk of Bias”. This tool assesses the quality of RCTs by addressing items such as: the methods of randomization, concealment of allocation, blinding, drop-out rate, intention to treat, and other forms of potential bias. Again, this assessment was made by two reviewers independently (SB and MV).

Outcome Measure: quality of life instruments

Studies were included if at least one of the following validated quality of life instruments was used: European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30; EORTC-QLQ-C38; Short Form-36 (SF-36); Gastro Intestinal Quality of Life Index (GIQ-LI); Quality of Life Index (QLI); EuroQoL-5D (EQ-5D); Symptom Distress Scale (SDS) and Global QoL. A summary of the four most commonly used questionnaires is given below.

The EORTC-QLQ-C30 questionnaire has been developed by the quality of life department of the EORTC. This is a self-reported patient questionnaire that included: five functional scales (physical, role, emotional, social, and cognitive); three symptom scales (fatigue, nausea
and vomiting and pain); a global health status/QoL scale; and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC-QLQ-C38 is an extra module used specifically for colorectal cancer. This questionnaire consists of 38 items covering symptoms and side-effects related to different treatment modalities, body image, sexuality and future perspective. The SF-36 consists of 36 items within eight dimensions: psychological functioning; role limitations due to physical problems; pain; general health perceptions; energy/vitality; social functioning; role limitations due to emotional problems and mental health. Lastly, the GIQLI assesses bowel related quality of life. It contains 36 items and covers symptoms, physical, emotional and social functioning.

Results

Literature search

A total of 594 potentially relevant titles were identified from the initial literature search in aforementioned electronic databases. After scanning of all titles by both reviewers independently, 117 abstracts were selected to be reviewed for inclusion criteria and of methodological quality. Hereafter, 25 full-text articles remained for assessment of inclusion criteria and of methodological quality. After this assessment 12 articles were excluded for the following reasons: four articles for being non-randomized studies; three for presenting data on similar patients; three for reporting on ongoing trials, i.e. not presenting data; one for not presenting quality of life data; and one could not be translated from Russian. A total of 13 full-text articles remained for final analysis and data extraction. These articles reported on the results of nine different RCTs. The long-term results of four of the nine included RCTs were presented in separate papers; therefore, 13 articles were included. Details of the search are shown in Figure 1.

Risk of bias in included trials

The methodological quality of the nine included trials is summarized in Figure 2. In general, overall study quality was good. All studies were properly randomized and in one, concealment of allocation was unclear. Patients were blinded for the approach in one out of nine studies, and in none of the studies the personnel (i.e. the surgeons) were blinded. In most studies, it was unclear if the outcome assessor was blinded; only one study stated adequate blinding of the outcome assessor. Eight out of nine studies were analyzed according to the intention to treat principle; in one study this was unclear. All predefined outcome parameters were reported in eight trials, and thus, free of selective reporting. Seven studies were free of other bias: baseline characteristics of the patients were comparable and treatment was similar apart from the intervention.

Description of trials

An overview of the included trials is given in Table 1. A total of 2263 patients (laparoscopic surgery n=1257, open surgery n=1006) were included in nine trials. Six trials reported on patients with colon or colorectal cancer and three reported on patients with diverticulitis, Crohn's disease and UC or FAP. Quality of life was a primary outcome measure in five of
the trials. The following validated questionnaires were used for measuring quality of life: EORTC-C30 (4 times), SF-36 (4 times), EORTC-C38 (2 times), GIQLI (2 times) and EQ-5D, QLI, SDS and Global Quality of Life, which were all used once.

**Figure 1** Flow chart of article inclusion

![Flow chart of article inclusion](chart.png)

RCTs=randomized controlled trials
Figure 2: Assessment of risk of bias of the nine included randomized clinical trials.
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<td>EORTC – C30 and C38</td>
</tr>
<tr>
<td>Guillou5</td>
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<td>2005</td>
<td>secondary</td>
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<tr>
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<td>Braga29</td>
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<td>190</td>
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<td>4.2</td>
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<td>SF-36</td>
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<td>Weeks32</td>
<td>Cost</td>
<td>2002</td>
<td>primary</td>
<td>228</td>
<td>221</td>
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<td>Colon resection</td>
<td>QLI, SDS, Global QOL</td>
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<td>Schwenk31</td>
<td></td>
<td>1998</td>
<td>primary</td>
<td>30</td>
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<td>RP &amp; IPAA</td>
<td>SF-36, GIQLI</td>
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<td>2007</td>
<td>secondary</td>
<td>26</td>
<td>27l</td>
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</tbody>
</table>

1Long term follow-up of same study population / 2Number of patients included in long term follow-up, data not specified for laparoscopic or open surgery / 3median / 4no data available / UC = ulcerative colitis / FAP = familial adenomatous polyposis / RP & IPAA = restorative proctocolectomy with ileo pouch anal anastomosis / QoL = Quality of Life / EORTC = European Organization for Research and Treatment of Cancer / SDS = Symptom Distress Scale / QLI = Quality of Life Index / GIQLI = Gastro Intestinal Quality of Life Index / SF-36 = Short Form 36
Quality of life

An outline of the results is shown in Table 2. The studies were heterogeneous in terms of variation in diseases treated, outcome measures, and timing of measurements. Hence, meta-analysis was not feasible. Preoperative quality of life was measured in eight out of the nine studies. In all but one of these, preoperative quality of life was similar between the groups. The study of Janson et al.\textsuperscript{28} reported a significantly better quality of life in 1 out of the 5 scales of the EQ-5D (‘usual activities’) for the group which was about to undergo open surgery (P=0.006). Postoperative follow-up in the different studies ranged from 2 days to 6.7 years. Except for Weeks et al.\textsuperscript{30}, all studies started measuring quality of life at least 1 week after surgery.

King et al.\textsuperscript{33,34}, Guillou et al.\textsuperscript{4}, Jayne et al.\textsuperscript{35}, Maartense et al.\textsuperscript{32}, Eshuis et al.\textsuperscript{36}, Maartense et al.\textsuperscript{2}, and Polle et al.\textsuperscript{37} showed no significant differences in postoperative quality of life following open or laparoscopic colorectal surgery on short-term (1 to 12 weeks) or long-term (3 months to 6.7 year) follow-up.

Five studies, Janson et al.\textsuperscript{28}, Braga et al.\textsuperscript{29}, Weeks et al.\textsuperscript{30}, Schwenk et al.\textsuperscript{31} and Klarenbeek et al.\textsuperscript{1}, did find a significant difference in postoperative quality of life in favor of laparoscopic surgery. Janson et al.\textsuperscript{28} showed a significant difference in favor of laparoscopic surgery in two (‘social function’ and ‘role function’) and one (‘social function’) of 15 subscales of the EORTC-C30 questionnaire at 2 and 4 weeks, respectively, following surgery. The authors also calculated the effect size (Cohen’s) of these subscales; the effect size of ‘role function’ was 0.51 (moderate) and the effect sizes of social function were 0.42 (low) and 0.38 (low) at 2 and 4 weeks, respectively. In the same study, there was no difference between the open and laparoscopic group as measured with EQ-5D.

Braga et al.\textsuperscript{29} measured quality of life at 1, 2 and 4 years postoperatively. Only three subscales (‘general health’, ‘physical functioning’ and ‘social functioning’) of the SF-36 were used for analysis. Two of three subscales (‘physical functioning’ and ‘social functioning’) scored significantly better in the laparoscopic group at 1 year after surgery; scores on one subscale (‘social functioning’) were still significantly better at 2 years postoperative, and no significant difference was found at 4 years following surgery.

Weeks et al.\textsuperscript{30} reported no difference between the groups measured with the SDS at 2 days postoperatively. At 2 weeks after surgery the authors reported a significantly better outcome for the laparoscopic group on the Global QoL questionnaire; at the same time point scores on the QLI and SDS were similar for both groups. At 8 weeks postoperatively no significant differences were found.

After 1 week Schwenk et al.\textsuperscript{31} found a significant difference in favor of laparoscopy as measured with the EORTC-C30 questionnaire. These differences were shown on four out of five functional scales (‘physical’, ‘emotional’, ‘social’, and ‘cognitive function’), on ‘global quality of life’ and on four of nine symptom- or single item scales (‘fatigue’, ‘pain’, ‘dyspnoea’ or ‘appetite loss’). After 4 weeks, two out of the five functional scales (‘social’ and ‘cognitive function’) and ‘global quality of life’ remained significantly better in the laparoscopic group. After 12 weeks, quality of life scores were similar.
Klarenbeek et al. performed one quality of life measurement after 6 weeks and reported a difference in four (‘pain’, ‘social functioning’, ‘role limitations due to physical health’ and ‘role limitations due to emotional problems’) of eight dimensions of the SF-36.

**Discussion**

This systematic review showed no substantial differences in quality of life, as measured two days to several years postoperatively, between laparoscopic and open surgical procedures for colorectal disorders. In only five out of the nine trials found, quality of life after laparoscopic colorectal surgery appeared slightly but significantly better during short-term follow-up compared to that with open colorectal surgery. However, this was not considered clinically relevant, because the observed differences were merely found in certain subscales at few and differing time intervals.

The clinical relevance of significant differences in quality of life is debatable. Osoba et al. have studied the outcomes of the EORTC-C30 by comparing changes in C-30 scores to a subjective significance questionnaire (SSQ). The SSQ asked patients to rate their own changes in physical, emotional and social functioning. These results were compared to the outcomes of the C-30, which resulted in a small change (5-10 points), moderate change (10-20 points) and large change (> 20 points). These results imply that statistical significance does not necessarily correlate with clinical relevance, which was illustrated in the trial of Janson et al. In that study, a low and moderate effect size was calculated for significant differences in quality of life outcomes in the EORTC-C30. They also stated that, due to the large number of subscales analyzed in multiple tests at different assessment points in time, the finding of false-positive results is likely to occur. Hence, the relatively small differences found in this review on sets of subscales were not considered to be clinically relevant findings.

Several studies have shown that laparoscopic surgery results in less perioperative blood loss, less inflammatory response, and smaller incisions. Obviously, laparoscopic surgery is associated with less perioperative trauma to the abdominal wall compared to open surgery. Therefore, differences in quality of life are expected to be more prominent in the first week after surgery. Unfortunately, in this review no conclusions could be drawn about that period, because almost all included studies started measuring quality of life after a minimum of 1 week. This is a possible explanation for the rare differences we found in quality of life, which is corroborated by the fact that nearly all of the reported differences in quality of life disappeared over time. If quality of life was indeed influenced by the surgical technique, another explanation for the marginal differences we found could be that in four out of the nine trials included, quality of life was not a primary outcome measure, which possibly lead to an underpowered quality of life analysis. Finally, quality of life is determined by many other postoperative factors, even if baseline characteristics are similar at the time of preoperative assessment. For example, the course of the disease differs per patient and may subsequently affect quality of life.

Results from this systematic review are in accordance with recent literature. Dowson et al. have shown no significant quality of life advantages after a laparoscopic approach com-
pared to open surgery, but also stated that there was a lack of good quality data. The authors did state that there was a possible trend of an improved quality of life after laparoscopic surgery. In a Cochrane systematic review on short-term benefits for laparoscopic colorectal surgery, Schwenk et al.\textsuperscript{40} found that quality of life might be improved in the early postoperative course. The authors, however, were not able to present a clear conclusion due to the low methodological quality of the studies that they included. In addition to the earlier review, the present systematic review included sufficient high-level evidence to state that there was no clinical relevant difference in quality of life on short- or long-term follow-up, measured 1 week to 6.7 years postoperatively.

A limitation of this review is the clinical heterogeneity among the included studies. Virtually every study used different quality of life instruments and did not present exact data. Furthermore, the recruited patients were treated for a range of different disorders. Therefore, it was impossible to recalculate the statistical analyses or to perform a meaningful meta-analysis. Future randomized trials comparing open with laparoscopic surgery are needed\textsuperscript{41}, and should be well-designed, sufficiently powered, and focus on quality of life; in particular shortly after the operation, i.e. within 1 week, in which period, most of the differences are likely to occur.

In conclusion, based on presently available high-level evidence, this systematic review showed no clinically relevant differences in postoperative quality of life between laparoscopic and open colorectal surgery.
References


11) Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2. 2009. Ref Type: Generic


19) Berdah SV, Mardion RB, Grimaud JC, Barthe J, Orsoni P, Moutardier V et al. Mid-term functional out-


Systematic review of laparoscopic versus open colonic surgery within an enhanced recovery programme

Malaika S. Vlug
Jan Wind
Edwin S. van der Zaag
Dirk T. Ubbink
Huib A. Cense
Willem A. Bemelman

Colorectal Dis. 2009 May;11(4):335-43
Abstract

Background
Fast track accelerates recovery, reduces morbidity and shortens hospital stay. It is unclear what the effects are of laparoscopic and open surgery within a fast track programme. Aim of this systematic review was to appreciate the existing evidence.

Methods
A systematic review was performed of all randomized (RCTs) and controlled clinical trials (CCTs) on laparoscopic and open surgery within a fast track setting. Primary endpoints were primary and overall hospital stay, readmission rate, morbidity and mortality. Study selection, quality assessment and data extraction were performed independently by two observers.

Results
Only 2 RCTs and 3 CCTs were eligible for final analysis, which reported on 400 patients. Data could not be pooled because of clinical heterogeneity. One RCT and one CCT stated a shorter primary hospital stay in the laparoscopic group of 3 and 2 days, respectively. In one RCT, the readmission rate was lower in the laparoscopic group; absolute risk reduction (ARR) 21.4% [95% confidence interval (CI): 6–42.3%] resulting in a number to treat (NNT) of 4.7 patients (95% CI: 2.4–176). Another study showed a 23% difference in favour of the laparoscopic group with regard to morbidity (95% CI: 6.3–39.1%), i.e. a NNT of 4.4 patients (95% CI: 2.6–15.9). There were no significant differences in mortality rates.

Conclusion
Due to the present lack of data, no robust conclusions can be made. A large randomized controlled trial is required to compare laparoscopic with open surgery within a fast track setting.
**Introduction**

A recent development in elective large bowel surgery is the introduction of an enhanced recovery programme after surgery (ERAS)\textsuperscript{1,2}, also referred to as fast track perioperative care. It combines a number of elements aiming at a faster recovery after surgery and a reduction in the surgical stress response.\textsuperscript{3-12} This multidisciplinary protocol was developed by Kehlet et al.\textsuperscript{4-6,9-11} for all patients undergoing a segmental colectomy enabling a faster recovery resulting in an earlier discharge as compared to traditional care. Furthermore, postoperative morbidity might be reduced in a fast track perioperative care setting.\textsuperscript{5-7,9,13,14} The essence of ERAS consists of extensive preoperative counselling, no bowel preparation, no sedative premedication, carbohydrate loaded liquids until two hours before operation, thoracic epidural anaesthesia, short acting anaesthetic, perioperative intravenous fluid restriction, small incisions, nonopioid pain management and no routine use of drains and nasogastric tubes. Postoperative care includes early oral feeding, enforced mobilization, early removal of bladder catheter and standard laxative.\textsuperscript{1-12,15}

Laparoscopic surgery was first described in 1991\textsuperscript{16} and is still increasingly popular. Advantages of laparoscopic surgery are a reduced hospital stay of about 4–8 days\textsuperscript{17-22}, less morbidity and less postoperative pain.\textsuperscript{17,21-26} After open colorectal surgery postoperative hospital stay is about 6–11 days.\textsuperscript{17-22} It is unclear what difference there is in hospital stay and clinical endpoints between laparoscopic and open surgery in a fast track programme. The aim of this systematic review was to appreciate the existing high-level evidence on these differences.

**Materials and Methods**

*Data search*

Medline database (from January 1950 to August 2007), EMBASE and the Cochrane Library (both from January 1980 to August 2007) were searched for randomized controlled trials (RCTs) or controlled clinical trials (CCTs) with a prospective intervention group comparing laparoscopic surgery with open surgery within an enhanced recovery programme, using the following MeSH (Medical Subject Headings) terms and free text words; fast track, enhanced recovery, ERAS, laparoscopy, laparoscopic, minimally invasive, surgery, laparotomy, open, colon, colonic, colorectal or rectal.
Electronic links to related articles and references of selected articles were hand-searched as well. Leading investigators in the field were contacted to enquire whether studies were ongoing or publications were recently submitted. A hand-search of relevant journals and conference proceedings was not performed. No language restriction was applied.

**Study selection, quality assessment and data extraction**

From the potentially eligible studies, two investigators (JW, MSV) independently selected suitable studies on the basis of their titles and abstracts. Studies were included if they investigated the following primary endpoints: age, gender, American Society of Anesthesiologists (ASA) classification, type of resection, primary (PHS) and/or overall hospital stay (OHS), readmission rate and/or morbidity and/or mortality, and whether at least four fast track (FT) elements were used in a FT protocol. If an eligible study did not specify at least one of these endpoints, it was excluded. The arbitrary number of four FT elements was chosen because fewer elements might represent ‘modern’ traditional care. Secondary endpoints were: quality of life, gastrointestinal function and pain medication.

In case of disagreement, full papers were obtained for final judgement. Discrepancies were resolved by discussion. Final inclusion was confirmed after consensus was reached. The remaining trials were critically appraised using the standard checklist from the Dutch Cochrane Collaboration. Subsequently, study data on the predefined endpoints were extracted, again independently by the two investigators.

**Data analysis**

Primary hospital stay (PHS) is expressed as a median value and inter-quartile range (IQR) or range for each surgical treatment group, calculated from the date of operation to the date of discharge. Overall hospital stay was defined as PHS including the hospitalization period of patients readmitted within 30 days of surgery. Readmission rate, morbidity and mortality are presented as a percentage of the included patients in each surgical treatment group. Morbidity was defined as the reported major and/or minor morbidity within 30 days after surgery. The authors of the papers included here were asked to send the median, interquartile range and range of their PHS and OHS for proper statistical analysis. For dichotomous outcomes (readmission, morbidity and mortality) the absolute risk reduction (ARR), number needed to treat (NNT) and 95% confidence intervals (CIs) were calculated. In the absence of clinical heterogeneity a meta-analysis was to be attempted.

**Results**

**Included studies**

The search identified 178 publications of which 171 were excluded, because those studies did not match the criteria for inclusion. From the 7 selected studies\(^{28-34}\), 2 studies\(^{33,34}\) were excluded because all data was used in one of the other selected studies. Of the 3 studies\(^{29,33,34}\) publishing on the same data, the study of Junghans et al.\(^{29}\) was selected, because both studies\(^{33,34}\) reported on a smaller sample size. Five studies\(^{28-32}\) remained for final analysis, two RCTs\(^{28,30}\) and three CCTs.\(^{29,31,32}\) The selection process of the studies included is summarized in Figure 1.
Included studies were published between 2004 and 2008 and reported on a total of 400 patients, ranging from 55 to 147 patients per study. In Table 1 overall quality assessment is presented. Patient characteristics and results of the included studies are shown in Table 2. The data could not be pooled because of clinical heterogeneity among the studies, for instance different inclusion criteria and different surgical procedures. Hence, only individual study results are presented.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Concealment of allocation</th>
<th>Intention to treat</th>
<th>Blinding and data collection</th>
<th>Comparability at baseline</th>
<th>Follow-up</th>
<th>Complete follow-up</th>
<th>Similar non-trial treatment</th>
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<td>Not blinded</td>
<td>Yes</td>
<td>3 months</td>
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<td>Yes</td>
<td>Not blinded</td>
<td>88%</td>
<td>3 months</td>
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<td>CCT</td>
<td>No</td>
<td>Yes</td>
<td>Not blinded</td>
<td>100%</td>
<td>30 days</td>
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<td></td>
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<td>2008</td>
<td>CCT</td>
<td>No</td>
<td>Yes</td>
<td>Not blinded</td>
<td>100%</td>
<td>30 days</td>
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</table>

RCT = randomized controlled trial / CCT = controlled clinical trial
Methodological quality of the studies
Two studies, Basse et al.\textsuperscript{28} and King et al.\textsuperscript{30}, were RCTs. The others by Mackay et al.\textsuperscript{31}, Junghans et al.\textsuperscript{29} and Polle et al.\textsuperscript{32} were CCTs. The five studies\textsuperscript{28-32} had several limitations. All had small sample sizes. One\textsuperscript{28} of the 2 RCTs\textsuperscript{28;30} did not describe how randomization was performed. Hence, concealment of allocation was unclear. Only one study (Basse et al.\textsuperscript{28}) was double-blinded, i.e. for patients and assessors. Their patients had an opaque dressing covering their whole abdomen, which was applied after surgery and was not removed until the decision about discharge had been taken. In the other studies the nonblinded study design and data collection may have caused observer bias, which theoretically could have been in favour of the laparoscopic group. In the study by Basse et al.\textsuperscript{28} the nontrial treatment differed between the groups. Patients in the open group received an additional epidural dose of morphine. Only three studies applied well-defined discharge criteria, which is of major importance as hospital stay is one of the outcome parameters. The analysis of Polle et al.\textsuperscript{32} was a subgroup analysis. In this study patients were included who underwent an elective open or laparoscopic segmental colorectal resection within an enhanced recovery programme or traditional care setting. The investigators mainly focused on the difficulties implementing FT surgery.

Primary outcome parameters
Primary and overall hospital stay
All five studies\textsuperscript{28-32} reported on primary hospital stay. One RCT\textsuperscript{30} and one CCT\textsuperscript{29} stated a shorter PHS after laparoscopy. The randomized trial of King et al.\textsuperscript{30} showed a significant difference in PHS of 5 (IQR 3–6) days in the laparoscopic surgery group vs 8 (IQR 5–9.25) in the open surgery group (Table 2). In the study of Junghans et al.\textsuperscript{29} the authors reported a PHS of 4 (range 3–123) days in the laparoscopic group vs 6 (range 3–79) days in the open group.

Overall the PHS varied widely between the studies. The largest difference was seen between the RCT of Basse et al.\textsuperscript{28} and the CCT of MacKay et al.\textsuperscript{31} Basse et al.\textsuperscript{28} reported a PHS of 2 (range 2–20) days in the laparoscopic group vs 2 (range 2–5) days in the open group. MacKay et al.\textsuperscript{31} reported a PHS of 6 (IQR 5–9) days in the laparoscopic group vs 6 (IQR 5–10) days in the open group.

Overall hospital stay was shown in 3 studies.\textsuperscript{28;30;32} The RCT of King et al.\textsuperscript{30} showed a significant shorter OHS in the laparoscopic group: 6 (IQR 3–11) days vs 8.5 (IQR 6–12.5) in the open group.

