During the past 20 years, fast-track care and the laparoscopic technique have been recognized as two major revolutions in colorectal surgery. The aims of this study were to investigate short and long term clinical outcomes of laparoscopic surgery and the impact of fast track care pathway on the recovery of patients undergoing elective colorectal surgery. In addition, this study examined survival of patients who underwent laparoscopic complete mesocolic excision for colon cancer.
Laparoscopic Colorectal Surgery
and Fast-Track Care
ANU EHRICH

Laparoscopic Colorectal Surgery

and Fast-Track Care

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To my mother
ABSTRACT

During last twenty years, several improvements have been made in colorectal surgery. The popularity of laparoscopic surgery is based on several randomized trials comparing the laparoscopic approach versus open resection for colorectal cancer. These studies demonstrated that the laparoscopic method could achieve an equivalent oncologic outcome, a faster short-time recovery, and a shorter hospital stay than the open method.

However, it has been evident for some time that surgery for colon cancer may not have been optimal with regard to oncologic outcome. Moreover, the conventional perioperative treatment provided in recent years has been based on traditions and is not evidence-based. While randomized trials and meta-analyses have demonstrated the safety and efficacy of fast track perioperative care in colorectal surgery, the role of laparoscopy in fast-track setting has remained controversial.

The aims of this study were to investigate short and long term clinical outcomes of laparoscopic surgery and impact of fast track care pathway on the recovery of patients undergoing elective colorectal surgery. In addition, this study examined survival and quality of laparoscopic surgery for colon cancer involving the complete mesocolic excision technique.

The material consisted of patients having been surgically operated for benign and malignant colorectal disease in the Central Hospital of Central Finland. In study I, 180 patients underwent laparoscopic or open bowel resection or laparoscopic ventral rectopexy in a fast-track setting, in study II, we assessed the outcomes and in-hospital costs of laparoscopic and open surgery for benign and malignant colonic diseases, clinical outcomes and in-hospital costs within fast track or traditional perioperative care pathways. In study III, 222 patients underwent laparoscopic resection for colon cancer involving complete mesocolic excision and central vascular ligation, and in study IV, we compared epidural and spinal analgesia for patients undergoing laparoscopic ventral rectopexy during the fast-track care setting.

Our results show that laparoscopic colonic resection within fast-track care is safe, improves postoperative recovery, results in a shorter hospital stay and is not more costly than open surgery. Laparoscopic complete mesocolic excision for colon cancer resulted in a good long-term oncologic outcome. Spinal analgesia for laparoscopic ventral rectopexy enhances postoperative mobilization and shortens the postoperative stay.

In conclusion, laparoscopic colorectal surgery within the fast-track setting improves short-term clinical outcomes and furthermore, laparoscopic complete mesocolic excision for colon cancer results in a good oncologic outcome, in line with international standards.

National Library of Medicine Classification: WI529, WI650

Medical Subject Headings: Analgesia; colonic neoplasms; colorectal surgery; mesocolon/surgery; epidural; length of stay; laparoscopy; injection, spinal.
Ehrlich Anu

Laparoskooppinen kolorektaalikirurgia ja nopeutettu hoitomalli.

Itä-Suomen yliopisto, terveystieteiden tiedekunta

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TIIVISTELMÄ

Viimeisen kahdenkymmenen vuoden aikana suolistokirurgia on kehittynyt merkittävästi. Videoavusteisen leikkaustekniikan (laparoskopia) läpimurto suolistokirurgiassa perustuu satunnaisesti suoritetuihin tutkimuksiin. Niillä voitiin osoittaa, että videoavusteinen, tähystystekniikkaan perustuva leikkausmenetelmä edistää potilaan toipumista ja lyhentää sairaalahoitoa syövän hoitotulosten huononematta.

Paksusuolisyövän perinteiset leikkausmenetelmät ja potilaiden leikkausta edeltävä valmistelu ja leikkaushäiriöt jälkeen osastohoito eivät välttämättä ole olleet optimaalisia eivätkä aina näytä toimivia. Nopeutetun hoitomallin (fast-track) käyttö suolistokirurgiassa on osoitettu olevan satunnaisten tutkimusten ja meta-analyysien perusteella työntämää nopeampia ja hyviä tuloksia. Sen sijaan videoavusteisen tähystysteekniikan edut ovat hieman rotunneissa nopeutetussa hoitomallissa, joten on tärkeää, että niitä pitäisi jatkida tutkimuksessa ja soveltaessa niitä. Tämän tutkimuskokonaisuuden tavoitteena oli selvittää videoavusteisen suolistokirurgian fast-tracked LEKP (laparoskooppinen) ja avoin LEKP (laparoskooppinen) menetelmät sekä nopeutetun hoitomallin vaikutusta potilaan toipumiseen. Lisäksi tavoitteena oli selvittää täydelliseen suolistokirurgiaan poistoon (CME) perustuvan leikkausmenetelmän etuja perinteiseen leikkaustekniikkaan verrattuna.