Readmission rate
Readmission rates were reported in four studies.\textsuperscript{28;30–32} A large variation was observed in readmission rates among the studies (Table 2). In the laparoscopic surgery group the highest readmission rate of 20\% was reported by Basse et al.\textsuperscript{28} and the lowest (0\%) was reported by MacKay et al.\textsuperscript{31} In the open surgery group the same studies reported the highest (26.6\%) and lowest (3.4\%) readmission rates, respectively. MacKay et al.\textsuperscript{31} who readmitted the lowest number of patients observed the longest primary hospital stay; 6 days in both treatment groups.
<table>
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<th>Reference</th>
<th>N</th>
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<th>% ASA I&amp;II Lap/Open</th>
<th>Type of surgery</th>
<th>PHS (days) Lap/Open</th>
<th>OHS (days) Lap/Open</th>
<th>Readmissions % (n) Lap/Open</th>
<th>Morbidity % (n) Lap/Open</th>
<th>Mortality % (n) Lap/Open</th>
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<td>Basse et al.</td>
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<td>83 / 63</td>
<td>RH, SR</td>
<td>2 (range 2-20) / 2 (range 2-5)</td>
<td>2 (NR) / 2 (NR)</td>
<td>20 (6) / 26.6 (8)</td>
<td>26.6 (8) / 20 (6)</td>
<td>0 / 10 (3)</td>
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<td>King et al.</td>
<td>41</td>
<td>72.3 / 70.4 (mean)</td>
<td>78 / 84</td>
<td>LH, RH, SR, AR, APR</td>
<td>5 (IQR 3-6) / 8 (IQR 5-9.25)*</td>
<td>6 (IQR 3-11) / 8.5 (IQR 6-12.5)*</td>
<td>4.6 (2) / 26.3 (5)*</td>
<td>14.9 (6) / 26.3 (5)</td>
<td>2.4 (1) / 5.3 (1)</td>
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<tr>
<td>MacKay et al.</td>
<td>21</td>
<td>72.0 / 73.2</td>
<td>77 / 74</td>
<td>LH, RH, AR, HC</td>
<td>6 (IQR 5-9) / 6 (IQR 5-10)</td>
<td>NR</td>
<td>0 / 3.4 (2)</td>
<td>27.2 (6) / 22.4 (13)</td>
<td>4.5 (1) / 1.7 (1)</td>
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<td>Junghans et al.</td>
<td>100</td>
<td>65 / 67</td>
<td>67 / 51.1</td>
<td>SR, RR</td>
<td>4 (range 3-123) / 6 (range 3-79)*</td>
<td>NR</td>
<td>NR</td>
<td>22 (22) / 44.7 (21)*</td>
<td>0 / 0</td>
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<td>29</td>
<td>46.4 / 50.4</td>
<td>100 / 100</td>
<td>SC, IR</td>
<td>4 (IQR 3-5.5) / 4.5 (IQR 4-8.25)</td>
<td>4 (IQR 3-6.5) / 5 (IQR 4-10.25)</td>
<td>10.3 (3) / 11.5 (3)</td>
<td>31.0 (9) / 23.1 (6)</td>
<td>0 / 0</td>
</tr>
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</table>

Continuous data: median (IQR or range) / Lap = laparoscopy / Open = open surgery / ASA = american society of anesthesiologists / PHS = primary hospital stay / OHS = overall hospital stay / LH = left hemicolectomy / RH = right hemicolectomy / SC = subtotal colectomy / SR = sigmoid resection / RR = rectal resection / IR = ileocolic resection / AR = anterior resection / APR = abdominoperineal resection / HC = hartmann closure / NR = not reported / *P < 0.05
In the study by King et al.\textsuperscript{30} readmission rate was significantly lower in the laparoscopic group; absolute risk reduction (ARR) 21\% (95\% CI: 0.6–42.3\%), resulting in a number needed to treat (NNT) of 4.7 patients (95\% CI: 2.4–176). The other studies did not show a significant difference in readmission rates between both surgical techniques.

\textit{Morbidity and mortality}

Morbidity rates were reported in all studies. Only in the study by Junghans et al.\textsuperscript{29} a 23 \% difference in favour of the laparoscopic group was shown (95\% CI: 6.3–39.1\%), i.e. a NNT of 4.4 patients (95\% CI: 2.6–15.9). There were no significant differences between the treatment groups with regard to mortality (Table 3).

<table>
<thead>
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<th>Reference</th>
<th>Readmissions</th>
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<th>Mortality</th>
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<tr>
<td></td>
<td>NNT (95% CI)</td>
<td>ARR (95% CI)</td>
<td>NNT (95% CI)</td>
</tr>
<tr>
<td><strong>RCTs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Basse et al.\textsuperscript{28}</td>
<td>NNT 15.0 (-6.8 , 3.6)</td>
<td>ARR 0.067 (-0.147 , 0.280)</td>
<td>NNT -15.0 (-3.5 , 6.8)</td>
</tr>
<tr>
<td>King et al.\textsuperscript{30}</td>
<td>NNT 4.7 (2.4 , 176)</td>
<td>ARR 0.214 (0.006 , 0.423)</td>
<td>NNT 8.5 (-9.2 , 2.9)</td>
</tr>
<tr>
<td><strong>CCTs</strong></td>
<td></td>
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<tr>
<td>MacKay et al.\textsuperscript{31}</td>
<td>NNT 28.5 (-76.9 , 12.0)</td>
<td>ARR 0.035 (-0.013 , 0.083)</td>
<td>NNT -17.3 (-3.6 , 6.1)</td>
</tr>
<tr>
<td>Junghans et al.\textsuperscript{29}</td>
<td>NR</td>
<td></td>
<td></td>
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<tr>
<td>Polle et al.\textsuperscript{32}</td>
<td>NNT 84.0 (-6.5 , 5.6)</td>
<td>ARR 0.012 (-0.153 , 0.177)</td>
<td>NNT 12.5 (-3.2 , 6.5)</td>
</tr>
</tbody>
</table>

| RCT = randomized controlled trial / CCT = controlled clinical trial / NNT = numbers needed to treat / ARR = absolute reduced risk / NP = not possible to calculate due to lack of data or zero in both groups / NR = not reported |

**Number of fast track items**

Application of the 17 FT elements applied varied among the studies (Table 4). The median number of FT items as applied in the five studies was 13 (IQR 11.5–14.5). Preoperative counselling, fluid restriction, no routine use of nasogastric tubes, enforced postoperative oral feeding/mobilization and early removal of the bladder catheter was required by protocol in all studies. Other FT items, like no bowel preparation and no premedication, were less frequently executed.
Secondary outcome parameters

Quality of life
In the study of King et al.\textsuperscript{30} and MacKay et al.\textsuperscript{31} quality of life after surgery was evaluated. Neither of these studies showed a statistical difference between the treatment groups. King et al.\textsuperscript{30} did report that quality of life in both groups deteriorated 2 weeks after surgery, but improved in both groups after 6 weeks.

Gastrointestinal function
Three studies\textsuperscript{28,29,31} reported about gastrointestinal function. Basse et al.\textsuperscript{28} and MacKay et al.\textsuperscript{31} did not find any significant difference between the treatment groups regarding nausea scores. Median time to first defecation was 2 days in both groups in the study of Basse et al.\textsuperscript{28} In the study of Junghans et al.\textsuperscript{29} the median time (range) to first defecation was 1 (0–6) days postoperatively in the laparoscopic group vs 2 (0–6) days in the open group. This difference was reported as significant. In MacKay et al.\textsuperscript{31} time to first flatus and first defecation were similar between the treatment groups; median (IQR) 68.7 (55.8–76.5) h vs 69.2 (56.0–86.7) h and 127.1 (99.3–148.7) h vs 101.2 (75.2–139.1) h, respectively.

Table 4 Summary of outcomes and FT items presented in the included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>Readmissions</th>
<th>Primary hospital stay</th>
<th>Total hospital stay</th>
<th>Minimum of 30 days follow-up</th>
<th>Preoperative counselling</th>
<th>Planned discharge</th>
<th>Preoperative feeding</th>
<th>No bowel preparation</th>
<th>No premedication</th>
<th>Fluid restriction</th>
<th>Active prevention of hypothermia</th>
<th>Epidural analgesia</th>
<th>Minimal invasive / transverse incisions</th>
<th>No routine use of nasogastric tubes</th>
<th>No use of drains</th>
<th>Local wound infiltration</th>
<th>Enforced postoperative mobilisation</th>
<th>Enforced postoperative oral feeding</th>
<th>No systemic morphine use</th>
<th>Standard laxatives</th>
<th>Early removal of bladder catheter</th>
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</thead>
<tbody>
<tr>
<td>Basse et al.\textsuperscript{28}</td>
<td>60</td>
<td>√</td>
<td>√</td>
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</tbody>
</table>

\(\text{RCT} = \text{randomized controlled trial} / \text{CCT} = \text{controlled clinical trial} / √ = \text{adequately described/present} / - = \text{not present/not studied} / ∼ = \text{not adequately described/partially present}\)
Pain medication

In the study by King et al.\textsuperscript{30} significantly more patients required additional opioid analgesics in the open group; ARR=52\% (95\% CI: 28.2–75.2\%) and NNT=1.9 patients (95\% CI: 1.3–3.5). There were no significant differences reported in use of morphine, paracetamol and tramadol between the groups in the study of MacKay et al.\textsuperscript{31}, mean difference 4 mg (95\% CI: –14.6–23.9 mg).

Discussion

This review points in the direction of superiority of laparoscopic surgery in fast track setting with respect to hospital stay, readmission rates and morbidity, based on a few, individual, study results. However, the available evidence is scarce due to a lack of good quality trials.

Of the two RCTs\textsuperscript{28;30} found, only one\textsuperscript{30} showed a significantly lower primary and overall postoperative hospital stay was significantly lower in the laparoscopic group. The differences between these RCTs\textsuperscript{28;30} in PHS and OHS were considerable. There are several possible explanations. In the study of King et al.\textsuperscript{30} only patients with diagnosed colorectal carcinoma are included. Basse et al.\textsuperscript{28} included patients with benign as well as malignant conditions. The condition of the patients in the study of King et al.\textsuperscript{30} could therefore be worse resulting in a longer postoperative recovery period. Patients requiring a rectal resection or not living independently were excluded in the study of Basse et al.\textsuperscript{28}, but were included by King et al.\textsuperscript{30}.

In the university hospital of Basse et al.\textsuperscript{28} fast track surgery has been developed. Therefore, the results of their programme are likely to be most favourable. Basse et al.\textsuperscript{28} demonstrated that a postoperative hospital stay of 2–3 days after colonic surgery can be achieved both after laparoscopic and open colectomy if performed in fast track setting. However, these results were achieved at the expense of readmission rates up to 26.6\%.

Basse et al.\textsuperscript{28} showed a remarkable high mortality rate in the open group (10\%). This can be explained by the higher ASA scores in that group.

The study of King et al.\textsuperscript{30} was not blinded. It is unclear how this affects hospital stay. On one hand an observer bias favouring the laparoscopic group, could have influenced the results of the study of King et al.\textsuperscript{30}, reporting a significantly worse PHS, OHS and readmission rate in the open group. On the other hand, blinding with large bandages might give the patient the impression they had open surgery hampering recovery and discharge.

In the three CCTs\textsuperscript{29;31;32} found, one study\textsuperscript{29} stated a significantly shorter PHS in the laparoscopic group. In this study\textsuperscript{29} however, almost 50\% of the patients in the open group had an ASA score III or IV and more patients in this group were operated because of a carcinoma (60\%). In their laparoscopic treatment group, 33\% of the patients had an ASA score of III or IV and 41\% had a carcinoma. This could be an explanation for the longer PHS and the higher morbidity in the open group. In the study of Polle et al.\textsuperscript{32} only patients with an ASA score of I and II were included.

Morbidity was around 20–30\% in four studies. Junghans et al.\textsuperscript{29} reported a 23\% reduction in morbidity in the laparoscopic group, but their morbidity of 44.7\% in the open group is
very high. However, it was not clear whether patients with more than one complication were counted twice resulting in this high morbidity percentage. A readmission rate of 0% in the laparoscopic group and 3.4% in the open group in the study of MacKay et al.\textsuperscript{31} indicates that the longer the mean hospital stay, the lower the readmission rate is. Recently, Kehlet’s group confirmed this relation between hospital stay and readmission rate achieving lower readmission rates when hospital stay was prolonged by 1 day.\textsuperscript{35} The longer hospital stay in the study of MacKay et al.\textsuperscript{31} may be caused by their use of patient-controlled instead of epidural analgesia.

Allocation bias could have influenced the results in favour of laparoscopic surgery in the three CCTs by MacKay et al.\textsuperscript{31}, Polle et al.\textsuperscript{32} and Junghans et al.\textsuperscript{39}, because the surgeon decided which patient would undergo laparoscopic or open surgery.

This systematic review was limited by a low number of studies. All studies had small sample sizes and only one study used a proper sample size calculation. Overall quality of the selected studies was found to be moderate. Of the five included studies\textsuperscript{28-32}, three studies were CCTs\textsuperscript{29;31;32}, which increases the probability bias will occur. Due to clinical heterogeneity the data could not be pooled. Mean differences and 95% CIs could not be calculated as data were not normally distributed.

Fast track periooperative care in colonic surgery has been introduced more then 10 years ago. In all studies\textsuperscript{28-32} the number of applied fast track items in the protocol were reported, but only one study, Polle et al.\textsuperscript{32}, reported the number of FT items actually achieved. In this study 15 fast track elements have been applied and 13 elements have been evaluated. An average of 7.4 of 13 fast track modalities were successfully achieved per patient. Nevertheless, despite this low success rate of implementing the fast track items, it was reported that a significantly faster recovery of the fast track group resulted in a shorter hospital stay. It is clear that a full implementation of all items encompassing the fast track protocol requires a learning curve and a dedicated multidisciplinary functioning team. Although there is evidence about most items of the programme, it seems hard to implement all different elements of fast track as every discipline has to break with longstanding traditions.

In conclusion, the presently available evidence does not allow a robust conclusion on the outcomes of laparoscopic vs open surgery within a fast track setting. Only five studies were available for analysis. So, the question remains whether fast track or modern traditional care, laparoscopic or open surgery, or a combination of both is the preferred strategy. This research question is the objective of the LAFA study\textsuperscript{36}, comprising over 400 patients, that will hopefully provide the answer to this question in the middle of 2009.
References

LAparscoopy in combination with FAst track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: A Randomized Clinical Trial (LAFA-study)
Abstract

Objective
To investigate which perioperative treatment, i.e. laparoscopic or open surgery combined with fast track (FT) or standard care, is the optimal approach for patients undergoing segmental resection for colon cancer.

Summary background data
Important developments in elective colorectal surgery are the introduction of laparoscopy and implementation of FT care, both focusing on faster recovery.

Methods
In a nine-centre trial, patients eligible for segmental colectomy were randomized to laparoscopic or open colectomy, and to FT or standard care, resulting in four treatment groups. Primary outcome was total postoperative hospital stay. Secondary outcomes were postoperative hospital stay, morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at two and four weeks, patient satisfaction and in-hospital costs. Four hundred patients were required to find a minimum difference of one day in hospital stay.

Results
Median total hospital stay in the laparoscopic/fast track group was 5 (inter-quartile range: 4-8) days; open/fast track 7 (5-11) days; laparoscopic/standard 6 (4.5-9.5) days, and open/standard 7 (6-13) days (P<0.001). Median postoperative hospital stay in the laparoscopic/fast track group was 5 (4-7) days; open/fast track 6 (4.5-10) days; laparoscopic/standard 6 (4-8.5) days and open/standard 7 (6-10.5) days (P<0.001). Secondary outcomes did not differ significantly among the groups. Regression analysis showed that laparoscopy was the only independent predictive factor to reduce hospital stay and morbidity.

Conclusions
Optimal perioperative treatment for patients requiring segmental colectomy for colon cancer is laparoscopic resection embedded in a FT program. If open surgery is applied, it is preferentially done in FT care.
**Introduction**

Worldwide, colon cancer is the second most common cancer. Its incidence is expected to rise with the increasing longevity of the Western population. Surgical resection is the first line strategy to treat colonic cancer and the implementation of screening programs is likely to further increase the number of patients requiring colonic surgery.

Over the past twenty years there have been two important developments in elective major abdominal surgery; the introduction of laparoscopic surgery and the implementation of an enhanced recovery after surgery (ERAS) program, also referred to as ‘fast track’ (FT) perioperative care, both focusing on accelerated recovery resulting in shorter hospital stay.\(^1\)\(^2\) Laparoscopic resection of bowel cancer was first described in 1991.\(^1\) Randomized clinical trials have shown that this technique is safe and effective for malignant disease, and results in a hospital stay shorter by about 1-4 days, and less morbidity and postoperative pain than open colorectal surgery.\(^3\)\(^-\)\(^5\)

During the mid-nineties FT perioperative care was pioneered by Henrik Kehlet.\(^2\)\(^,\)\(^6\)\(^-\)\(^8\) FT programs consist of a multidisciplinary approach, involving dieticians, nurses, surgeons and anesthesiologists and are aimed at reducing surgical stress response, organ dysfunction and morbidity, thereby promoting a faster recovery after surgery.\(^7\)\(^,\)\(^9\) FT perioperative care comprises extensive preoperative counseling, no bowel preparation, no sedative premedication, carbohydrate-loaded liquids up to two hours before surgery, effective multimodal pain management, short acting anaesthetics, adequate perioperative fluid management, small incisions, and no routine use of drains and nasogastric tubes. Postoperative care includes early oral feeding, enforced mobilization, early removal of urinary catheter, and standard laxatives.

Similar or even faster rates of recovery have been reported for FT open colectomy on comparison with laparoscopic colectomy in a standard perioperative care setting.\(^10\)\(^-\)\(^12\) Since the leading trials\(^3\)\(^-\)\(^5\) comparing laparoscopic with open surgery have been done in a traditional perioperative care setting, this comparison needs to be re-evaluated within an enhanced recovery program.

There are no trials to be found in literature addressing the four combinations of standard or FT care with laparoscopic or open surgery. The longstanding question of which of the four perioperative treatment options is the optimal one for the patient with respect to postopera-
tive recovery remains unanswered.\textsuperscript{13,14} Two systematic reviews looked at all available studies comparing open surgery with laparoscopic surgery within a FT program, but no firm conclusion could be made due to lack of data.\textsuperscript{15,16}

Hypothetically, combining the two new developments, i.e. FT care and laparoscopy, will result in the fastest postoperative recovery. At the same time, it is questionable if both of them are as important with respect to postoperative recovery.

Hence, our aims were to determine which form of perioperative treatment, laparoscopic or open surgery combined with FT or standard care, is the optimal approach for patients undergoing segmental resection for colon cancer, and to investigate if either laparoscopy, FT care, or the combination of both is the main predictive factor for a faster postoperative recovery.

\textbf{Methods}

Patients treated in nine Dutch hospitals (three University hospitals and six teaching hospitals) were eligible if they were between 40 and 80 years of age, had an American Society of Anesthesiologists (ASA) grade of I, II or III, were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma, and without evidence of metastatic disease. Exclusion criteria were prior midline laparotomy, unavailability of a laparoscopic surgeon, emergency surgery, or a planned stoma. The study was conducted in accordance with the principles of the Declaration of Helsinki and according to the CONSORT statement.\textsuperscript{17} The independent medical ethics review boards of the participating hospitals approved the study protocol. The study was registered under NTR222.\textsuperscript{18}

\textbf{Design}

A randomized trial of a 2 x 2 balanced factorial design was performed. After written informed consent had been obtained, patients were randomized by means of an internet randomization module. Block-randomization was used and randomization was stratified for the randomizing centers. Patients were randomized to laparoscopic or open colectomy, and to the FT program or standard care. This resulted in four treatment groups: (a) laparoscopic colectomy with FT care (Lap/FT) (b) open colectomy with FT care (Open/FT) (c) laparoscopic colectomy with standard care (Lap/Standard), and (d) open colectomy with standard care (Open/Standard). Patients and nursing staff were routinely informed about the perioperative care program, i.e. FT care or standard care, but were blinded to the type of intervention, i.e. laparoscopic or open surgery.

\textbf{Outcomes}

Primary outcome was total postoperative hospital stay (THS), measured in days. THS was defined as postoperative hospital stay plus the additional hospitalization period in case patients were readmitted within 30 days of surgery. All patients were discharged if they complied with the following predefined discharge criteria: (1) adequate pain control with paracetamol and/or non-steroidal anti-inflammatory drugs (2) ability to tolerate solid food (3) absence of nausea (4) passage of first flatus and/or first stool (5) mobilization as preoperative, and (6) acceptance of discharge by the patient.
Secondary outcomes were postoperative hospital stay (PHS), overall morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at two and four weeks, patient satisfaction four weeks postoperatively and in-hospital costs.

General quality of life was assessed with the validated and widely-used Short Form-36 (SF-36).\textsuperscript{19} Bowel-related quality of life was assessed with the validated Gastro-Intestinal Quality of Life Index (GIQLI).\textsuperscript{20} Physical functioning, bodily pain and social functioning scales (SF-36), and social functioning scale (GIQLI) were secondary outcomes.

Additionally, a self-reported patient satisfaction questionnaire, routinely used at our center, was sent to all patients. It comprises 16 items, addressing issues including satisfaction with personal attention from the surgeon and nurses and medical information. Total patient satisfaction scores ranged from 16 (lowest patient satisfaction) to 80 (highest patient satisfaction).

The marginal direct medical in-hospital costs were calculated per patient for the four treatment strategies. These costs included outpatient care, operating time, patient-days, the additional costs of laparoscopy and of fast track care, as well as the costs of complications, reoperations and readmissions within 30 days after the index operation.

\textit{FT care versus standard care}

In order to avoid cross-over treatment by the nursing staff, patients were admitted either to a ward providing FT care or a ward providing standard care, depending on randomization. These treatment protocols are described in detail elsewhere.\textsuperscript{18} Nursing and medical staff working on the FT care ward were already familiar with FT care prior to this study.

\textit{Surgical technique}

The technique of the open or laparoscopic procedure was at the discretion of the local surgeon. Participating laparoscopic surgeons were required to have performed a minimum of 20 laparoscopic colectomies for benign disease as stated in the proclamation of the American Society of the Colon and Rectum Surgeons in 2004, before they were allowed to perform laparoscopic colectomy for cancer. A laparoscopic procedure was considered converted if there was an unplanned enlargement of the incision. No quality requirements were set for open surgery as this was standard care in all centers. A right colectomy was typically done via midline laparotomy. At the end of surgery the abdomen was covered with a large dressing to hide the type of approach in order to blind the patient, doctors and nurses on the ward.

\textit{Data collection}

Data were collected via a secured dedicated website. Up to discharge, nursing staff reported daily on the patient’s progress, i.e. intake, passage of flatus, and predefined discharge criteria were checked. After 30 days of follow-up, the anesthetic and clinical dossiers (nursing and medical) were checked for missing data. Outpatient medical dossiers were checked for any complication that had occurred after discharge within 30 days of the operation. The SF-36 and GIQLI were mailed to the patients prior to and at two and four weeks following the operation. The patient satisfaction questionnaire was mailed four weeks postoperatively. All quality of life data from patients who had returned baseline questionnaires were incorporated into the analysis, even if one or two follow-up measurements were missing.
Sample size calculation
Since both FT care and laparoscopy aim at faster recovery resulting in a reduction of hospital stay, hospital stay was used as the primary efficacy parameter. Using a 5% significance level, a total sample size of 400 had a power of >95% to detect a minimum reduction in THS of one day between laparoscopic and open surgery, one day reduction in THS between FT and standard care, and a power of 80% to detect the same difference between the combination of FT with laparoscopic surgery and open surgery with standard care.18

Statistical analysis
Statistical analyses of any differences between the four groups were performed using SPSS for Windows version 16 (SPSS Inc. Chicago, Ill., USA). Data were analyzed in according to the intention to treat principle. Data were presented as means ± standard deviations or as medians and inter-quartile ranges where appropriate. For dichotomous outcomes, treatment groups were compared by means of the Chi-square test. The Mann-Whitney U test and Kruskal Wallis tests were used for continuous, not normally distributed outcomes. For continuous normally distributed data, the ANOVA test was used. Univariate and multiple linear or logistic regression analyses were performed to analyze the effect of laparoscopy, FT care and the combination of both on the primary and secondary endpoints. As the length of hospital stay was not normally distributed, these data were log-transformed. Quality of life was investigated through multilevel modeling, with fixed measurement occasions (level one) nested within patients (level two). The appropriate covariance structure for the data was unstructured and all models included time and treatment interactions. In-hospital costs were separately analyzed for the university and teaching hospitals. A two-sided P-value <0.05 was considered to be statistically significant.

Results
Between July 2005 and August 2009, 427 patients were randomly assigned to one of the four treatment groups (Figure 1). Baseline characteristics between the four treatment groups did not differ significantly (Table 1).
**Figure 7.1 Study Flow**

- Excluded n = 106
  - Laparoscopy/Past Track

- Excluded n = 103
  - Open/Past Track

- Excluded n = 110
  - Laparoscopy/Standard Care

- n = 108
  - Open/Standard Care

- Analyzed n = 601
  - Emergency operation
  - Withdrawal
  - Previous medical history
  - Death

- Excluded n = 93
  - Uninterpretable
  - Incomparable
  - Withdrawal
  - Death

- Analyzed n = 86
  - Emergency operation
  - Incomparable
  - Withdrawal
  - Death

- Excluded n = 10
  - Incomparable
  - Uninterpretable
  - Death

- n = 427 Randomized
Table 1 Baseline characteristics and surgical aspects of the included patients per group

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy &amp; Fast Track (n = 100)</th>
<th>Open &amp; Fast Track (n = 93)</th>
<th>Laparoscopy &amp; Standard care (n = 109)</th>
<th>Open &amp; Standard care (n = 98)</th>
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<td>Age – yr*</td>
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<td>68±8.8</td>
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<td>55</td>
<td>50</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>- T3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>- T4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stage – %</td>
<td>64</td>
<td>61</td>
<td>68</td>
<td>70</td>
<td>0.893³</td>
</tr>
<tr>
<td>- N0</td>
<td>29</td>
<td>31</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>- N1</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>M stage – %</td>
<td>98</td>
<td>96</td>
<td>94</td>
<td>94</td>
<td>0.509⁰</td>
</tr>
<tr>
<td>- M0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Conversion – n (%)</td>
<td>12 (12)</td>
<td>12 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>171</td>
<td>129</td>
<td>165</td>
<td>129</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>139 – 198</td>
<td>101 – 175</td>
<td>135 – 204</td>
<td>110 – 151</td>
<td></td>
</tr>
<tr>
<td>Blood loss</td>
<td>50</td>
<td>200</td>
<td>100</td>
<td>200</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>0 – 150</td>
<td>100 – 306</td>
<td>0 – 200</td>
<td>100 – 350</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± standard deviation / BMI = Body Mass Index / ASA = American Society of Anesthesiologists / IQR = inter-quartile range / ANOVA test / Chi-square test / Kruskal-Wallis test
Protocol compliance

Fifteen FT elements were evaluated per patient. The following elements were scored if successfully applied; preoperative counseling, omission of bowel preparation, intake of carbohydrate-loaded drinks at the day before surgery, intake of carbohydrate-loaded drinks at the morning before surgery, no preoperative fasting since midnight, omission of premedication, thoracic epidural analgesia, prevention of hypothermia, adequate perioperative fluid loading, removal of nasogastric tube before extubation, omission of abdominal drains, suprapubic catheter or no catheter, more than 500 ml of intake at postoperative day (POD) 0 including 200 ml carbohydrate-loaded drink, more than 15 minutes mobilization at POD 0, and starting with laxative at POD 1. In the Lap/FT group 11.2 ± 2.2 out of the 15 elements and in the Open/FT group 11.1 ± 2.2 elements were successfully applied per patient (Table 2).

As illustrated in Table 2 some FT elements have also been implemented in the standard care group; in the Lap/Standard 6.0 ± 1.5 elements and in the Open/Standard 5.8 ± 1.4 elements per patient. Other applied elements were; prevention of hypothermia in 97% of the patients, removal of the nasogastric tube before extubation in 82%, and omission of abdominal drains in 93%. Although thoracic epidural analgesia was applied at an equal rate in all groups, the epidural catheter remained significantly longer in situ in the standard care groups (a median (IQR) i.e. 3 (2-4) days compared with 2 (2-3) days in the FT groups (P<0.001)).

Primary outcome

THS and PHS in patients randomized to the Lap/FT group was significantly (median 1 day) shorter than in the other three treatment groups (P<0.001). There was no significant difference in THS or PHS between patients treated with Open/FT and patients treated with Lap/Standard. Patients who underwent Open/Standard treatment had a significantly longer PHS than Lap/FT, Open/FT, and Lap/Standard. THS after Open/Standard treatment was significantly longer than Lap/FT and Lap/Standard (Table 3).

Linear regression analysis identified laparoscopy as the only independent factor to influence THS (B=0.79, confidence interval (CI): 0.69-0.91, P=0.001), i.e. laparoscopic surgery would lead to a reduction in THS of 21% (CI: 9-31%). FT care showed a trend toward a shorter THS (B=0.88, CI: 0.77-1.01, P=0.070), but the combination of both showed no additional benefit. PHS was significantly influenced by both laparoscopy (B=0.80, CI: 0.70-0.91, P=0.001), i.e. leading to a reduction in PHS of 20% (CI: 9-30%), and FT care (B=0.86, CI: 0.76-0.98, P=0.025), i.e. a reduction of 14% (CI: 10-20%). The combination of both did not add any benefit.
### Table 2 Protocol compliance

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy &amp; Fast Track (n = 100)</th>
<th>Open &amp; Fast Track (n = 93)</th>
<th>Laparoscopy &amp; Standard care (n = 109)</th>
<th>Open &amp; Standard care (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross-over</strong> ^1 – n (%)</td>
<td>3^a (3)</td>
<td>3^b (3)</td>
<td>3^c (2)</td>
<td>2^d (2)</td>
</tr>
<tr>
<td><strong>Preoperative phase</strong> – Yes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative counseling</td>
<td>96 (96)</td>
<td>92 (99)</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Omission of bowel preparation</td>
<td>96 (96)</td>
<td>90 (97)</td>
<td>85 (78)</td>
<td>83 (85)</td>
</tr>
<tr>
<td>Intake of CHL – day before surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – liter</td>
<td>0.8 (0.3-0.8)</td>
<td>0.8 (0-0.8)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td><strong>Day of surgery</strong> – Yes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intake of CHL – 2 hours before surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – liter</td>
<td>0.4 (0.2-0.4)</td>
<td>0.4 (0-0.4)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>No preoperative fasting since midnight</td>
<td>87 (87)</td>
<td>77 (83)</td>
<td>29 (27)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>Omission of premedication</td>
<td>69 (69)</td>
<td>61 (66)</td>
<td>23 (21)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Thoracic epidural analgesia</td>
<td>87 (87)</td>
<td>84 (90)</td>
<td>72 (66)</td>
<td>74 (76)</td>
</tr>
<tr>
<td>Intraoperative fluid loading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – liter</td>
<td>2.2 (1.6 – 3)</td>
<td>2.5 (2 – 3)</td>
<td>2.5 (2 – 3.1)</td>
<td>2.6 (2 – 3.5)</td>
</tr>
<tr>
<td>Suprapubic catheter or no catheter</td>
<td>47 (47)</td>
<td>54 (58)</td>
<td>42 (39)</td>
<td>30 (31)</td>
</tr>
<tr>
<td>Intake of CHL – after surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – liter</td>
<td>0.0 (0-0.2)</td>
<td>0.0 (0-0.2)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>Total oral intake – after surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – liter</td>
<td>0.5 (0.1-0.8)</td>
<td>0.3 (0-0.8)</td>
<td>0.05(0-0.2)</td>
<td>0.0 (0-0.2)</td>
</tr>
<tr>
<td>Mobilization – after surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR] – minutes</td>
<td>0.0 (0-19)</td>
<td>0.0 (0-20)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>Start laxative POD 1 – Yes, n (%)</td>
<td>85 (85)</td>
<td>77 (83)</td>
<td>9 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Intake of CHL – liter (median [IQR])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- POD 1</td>
<td>0.2 (0-0.4)</td>
<td>0.2 (0-0.4)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>- POD 2</td>
<td>0.2 (0-0.4)</td>
<td>0.2 (0-0.4)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>- POD 3</td>
<td>0.0 (0-0.4)</td>
<td>0.0 (0-0.4)</td>
<td>0.0 (0-0)</td>
<td>0.0 (0-0)</td>
</tr>
<tr>
<td>Total oral intake – liter (median [IQR])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- POD 1</td>
<td>1.5 (0.9-1.9)</td>
<td>1.1 (0.7-1.6)</td>
<td>0.9 (0.5-1.5)</td>
<td>0.7 (0.3-1.0)</td>
</tr>
<tr>
<td>- POD 2</td>
<td>1.7 (1.0-2.0)</td>
<td>1.4 (0.8-2.0)</td>
<td>1.2 (0.8-1.7)</td>
<td>1.0 (0.4-1.5)</td>
</tr>
<tr>
<td>- POD 3</td>
<td>1.8 (1.2-2.0)</td>
<td>1.8 (1.0-2.0)</td>
<td>1.5 (1.0-2.0)</td>
<td>1.0 (0.7-1.8)</td>
</tr>
<tr>
<td>Mobilization – minutes (median [IQR])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- POD 1</td>
<td>120 (50-240)</td>
<td>120 (60-215)</td>
<td>30 (15-60)</td>
<td>20 (0-60)</td>
</tr>
<tr>
<td>- POD 2</td>
<td>200 (90-360)</td>
<td>120 (60-240)</td>
<td>90 (45-180)</td>
<td>60 (20-115)</td>
</tr>
<tr>
<td>- POD 3</td>
<td>300 (120-400)</td>
<td>220 (100-360)</td>
<td>135 (60-240)</td>
<td>100 (53-195)</td>
</tr>
</tbody>
</table>

---

^2 pt. received Open FT / 1 pt. received Lap Standard ; ^3 pt. received Open Standard / 1 pt. received Lap FT ; ^4 pt. received Open Standard / 1 pt. received Lap FT ; ^1 Analysis according to intention to treat ; ^5 Preoperative counseling = separate consultation before admission with a ‘fast track’ trial nurse to discuss the essence of the fast track program ; CHL = carbohydrate-loaded drink / IQR = inter-quartile range / POD = postoperative day
### Table 3: Postoperative data

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy &amp; Fast Track (n = 100)</th>
<th>Open &amp; Fast Track (n = 93)</th>
<th>Laparoscopy &amp; Standard care (n = 109)</th>
<th>Open &amp; Standard care (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total hospital stay</strong></td>
<td>Days (4 – 8)</td>
<td>Days (5 – 11)</td>
<td>Days (4.5 – 9.5)</td>
<td>Days (6 – 13)</td>
</tr>
<tr>
<td><strong>Postoperative hospital stay</strong></td>
<td>Days (4 – 7)</td>
<td>Days (4.5 – 10)</td>
<td>Days (4 – 8.5)</td>
<td>Days (6 – 10.5)</td>
</tr>
<tr>
<td><strong>Days to fulfill discharge criteria</strong></td>
<td>Pain control with oral medication</td>
<td>Pain acceptance of discharge</td>
<td>Migration as pre-operative</td>
<td>Passage of first stool</td>
</tr>
<tr>
<td><strong>In-hospital costs</strong></td>
<td>University hospitals – €</td>
<td><em>Median (IQR)</em></td>
<td>Teaching hospitals – €</td>
<td><em>Median (IQR)</em></td>
</tr>
<tr>
<td></td>
<td>10 594</td>
<td>(5 461 – 16 763)</td>
<td>5768</td>
<td>(4873 – 8917)</td>
</tr>
<tr>
<td></td>
<td>12 805</td>
<td>(6 847 – 20 658)</td>
<td>5497</td>
<td>(4506 – 6513)</td>
</tr>
<tr>
<td></td>
<td>11 967</td>
<td>(6 222 – 17 039)</td>
<td>6228</td>
<td>(5280 – 6604)</td>
</tr>
<tr>
<td></td>
<td>10 479</td>
<td>(6 608 – 16 875)</td>
<td>5650</td>
<td>(4836 – 8003)</td>
</tr>
</tbody>
</table>

Values median (inter-quartile range) / ±Kruskal-Wallis test / ≠Significant difference (Mann Whitney U) between Lap/FT & Open/FT

Difference (Mann Whitney U) between Lap/FT & Open/FT (0.008); Lap/FT & Open/Standard (0.000); Lap/FT & Lap/Standard (0.010); Lap/Standard & Open/Standard (0.000); Lap/Standard & Open/Standard (0.000).

<table>
<thead>
<tr>
<th>Postoperative laparoscopic stay – days</th>
<th>P = 0.048</th>
<th>P = 0.009</th>
<th>P = 0.010</th>
<th>P = 0.006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hospital stay – days</td>
<td>(n = 99)</td>
<td>(n = 109)</td>
<td>(n = 93)</td>
<td>(n = 98)</td>
</tr>
<tr>
<td>Fast Track</td>
<td>6 (4.5 – 7)</td>
<td>5 (4.5 – 7)</td>
<td>6 (4.5 – 7)</td>
<td>5 (4.5 – 7)</td>
</tr>
<tr>
<td>Standard care</td>
<td>7 (6 – 1.3)</td>
<td>7 (6 – 1.3)</td>
<td>7 (6 – 1.3)</td>
<td>7 (6 – 1.3)</td>
</tr>
<tr>
<td>Open</td>
<td>8 (7 – 9.5)</td>
<td>8 (7 – 9.5)</td>
<td>8 (7 – 9.5)</td>
<td>8 (7 – 9.5)</td>
</tr>
</tbody>
</table>

Chapter 7
Secondary outcomes
There were no significant differences between the four treatment groups regarding overall-, major-, or minor morbidity, reoperation rate, readmission rate and in-hospital mortality (Table 4). Logistic regression analysis showed that laparoscopic resection resulted in a significantly lower overall- and major morbidity (OR 1.53, CI: 1.02-2.29, P=0.041, and OR 1.73, CI: 1.01-2.95, P=0.045, respectively). Neither FT care nor the combination of both reduced overall- and major morbidity. Minor morbidity, reoperation and readmission rate were not significantly influenced by the different surgical regimens.

There were no statistically significant differences, adjusted for the type of hospital, in in-hospital costs among the treatment groups as tested with the Kruskall Wallis test and linear regression analysis (Table 3).

The discharge criterion ‘absence of nausea’ was achieved at the same postoperative day in all groups. Lap/FT patients had a significantly faster recovery, i.e. achieved five discharge criteria earlier, than patients in the Lap/Standard or Open/Standard groups. Lap/FT patients showed a significantly quicker ‘passage of first stool’ and ‘acceptance of discharge’ than those in the Open/FT group (Table 3).

Five discharge criteria were achieved significantly earlier in Open/FT than in Open/Standard treatment; the criteria ‘tolerate solid food’ and ‘mobilization as preoperative’ were achieved significantly earlier in Open/FT than in Lap/Standard.

Apart from the criteria ‘absence of nausea’, ‘tolerate solid food’ and ‘passage of first flatus’, Lap/Standard patients achieved all other discharge criteria significantly earlier than Open/Standard patients.

Due to missing data at baseline, the overall analysis of data generated by the SF-36 and GIQLI was conducted in 352 patients (88%). At follow-up there was an overall response rate of 80% and 84% at two and four weeks postoperatively. Quality of life at baseline was not significantly different among the groups for the scales assessed. Overall, physical functioning, bodily pain, and social functioning measured with the SF-36, and social functioning measured with the GIQLI, significantly declined at two weeks postoperatively. Four weeks following surgery bodily pain and social functioning measured with the SF-36 returned to baseline values. The other functioning scales remained significantly lower. There were no statistically significant differences on any of the scales among the four treatment groups at any time point. Patient satisfaction was similar across all groups.
Discussion
This trial showed that the combination of laparoscopic surgery with FT care resulted in a significantly faster recovery after colonic surgery than all other combinations, i.e. Open/FT, Lap/Standard, or Open/Standard. Patients treated with Open/FT or Lap/Standard had a similar postoperative recovery; Open/Standard treatment resulted in the worst outcome. Treatment
groups had similar morbidity, reoperation and readmission rates, equal in-hospital mortality, comparable levels of quality of life and patient satisfaction, and similar in-hospital costs. Laparoscopy was found to be the only significant independent factor to reduce postoperative hospital stay and morbidity.

The main goal of the FT concept is not to discharge patients earlier, but to accelerate the patient’s postoperative recovery resulting in a shorter hospital stay. The primary outcome, total postoperative hospital stay, was standardized by predefined objectively quantified discharge criteria, which is in contrast to other studies where discharge criteria have not been defined properly.9;13;21-23 In our study, discharge criteria were scored daily.

Length of hospital stay after a Lap/FT or Open/FT treatment in our study was in accordance with the literature,13;22;24;25 but longer than that reported by Kehlet et al.9;21;26 It should be pointed out that Kehlet’s results were achieved at the center where FT was developed, and at the expense of a higher readmission rate. Our study might therefore reflect daily practice more accurately.

On comparison with the literature overall morbidity in the four treatment groups was relatively high. This can be explained by the fact that all complications both intra- and extramural, were scored prospectively and by the inclusion of patients aged up to 80. Two systematic reviews comparing FT with standard care suggest reduced morbidity and mortality in FT.10;11 We found no significant difference in overall morbidity and mortality between the four groups. However, less morbidity was associated with laparoscopic surgery, while this was not the case for FT care. It is remarkable and yet unexplained, that in this trial patients treated in the Open/Standard group underwent reoperation more frequently (18%) than literature reports. In the Netherlands the mean figure is 11%.

Quality of life two and four weeks postoperatively were similar across the groups, which is in accordance with a recently published systematic review.27 This is probably explained by the fact that all patients were operated for cancer and therefore the most important aim for them was to get cured. Another explanation is that differences in quality of life are expected to be the most prominent in the first week after surgery.

Most studies investigating the effectiveness of FT protocols did not assess how many of the FT elements were actually implemented in practice. It is important to evaluate this, particularly as implementation of this multidisciplinary protocol in clinical practice has proven difficult.7;28-30 Eleven of the 15 predefined FT elements were successfully applied in our FT groups. Four systematic reviews10-12;16 reported means of between 8.5 and 13 FT elements applied, whereby applied does not necessarily mean achieved. The reduction in hospital stay of only 1 day, as found in the Lap/FT group, is probably due to the fact that standard care actually meant modern care. In the participating centers, standard care included 6 of the 15 predefined FT items. Based on existing evidence we felt that it would have been unethical and unreal to withhold these in trial setting.31;32

Laparoscopy as well as FT care is more expensive than open surgery and standard care. Nevertheless, in-hospital costs were similar between the groups. A cost-effectiveness analysis
was therefore not performed. The higher costs of laparoscopy and FT care were most likely
counterbalanced by a shorter hospital stay and, although not significant, less overall morbid-
ity. Moreover, saving 1-2 days per treated patient, hospital bed utilization will be reduced by
20%.

Apart from the set of items applied, the discriminating feature of the FT program is the re-
habilitation process which is always implemented in the same way. For example, the protocol
precluded the discussion of, if, and when the patient could eat and mobilize after surgery, or
the time of removal of the epidural. It is likely to be the fact that perioperative care is pro-
tocolized, rather than the combination and number of applied FT elements, that is the true
source of the success of the FT program. Further study is required to distinguish which of the
FT items are essential for enhanced recovery.

The limitations of our study were the blinding of the treatment, which was difficult to
achieve as the majority of the patients could not resist looking under the abdominal dress-
ing. Wound inspection was not a limiting factor as this was not carried out until the day of
discharge, but obviously only in those patients without wound complaints or complications.
Nonetheless, this possible failure has not influenced our primary outcome as discharge was
clearly defined by applying strict discharge criteria. Secondly, after randomization more pa-
tients in the open groups (n=20) than in the laparoscopic groups (n=7) were excluded, nev-
ertheless we can assume that this is coincidental. Thirdly, as patients have been enrolled for
over four years, there might have been in drift in care, i.e. patients included in a later phase
of the study, allocated to standard care, might have received more FT elements than patients
included at the start of the study. We tried to avoid this though by admitting patients to a
ward providing FT care or a ward providing standard care.

In conclusion, the optimal treatment combination for patients requiring segmental colec-
tomy for malignancy is a laparoscopic approach within a FT perioperative care program. If
open surgery has to be performed, for example because of the lack of laparoscopic expertise or
patient-related factors, then this should preferentially be embedded in a FT protocol.

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The authors would like to thank all investigators of the LAFA study group and all patients
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References


Gastrointestinal motility recovers faster after laparoscopy and fast track care in patients undergoing co- lonic surgery

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Submitted
Abstract

Background
Postoperative ileus characterized by delayed gastrointestinal (GI) transit and is a major determinant of recovery after colorectal surgery. Both laparoscopic surgery and fast track multimodal perioperative care have been reported to improve clinical recovery, i.e. earlier occurrence of flatus and defecation and tolerance of food. However, objective measures supporting faster GI recovery are lacking. The aim of this study was to objectively assess, using a scintigraphic technique, which perioperative strategy, laparoscopic or open surgery combined with fast track or standard care, leads to a faster recovery of the gut after colonic surgery.

Methods
Patients requiring elective colonic surgery were enrolled in the Academic Medical Center as part of the LAFA (LAparoscopy in combination with FAst track multimodal management is the best perioperative strategy in patients undergoing colonic surgery) multicenter trial. Colonic transit and gastric emptying were scintigraphically assessed from day 1 to 3. Colonic transit at day 2 and 3 was represented as geometrical center (GC) of activity (segment 0=small intestine, 1=proximal colon, 2=distal colon, 3=toilet). Secondary endpoints were time to toleration of solid food and/or bowel movement, and time until (ready for) discharge.

Results
In total 93 patients participated. The median colonic transit at day 3 of patients undergoing laparoscopic/fast track care (GC: 2.6 (2.0-2.9)) was significantly faster, compared to laparoscopic/standard (GC: 2.2 (1.6-2.5), P=0.044), open/fast track (GC: 2.0 (1.6-2.4), P=0.010), and open/standard group (GC: 1.3 (1.0-1.5, P<0.001). Multivariate regression analysis showed that both laparoscopic surgery and fast track care were significant independent predictive factors of improved colonic transit, resulted in significantly shorter time until toleration of solid food and bowel movement and faster clinical recovery.

Conclusions
These data demonstrate that colonic transit recovers fastest after laparoscopic surgery embedded in the fast track program, providing objective data that this combination leads to faster recovery of GI motility and concomitant enhanced clinical recovery.
Introduction

Each patient undergoing an abdominal surgical procedure will develop a transient episode of impaired gastrointestinal (GI) motility or postoperative ileus (POI). Importantly, POI is the single most important determinant of hospital stay after abdominal surgery and consequently significantly contributes to postoperative morbidity and hospitalization costs. Laparoscopic surgery and the implementation of an enhanced recovery after surgery (ERAS) program, also referred to as ‘fast-track’ (FT) perioperative care are the two most important recent advances in modern surgical care. Both have been reported to be safe and effective and to result in a shorter hospital stay with earlier recovery of GI function and less morbidity compared to open colorectal surgery and standard care.

FT programs in colonic surgery were introduced to reduce surgical stress response, organ dysfunction and morbidity, thereby promoting a faster recovery after surgery. This multimodal perioperative care strategy constitutes a multidisciplinary approach involving dieticians, nurses, surgeons and anaesthesiologists. It mostly focuses on fluid restriction, optimized analgesia, early oral nutrition and early mobilization. Similarly, faster postoperative clinical recovery has been reported following laparoscopic procedures most likely due to decreased tissue trauma compared to open procedures. It should be emphasized though that most studies assessing POI have used rough clinical parameters such as return of bowel sounds and time to first flatus or defecation as primary outcomes. These parameters are not only difficult to assess accurately, but it is also questionable to what extent they reflect restoration of GI motility. For example, the occurrence of first flatus may rather reflect emptying of rectal gas rather than recovery of colonic transit. To date, only two clinical studies comparing laparoscopic and open colectomies objectively measured postoperative GI motility and at best showed only a modest increase in the recovery of GI motility. With regard to the comparison between the current standard approach and the FT care concept, there are no clinical controlled trials providing objective measures on postoperative bowel recovery. Therefore, the question whether laparoscopic surgery and/or FT care lead to a faster recovery of GI motility measured by postoperative GI transit remains unanswered. Hence, our aim was to objectively assess using a scintigraphic technique which perioperative strategy, laparoscopic or open surgery combined with FT or standard care, leads to a faster recovery of the gut after colonic surgery.
Methods

Patients enrolled in the Academic Medical Center Amsterdam as part of the LAFA (LAparoscopy in combination with FAst track multimodal management is the best perioperative strategy in patients undergoing colonic surgery) multicenter trial were eligible for this study. Patients between 40 and 80 years of age, with an American Society of Anesthesiologists Physical Health status (ASA-PS) status < IV, were invited to participate if they were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma without evidence of metastatic disease. Exclusion criteria were prior midline laparotomy, unavailability of a laparoscopic surgeon, emergency surgery, or a planned stoma.

The study was registered under NTR1884 and was conducted in accordance with the principles of the Declaration of Helsinki and according to the CONSORT statement. The protocol was approved by the independent medical ethics review board of the Academic Medical Center Amsterdam, the Netherlands.

Study design

A 2 x 2 balanced factorial block design was used to randomize patients to laparoscopic or open colectomy, and to the FT program or standard care. This resulted in four treatment groups: (I) laparoscopic colectomy with FT care (Lap/FT), (II) laparoscopic colectomy with standard care (Lap/Standard), (III) open colectomy with FT care (Open/FT), and (IV) open colectomy with standard care (Open/Standard). All procedures were performed by one of three staff surgeons with a fellow and/or a resident. Patients and nursing staff were routinely informed about the perioperative care program, i.e. FT care or standard care, but were blinded to the type of surgical intervention, i.e. laparoscopic or open surgery by covering the abdomen with a large dressing.

In order to avoid cross-over treatment of FT and standard care by the nursing staff, patients were admitted either to a ward providing FT care or a ward providing standard care, depending on randomization. Nursing and medical staff working on the FT care ward were already familiar with FT care prior to this study. The principles of the standard care and FT multimodal management are described in detail elsewhere.

Twenty-four hours after surgery, patients underwent a solid gastric emptying test (99mTc labelled pancake, 115 Kcal) directly followed by the ingestion of 60 ml of indium-111 labelled water to assess colonic transit on postoperative day 2 and 3 (see section Gastrointestinal transit studies for details). During hospital admission, patients were visited at least once daily by a trial nurse and/or a research physician for clinical evaluation (i.e., diet, first bowel movement, nausea and vomiting). Clinical symptoms of upper and lower GI motility were evaluated via self-designed questionnaires. Patients were assisted to fill in this self-assessment sheet daily at the time of the scintigraphical scan until discharge. Until discharge, nursing staff reported daily on the patient’s progress, i.e. intake, passage of stool, and predefined discharge criteria were checked.

Outcomes

The primary outcome of efficacy was postoperative GI transit on postoperative day 1 to 3. GI
transit endpoints were: (I) colonic transit on day 3, depicted as geometrical center of intracolonic mass 48 hours postprandially of 111In-DTPA labeled water; (II) gastric retention at 24 hours after surgery, formulated as the percentage of 99mTc labelled pancake present in the stomach two hours after ingestion.

The secondary endpoints of this study were: (I) time until first bowel movement in hours after surgery; (II) time until first tolerance of solid food in hours after surgery; (III) the composite outcome of time to tolerate solid food and bowel movement; (IV) postoperative hospital stay, i.e. days until discharge; (V) time until ready for hospital discharge in hours after surgery. Patients were daily questioned about the occurrence and severity of nausea, vomiting, and abdominal bloating. All patients were discharged if they complied with the following predefined discharge criteria: (1) adequate pain control with paracetamol and/or nonsteroidal anti-inflammatory drugs (2) ability to tolerate solid food (3) absence of nausea (4) passage of first flatus and/or first stool (5) mobilization as preoperative, and (6) acceptance of discharge by the patient. Time until ready for discharge was defined as the time when patients were able to tolerate solid food without reversal to enteral fluids, were without complications, and pain was adequately controlled with oral analgetics.

Gastrointestinal transit studies
On postoperative day 1, patients underwent a solid gastric emptying test. Two hours after ingestion of a 99mTc labelled pancake (115 Kcal), a 5-min acquisition was performed in a 128 matrix with the patient in a supine position using a single head gamma camera (Siemens OrbiRun, or Diacam, Siemens, Hoff man Estates, IL) fitted with a medium energy collimator. The relative gastric content of the pancake 2 hours after ingestion was calculated as previously described.20 Briefly, to depict the percentage of activity present in the stomach compared with the total activity in the abdominal region of interest, the counts in the stomach were divided by the counts in the complete abdominal region, corrected for background.

Directly after completion of the gastric emptying test patients were asked to drink 60 ml of tap water labeled with 4 MBq 111In-DTPA (DiethyleneTriaminePentaAcetate, Covidien, Petten, The Netherlands). A cobalt marker was placed on the iliac crest for anatomical reference and a baseline scan was performed to determine total amount of indium activity present in the abdomen 5 minutes after ingestion. To determine colonic transit, two 5-min acquisitions were performed 24 and 48 h after ingestion of the radiolabelled water using the same single head gamma camera.

To enable calculation of colonic transit, the gut was subdivided into three segments (i.e., 0 = small intestine; 1 = proximal colon; 2 = distal colon; 3 = stool). The center of mass model21 was applied expressing colonic transit at 24 and 48 hours postprandial as geometrical center (GC) of activity. The primary variable of interest in overall colonic transit was the GC at 48 hours. The GC is the weighted average of counts in the different colonic regions: proximal colon, distal colon and stool. Quantification of the counts in each region was performed using a Hermes Gold software program (Hermes Medical Solutions, Stockholm, Sweden). At any time, the portion of colonic counts in each colonic region (corrected for background activ-
ity and isotope decay) was multiplied by the corresponding weighting factors as follows: GC = (% proximal colon x 1 + % distal colon x 2 + % stool x 3)/100. Thus, a high GC implies faster colonic transit. A GC of 0 implies that none of the isotope has reached the colon, and a GC of 3 implies that all isotope is in the stool. The amount of 111In-DTPA tracer defecated before day 4 was computed by subtraction of decay corrected abdominal counts on day 3 from total abdominal counts on day 1. Interpretation and calculation of gastric retention and colonic transit was performed blinded by two researchers independent from each other (research physician S.v.B. & staff physician of the Nuclear Medicine Department R.J.B.) on a Hermes workstation.

**Sample size calculation and statistical analysis**

Since resumption of colonic motility occurs on postoperative days 3 through 5 and typically is the rate-limiting factor for the resolution of ileus (reviewed in\(^\text{22}\)), the colonic transit on day 3 was used as the primary efficacy parameter. Sample size calculation was based on earlier studies on GI transit after abdominal surgery\(^\text{16,20}\) and indicated that 18 patients per group were required to identify a >15% significant (P<0.05) difference in colonic transit on day 3 between the different treatment modalities, providing 80% power.

Per protocol analysis was applied on all data as this study was designed and powered to detect a difference in postoperative GI transit between patients who actually received the treatment of interest and had no major surgical complications of the intestinal tract.

Data were presented as means ± standard deviations or as medians and interquartile ranges according to data type. For dichotomous outcomes, treatment groups were compared by means of the Chi-square test or Fisher’s Exact test. The Kruskal-Wallis test and Mann-Whitney U tests were used for continuous, not normally distributed outcomes. For continuous normally distributed data, the ANOVA test was used. Multiple linear regression was used to analyze the effect of laparoscopy, FT care and the combination of both on the primary and secondary endpoints. As the measurements of gastric emptying and clinical parameters (except time until defecation) were skewed, linear regression analysis of these endpoints was carried out after logarithmic transformation of the dependent variable. Statistical analysis was performed using SPSS for Windows version 17 (SPSS Inc. Chicago, Ill., USA). A two-sided P-value < 0.05 was considered to be statistically significant.

**Results**

**Patients**

Between October 2005 and August 2009 a total of 93 patients were randomly assigned to one of the four treatment groups. Fifteen patients (n=1 Lap/FT; n=3 Lap/Standard; n=6 Open/FT; n=5 Open/Standard) were withdrawn for various reasons: two had resection of the small intestine, one a delirium, one abdominal dehiscence, four had metastasis at time of admission, five had a protocol violation and two withdrew informed consent. GI transit was assessed in 78 patients. Seven of these developed a paralytic POI requiring surgical intervention within the first five days: three Lap/FT patients (two internal herniation & one adhesion); one Lap/
Standard patient (anastomotic leakage); one Open/FT patient (anastomotic leakage); two Open/Standard patients (intraperitoneal bleeding & adhesion). Therefore, data from 71 patients without major surgical complications were available for per protocol analysis.

In one patient laparoscopy had to be converted to open colectomy because of the extent of tumour invasion. Baseline characteristics and surgical aspects did not differ significantly between the four treatment groups, except duration of surgery (P<0.001, Table 1).

| Table 1 Baseline characteristics and surgical aspects of the included patients per group |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | Laparoscopy & Fast Track (n = 18) | Laparoscopy & Standard care (n = 17) | Open & Fast Track (n = 18) | Open & Standard care (n = 18) |
| Age – yr*                        | 65±9.4                           | 66±10.2                           | 64±10.1                       | 66±6.9                           | 0.920*                          |
| Male sex – %                     | 50                               | 53                                | 61                            | 61                               | 0.872*                          |
| BMI – kg/m²*                     | 26.5±4.4                         | 24.0±3.9                          | 24.6±3.5                      | 25.0±3.6                         | 0.246*                          |
| ASA – %                          | 89                               | 88                                | 89                            | 89                               |                                  |
| - Grade I or II                  |                                  |                                   |                               |                                  | 0.436*                          |
| Co-morbidity – %                 | 72                               | 53                                | 56                            | 50                               | 0.331*                          |
| Type of colectomy – %           |                                  |                                   |                               |                                  |                                  |
| - Right-sided                    | 28                               | 55                                | 28                            | 39                               | 0.345*                          |
| - Left-sided                     | 6                                | 14                                | 17                            | 22                               |                                  |
| - Sigmoid                        | 67                               | 32                                | 56                            | 39                               |                                  |
| Duration of surgery             |                                  |                                   |                               |                                  |                                  |
| Median [IQR]                     | 191                              | 179                               | 146                           | 139                              | <0.001*                          |
|                                 | 176-205                          | 157-202                           | 122-180                       | 122-165                          |                                  |

*Values are mean ± standard deviation / BMI = Body Mass Index / ASA = American Society of Anesthesiologists / IQR = inter-quartile range / *ANOVA test / *Chi-square test / *Kruskal-Wallis test

**Gastrointestinal transit**

**Colonic transit**

The median calculated GC of activity at day 2 are shown in Figure 1a. Colonic transit at day 2 was significantly faster in the Lap/FT patients (2.2 (1.8-2.6)) compared to the Lap/Standard (1.3 (1.2-2.0), P=0.005), Open/FT (1.5 (1.2-1.9), P=0.002), and Open/Standard patients (1.1 (1.0-1.4), P<0.001). These data indicate that most of the radiolabelled material was still located in the proximal part of the colon at day 2 in the latter three groups, while in the Lap/FT group it had already moved to the distal part of the colon.
On postoperative day 3, most of the Indium was still present in the proximal colon in the Open/Standard group, but had moved into the distal colon in the other three groups. The median GC for patients in the Lap/FT (2.6 (2.0-2.9)) was significantly higher, compared to the Lap/Standard (2.2 (1.6-2.5), P=0.044), Open/FT (2.0 (1.6-2.4), P=0.010), and those in the Open/Standard group (1.3 (1.0-1.5), P<0.001).

**Figure 1** Postoperative gastrointestinal transit
Scintigraphical evaluation of gastrointestinal transit of an In-111 labelled non-caloric liquid test-meal and gastric emptying of a \(^{99m}\text{Tc}\) labelled pancake 24 hrs after surgery. Lines represent inter-quartile-ranges in corresponding treatment groups. Mann-Whitney U test. *P <0.05, **P<0.001

Colonic transit on day 3 was significantly influenced by both laparoscopy (B=0.64; CI: 0.36-0.92, P<0.001; i.e. laparoscopic surgery would lead to an increase in the GC of 0.64) and FT care (B=0.53; CI: 0.24-0.81, P<0.001; i.e. leading to an increase in the GC of 0.53 compared to patients receiving standard care). The combination of both did not add any benefit.

Colonic transit is considered to mainly determine clinical recovery.\(^{22}\). The latter (i.e. time until ready for discharge) correlated significantly with colonic GC on day 3 (r= -0.56, P<0.001; Spearman’s rank correlation). As depicted in Figure 1b, the median percentage of \(^{111}\text{In-DTPA}\) tracer defecated 48 hours after intake was 70% (36-49) in the Lap/FT treated group com-
pared to 37% (0-58), 26% (0-57) and 0% (0-0) in the Lap/Standard, Open/FT and Open/Standard treated groups respectively, showing a significant difference of the Lap/FT treated patients with the Open/FT group (P=0.043) and the Open/Standard group (P=0.001).

Figure 1b Amount of $^{111}\text{In}$-DTPA tracer defecated before day 4, depicted as median percentage of $^{111}\text{In}$ defecated on day 3

![Graph showing the amount of indium defecated before day 4 (%)](image)

Figure 1c Gastric retention determined 2 hr postprandial, depicted as median percentage in stomach compared to total abdominal region corrected for background

![Graph showing gastric retention day 1](image)
Gastric retention day 1
The residual gastric content two hours after ingestion of the pancake varied from almost complete emptying to gastric stasis with more than 99% of the radiolabelled pancake still present in the stomach. The median gastric retention did not differ between groups (P=0.61) (Figure 1c). Gastric retention was 70% (IQR: 36-94), 81% (34-95), 58% (26-71), 58% (31-100) in patients treated with Lap/FT, Lap/Standard, Open/FT and Open/Standard respectively.

Clinical evaluation
Symptoms of upper and lower GI motility and time until (ready for) discharge
Visual-analogue scores for nausea and bloating were comparable in the four groups at day 1 (P=0.735 and P=0.359, respectively). Median time until first defecation and tolerance of solid food, length of hospital stay, and ready for discharge were significantly shorter for patients who underwent Lap/FT treatment compared to the other groups (Figure 2). In a second analysis patients with a major surgical complication (n=7) were included and similar differences between groups were found. Linear regression analysis showed that laparoscopic resection and FT care both independently resulted in a significantly shorter time until first defecation, tolerance of solid food, first defecation & tolerance of solid food, length of stay and time until ready for discharge.

There was no significant difference between the groups in readmission rate (P=0.850) and overall morbidity (P=0.217) until 30 days after surgery.

Overall compliance of surgical, anesthesiological and nursing care personnel with the multimodal perioperative rehabilitation pathway was very good. Intra-operative fluid loading was similar (P=0.092) and restricted in all four treatment groups with a median of 2.0 (IQR: 1.3-3.0) liter.

Figure 2 Clinical (secondary) endpoints
Lines represent inter-quartile-ranges in corresponding treatment groups. Per protocol analysis. Mann-Whitney U test. *P<0.05, **P<0.001

Figure 2a Hrs until first defecation
Figure 2b Hrs until first tolerance solid food

Figure 2c Hrs until first defecation & tolerance solid food

Figure 2d Days until discharge
The results of this study provide objective data indicating that laparoscopic surgery and FT care improve recovery of GI transit associated with faster clinical recovery compared to open colectomy and standard care. In a multivariate analysis, the present study shows that both are significant predictors of improved colonic transit, and reduced time to tolerance of solid food and bowel movement. These data suggest that laparoscopic resection embedded in a FT program leads to the most optimal recovery of GI transit.

In our study clinical hallmarks were not the primary outcome measures for POI as these are non-specific. Parameters such as nausea, vomiting and tolerance of solid food strongly depend on patient reporting, whereas first passage of stool or flatus may simply reflect rectal emptying and therefore not necessarily inform on recovery of effective GI contractile activity. For this reason nuclear scintigraphy was used to assess postoperative GI motility in a detailed and objective manner.

In the present study gastric retention on day 1 did not differ significantly between groups. A possible explanation for the discrepancy between gastric emptying and the time until ready for discharge could be a difference in the dosage of opioids or anti-emetics between the groups before day 1. However, there was no difference in analgesia or dosage of anti-emetics in this period. Therefore, it is more likely that the time frame in which the beneficial effect of laparoscopy and FT care on GI motility can be detected starts after day 1. This indicates that gastric emptying, in contrast to colonic transit, is not a good parameter to predict clinical recovery.

The study of Basse et al, is the only study that evaluated recovery of GI transit after open and laparoscopic colectomy.\textsuperscript{16} They used scintigraphy in patients who underwent elective

\textbf{Discussion}

Figure 2e Days until ready for discharge

![Days until ready for discharge](image)

The results of this study provide objective data indicating that laparoscopic surgery and FT care improve recovery of GI transit associated with faster clinical recovery compared to open colectomy and standard care. In a multivariate analysis, the present study shows that both are significant predictors of improved colonic transit, and reduced time to tolerance of solid food and bowel movement. These data suggest that laparoscopic resection embedded in a FT program leads to the most optimal recovery of GI transit.

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The study of Basse et al, is the only study that evaluated recovery of GI transit after open and laparoscopic colectomy.\textsuperscript{16} They used scintigraphy in patients who underwent elective
laparoscopic or open colonic resection within a FT program, but did not address the question what the individual contribution of laparoscopic surgery and/or FT was on GI transit. Their results demonstrated no significant difference in the amount of $^{111}$In-tracer defecated, but showed a significantly higher colonic transit 48 hours after surgery in the laparoscopic group. Based on these results Basse et al. concluded that there was no significant difference between an open and laparoscopic approach. However it is likely that the sample size was too small to find a difference in amount of $^{111}$In-tracer defecated within the first 48 hours after surgery. As the amount of $^{111}$In-tracer defecated is not only dependent on colonic transit, but also whether or not rectal emptying of rectal $^{111}$In-tracer has occurred and therefore may be less precise in reflecting recovery of GI transit. Secondly, determining the amount of $^{111}$In-tracer defecated within only the first 48 hours postoperatively might be too short since colonic motility is impaired between 48-72 hours after surgery. We found a significantly higher colonic transit and amount of $^{111}$In-tracer defecated before day 4 after laparoscopic surgery compared to open colonic resection with FT rehabilitation. In addition, our finding that there was a clear difference in the amount of $^{111}$In-tracer defecated between patients in the FT care and standard care groups confirms the beneficial effect of FT care on GI transit. These scintigraphical data were consistent with the results on the clinical outcome measures and of previous randomized clinical trials, confirming in an objective manner that laparoscopic surgery and FT care fasten postoperative bowel motility.

The pathophysiological mechanisms involved in POI are still not completely understood, but recent studies have shown the importance of inflammation of the intestinal muscularis resulting from surgical handling. The faster clinical recovery observed after laparoscopic surgery compared with open surgery could be explained by decreased tissue trauma with concomitant decreased mast cell activation leading to attenuated intestinal inflammation and thus a quicker GI recovery. The beneficial effect of the FT program may not only be explained by the set of FT elements actually applied but also by the discriminating aspect of the FT program that the perioperative care is protocolized. For example, the protocol precluded the discussion of if and when the patient could mobilize after surgery, or the time of removal of the epidural. Thus, the fact that the rehabilitation process is always implemented in the same way can be an important explanation for the success of the FT program. Further study is required to distinguish which of the FT elements have the greatest impact upon POI.

Limitations of this study were the omission of baseline GI transit measurements. This design would have allowed comparison before and after surgery in each individual patient, possibly reducing the variability and increasing the power of the study. However such a design was not possible as this would place too high a burden on patients and logistics. Second, with regard to the (secondary) clinical endpoints total blinding for the type of surgery was difficult to achieve by an opaque abdominal dressing as the majority of the patients could not resist looking under the abdominal dressing. Wound inspection was not a limiting factor as this was not carried out until the day of discharge, but obviously only in those patients without wound complaints or complications.
In conclusion, these data demonstrate that colonic transit recovers fastest after laparoscopic surgery embedded in the fast track program, providing objective data that this combination leads to faster recovery of GI motility and concomitant enhanced clinical recovery.

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References

24) The FO, Bennink RJ, Ankum WM, Buist MR, Busch OR, Gouma DJ et al. Intestinal handling-induced


CHAPTER 9

Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: A randomized trial

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Submitted
Abstract

Purpose
To evaluate the effect of laparoscopic or open colectomy with fast track or standard perioperative care on patient’s immune status and stress response following surgery.

Methods
Patients with non metastasized colon cancer were randomized to laparoscopic or open colectomy with fast track or standard care, resulting in four different treatment groups. Blood samples were taken preoperatively (baseline), 1 hour, 2 hours, 24 hours and 72 hours following surgery. Systemic HLA-DR expression on monocytes, C-reactive protein, Interleukin-6, growth hormone, prolactin and cortisol were analyzed.

Results
Nineteen patients were randomized for laparoscopy and fast track care (LFT), 23 for laparoscopy and standard care (LS), 17 for open surgery and fast track care (OFT) and 20 for open surgery and standard care (OS). Patient characteristics in terms of age, gender, ASA classification, localization of the tumor and type of resection were comparable for all groups. HLA-DR expression on monocytes was best preserved in the LFT group 2 hours (P=0.002) and 24 hours (P=0.003) postoperatively. Interleukin-6 was significantly increased in the OS group 24 hours (P=0.048) and 72 hours (P=0.05) postoperatively. C-reactive protein was significantly increased in the OS group 1 hour (P=0.002), 2 hours (P=0.011), 24 hours (P=0.048) and 72 hours (P=0.009) postoperatively. No differences between the groups were seen regarding growth hormone, prolactin, or cortisol levels. No differences in (infectious)complication rates were observed between the groups.

Conclusion
This randomized trial showed that immune function is best preserved in patients having laparoscopic colectomy within a fast track program. Patients treated by open surgery in combination with standard care do worst. There are no differences between the groups concerning the hormonal response to surgery. These results support the accelerated recovery of patients treated laparoscopically within a fast track program.
**Introduction**

The first minimally invasive colon resection was described in 1991 by Jacobs et al. The short term advantages of minimally invasive colon resection have been well established in several randomized trials. However, major surgery still remains associated with postoperative morbidity and undesirable side effects such as pain, cardiopulmonary, infective, and thromboembolic complications. A major factor in the development of morbidity is the surgical stress response with subsequent increased demand on the patient’s reserves and immune competence. Increased demands in organ functions are thought to be mediated by trauma induced endocrine and metabolic changes.

HLA-DR expression on monocytes is a measure for immune competence and is associated with adequate presentation of antigen and specific immune response in humans. Levels of C-reactive protein and cytokines are closely related with the inflammatory response and the extent of the inflamed tissue involved, as well with the activity of the immune reaction. Interleukin-6 levels are associated with postoperative complication rates and are a predictor of morbidity following surgical intervention.

Previously, Harmon et al. and Wu et al. have described lower interleukin-6 levels following laparoscopic colectomy in smaller trials. Schwenk et al. reported lower concentrations of both interleukin-6 and C-reactive protein following laparoscopic colectomy.

Following the introduction of minimally invasive techniques, in 2001 Kehlet introduced the second major advancement in modern elective colorectal surgery; the implementation of the ‘fast track’ perioperative care. The fast track recovery program comprises a multidisciplinary approach aiming to reduce surgical stress response, enhance immune function, and thereby reduce organ dysfunction and allow for a faster recovery following surgery.

Up to date there is little evidence for a better preserved immune status, which is in line with the observed lower morbidity and faster recovery of minimally invasive colectomy. In addition, no previous studies have investigated immune status and stress response following fast track recovery programs. Hence, the aim of this study was to evaluate the effect of laparoscopic or open colectomy with fast track or standard perioperative care on patient’s immune status and stress response following surgery.
Materials and methods

Eligible patients were those with a histologically confirmed malignancy or adenoma planned for an elective, segmental, curative colectomy. Patients had to be between 40 and 80 years of age with an American Society of Anaesthesiologists (ASA) grade I through III. Patients with a previous midline laparotomy, emergency surgery, a planned stoma or immune depressant disease or medication were excluded from this study. Once informed consent was obtained, patients included in the VU University Medical Center and Academic Medical Center were randomized. This was done as a substudy of the LAFA trial, a randomized trial of a 2 x 2 balanced factorial design. Randomization was achieved by means of an internet module. Patients were randomized to 4 different treatment groups: laparoscopic colectomy with fast track care (LFT), laparoscopic colectomy with standard care (LS), open colectomy with fast track care (OFT), and open colectomy with standard care (OS). The study was conducted in accordance with the principles of the Declaration of Helsinki and the present protocol was approved by the local medical ethics review boards (protocol NTR222).

Peripheral blood and serum (BD Vacutainer Systems, Plymouth, UK) were collected preoperatively (baseline), 1 hour, 2 hours, 24 hours, and 72 hours after surgery. All samples had to be collected within 10 minutes of the exact preset postoperative times. Transportation of the serum to the laboratory had to be accomplished within 10 minutes. Serum interleukin-6, C-reactive protein, prolactin, cortisol, and growth hormone samples were obtained by centrifugation for 10 minutes at 3 000 rpm at 4 degrees Celsius. All samples were stored in aliquots at -80 degrees Celsius until tested in a one block fashion. HLA-DR expression on monocytes were analysed directly on full blood samples.

Immune status

HLA-DR expression on monocytes

Numbers and phenotype of white blood cells and monocytes were determined in fresh (<2 hrs) heparinised venous blood. Phenotyping was performed by using CD14-PE and HLA-DR-FITC moAbs (Becton Dickinson), subsequent lysis of erythrocytes and fixation with paraformaldehyde. Monocyte HLA-DR expression was evaluated by FACS analysis (FACS Calibur, Becton Dickinson, San Jose, CA, USA) quantified by using calibration beads (Quantum-TM 26, Flow Cytometry Standards Corp, Bangs Laboratories, Inc, Fisher IN) and expressed as ratio of the mean fluorescence intensity post/pre surgery.

Interleukin-6 (IL-6)

IL-6 concentrations in serum were measured using commercially available enzyme-linked immunosorbent assay kits (Pelikine compact human ELISA kits, Sanquin, Amsterdam, the Netherlands).

C-reactive protein (CRP)

Plasma CRP levels were measured by immunoturbidimetric method, using the BM/Hitachi 705 (Boeingher, Mannheim, Germany).
Stress response

Cortisol
Cortisol concentrations in serum were measured by competitive immunoassay (Bayer Diagnostics, Mijdrecht, The Netherlands).

Prolactin
Prolactin concentrations in serum were measured by immunometric assay (DPC, Los Angeles, USA).

Growth hormone
Growth hormone concentrations in serum were measured by immunometric assay (Bayer Diagnostics, Mijdrecht, The Netherlands).

Statistical analysis
Statistical analysis was performed using the SPSS software package (SPSS 16.0 for Windows; SPSS, Chicago, IL, USA). Medians, means, ranges, and inter-quartile ranges were calculated and subsequently depicted when appropriate. The Mann Whitney U test, Chi-squared test, Fisher’s exact test, independent samples T-test or ANOVA test were applied when appropriate for group comparisons. An intention to treat principle was applied. Significance was set at p<0.05.

Results

Patients
A total of 79 patients were randomized. Nineteen patients were randomized for laparoscopic surgery with fast track care (LFT), 23 for laparoscopic surgery with standard care (LS), 17 for open surgery with fast track care (OFT) and 20 for open surgery with standard care. Patient characteristics in terms of age, body mass index (BMI), gender, ASA classification or operative procedure were comparable for all groups and are depicted in Table 1. Of all blood sample accrual times described by protocol, 94.9% of samples were collected and analysed on time as described by study protocol.

Immune Status
All exact values for immune competence are depicted in Table 2. Monocyte HLA-DR expression was used as a parameter for surgery induced attenuated immune competence. Two hours and 24 hours following surgery HLA-DR expression on monocytes was significantly better preserved in the LFT group (P=0.002 and P=0.003, respectively). After 72 hours a trend was observed for better preservation of immune competence in the LFT group (P=0.07, Figure 1).

IL-6 levels did not significantly differ between the groups 1 hour and 2 hours following surgery. After 24 hours and 72 hours a significant increase in IL-6 levels was observed for the OS group (P=0.048 and P=0.05, respectively, Figure 2).

CRP levels were significantly increased for the OS group at 1 hour, 2 hours, 24 hours and 72 hours following surgery (P=0.002, P=0.011, P=0.048 and P=0.009, respectively, Figure 3).

Stress response
All values regarding stress response are depicted in Table 2. Growth hormone, prolactin and
cortisol levels did not differ during the postoperative follow-up between the 4 groups at any time-interval.

**Operative and hospital data**

Duration of the operative procedure was significantly longer for laparoscopy, whereas blood loss was significantly lower. In-hospital morbidity for the first 72 hours was similar for all groups. One patient in the LS group required a conversion due to a bulky tumor with minor ingrowth in the abdominal wall. The results of this patient were analyzed in an intention to treat principle (Table 3).

### Table 1 Patient and tumour characteristics

<table>
<thead>
<tr>
<th></th>
<th>LFT (n=19)</th>
<th>LS (n=23)</th>
<th>OFT (n=17)</th>
<th>OS (n=20)</th>
<th>P</th>
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<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Male</td>
<td>10 (53)</td>
<td>19 (82)</td>
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<td>4 (18)</td>
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<td>Age, years</td>
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<td>- 3</td>
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<td>Operation, n (%)</td>
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Values are mean (range) / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard / BMI = Body Mass Index / ASA = American Society of Anaesthesiologists
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<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
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<th>2 hours</th>
<th>24 hours</th>
<th>72 hours</th>
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<td><strong>HLA-DR</strong></td>
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<td>180 (48-608)</td>
<td>184 (16-580)</td>
<td>141 (48-326)</td>
</tr>
</tbody>
</table>

Values are depicted as percentage with the preoperative value set at 100% / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard / IL-6 = interleukine 6 / CRP = C-reactive protein
Figure 1 HLA-DR expression on monocytes in percentage with baseline set at 100%

![Graph showing HLA-DR expression over postoperative hours]

Figure 2 Interleukine-6 levels in percentage with baseline set at 100%

![Graph showing IL-6 levels over postoperative hours]
Figure 3  C-reactive protein in percentage with baseline set at 100%

![Graph showing C-reactive protein levels with different operations and time intervals.]

Table 3 Operative and morbidity data

<table>
<thead>
<tr>
<th>Operation</th>
<th>LFT (n=19)</th>
<th>LS (n=23)</th>
<th>OFT (n=17)</th>
<th>OS (n=20)</th>
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<td>Blood loss, ml</td>
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<td>Complications, n (%)</td>
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<td>5 (29)</td>
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<td>Total No. of complications</td>
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</table>

Values are mean (range) / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard
Discussion

This randomized trial showed that patients undergoing laparoscopic colectomy combined with perioperative fast track care have a significantly better preserved immune competence (HLA-DR presentation on monocytes) until 3 days after surgery. Laparoscopic surgery with standard care seemed marginally superior to open colectomy with fast track care, followed by open colectomy with standard care. Inflammatory parameters such as IL-6 and CRP were significantly increased in patients undergoing open colectomy with standard care. Differences in the other 3 groups were marginal, therefore a clear order could not be discriminated.

These results might reflect a biological substrate to the longstanding question as to why patients undergoing minimally invasive techniques with fast track perioperative care have been described to have an accelerated recovery. In addition, a better preserved immune competence, including specific HLA-DR immune response, may protect against potential consequences of seeding free tumor cells and thus distant metastases. As described by Wind et al., this is most important during surgery, as circulating tumor cells are highest directly after the onset of surgery. It will therefore be interesting to investigate whether patients in the laparoscopic group with fast track perioperative care will have a lower cancer recurrence rate during long-term follow-up.

The complex interaction between inflammatory cytokines and the hypothalamic-pituitary-adrenal axis is still difficult to assess. In this study, stress response in terms of growth hormone, cortisol, and prolactin were not different between the groups. Therefore the ‘fast track theory’ including a reduced stress response due to epidural anaesthesia could not be demonstrated. However, cortisol, growth hormone, and prolactin are anterior pituitary hormones and secretion is stimulated by hypothalamic releasing factors. Therefore, the standard epidural in fast track recovery programs may not have had any effect on these hormones. It would be interesting to evaluate the secretion of catecholamines and/or its metabolized products in future studies as the epidural would have been more likely to have had an effect on these adrenal gland stress hormones.

Morbidity within 72 hours was lower in the laparoscopic group with fast track perioperative care, but did not reach a statistical difference between the 4 groups. It is however unlikely that the clear differences in immune response are simply based on morbidity percentages. The hypothesis that laparoscopic surgery in combination with fast track perioperative care reduces demand on the patient’s immune reserves is supported by the results of the present study. Other authors have described lower morbidity following fast track postoperative care.

In the present study, 94.9% of all samples were obtained and analysed according to study protocol. All obtained samples were analysed in a one block analysis, therefore the presented differences could not have been due to altered analyzing techniques or modified analyzing apparatus.

Smaller trials investigating immune response following laparoscopic and open colectomy have previously been presented. Harmon et al. were the first to describe differences in postop-
operative IL-6 levels when laparoscopic colectomy was compared to open techniques in favor of laparoscopic surgery. Wu et al. measured cytokine levels both in serum and peritoneal drain fluid and found significantly lower levels of IL-6 after laparoscopic surgery confirming the previous studies. A randomized study by Schwenk et al. showed significantly lower peak concentrations of IL-6 and CRP two days after laparoscopic colon surgery. To our knowledge no previous randomized studies have presented advantages for laparoscopic colectomy in HLA-DR presentation on monocytes. In addition, no previous studies have investigated the effect on fast track perioperative care on patient’s postoperative immune status.

In conclusion, this randomized trial showed that immune function is best preserved in patients having laparoscopic colectomy within a fast track program. Patients treated by open surgery in combination with standard care do worst. These results support the accelerated recovery which can be observed when patients are treated laparoscopically within a fast track program.
References


CHAPTER 10

Which fast track elements predict early recovery after colon cancer surgery?

Malaika S. Vlug
Sanne A.L. Bartels
Jan Wind
Dirk T. Ubbink
Markus W. Hollmann
Willem A. Bemelman
on behalf of the LAFA study group

Submitted
Abstract

Background
To determine which baseline characteristics and/or which successfully achieved fast track elements are independent predictors of faster postoperative recovery in patients undergoing colonic resection for colon cancer.

Methods
Data from the LAFA-trial database were used. In this trial, fast track care was compared with standard perioperative care in 400 patients undergoing laparoscopic or open surgery for colonic cancer. During admission 19 fast track elements were prospectively evaluated per patient and scored whether or not successfully applied. To identify predictive factors 6 baseline characteristics and those fast track items that were successfully achieved were entered in a univariable and multivariable linear regression analysis with total postoperative hospital stay (THS) as primary outcome.

Results
Mean number of successfully achieved fast track elements in the fast track group was 12.6 out of 19 elements. In 400 patients, 2 baseline characteristics and 2 fast track elements were found to be significant independent predictors on THS; female sex was leading to a 15% (CI: 4-25%) reduction in THS, laparoscopic resection in a 15% (CI: 4-25%) reduction in THS, ‘normal diet at postoperative days 1, 2 & 3’ in a 30% (CI: 19-39%) reduction in THS, and ‘enforced mobilisation at postoperative days 1,2 & 3’ in 32% (CI: 20-41%) reduction in THS.

Conclusion
Evaluating only those fast track elements that were successfully achieved, showed that enforced advancement of oral intake, early mobilisation and laparoscopic surgery and female sex were independent determinants of early recovery.
Introduction

An important development in elective large bowel surgery is the introduction of an enhanced recovery programme after surgery, also referred to as fast track perioperative care.\textsuperscript{1-4} This multidisciplinary protocol, involving dieticians, nurses, surgeons and anaesthesiologists, is developed by Kehlet et al. during the mid-nineties and aims at a reduced surgical stress response, less organ dysfunction, reduced morbidity and thereby a faster recovery after surgery.\textsuperscript{2,5} Essentially, the fast track programme consists of extensive preoperative counselling, no bowel preparation, no sedative premedication, carbohydrate-loaded liquids until two hours before surgery, effective multimodal pain management, short acting anaesthetics, adequate perioperative fluid management, small incisions, and no routine use of drains and nasogastric tubes. Postoperative care includes early oral feeding, enforced mobilisation, early removal of bladder catheter and standard laxative.\textsuperscript{6}

To date, several randomised controlled trials have shown that fast track care compared to standard care resulted in a reduced postoperative hospital stay in colorectal surgery without an increased morbidity or mortality.\textsuperscript{7} Nevertheless, full implementation of this multidisciplinary protocol appeared difficult, which was most likely explained by the need to break with longstanding traditions.\textsuperscript{3,8,9} Within a fast track programme a set of at least 15 perioperative elements can be identified. The extent of which of these elements are truly implemented determines the effectiveness of the fast track programme. It is unknown which (set of the) elements are crucial with respect to recovery. Additionally, it is questioned whether all separate fast track elements are actually essential for the enhanced postoperative recovery. It can be hypothesized that the key to success in the fast track perioperative care programme is not the combination and number of applied fast track elements, but rather the fact that perioperative care is protocolised.

The aim of this study was to determine which baseline and/or which successfully achieved fast track elements are independent predictors of faster postoperative recovery in patients undergoing a colonic resection for colon cancer.
Methods and materials

Study design

This study is based on data from the LAFA-trial (LAparoscopy in combination with FAst track multimodal management is the best perioperative strategy in patients undergoing colonic surgery). This was a nine-centre randomised trial set up as a 2 x 2 balanced factorial design. Aim was to determine which combination of care, laparoscopic or open surgery combined with fast track or standard care, was the optimal treatment for patients undergoing a segmental resection for colon cancer. Patients were randomised into 4 groups: (a) laparoscopic colectomy with fast track care (b) open colectomy with fast track care (c) laparoscopic colectomy with standard care, and (d) open colectomy with standard care. Patients and nursing staff were routinely informed about the perioperative care programme, i.e. fast track care or standard care, but were blinded to the type of intervention, i.e. laparoscopic or open surgery. Nurses working on the fast track ward were extensively trained in fast track care before the start of the study in 2005. In order to avoid cross-over treatment by the nursing staff, patients were admitted either to a ward providing fast track care or a ward providing standard care, depending on randomisation. Primary outcome was total postoperative hospital stay (THS), measured in days, warranted by applying predefined objectively quantified discharge criteria.

In the present study, we merged all patients that were randomised to fast track care (n=193) and standard care (n=207) and analysed whether one single item or a set of items independently predicted enhanced recovery.

Fast track elements

Patients allocated to fast track care were treated according to a fast track protocol, which has been described in detail elsewhere. Patients randomised to standard care were treated according to traditional perioperative care. The applied perioperative fast track items were scored both in the fast track as well as the standard care groups; up to discharge, nursing staff reported daily on the patient’s status, i.e. preoperative counselling yes/no, thoracic epidural removed yes/no, amount of intake, and the predefined discharge criteria were checked. In Table 1 all fast track elements, which were prospectively checked and scored if successfully achieved per patient, are listed. After 30 days of follow-up, the anaesthetic and clinical dossiers (nursing and medical) were checked for missing data. Outpatient medical dossiers were checked for any complication or readmission that had occurred after discharge within 30 days of the operation.

Statistical analysis

Analyses were performed according to the intention to treat principle. Data were presented as means ± standard deviations or as medians and inter-quartile ranges where appropriate. For dichotomous outcomes, treatment groups were compared by means of the Chi-square test. The Mann-Whitney U test was used for continuous, not normally distributed outcomes. For continuous normally distributed data, the ANOVA test was used.

THS was calculated from the day of surgery until the day of discharge, including additional hospital days in case of readmission within 30 days of surgery. As THS was not normally dis-
tributed, these data were log-transformed.

In a univariable linear regression analysis, 6 baseline characteristics; sex, age, American Society of Anesthesiologists (ASA) grade, body mass index (BMI), type of surgery (open, laparoscopic), and type of resection (right-sided, left-sided), and all individual prospectively scored fast track elements that were successfully achieved were entered. All variables with P<0.10 were then entered in a multivariable linear regression analysis. Stepwise backwards elimination was used to create a final multivariable model retaining only variables with P<0.050, as this was considered to be statistically significant. B-values of significant predictive parameters were converted into percentages difference in THS they would result in if present, with their 95% confidence intervals (CI). Statistical analyses were done by using SPSS for Windows version 16.0.2. (SPSS Inc. Chigago, III., USA).

<table>
<thead>
<tr>
<th>Table 1 Number of achieved fast track elements</th>
<th>Fast Track (n = 193)</th>
<th>Standard care (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Separate consultation with a fast track trial nurse before admission to discuss the essence of the fast track programme – n (%)</td>
<td>188 (97)</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>Day of admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. No bowel preparation – n (%)</td>
<td>186 (96)</td>
<td>168 (81)</td>
</tr>
<tr>
<td>3. Intake of at least 0.4 litre carbohydrate-loaded liquids – n (%)</td>
<td>141 (73)</td>
<td>9 (4)</td>
</tr>
<tr>
<td><strong>Day of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. No preoperative fasting – n (%)</td>
<td>164 (85)</td>
<td>57 (28)</td>
</tr>
<tr>
<td>5. Intake of at least 0.2 litre carbohydrate-loaded drinks 2 h before surgery – n (%)</td>
<td>143 (74)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>6. No sedative premedication – n (%)</td>
<td>130 (67)</td>
<td>43 (21)</td>
</tr>
<tr>
<td>7. Thoracic epidural analgesia – n (%)</td>
<td>171 (89)</td>
<td>146 (71)</td>
</tr>
<tr>
<td>8. Adequate perioperative fluid management (about 20 ml/kg in the 1st hours, followed by 6 ml/kg in the next hours) – n (%)</td>
<td>123 (64)</td>
<td>123 (59)</td>
</tr>
<tr>
<td>9. Forced body heating – n (%)</td>
<td>190 (98)</td>
<td>201 (97)</td>
</tr>
<tr>
<td>10. Removal of nasogastric tube before extubation – n (%)</td>
<td>157 (81)</td>
<td>169 (82)</td>
</tr>
<tr>
<td>11. No use of abdominal drains – n (%)</td>
<td>171 (89)</td>
<td>192 (93)</td>
</tr>
<tr>
<td>12. Suprapubic catheter or no catheter – n (%)</td>
<td>101 (52)</td>
<td>72 (35)</td>
</tr>
<tr>
<td>13. Intake of at least 0.5 litre liquids of which 0.2 litre carbohydrate-loaded drinks – n (%)</td>
<td>62 (32)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>14. At least 15 minutes of mobilisation in the evening – n (%)</td>
<td>58 (30)</td>
<td>10 (5)</td>
</tr>
<tr>
<td><strong>Days after surgery (postoperative days 1, 2 &amp; 3)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Laxative at postoperative days 1, 2 &amp; 3 – n (%)</td>
<td>128 (66)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>16. Normal diet at postoperative days 1, 2 &amp; 3 – n (%)</td>
<td>111 (58)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>17. Enforced mobilisation (a minimum of 540 minutes at postoperative days 1,2 &amp; 3 together) – n (%)</td>
<td>95 (49)</td>
<td>31 (15)</td>
</tr>
<tr>
<td>18. Enforced intake of liquids (a minimum of 4.5 litre of which 0.6 litre carbohydrate-loaded drinks at postoperative days 1,2 &amp; 3 together) – n (%)</td>
<td>84 (44)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>19. Removal of thoracic epidural at postoperative day 2 – n (%)</td>
<td>105 (61) of 171</td>
<td>40 (27) of 146</td>
</tr>
</tbody>
</table>
**Results**

Between July 2005 and August 2009, 427 patients were randomly assigned to either the fast track or standard treatment groups. Twenty-seven patients were excluded due to various reasons, the remaining 400 patients were analysed in the principal study. Patient characteristics and the main clinical outcomes are shown in Table 2.

A total of 193 patients were randomised to fast track care, of whom 2 patients (1%) still received standard care; in the standard care group 3 patients (1.4%) received fast track care. In the fast track group there was a higher overall compliance to the preoperative and perioperative fast track elements (mean 9.7 elements out of 12; ranging from 52% to 97%) than to the postoperative elements (mean 2.9 elements out of 7; ranging from 30% to 66%). Some elements (no bowel preparation, thoracic epidural, forced body heating, removal of nasogastric tube and no abdominal drains) were applied in standard care group. Table 1 illustrates in how many patients each fast track element had successfully been achieved.

Six baseline characteristics and the prospectively scored successful achieved fast track elements were entered in a univariable linear regression analysis. Results of this analysis are shown in Table 3. Items with a P<0.10 were subsequently entered in a multivariable linear regression analysis. These items were: sex, age, ASA, type of surgery, no bowel preparation, removal of nasogastric tube before extubation, intake of at least 0.5 litre liquids of which 0.2 litre carbohydrate-loaded drinks, standard laxative, enforced postoperative care (normal diet, intake of liquid, and mobilisation), and removal of the thoracic epidural at postoperative day 2. Multivariable linear regression analysis identified the following independent predictors of THS: female sex \( [B=0.85; 95\% \text{ CI} 0.75 \text{ to } 0.96; P=0.010, \text{ i.e. leading to a } 15\% \text{ (CI: 14-25\%) reduction in THS}] \), laparoscopic resection \( [B=0.85; 95\% \text{ CI } 0.75 \text{ to } 0.96; P=0.009, \text{ i.e. a reduction of } 15\% \text{ (CI: 14-25\%) in THS}] \), ‘normal diet at postoperative days 1, 2 & 3’ \( [B=0.70; 95\% \text{ CI } 0.61 \text{ to } 0.81; P<0.001, \text{ i.e. a reduction of } 30\% \text{ (CI: 19-39\%) in THS}] \) and ‘enforced mobilisation at postoperative days 1, 2 & 3’ \( [B=0.68; 95\% \text{ CI } 0.59 \text{ to } 0.80; P<0.001, \text{ i.e. a reduction of } 32\% \text{ (CI: 20-41\%) in THS}] \). Mean difference (95% CI) in THS between males (n=234) and females (n=166) was 3.84 (95% CI: 0.77 to 6.91) days and mean difference between laparoscopic (n=209) and open resection (n=191) was 3.45 (95% CI: 0.42 to 6.48) days. Patients with a normal diet and patients that mobilised at least 540 minutes (together) at postoperative days 1, 2 and 3 recovered significantly faster, with a mean difference (95% CI) in total hospital stay of 4.58 (1.48 to 7.68) days and 6.51 (3.30 to 9.72) days, respectively.

A new variable was created for those patients that had achieved ‘normal diet at postoperative days 1, 2 & 3’ and ‘enforced mobilisation at postoperative days 1, 2 & 3’. This new variable, named ‘perfect protocol’, plus the predictive baseline characteristics, sex and type of surgery, were entered in a new multivariable linear regression model. In total, 90 (22.5%) of the 400 patients had achieved both elements. All parameters remained independent predictors on total postoperative hospital stay (Table 4); if a patient was able to achieve the ‘perfect protocol’, THS was reduced with 44% (95% CI: 35 to 52%) compared to the patients who
had not achieved a normal diet and enforced mobilisation at postoperative days 1, 2, and 3. In the second part, multivariable regression analysis was performed in the patients without postoperative morbidity; sex no longer came out as an independent predictor (P=0.067). Laparoscopic resection [B=0.86; 95% CI 0.80 to 0.93; P<0.001, i.e. a reduction of 14% (CI: 7-20%) in THS] and ‘perfect protocol’ [B=0.72; 95% CI 0.66 to 0.78; P<0.001, i.e. a reduction of 28% (CI: 12-28%) in THS] remained independent predictors.

**Table 2 Included Patients**

<table>
<thead>
<tr>
<th></th>
<th>Fast Track (n = 193)</th>
<th>Standard care (n = 207)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr*</td>
<td>66±9.5</td>
<td>67±8.1</td>
<td>0.548*</td>
</tr>
<tr>
<td>Male sex – %</td>
<td>55</td>
<td>61</td>
<td>0.562*</td>
</tr>
<tr>
<td>Body mass index – kg/m²*</td>
<td>26.6±4.1</td>
<td>26.0±4.5</td>
<td>0.177*</td>
</tr>
<tr>
<td>ASA – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grade I or II</td>
<td>80</td>
<td>77</td>
<td>0.436*</td>
</tr>
<tr>
<td>Co-morbidity – %</td>
<td>65</td>
<td>68</td>
<td>0.331*</td>
</tr>
<tr>
<td>Type of surgery – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Open</td>
<td>48</td>
<td>47</td>
<td>0.866*</td>
</tr>
<tr>
<td>- Laparoscopic</td>
<td>52</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Type of colectomy – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Right-sided</td>
<td>40</td>
<td>49</td>
<td>0.055*</td>
</tr>
<tr>
<td>- Left-sided</td>
<td>60</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>T stage – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- T0</td>
<td>15</td>
<td>15</td>
<td>0.879*</td>
</tr>
<tr>
<td>- T1</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>- T2</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>- T3</td>
<td>51</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>- T4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>N stage – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- N0</td>
<td>62</td>
<td>70</td>
<td>0.893*</td>
</tr>
<tr>
<td>- N1</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>- N2</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>M stage – %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- M0</td>
<td>97</td>
<td>94</td>
<td>0.509*</td>
</tr>
<tr>
<td>- M1</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total hospital stay – days</td>
<td>5 (4 – 10)</td>
<td>7 (5 – 10)</td>
<td>&lt;0.004*</td>
</tr>
<tr>
<td>Overall morbidity &lt; 30 days – n (%)</td>
<td>77 (39.9)</td>
<td>78 (37.7)</td>
<td>0.650*</td>
</tr>
<tr>
<td>Reoperations – n (%)</td>
<td>23 (11.9)</td>
<td>29 (14.0)</td>
<td>0.534*</td>
</tr>
<tr>
<td>Readmission &lt; 30 days – n (%)</td>
<td>13 (6.7)</td>
<td>14 (6.8)</td>
<td>0.991*</td>
</tr>
<tr>
<td>In-hospital mortality – n (%)</td>
<td>6 (3.1)</td>
<td>4 (1.9)</td>
<td>0.451*</td>
</tr>
</tbody>
</table>

*Values are mean ± standard deviation / ASA = American Society of Anesthesiologists / IQR = inter-quartile range / *ANOVA test / ^Chi-square test / ~Mann-Whitney U test
Table 3 Univariable linear regression analysis of baseline characteristics and achieved fast track elements on total postoperative hospital stay (after log-transformation)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>B (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.84 (0.73 – 0.97)</td>
<td>0.017</td>
</tr>
<tr>
<td>Age – years</td>
<td>1.01 (1.00 – 1.02)</td>
<td>0.033</td>
</tr>
<tr>
<td>ASA, grade III</td>
<td>0.82 (0.70 – 0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00 (0.99 – 1.02)</td>
<td>0.648</td>
</tr>
<tr>
<td>Laparoscopic operation</td>
<td>0.79 (0.69 – 0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Right-sided resection</td>
<td>1.01 (0.88 – 1.17)</td>
<td>0.842</td>
</tr>
<tr>
<td>Fast track elements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative counselling</td>
<td>0.90 (0.78 – 1.03)</td>
<td>0.119</td>
</tr>
<tr>
<td>No bowel preparation</td>
<td>0.75 (0.61 – 0.94)</td>
<td>0.010</td>
</tr>
<tr>
<td>Intake of at least 0.4 litre carbohydrate-loaded liquids</td>
<td>0.90 (0.78 – 1.04)</td>
<td>0.144</td>
</tr>
<tr>
<td>No preoperative fasting</td>
<td>0.93 (0.81 – 1.02)</td>
<td>0.295</td>
</tr>
<tr>
<td>Intake of at least 0.2 litre carbohydrate-loaded drinks 2 h before surgery</td>
<td>0.92 (0.80 – 1.06)</td>
<td>0.265</td>
</tr>
<tr>
<td>No sedative premedication</td>
<td>0.89 (0.77 – 1.03)</td>
<td>0.109</td>
</tr>
<tr>
<td>Thoracic epidural analgesia</td>
<td>0.97 (0.81 – 1.15)</td>
<td>0.699</td>
</tr>
<tr>
<td>Adequate perioperative fluid management</td>
<td>1.09 (0.94 – 1.26)</td>
<td>0.251</td>
</tr>
<tr>
<td>Forced body heating</td>
<td>0.76 (0.48 – 1.22)</td>
<td>0.262</td>
</tr>
<tr>
<td>Removal of nasogastric tube before extubation</td>
<td>0.84 (0.70 – 1.01)</td>
<td>0.060</td>
</tr>
<tr>
<td>No use of abdominal drains</td>
<td>0.89 (0.70 – 1.13)</td>
<td>0.321</td>
</tr>
<tr>
<td>Suprapubic catheter or no catheter</td>
<td>0.94 (0.82 – 1.08)</td>
<td>0.393</td>
</tr>
<tr>
<td>Intake of at least 0.5 litre liquids of which 0.2 litre carbohydrate-loaded drinks</td>
<td>0.85 (0.70 – 1.02)</td>
<td>0.084</td>
</tr>
<tr>
<td>At least 15 minutes of mobilisation in the evening</td>
<td>0.86 (0.72 – 1.04)</td>
<td>0.113</td>
</tr>
<tr>
<td>Laxative at postoperative days 1, 2 &amp; 3</td>
<td>0.78 (0.67 – 0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Normal diet at postoperative days 1, 2 &amp; 3</td>
<td>0.58 (0.51 – 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enforced mobilisation at postoperative days 1, 2 &amp; 3</td>
<td>0.57 (0.50 – 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enforced intake of liquids at postoperative days 1, 2 &amp; 3</td>
<td>0.67 (0.55 – 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Removal of thoracic epidural at postoperative day 2</td>
<td>0.71 (0.62 – 0.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Table 4** Multivariable linear regression analysis of remaining baseline characteristics and achieved fast track elements on total postoperative hospital stay (after log-transformation)

<table>
<thead>
<tr>
<th></th>
<th>Total hospital stay (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.83 (0.73 – 0.94)</td>
</tr>
<tr>
<td>Laparoscopic resection</td>
<td>0.82 (0.72 – 0.94)</td>
</tr>
<tr>
<td>‘Perfect protocol’</td>
<td>0.56 (0.48 – 0.65)</td>
</tr>
</tbody>
</table>

**Discussion**

The present study showed that two baseline characteristics; female sex and laparoscopic surgery, and two successfully achieved fast track elements; enforced mobilisation and enforced diet, were independent predictors of total postoperative hospital stay.

The two identified predictive fast track elements were both postoperative items, and therefore likely to be confounders on the outcome. First of all, these elements were a direct reflection of a patients’ postoperative recovery; if a patient was feeling well, he/she was more likely to comply with the postoperative elements compared to a patient who was nauseated. Secondly, although patients were actively stimulated by the nurses and surgeons to mobilise and eat, the patient himself was responsible for actually doing it. Therefore, the attitude of a patient and the amount of effort a patient was willing to make was determining as well.

For some fast track items, like ‘prevention of hypothermia’ and ‘no abdominal drains’, available evidence is so convincing, that it would have been unethical to withhold these in trial setting. Therefore, some elements have been applied in the majority of the patients in the standard care group as well. This probably explains why these items have not been identified as independent predictors; due to the high compliance in both groups, the statistical significance was lost.

A laparoscopic resection as independent predictor was in accordance with the results of the principal study. Sex as an independent predictor was more surprising. After exploring the data, this difference could be explained by the higher percentage of morbidity in male patients (44%) compared to female patients (32%), in particular major morbidity (21% and 10%, respectively), which was defined as any complication requiring a surgical or percutaneous intervention or an admission to the intensive care unit. This contrast in morbidity can be clarified in several ways. First of all, significantly more men in this study were classified with an ASA grade III; several studies have shown that an ASA III grade or higher is associated with an increased postoperative morbidity. Second, a recently published multivariable analysis has identified the male sex itself as a potential risk factor for postoperative complications in elec-
tive laparoscopic colorectal procedures. In addition, some studies have stated an increased risk for anastomotic leakage in men, which is consistent with the results of this study (10% of the males were reoperated for an anastomotic leakage versus 3% of the females). Third, the difference in body fat distribution, i.e. males have got more visceral fat, while women have more subcutaneous fat. Up to date, there is some literature demonstrating that a higher degree of visceral fat is associated with more postoperative morbidity.

It is our opinion, that the protocolised way of working (i.e. the preclusion of discussion if, when, and how) and enforced postoperative care, are, above all, the most important distinguishing factors compared to standard care. The data of the systematic review by Wind et al. support this. Despite having implemented only 9 out of the 17 fast track elements, hospital stay was significantly reduced. Another recently published study support this as well; Ahmed et al. evaluated the difference in compliance to a fast track protocol between patients operated in a trial setting and those not participating in a trial. The authors concluded that fewer items were achieved in the non-trial group. Nonetheless, this made little difference on patient outcome. In addition, one observational study examined the relationship between protocol compliance and hospital stay. Their results were comparable to ours; compliance with postoperative fast track elements was predictive of length of hospital stay. The same study group also investigated which patient factors were related to a prolonged hospital stay within an enhanced recovery programme; male sex was found to be an independent predictor, which is in accordance with our study. It can be hypothesized that laparoscopic surgery combined with a protocolised way of enforced mobilisation and oral intake might be as efficient as successful implementation of all fast track items. This needs to be studied in more detail.

Limitations of our study were that some, mainly postoperative, fast track items were patient dependent, which means that if a patient was feeling nausea or did not feel like mobilising or drinking, the item was less likely to be achieved. Secondly, we could not assess the predictive character of elements that were applied in the majority of patients in the fast track group and in the standard care group, e.g. epidural analgesia.

In conclusion, evaluating only those fast track elements that were successfully achieved, showed that enforced advancement of oral intake, early mobilisation and laparoscopic surgery and female sex were independent determinants of early recovery.

Acknowledgements
The authors would like to thank all investigators of the LAFA study group and all patients that participated in the LAFA-trial, without them the study would not have been possible. Further we are grateful for the governmental subvention (ZonMW) and the financial support of Johnson and Johnson International and Nutricia.
References


Feasibility of a laparoscopic Nissen fundoplication as a day-case procedure

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Abstract

Background
The aim of this prospective double-cohort pilot study is to evaluate the feasibility and desirability of laparoscopic Nissen fundoplication (LNF) performed in day-care when compared to laparoscopic cholecystectomy (LC) in day-care.

Methods
Patients who underwent a LNF in day-care were prospectively evaluated. LNF patients were treated according to LC in day-care protocol. Outcome parameters were EQ-5D, Visual Analogue Scale (VAS) and patient satisfaction.

Results
From October 2005 to March 2008, 22 patients underwent LNF and 48 patients LC in day-care. After LNF, 21 out of 22 (95%) patients were discharged the same day. Seven (32%) patients were seen postoperatively on the Emergency Department with dysphagia or pain and two (9%) patients were readmitted. After LC, 45 out of 48 (94%) patients were discharged the same day. Six (12.5%) patients were seen postoperatively on the Emergency Department because of wound infection or pain and three (6%) were readmitted. EQ-5D and VAS scores were significantly worse after LNF in day-care, repeated measurements P<0.0001 and P<0.0001. In a telephone survey 66.7% preferred a short hospital stay over day-care surgery after LNF compared to 30.9% after LC (P=0.011).

Conclusions
LNF in day-care is feasible and safe, but postoperative pain scores are high and most prefer short hospital stay.
**Introduction**

The incidence of gastro esophageal reflux disease (GERD) has increased in the Western world for the last 50 years.\(^1\) A 360° Nissen fundoplication is the most common surgical treatment for this disease nowadays\(^2\), and the first laparoscopically performed Nissen fundoplication was performed in 1991.\(^3\) Randomized controlled trials have shown that the success rate of surgery is similar for the open and laparoscopic approach. Advantages for a laparoscopic procedure were less morbidity, a shorter hospital stay and a better cosmetic result.\(^4\) Nowadays, the preferred treatment for GERD is a laparoscopic Nissen fundoplication (LNF).

As surgical and anesthesiology techniques get better, day-care surgery is gaining popularity. Laparoscopic cholecystectomy (LC), for example, is performed routinely in day-care surgery in many centers. Several randomized studies\(^5\) have demonstrated that there is no difference in morbidity, number of readmissions and quality of life between inpatient or outpatient procedure. Advantages of a day-care procedure are lower costs and, in some countries, shorter waiting lists. In 1995 Milford et al.\(^6\) performed the first LNF as a day-care procedure. This article has been included in the only systematic review published\(^7\), which concluded that LNF in day-care was feasible and safe.

Very few papers have been published describing the results of LNF in day-care and only one of those studies is a double cohort study.\(^8\)

Therefore, the aim of this prospective double-cohort pilot study was to evaluate the feasibility and desirability of LNF in day-care with respect to postoperative pain, quality of life and patient satisfaction when compared to LC in day-care.

**Materials and Methods**

Patients undergoing LNF or LC in day-care from September 2005 to March 2008 were included in this prospective double-cohort pilot study. Clinical indications for LNF were: symptoms of GERD confirmed by gastroscopy, manometry, and 24-hours pH-metry. Symptomatic cholelithiasis proven by abdominal ultrasound was an indication for LC. The surgeon and anesthesiologists decided if a patient was suitable for day-care surgery. Inclusion criteria for day-care surgery were: American Society of Anesthesiologists (ASA) grade I, II or stable III\(^9\), Body Mass Index (BMI) below 40 kg/m\(^2\), living no more than 1.5 h away from the hosp-
pital, the company of a responsible adult for a minimum of 24 h after the operation, being under medical attention of a general practitioner, and telephonic accessibility. Presence of a large hiatus hernia or a prior abdominal operation was not an exclusion criteria.

At the day of surgery patients had to be present at 7.30 a.m. Intervention started at 8.00 or 10.00 a.m. for the first and second case, respectively. As premedication 1g acetaminophen and 50 mg tramadol was administered. Benzodiazepines were not part of the standard premedication and were only administered if the patient was anxious, as evaluated by the attending anesthesiologist. General anesthesia was induced and maintained by target-controlled infusion of 2.5-3 µgram propofol plus remifentanil. To facilitate endotracheal intubation mivacurium or rocuronium was used. Patients were mechanically ventilated with oxygen air.

Prophylactic medication for postoperative nausea and vomiting (PONV) was administered peroperatively using the following medication scheme: at the start of the operation 10 mg dexamethason, and at the end 15 µgram/kg dehydrobenzperidol plus 4 mg ondansetron. Forty-five minutes before closing 0.15 mg/kg morphine was given as postoperative pain medication. Nasogastric tubes were used to decompress the stomach during operation and removed before extubation. Urinary catheters were not utilized.

Surgical technique

For a LNF, three 10-mm and two 5-mm trocars were inserted in the umbilicus and upper abdomen. For LC, two 10-mm and two 5-mm were used. At the end of the operation the port sites were infiltrated with a long-acting local anesthetic (bupivicaine). All LNF were performed or supervised by a senior surgeon (W.A.B.). At the recovery room, postoperative pain management consisted of 150 mg acetaminophen intravenously and, if required, for PONV, 2 mg ondansetron, 15 µgram/kg dehydrobenzperidol, and/or metoclopramide intravenously.

Patients were permitted to drink and eat shortly after discharge from the Post Anesthesia Care Unit (PACU) and were scheduled to leave the day-care center before 7.30 p.m. Discharge criteria according to Post Anaesthesia Discharge Score System\textsuperscript{10} were: <20% deviation of blood pressure and pulse compared with preoperative values, balanced gait without dizziness, pain acceptable and pain regulated with oral analgesics, no excessive nausea or vomiting, and minimal blood loss. Before discharge patients were seen both by the surgeon as well as the anesthesiologist. Postoperative pain medication differed between the first group of 10 LNF patients (group I) and the last group of 10 LNF patients (group II). Group I received 1 g acetaminophen and 50 mg tramadol, both 4 times a day. Group II and all LC received the same analgesics plus 50 mg diclofenac and 40 mg esomeprazol three times a day. Pain medication was reduced as agreed with each patient. Information about alarm symptoms plus relevant telephone numbers was given to the patient and their companion. Patients were called the next day by a nurse of the day-care center. Two months after surgery patients were seen for outcome assessment by the responsible surgeon.

Primary endpoints were: health related quality of life, postoperative pain and patient satisfaction. Health related quality of life was assessed by EQ-5D, which is a simple, self-administered questionnaire in which a patient scores 1, 2, or 3, reflecting no problems, moderate
problems and extreme problems, respectively, scored on five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. These scores were used to generate a tariff reflecting the preference value associated with a given health state. The utility by Dolan et al.\textsuperscript{11} was used to calculate the overall health status (i.e., the EQ-5D tariff), in which a tariff of -0.6 represented the worst quality of life and 1.0 best quality of life. Postoperative pain was assessed by the Visual Analogue Scale (VAS), were 0 means no pain and 10 worst pain. Both had to be filled out at postoperative day 1 until 7, and at day 14. To assess patient satisfaction, patients with a successful discharge were contacted by telephone and asked for their preference for either day-care or short hospital stay. Secondary endpoints were percentage of successful discharges before 7.30 p.m. at the day of surgery, number of unplanned visits to the Emergency Department, readmission rate, and morbidity within 30 days.

Results for this pilot study for continuous data were expressed as median and range. Analyses of EQ-5D tariff and VAS were only done on the responding patients by linear mixed repeated-measure models. Other data were compared by Mann Whitney U and Chi-square tests. In all analyses, P<0.05 was considered as statistically significant.

\textit{Results}

Between September 2005 and March 2008, 22 consecutive patients underwent a LNF for GERD as a day-case procedure. All these patients were included in this study. Of the 22 LNF patients, 20 completed and returned the EQ-5D questionnaire and VAS (response rate 91%). A group of 48 patients underwent a LC as a day-case procedure, of whom 83% (n=40) responded. The 10 non-responding patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Convalescence of the non-responders</th>
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<tbody>
<tr>
<td><strong>Laparoscopic cholecystectomy</strong></td>
</tr>
<tr>
<td>Included, n</td>
</tr>
<tr>
<td>Responders, % (n)</td>
</tr>
<tr>
<td>Non-responders, % (n)</td>
</tr>
<tr>
<td>- Postoperative complication</td>
</tr>
<tr>
<td>- No postoperative complication</td>
</tr>
</tbody>
</table>

Except for the sex distribution, there were no significant differences in baseline characteristics between the groups (Table 2). None of the operations were converted to an open procedure in either group. In the LNF group, all but one (95%) were discharged before 7.30 p.m. at the day of surgery. One patient had to stay for an overnight observation, because of the development of subcutaneous emphysema in the face and neck peroperatively. This patient was discharged the next day without any complications. Successful discharge was achieved in 94% (n=45)
after LC. Two patients had to stay for observation because of peroperative complication managed nonoperatively and one because of excessive pain. In the LNF group 32% (n=7) of the patients visited the Emergency Department; one with bladder retention and six with dysphagia or pain, of whom two (9%) patients were readmitted. One patient required a laparoscopic drainage of a parahiatal abscess and one patient had infection of the umbilical port site. These postoperative complications resulted in hospital stay of 17 and 7 days, respectively. Of the patients in the LC group, 12.5% (n=6) visited the Emergency Department because of pain. Readmission occurred in 6% (n=3); one patient had acute pancreatitis, one a wound infection of the umbilical port site and one was admitted for adequate pain management. This resulted in hospital stay of 5, 3, and 3 days, respectively. The complication rate after LNF and LC was 14% (n=3; bladder retention, parahiatal abscess, wound infection) and 4% (n=2; pancreatitis, wound infection), respectively. None of these differences were significant.

<table>
<thead>
<tr>
<th>Table 2 Demographics of patients undergoing LC or LNF</th>
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<tr>
<td><strong>Laparoscopic cholecystectomy</strong></td>
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<tr>
<td>N</td>
</tr>
<tr>
<td>Male : female</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>ASA I : II : III</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Surgery time</td>
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</tbody>
</table>

Data: median (range) / †Mann Whitney U test / ‡Kruskal-Wallis test / LC = laparoscopic cholecystectomy / LNF = laparoscopic Nissen fundoplication / ASA = American Society of Anaesthesiologists / BMI = Body Mass Index

Interim analysis was performed after the first group of ten LNF patients (group I). In this group postoperative EQ-5D tariff and VAS were high at all postoperative days. After the interim analysis 50 mg diclofenac three times daily and 40 mg esomeprazol once daily was added to the postoperative pain medication (group II). Visual judgement of group I compared to group II did not show a different relation between time point and EQ-5D tariff or VAS score (Figure 1). Therefore, LNF subgroups were combined for further analysis, but an interaction term (treatment group x dose) was included as a covariate in the estimation of the average score difference over time between LNF and LC. Figures 2 and 3 show the EQ-5D tariff and VAS scores of all LNF patients and LC patients. On all postoperative days on both scales patients in the LNF group scored significantly worse (Figures 2 and 3). Repeated measures (mixed model) analysis indicated that the average increase per day in EQ-5D tariff was 0.033 points for both treatment groups. Corrected for the interaction between dose and treatment group, the average difference between the groups was 0.024 tariff points (Figure 2;
P<0.0001); without correction, the difference was the same. On the VAS patients scored on average -0.161 per day lower. Corrected average difference between the two interventions was 2.41 points on the VAS in advantage of the LC group (Figure 3; P<0.0001); without correction, this difference was 2.93 VAS points.

When asked for their preference in case of the hypothetical situation of having the same procedure again, 14 out of 21 (66.7%) LNF patients preferred a short hospital stay. In the LC group this was 13 out 42 (30.9%) patients. This difference was statistically significant (P=0.011).

**Figure 1** Postoperative EQ-5D tariff of first 10 LNF versus last 10 LNF

LNF = laparoscopic Nissen fundoplication / Group I = first 10 LNF patients / Group II = last 10 LNF patients
**Figure 2** Postoperative EQ-5D tariff of LC versus LNF

![EQ-5D tariff graph](image)

P < 0.0001, regression coefficient 0.033; linear mixed model
LC = laparoscopic cholecystectomy / LNF = laparoscopic Nissen fundoplication

**Figure 3** Postoperative VAS of LC versus LNF

![VAS graph](image)

P < 0.0001, regression coefficient -0.161, linear mixed model
VAS = Visual Analogue Scale / LC = laparoscopic cholecystectomy / LNF = laparoscopic Nissen fundoplication


**Discussion**

This study evaluated the feasibility and desirability of LNF in day-care surgery. The results were compared with a prospective cohort of day-care LC. Although LNF in day-care was successful in terms of discharge rate and morbidity, postoperative pain scores were higher despite adequate pain medication. Quality of life and patient satisfaction were much lower when compared with LC. In general in day-care, VAS for pain at home should not exceed 4. In the present study pain scores after LNF exceeded 4, and therefore LNF in day-care might not be desirable.

There are several conditions that an operation in day-care surgery has to meet in order to obtain acceptance by physicians: no increased morbidity or mortality compared with inpatient procedure, high success rate of same-day discharge, and satisfied patients.

Only one systematic review \(^6\)\(^{12-14}\) has been published about LNF in day-care. However, only four \(^6\)\(^{12-14}\) out of the seven studies were truly day-care surgery, as three studies \(^8\)\(^{15-16}\) defined discharge within 24 h after surgery as day-care surgery, when an overnight hospital admission is actually a short hospital stay. Of a total of 61 patients, questioned in two studies \(^8\)\(^{14, 45}\) (73%) would undergo the same procedure in day-care again. This review concluded that LNF in day-care was feasible and safe, but a judgment about patient satisfaction and preference could not be made.

Six studies \(^6\)\(^{12-14, 17-18}\) have been published about LNF in true day-care. In these studies morbidity and readmissions ranged from 0% to 11% and discharge rates from 82.5% to 100%. Our results were comparable with these data from literature.

Preference to undergo the same procedure in day-care again was only 33.3% in the present study. This is very low compared to other studies \(^12\)\(^{14, 17-18}\), which report preference for day-care surgery of 63.4-95%. In one study \(^17\) patients were asked to complete an 11-point numeric rating scale for pain and nausea within 5 days postoperatively, ranging from 0 (no pain/ no nausea) to 10 (worst pain/uncontrollable vomiting). The reported pain scores in that study were similar to those reported in the study by Keulemans et al. \(^19\), who studied LC in day-care. A possible explanation for the difference in pain between this present study and the study of Marriete et al. \(^17\) was the infiltration of the diaphragm with bupivcaine (long-acting local anesthetic) before closure apart from the routine infiltration of the port-site wounds. The highest patient satisfaction (95%) was achieved in the study of Bailey et al. \(^12\). In this study however, patients were asked for their preference at the evening of discharge, which might be not the optimal moment to evaluate this question.

The only other double-cohort study is done by Narain et al. \(^8\). It is of great importance to perform a double-cohort study when comparing postoperative pain. Postoperative pain after a laparoscopic procedure is thought to be caused by the port-site wounds. \(^20\) LC is performed with four trocars. For LNF, only one more 10-mm trocar is needed. The expectation of this study that postoperative pain after LNF would be comparable to that after LC, as there is only one additional port-site, proved to be incorrect. This difference might be caused by the intra-abdominal dissection in front of the aorta freeing the distal thoracic esophagus in LNF.
Another possible explanation for the difference in pain between LNF and LC could be the duration of operation and anesthesia, assuming more postoperative pain when surgery takes longer.\textsuperscript{21} In this study, however, median duration of surgery was actually 3 minutes shorter in the LNF group.

After the interim analysis pain medication had to be adjusted as VAS exceeded 4 and quality of life was low. The aim of this study was to compare LNF to LC in day-care. Nevertheless, postoperative pain medication was different for the first group of ten LNF patients. The reason for this was the restraining attitude of the anesthesiologists to prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) to patients with GERD and, as Trondsen et al.\textsuperscript{14} had shown excellent patient results and satisfaction with minimal pain medication (acetaminophen and codeine), alternative medication was not given. This difference in pain medication for the first ten LNF patients could have been a bias. However, corrected analysis taking the difference in pain medication into account did not relevantly alter the results.

Recently new interventions to treat GERD have been developed. One of the new surgical antireflux devices is a magnetic sphincter\textsuperscript{22}, positioned around the distal esophagus laparoscopically. It might be of interest to study postoperative pain in these patients, since periesophageal dissection is minimal and therefore postoperative pain might be less in these patients.

In conclusion, LNF in day-care is feasible and safe but, once at home, patients have high pain scores and quality of life is diminished in comparison with LC. Since more than two-thirds of the patients preferred a short hospital admittance, conventional LNF can best be performed in a short-stay setting. In order to justify LNF in day-care further research is needed to adjust postoperative analgesia.\textsuperscript{23}
References


Summary and conclusions

In this thesis several aspects of abdominal surgery for benign and malign diseases were highlighted. The aim of part I was to evaluate the clinical and functional outcome of abdominal surgery in patients with ulcerative colitis (UC) and familiar adenomatous polyposis (FAP). In part II, the aim was to critically appraise the effects of the two new major developments in elective abdominal surgery.

Surgery for Ulcerative Colitis and Familial Adenomatous Polyposis (part I)

In chapter 1, a pilot study was performed to determine whether the type of approach, open or laparoscopic, and the order of devascularisation in laparoscopic colectomy, affects intestinal barrier function, local inflammatory response and clinical outcome. Twenty-two patients scheduled for laparoscopic colectomy were randomized to start with inferior mesenteric artery or ileocolic artery devascularisation. Eighteen patients scheduled for open surgery served as a prospective control group. To assess the intestinal barrier function release of intestinal fatty acid binding protein (I-FABP; marker of mucosal injury and ischemia) was measured pre- and postoperatively. Mesenteric lymph nodes were harvested to detect changes in RNA expression of genes encoding for inflammatory mediators using Multiplex Ligation Probe Amplification. After a right-sided start, excretion of I-FABP was significantly increased over time (P=0.002). In this group I-FABP levels were significantly increased on postoperative days 1 and 3 compared to preoperative values (P=0.011 and P=0.001, respectively). There were no differences in expression of inflammatory mediator-related genes or postoperative morbidity among the groups. This pilot study demonstrated that devascularisation started at the ileocolic artery during laparoscopic colectomy was associated with prolonged intestinal mucosal ischemia.

After a proctocolectomy with ileo-pouch anal anastomosis (IPAA) for ulcerative colitis (UC), patients are still at risk for the development of dysplasia and cancer in the pouch, the anastomotic site, or remaining rectal cuff. In chapter 2 the prevalence of dysplasia in UC patients who have undergone a proctocolectomy with IPAA and who demonstrated dysplasia or cancer in their resection specimen was assessed. Between 1988 and 2008, 290 patients with inflammatory bowel disease underwent a proctocolectomy with IPAA in the Academic Medical Center Amsterdam. A total of 64 patients with UC underwent surgery and had (indefinite for) dysplasia or carcinoma in their resection specimen. Forty-four patients (mean age 49 years) underwent surveillance pouch-endoscopy. The mean time between surgery and pouch surveillance was 8.6 (median 7.9, range 1-19) years. In 2 patients low-grade dysplasia was detected (4.5%). Based on this study the benefit of routine surveillance for dysplasia in the IPAA is uncertain.

A common complication after a proctocolectomy with IPAA is sexual dysfunction. This may have a large impact as most of the patients are young and sexually active. The most systematic physical reaction to sexual stimulation is an increase in vaginal vasocongestion, which can be assessed by vaginal pulse amplitude (VPA) using vaginal photoplethysmog-
raphy. Chapter 3 was designed to assess whether a proctocolectomy with IPAA was associated with autonomic pelvic nerve damage, as objectified with VPA during sexual stimulation (visual and vibrotactile), and with changes in subjective indices of sexual function, assessed with validated questionnaires. For 8 patients (median age 37) pre- and postoperative data was collected. VPA analysis showed a significant reduction in vaginal vasocongestion during sexual stimulation postoperatively, P=0.012. There were no differences in subjective sexual arousal and estimated lubrication during the experiment, and reported psychological and sexual functioning pre- and postoperatively. In conclusion, vaginal vasocongestion after IPAA was significantly reduced in this study. This indicates that IPAA in women is possibly associated with autonomic pelvic nerve damage or partial devascularisation of the vagina.

Most patients are young and in their reproductive years at the time of operation. In these patients, the optimal method of childbirth has yet to be determined. It is demonstrated that anal sphincter defects occur after vaginal deliveries. In patients with UC or FAP that have undergone or still have to undergo a proctocolectomy with IPAA, damage to the anal sphincter, pelvic floor or pudendal nerves will probably have more clinical impact at an earlier age compared to 'normal' women. A retrospective study was initiated, described in chapter 4, to evaluate the effect of vaginal delivery and its potential complications both before and after a proctocolectomy with IPAA on the pouch function. All women (n=267) who underwent a proctocolectomy with IPAA between January 1985 and November 2004 were retrospectively recruited from 3 academic medical centers in the Netherlands. Hundred seventy-two patients were available for analysis. Patients were asked about their pregnancies and risk factors for obstetric injury. Functional outcome was assessed by the colorectal functional outcome questionnaire. Median follow-up after pouch surgery was 7.2 (range 1.0–19.7) years. One hundred patients had at least one delivery; 86 of these 100 patients attempted a vaginal delivery of which 52 patients had an increased risk of obstetric injury according to the predefined risk factors. In patients with an increased risk of obstetric injury, ageing and longer follow-up appeared to be significant risk factors for impaired incontinence. Based on these results, patients with proctocolectomy with IPAA should be informed about the considerable risk of vaginal delivery on long-term pouch function.

Enhanced Recovery After Surgery (part II)

In chapter 5 the latest evidence of quality of life in patients after laparoscopic or open colorectal surgery was examined. After a systematic search 9 randomized clinical trials (RCTs) remained for analysis, comprising 2263 patients. Short- and long-term results of these 9 RCTs were described in 13 articles. Due to clinical heterogeneity, it was not possible to conduct a meta-analysis. Postoperative follow-up ranged from 2 days to 6.7 years. Four RCTs showed no significant differences in postoperative quality of life following open or laparoscopic colorectal surgery on short-term (1 to 12 weeks) or on long-term (3 months to 6.7 year) follow-up. The remaining 5 studies reported a better quality of life in favour of the laparoscopic group on a few quality of life scales at time points ranging from 1 week to 2 years after surgery. Based
on presently available high-level evidence, this systematic review showed no clinical relevant differences in quality of life on short- or long-term follow-up between open and laparoscopic colorectal surgery.

In chapter 6 another systematic review was performed of all RCTs and controlled clinical trials (CCTs) on laparoscopic versus open surgery within fast track perioperative care. Primary endpoints were primary and overall hospital stay, readmission rate, morbidity and mortality. Only 2 RCTs and 3 CCTs were eligible for final analysis, which reported on 400 patients. Data could not be pooled because of clinical heterogeneity. One RCT and one CCT stated a shorter primary hospital stay in the laparoscopic group of three and two days, respectively. In one RCT readmission rate was lower in the laparoscopic group; absolute risk reduction 21.4% and a number to treat of 4.7 patients. Another study showed a 23% difference in favour of the laparoscopic group with regard to morbidity, i.e. a number to treat of 4.4 patients. There were no significant differences in mortality rates. Based on this evidence, no conclusion could be made. So, whether laparoscopic surgery is still of added benefit when concurrently a fast track program is applied, remained a matter of debate.

To answer this question a multicenter randomized controlled trial of a 2 x 2 balanced factorial design was initiated at the Academic Medical Center. This study, presented in chapter 7, aimed to determine which perioperative treatment, i.e. laparoscopic or open surgery combined with fast track or standard care, was the optimal approach for patients undergoing segmental resection for colon cancer, and to investigate if either laparoscopy, FT care, or the combination of both is the main predictive factor for a faster postoperative recovery. Patients between 40 and 80 years of age, with an American Society of Anaesthesiologists grade of I, II or III, that were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma, and without evidence of metastatic disease were eligible. After informed consent patients were randomized to laparoscopic or open colectomy, and to fast track or standard care, resulting in four treatment groups. Patients, nursing and medical staff were informed about the applied care program, but blinded to type of intervention. In total 427 patients (mean age 66.5 years, 234 males) were randomized in 9 Dutch hospitals. Our primary endpoint was total postoperative hospital stay, including hospitalization period in case of readmission. Four hundred patients were available for analysis. Median total postoperative hospital stay was 5 days after a laparoscopic resection combined with fast track care, 7 days after an open/fast track treatment, 6 days after a laparoscopic/standard treatment, and 7 days after an open/standard treatment. Median postoperative hospital stay was similar to total postoperative hospital stay for all treatment groups, except for the open/fast track group in whom hospital stay was 6 days instead of 7 days. Linear regression analysis identified laparoscopy as the only independent factor to influence total postoperative hospital stay, i.e. a reduction of 21% (CI: 9-31%). FT care showed a trend, but the combination of both showed no additional benefit. Median postoperative hospital stay was significantly influenced by both, i.e. reduction of 20% (CI: 9-30%), and FT care, i.e. a reduction of 14% (CI: 10-20%). The combination of both did not add any benefit. Other secondary outcomes; overall morbidity,
reoperation rate, readmission rate, in-hospital mortality and in-hospital costs did not differ significantly among the groups. Logistic regression analysis showed that only laparoscopic resection resulted in a significantly lower overall- and major morbidity. The other endpoints were not significantly influenced by the different surgical regimens. Quality of life and patient satisfaction were similar. This study showed that a laparoscopic resection within a fast track perioperative care program is the optimal treatment for patients requiring a segmental colectomy for malignancy. If open surgery has to be performed, for example because of the lack of laparoscopic expertise or patient-related factors, then this should be embedded in a fast track protocol. In addition, laparoscopy was found to be the only significant independent factor to reduce postoperative hospital stay and morbidity.

As RCT’s comparing the effect on postoperative gastrointestinal motility are lacking a side-study of the LAFA-study was performed in **Chapter 8**. In this study it was evaluated which perioperative treatment, i.e. laparoscopic or open surgery combined with fast track or standard care, leads to faster recovery of the gut after colonic surgery. Primary endpoints were colonic transit and gastric emptying. This was scintigraphically assessed from day 1 to 3. Colonic transit at day 2 and 3 was represented as geometrical center of activity (segment 0=small intestine, 1=proximal-, 2=distal colon, 3=toilet). Secondary endpoints were time to tolation of solid food and/or bowel movement, and time until (ready for) discharge. In total 93 LAFA patients participated. The median colonic transit at day 3 of patients undergoing laparoscopic/fast track care (2.6 (2.0-2.9)) was significantly higher, compared to the laparoscopic/standard (2.2 (1.6-2.5), P=0.044), open/fast track (2.0 (1.6-2.4), P=0.010), and open/standard care group (1.3 (1.0-1.5), P<0.001). Median gastric retention did not differ between groups (P=0.61). Multivariate regression analysis showed that both laparoscopic surgery and fast track care were significant independent predictive factors of improved colonic transit, resulted in significantly shorter time until tolation of solid food and bowel movement and recovered significantly faster. This study showed that laparoscopic surgery as well as fast track care result in a better recovery of the gut after colorectal surgery, leading to a more rapid clinical recovery. The optimal perioperative treatment with the fastest recovery of gastrointestinal function is laparoscopic resection embedded in a fast track program.

To even further assess why laparoscopic surgery combined with fast track care is the optimal treatment, another side-study of the LAFA-study was performed in **Chapter 9**. In this study the effect on patient’s immune status and stress response after the 4 treatment combinations was evaluated. In each treatment group around 17 to 23 comparable patients were available for analysis. HLA-DR expression on monocytes is a measure for immune competence and was best preserved 2 and 24 hours after a laparoscopic/fast track treatment. Interleukin-6 is associated with postoperative complication rates and was significantly increased in the open/standard group at 24 hours and 72 hours postoperatively. C-reactive protein was significantly increased at all time points (1 hour, 2 hours, 24 hours and 72 hours) in the open/standard group. There were no differences regarding growth hormone level, prolactin level, cortisol level and rate of (infectious)complications between the groups. This study showed that im-
mune function is best preserved in patients having laparoscopic colectomy within a fast track program. Therefore, these data are supportive to chapter 7 & 8, in which an accelerated postoperative recovery was found in patients treated laparoscopically within a fast track program.

As illustrated by the previous chapters, implementation of fast track care is important, because it is associated with a shorter hospital stay and possibly less complications. In chapter 10 it was determined which baseline characteristics and/or which successfully achieved fast track elements are independent predictors of faster postoperative recovery in patients undergoing colonic resection for colon cancer. For this purpose data from the LAFA-study were used. During admission the fast track elements were prospectively evaluated per patient and scored whether or not successfully applied. In the fast track group there was a higher overall compliance to the preoperative and perioperative fast track elements (mean 9.7 elements out of 12; ranging from 52% to 97%) than to the postoperative elements (mean 2.9 elements out of 7; ranging from 30% to 66%). Some elements (no bowel preparation, thoracic epidural, forced body heating, removal of nasogastric tube, no abdominal drains) were also applied in standard care group as available evidence is so convincing, that it would have been unethical to withhold these in a trial setting. Two baseline characteristics and 2 fast track elements were found to be significant independent predictors on total postoperative hospital stay (THS); female sex was leading to a 15% (CI: 4-25%) reduction in THS, laparoscopic resection in a 15% (CI: 4-25%) reduction in THS, ‘normal diet at postoperative days 1, 2 & 3’ in a 30% (CI: 19-39%) reduction in THS, and ‘enforced mobilisation at postoperative days 1,2 & 3’ in 32% (CI: 20-41%) reduction in THS. In conclusion, evaluating only those fast track elements that were successfully achieved, showed that enforced advancement of oral intake, early mobilisation and laparoscopic surgery and female sex were independent determinants of early recovery.

Finally in chapter 11, the ultimate level of fast track care, namely day-care surgery, has been evaluated. The main goal of the fast track concept is to accelerate patient’s postoperative recovery resulting in a shorter hospital stay. Day-care surgery is a feasible option for some surgical procedures. In this prospective double-cohort study we evaluated the feasibility and desirability of 360° laparoscopic Nissen fundoplication (LNF) performed in day-care compared to a laparoscopic cholecystectomy (LC) in day-care. LC was chosen as cohort, because this procedure is performed routinely in day-care surgery. Twenty-two patients underwent LNF and 48 patients LC in day-care. After LNF, 21 out of 22 (95%) patients were discharged the same day. After LC, 45 out of 48 (94%) patients were discharged the same day. EQ-5D (a measure of health-related quality of life) and VAS scores were significantly worse after LNF in day-care (repeated measurements, P<0.0001 and P<0.0001). In a telephone survey 66.7% of the LNF patients preferred a short hospital stay over day-care surgery, compared with 30.9% after LC (P=0.011). In conclusion, LNF in day-care is feasible and safe, however postoperative pain scores were high and quality of life was diminished in comparison with LC. Since more than two-thirds of patients preferred short hospital admittance, conventional LNF can best be performed in a short-stay setting.
Samenvatting

In dit proefschrift zijn de verschillende aspecten van de abdominale chirurgie voor benigne en maligne ziekten belicht. Het doel van deel I was om de klinische en functionele uitkomsten van abdominale chirurgie in patiënten met ulceratieve colitis (UC) en familiare adenomateuze polyposis (FAP) te evalueren. Deel II had tot doel om de effecten van twee belangrijke ontwikkelingen binnen de electieve abdominale chirurgie te evalueren.

Chirurgie voor Ulceratieve Colitis en Familiaire Adenomateuze Polyposis (deel I)

Hoofdstuk 1 beschrijft een pilot-studie. In deze studie is bepaald of het type operatie, open dan wel laparoscopisch, en de volgorde van devascularisatie in een laparoscopische colectomie, de intestinale barrière functie, de lokale inflammatoire respons en klinische uitkomsten beïnvloedt. Tweeëntwintig electief geplande laparoscopische colectomie patiënten, zijn gerandomiseerd naar rechts- of linkszijdig starten met devasculariseren. Achtien patiënten, gepland voor open chirurgie, dienden als prospectieve controle groep. Ter bepaling van de intestinale barrière functie is de excretie van ‘intestinal fatty acid binding protein’ (I-FABP; een maat voor mucosale schade en ischemie) preoperatief en op postoperatieve dagen 1, 3 en 7 in de urine gemeten. Na verwijdering van het resectie preparaat is een lymfklier uit het mesenterium geoogst om de expressie van mediator-gerelateerde inflammatie genen te bepalen door middel van Multiplex Ligation Probe Amplification. De excretie van I-FABP bleek na een rechtszijdige start significant in de tijd te zijn toegenomen (P=0.002). In deze groep was I-FABP significant verhoogd op de postoperatieve dagen 1 en 3 ten opzichte van preoperatieve waarden (P=0.011 en P=0.001, respectievelijk). De expressie van inflammatoire mediator-gerelateerde genen en morbiditeit was niet verschillend tussen de drie benaderingen. De conclusie van deze pilot-studie is dat een rechtszijdige benadering bij een laparoscopische colectomie geassocieerd is met meer mucosale intestinale schade.

Hoofdstuk 2 beschrijft een prospectieve studie om de prevalentie van dysplasie in ulceratieve colitis (UC) geopereerde patiënten te bepalen. Een in 2007 verschenen systematisch review suggereerde dat patiënten met UC na een proctocolectomie met ileoanal pouch (IPAA) het risico blijven houden op het ontwikkelen van dysplasie of een carcinoom in de IPAA of rectale cuff. Patiënten die tussen 1988 en 2008 geopereerd zijn in het Academisch Medisch Centrum Amsterdam met bewezen dysplasie of carcinoom in hun resectiepreparaat zijn uitgenodigd voor een surveillance endoscopie. Vierenzestig patiënten kwamen in aanmerking, waarvan 44 patiënten (gemiddelde leeftijd 49 jaar) de surveillance endoscopie hebben ondergaan. De gemiddelde tijd tussen de operatie en surveillance was 8.6 (mediaan 7.9, range 1-19) jaar. Bij 2 patiënten is laag-gradige dysplasie gevonden (4.5%). De conclusie is dat het risico voor het ontwikkelen van dysplasie in de IPAA laag is. Het is daarom niet duidelijk of routinematige surveillance naar dysplasie in de IPAA noodzakelijk is.

Seksuele disfunctie na een proctocolectomie met IPAA komt vaak voor. Deze complicatie kan een grote impact hebben, omdat de meeste patiënten jong en seksueel actief zijn. De
belangrijkste lichamelijke verandering in reactie op seksuele prikkels is een toename van doorbloeding van de geslachtsdelen. De genitale respons kan worden vastgesteld door het meten van de doorbloeding van de vaginawand. Dit wordt gedaan door middel van een vaginale fotoplethysmograaf en wordt uitgedrukt als vaginale pulse amplitude (VPA). Het doel van de in hoofdstuk 3 beschreven studie was om te bepalen of een proctocolectomie met IPAA geassocieerd is met schade aan de autonome zenuwen in het kleine bekken. Deze schade is geobjectiveerd door het meten van VPA tijdens zowel visuele als vibrotactiele seksuele stimulatie, en door het afnemen van gevalideerde vragenlijsten om veranderingen te detecteren in de subjectieve indices van de seksuele functie. Acht patiënten (mediane leeftijd 37 jaar) ondergingen een pre- en postoperatieve meting. VPA analyse liet postoperatief een significante reductie zien van vaginale vasocongestie tijdens seksuele stimulatie (P=0.012). Subjectieve seksuele opwinding en zelf geschatte vaginale lubricatie tijdens het experiment, en gerapporteerd psychologisch en seksueel functioneren waren pre- en postoperatief niet verschillend. De conclusie van deze studie is dat de vaginale vasocongestie na IPAA significant afneemt. Dit duidt erop dat de seksuele disfunctie die vaak optreedt na deze ingreep wordt veroorzaakt door schade aan de autonome zenuwen in het kleine bekken of door partiële devascularisatie van de vagina.

Het is aangetoond dat na een vaginale bevalling anale sfincter defecten kunnen zijn opgetreden. In UC en familiare adenomeuze polyposis (FAP) patiënten, die een proctocolectomie met IPAA hebben of nog moeten ondergaan, is het waarschijnlijker dat schade aan de anale sfincter, danwel bekkenbodem of nervus pudendus een grotere klinische impact heeft vergeleken met ‘normale’ vrouwen. Een retrospectieve studie is uitgevoerd om het effect van een vaginale bevalling en de mogelijke complicaties, zowel vóór als na een proctocolectomie met IPAA op de functie van de pouch te evalueren. Deze studie staat beschreven in hoofdstuk 4. Alle vrouwen (n=267) die een proctocolectomie met IPAA ondergingen tussen januari 1985 en november 2004 zijn retrospectief geïdentificeerd. Honderd tweeënzeventig patiënten waren beschikbaar voor analyse. Patiënten werden gevraagd naar hun zwangerschappen, naar mogelijk opgelopen risicofactoren voor obstetrisch letsel, en naar het functionele resultaat van hun IPAA. Mediane follow-up na de operatie was 7.2 (range 1.0-19.7) jaar. Honderd patiënten waren ten minste één keer bevallen, waarvan 86 patiënten gestart waren met een vaginale bevalling. In 52 van deze 86 patiënten is de bevalling gecompliceerd verlopen (zoals gedefinieerd volgens vooraf opgestelde risicofactoren). In de groep ‘gecompliceerde bevallingen’ hadden patiënten meer incontinentieklachten met het toenemen van de leeftijd en langere follow-up. In het licht van deze bevindingen moeten patiënten met een proctocolectomie met IPAA ingelicht worden over de aanzienlijke risico’s van een vaginale bevalling op de lange termijn functie van de pouch.

Versneld herstel na chirurgie (deel II)
In hoofdstuk 5 zijn alle studies die de kwaliteit van leven bij patiënten na laparoscopische of open colorectale chirurgie hebben onderzocht systematisch beschreven. Na een systematische
search zijn 9 gerandomiseerde klinische trials (RCT’s) overgebleven voor analyse, bestaande uit 2 263 patiënten. Korte en lange termijn resultaten van deze 9 RCT’s zijn beschreven in 13 artikelen. Als gevolg van klinische heterogeniteit, was het niet mogelijk een meta-analyse uit te voeren. Postoperatieve follow-up varieerde van 2 dagen tot 6.7 jaar. Vier RCT’s toonden geen significante verschillen in postoperatieve kwaliteit van leven na open of laparoscopische colorectale chirurgie op korte termijn (1 tot 12 weken) of op lange termijn (3 maanden tot 6.7 jaar). De overige 5 studies rapporteerden op een paar schalen een betere kwaliteit van leven ten voordele van de laparoscopische groep, op tijdstippen variërend van 1 week tot 2 jaar na de operatie. Deze studie bewijst dat er geen klinisch relevante verschillen zijn in kwaliteit van leven op korte of lange termijn tussen open en laparoscopische colorectale chirurgie.

Een tweede systematische review is beschreven in hoofdstuk 6. Alle RCT’s en klinische gecontroleerde studies (CCT’s) die laparoscopische chirurgie met open chirurgie binnen fast track zorg hebben vergeleken zijn geïncludeerd. Primaire eindpunten waren primaire en totale ziekenhuisduur, het aantal heropnames, morbiditeit en mortaliteit. Slechts twee RCT’s en drie CCT’s, rapporterend over in totaal 400 patiënten, konden geanalyseerd worden. Vanwege klinische heterogeniteit bleek het niet mogelijk de data van deze studies te ‘poolen’. Eén RCT en één CCT lieten in de laparoscopische groep een kortere primaire ziekenhuisduur van respectievelijk drie en twee dagen zien. Het aantal heropnames was in één RCT significant lager in de laparoscopische groep, met een absolute risico reductie van 21.4% en een ‘aantal te behandelen patiënten’ (=numbers needed to treat) van 4.7 patiënten. Een andere studie toonde een verschil in morbiditeit van 23% in het voordeel van de laparoscopische groep aan, resulterend in een ‘numbers needed to treat’ van 4.4 patiënten. Mortaliteit tussen de twee behandelstrategieën was vergelijkbaar. Op basis van deze data konden we geen conclusie trekken. De vraag of laparoscopie nog van additioneel voordeel is als er tevens een fast track programma wordt toegepast, bleef bestaan.

Om deze vraag te beantwoorden is er in 2005 een multicentrum gerandomiseerde studie geïnitieerd vanuit het Academisch Medisch Centrum. Deze studie, beschreven in hoofdstuk 7, had tot doel te onderzoeken welke perioperatieve behandeling, i.e. laparoscopie of open chirurgie gecombineerd met fast track of standaard zorg, optimaal is voor patiënten die een segmentale resectie moeten ondergaan voor een coloncarcinoom, en om te onderzoeken wat de belangrijkste voorspeller is voor een versneld postoperatief herstel, laparoscopie, fast track zorg, of de combinatie van beiden. Patiënten tussen de 40 en 80 jaar, die in aanmerking kwamen voor een curatieve segmentale colon resectie wegens een maligniteit werden gevraagd deel te nemen aan dit onderzoek. Na toestemming van de patiënt vond randomisatie plaats naar één van de vier behandelgroepen; (1) laparoscopie/fast track, (2) open/fast track, (3) laparoscopie/standaard zorg, of (4) open/standaard zorg. De patiënten, de verpleegkundigen en de medische staf werden geïnformeerd over het toegewezen zorgprogramma, maar geblindeerd voor het type interventie. In totaal zijn 427 patiënten (gemiddeld 66.5 jaar, 234 mannen) gerandomiseerd in 9 Nederlandse ziekenhuizen (Onze Lieve Vrouwe Gasthuis, Sint Lucas Andreas Ziekenhuis, Zaanse Medisch Centrum, Tergooi Ziekenhuizen, Rode Kruis
Ziekenhuis, VU Medisch Centrum, Academisch Ziekenhuis Maastricht, Gelre Ziekenhuzen). Uiteindelijk waren 400 patiënten beschikbaar voor analyse. Ons primaire eindpunt, mediane totale postoperatieve ziekenhuisduur (ziekenhuisduur inclusief het aantal heropnames), was 5 dagen na een laparoscopie/fast track behandeling, 7 dagen na een open/fast track behandeling, 6 dagen na een laparoscopie/standaard behandeling, en 7 dagen na een open/standaard behandeling. In alle groepen was de mediane directe postoperatieve ziekenhuisduur hetzelfde als de totale postoperatieve ziekenhuisduur, behalve na een open/fast track behandeling waarin de postoperatieve ziekenhuisduur 6 dagen telde in plaats van 7 dagen. Lineaire regressie analyse identificeerde laparoscopie als enige onafhankelijke factor op de totale postoperatieve ziekenhuisduur, dit gaf een reductie van 21% (CI: 9-31%). De factor fast track zorg liet een (niet-significante) trend zien naar kortere ziekenhuisduur. De combinatie van beiden gaf echter geen additioneel voordeel. De mediane directe postoperatieve ziekenhuisduur werd door zowel laparoscopie als fast track zorg significant verkort. Dit leidde tot een reductie van 20% (CI: 9-30%) en 14% (CI: 10-20%), respectievelijk. Andere secundaire uitkomsten als morbideiteit, aantal heroperaties, aantal heropnames, ziekenhuis mortaliteit, ziekenhuiskosten, kwaliteit van leven en patiënt tevredenheid waren niet significant verschillend tussen de groepen. Logistische regressie liet zien dat alleen een laparoscopische resectie leidde tot een significant lagere morbiditeit. De overige secundaire eindpunten werden niet significant beïnvloed door laparoscopie, fast track of de combinatie van beiden. Deze studie heeft aangetoond dat een laparoscopische resectie gecombineerd met fast track zorg de optimale perioperatieve behandeling is voor patiënten die een segmentele colectomie voor een coloncarcinoom moeten ondergaan. In het geval dat open chirurgie moet worden toegepast, dan heeft het de voorkeur dit binnen een fast track programma te doen. De enige onafhankelijke voorspeller die invloed heeft op de postoperatieve ziekenhuisduur en morbiditeit is een laparoscopische resectie.

RCT’s die het effect van de verschillende behandelstrategieën op de postoperatieve gastro-intestinale motiliteit vergelijken ontbreken. In hoofdstuk 8 is een side studie van de LAFA-studie uitgevoerd met als doel te evalueren welke perioperatieve behandeling, laparoscopie of open chirurgie gecombineerd met fast track of standaard zorg, resulteert in sneller herstel van het maag darmstelsel na colon chirurgie. Primaire eindpunten waren colon transit en maaglediging. Dit werd scintigrafisch beoordeeld op postoperatieve dagen 1, 2 en 3. Colon transit werd geregistreerd door middel van een geometrische centrum van de activiteit (0 = segment dunne darm, 1 = proximale colon, 2 = distale colon, 3 = toilet). Secundaire eindpunten waren; verdragen van vast voedsel en/of stoelgang, en tijd tot (of klaar voor) ontslag. In totaal hebben 93 LAFA patiënten deelgenomen. De colon transit op postoperatief dag 3 in patiënten na een laparoscopie/fast track behandeling (2.6 (2.0-2.9)) was significant hoger vergeleken met laparoscopie/standaard (2.2 (1.6-2.5), P=0.044), open/fast track (2.0 (1.6-2.4), P=0.010), en open/standaard behandeling (1.3 (1.0-1.5), P<0.001). Mediane maaglediging verschilde niet tussen de groepen (P=0.61). Multivariaat regressie analyse identificeerde zowel laparoscopie als fast track als significant onafhankelijk voorspellende factoren op een
versnelde colon transit, een significant kortere duur tot verdragen van vast voedsel en de stoelgang, en herstelde significant sneller. Concluderend toonde deze studie aan dat laparoscopie en fast track in beter postoperatief herstel van de darm na colorectale chirurgie, wat resulteerde in een sneller klinisch herstel. De optimale perioperatieve behandeling ten aanzien van het snelste herstel van de gastro-intestinale functie is een laparoscopische resectie gecombineerd met fast track.

Een andere substudie van de LAFA is beschreven in hoofdstuk 9. Het doel van deze studie was de invloed van de vier behandelstrategieën op het afweersysteem en de daaruit volgende stressreactie te onderzoeken. In elke behandelgroep zijn 17 tot 23 vergelijkbare patiënten geïncludeerd. HLA-DR expressie op de monocytten is een maat voor de immuun competentie. Twee uur en 24 uur na een laparoscopie/fast track behandeling was HLA-DR expressie op de monocytten significant beter behouden. Interleukine-6 wordt geassocieerd met postoperatieve complicaties. Vierentwintig uur en 72 uur postoperatief was interleukine-6 significant verhoogd in de open/standaard groep. C-reactief proteïne was significant verhoogd op alle tijdstippen (1 uur, 2 uur, 24 uur en 72 uur) in de open/standaard groep. De stressreactie is gemeten aan de hand van de hoeveelheid groeihormoon, prolactine en cortisol in het bloed. Er waren geen verschillen tussen de groepen. Het aantal (infectieuze) complicaties was ook niet verschillend. Deze studie heeft aangetoond dat het immuunsysteem het best wordt behouden in patiënten die een laparoscopische resectie in combinatie met fast track zorg ondergaan. Deze bevinding is ondersteunend aan de conclusies van hoofdstuk 7 & 8, waarin een versneld postoperatief herstel is gevonden in patiënten behandeld door middel van laparoscopie en fast track.

In de vorige hoofdstukken is aangetoond dat fast track zorg geassocieerd is met een kortere ziekenhuisduur en wellicht ook met minder complicaties. Uit literatuur blijkt echter dat de implementatie van dit multidisciplinaire protocol niet gemakkelijk is. In hoofdstuk 10 is onderzocht welke patiëntkarakteristieken en welke succesvol behaalde fast track elementen onafhankelijke voorspellers waren op een sneller postoperatieve herstel. Voor deze studie, zijn de data van de LAFA-studie gebruikt. In elke patiënt is prospectief geëvalueerd hoeveel fast track elementen succesvol waren behaald. De preoperatieve en perioperatieve fast track elementen (gemiddeld 9.7 elementen van de 12; variërend van 52% tot 97%) zijn beter nageleefd dan de postoperatieve elementen (gemiddeld 2.9 elementen van de 7; variërend van 30% tot 66%). Sommige elementen (geen darmvoorbereiding, thoracale epiduraal, vermijden van hypothermie, geen maagsonde, geen abdominale drains) zijn ook toegepast in de standaard zorg groep. Het beschikbare wetenschappelijk bewijs hiervoor is namelijk zo overtuigend, dat het onethisch zou zijn deze elementen voor studie doeleinden achterwege te laten. Twee patiëntkarakteristieken en twee fast track elementen bleken significant onafhankelijke voorspellers op de totale postoperatieve ziekenhuisduur (THS); het vrouwelijk geslacht resulteerde in een 15% (CI: 4-25%) reductie in THS, een laparoscopische resectie ook in 15% (CI: 4-25%) reductie, ‘normaal dieet op postoperatieve dagen 1, 2 & 3’ in een 30% (CI: 19-39%) reductie en ‘gedwongen mobilisatie op postoperatieve dagen 1,2 & 3’ in 32% (CI: 20-41%) reductie.
Concluderend zijn laparoscopische chirurgie, het vrouwelijk geslacht, geforceerde orale intake en vroeg mobiliseren onafhankelijke voorspellers op een versneld herstel.

Ten slotte, is in hoofdstuk 11 de hoogste en snelste variant van fast track zorg, namelijk de chirurgische dagbehandeling, geëvalueerd. Het belangrijkste doel van fast track is het versnellen van het postoperatieve herstel van de patiënt, hetgeen resulteert in een kortere ziekenhuisopname. De chirurgische dagbehandeling is voor sommige procedures (bijvoorbeeld laparoscopische cholecystectomie) een haalbare en veilige optie. In deze prospectieve dubbel cohortstudie is de haalbaarheid en wenselijkheid van een 360° laparoscopische Nissen fundoplicatie (LNF) in dagbehandeling vergeleken met een laparoscopische cholecystectomie (LC) in dagbehandeling. LC wordt routinematig in dagbehandeling uitgevoerd. Tweeëntwintig patiënten ondergingen LNF en 48 patiënten LC in dagbehandeling. Na LNF, zijn 21 van de 22 (95%) patiënten op dezelfde dag ontslagen. Na LC, waren dit 45 van de 48 (94%) patiënten. Tot 14 dagen na de operatie hielden patiënten de EQ-5D (een maat voor de gezondheid gerelateerde kwaliteit van leven) en VAS (een instrument om de hoeveelheid pijn aan te geven) bij; na LNF in dagbehandeling scoorden patiënten significant slechter op beide schalen (herhaalde metingen, P<0.0001 en P<0.0001). Na de ingreep is een telefonische enquête afgenomen, waarin patiënten werd gevraagd of zij achteraf gezien liever een dagbehandeling of een korte opname zouden prefereren. Significante meer LNF patiënten (66.7%) gaven de voorkeur aan een korte ziekenhuisopname vergeleken met 30.9% van de LC patiënten (P=0.011). Uit de studie blijkt dat LNF in dagbehandeling veilig en haalbaar is, maar omdat dit gepaard gaat met hoge postoperatieve pijnscores, een verminderde kwaliteit van leven, alsmede de voorkeur van meer dan twee derde van de patiënten aan een korte ziekenhuisopname, is een korte opname te prefereren.
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Curriculum vitae


In het derde studiejaar startte zij als wetenschappelijke stagiaire bij haar latere promotor Prof. dr. W.A. Bemelman (Academisch Medisch Centrum Amsterdam) met een onderzoek naar het effect van bevallingen op de lange termijn functie van de pouch. Dit onderzoek was de opstap naar het promotietraject. Van november 2007 tot mei 2010 was ze fulltime onderzoekster, met als resultaat dit proefschrift. Malaika vervult eind dit jaar haar laatste coschap in het St Francis Hospital Mutolere in Kisoro, Oeganda. In 2011 breekt er een nieuwe periode aan, dan gaat ze als dokter aan de slag.