Aineisto koostuu Keski-Suomen keskussairaalaalasta paksu- ja peräsuolilääketiede-osastolta. Tutkimuksessa I 180 potilaalle tehtiin laparoskooppinen tai avoin paksusuolileikkaus tai paksusuolihuoltotuki osana keskussairaalan potilaiden osastohoitojärjestelmää. Tutkimuksessa II verrattiin kolorektaalikirurgian osana tuloksia ja sairaalakustannuksia laparoskooppisessa ja avoimessa kirurgiassa, sekä perinteisessä ja nopeutetussa hoitomallissa. Tutkimuksessa III tutkittiin 22 laparoskooppisella CME tekniikalla leikattujen potilaiden seurantatuloksi ja tutkimuksessa IV verrattiin epiduralia ja spinaalipuudutuet tuloksia ja potilailla, joille oli tehty laparoskooppinen peräsuolihoidon fast-track. Tuloksemme osoittivat, että laparoskooppinen kolorektaalikirurgia yhdistettynä nopeutettuun hoitomalliin on turvallinen, johtaa lyhyempään sairaalahaotoon, eikä ole kustannukseltaan kalliimpaa kuin avokinnoilla. Laparoskooppinen CME teekniikka soveltuu hyvin paksusuolisyövällä ja spinaalipuudutuksella leikkaus potilailla parantaa leikkausen jälkeistä mobilisointia ja lyhentää leikkausen jälkeistä hoitoa.

Laparoskooppinen kolorektaalikirurgia yhdistettynä nopeutettuun hoitomalliin paransi lyhyen aikavälin tuloksia ja laparoskooppinen CME tekniikka paksusuolisyövä leikkausosassa tuotti kansainvälisiin standardeihin verrattavan ongelmisen tuloksen.

Luokitus: WI529, WI650

Yleinen Suomalainen asiasanasto: Hoitoaika; kivunhoito; paksusuolinsyöpä; tähystysteekniikka
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List of the original publications

This dissertation is based on the following original publications:


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### Abbreviations

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<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ALCCaS</td>
<td>The Australian Laparoscopic Colon Cancer Surgical trial</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BRAF</td>
<td>V-raf murine sarcoma viral oncogene homolog B1</td>
</tr>
<tr>
<td>CHCF</td>
<td>Central Hospital of Central Finland</td>
</tr>
<tr>
<td>CME</td>
<td>Complete mesocolic excision</td>
</tr>
<tr>
<td>COLOR</td>
<td>Colon cancer Laparoscopic or Open Resection</td>
</tr>
<tr>
<td>COST</td>
<td>Clinical Outcomes of Surgical Therapy Study Group</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CRS</td>
<td>Colorectal surgery</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease-free survival</td>
</tr>
<tr>
<td>DSS</td>
<td>Disease-specific survival</td>
</tr>
<tr>
<td>ERAS</td>
<td>Enhanced Recovery After Surgery</td>
</tr>
<tr>
<td>FU</td>
<td>Follow up</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low–molecular-weight heparin</td>
</tr>
<tr>
<td>MRC CLASSIC</td>
<td>The medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer</td>
</tr>
<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroid antiinflammatory drugs</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PCA</td>
<td>Patient controlled analgesia</td>
</tr>
<tr>
<td>POD</td>
<td>Postoperative day</td>
</tr>
<tr>
<td>PONV</td>
<td>Postoperative nausea et vomiting</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TAP</td>
<td>Transversus abdominal plane</td>
</tr>
<tr>
<td>TIVA</td>
<td>Intravenous anesthesia</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue</td>
</tr>
</tbody>
</table>
1 Introduction

During the past 20 years, fast-track care and the laparoscopic technique have been recognized as two major revolutions in colorectal surgery. Following the introduction of laparoscopic cholecystectomy in the late 1980s, it soon became the most common laparoscopic procedure. In colorectal surgery, the laparoscopic technique was adopted after its successful application in gallbladder and biliary surgery. Laparoscopic colectomy has been performed since 1990; initially the laparoscopic approach was used for bowel mobilization and simple resection to remove benign lesions. However, after technological advances, laparoscopic surgery was soon being applied to the full spectrum of colorectal operations.

Several randomized trials and meta-analysis comparing laparoscopic versus open resection for colon cancer have demonstrated that the laparoscopic method can provide an equivalent long term oncologic outcome, with a similar number of complications, but with a faster short-term recovery than the open method (Bonjer et al. 2007, Fleshman et al. 2007). There are published studies indicating that patient survival after open colon cancer surgery is directly related to the extent and completeness of mesenteric excision (Hohenberger et al. 2003, Bokey et al. 2003). A complete mesocolic excision (CME) involves wide mesenteric excision including a central vascular ligation to remove the central lymph nodes as well as a resection of an adequate length of bowel in a longitudinal direction (Hohenberger et al. 2009).

In 2008, West et al. demonstrated that intact mesocolic plane surgery was associated with a 15% greater 5-year overall survival compared with cases where defects in the mesocolon extended down into the muscularis propria. At present, there are no randomized controlled trials comparing CME to standard colon surgery (Killeen et al. 2014). The most recent retrospective study confirmed that CME surgery was associated with better disease-free survival than conventional colon cancer surgery for patients with stage I-III colon adenocarcinoma (Bertelsen et al. 2015)

Fast-track perioperative care, initiated by Kehlet and coworkers in 1999, can be considered as the second major improvement of colorectal patients (Kehlet et al. 1999). Fast-track or enhanced recovery protocols have been used to reduce the surgical stress response and organ dysfunction (Kehlet et al. 2008). Randomized trials have now demonstrated the safety and efficacy of fast-track care in colorectal surgery, not only by reducing postoperative hospital stay and morbidity, but also by improving patient convalescence and satisfaction when compared to traditional care (Zutshi et al. 2005, Anderson et al. 2003, Gatt et al. 2005).

Despite convincing clinical evidence, the effective implementation of all fast-track elements has proven to be difficult because it demands a multidisciplinary collaboration between surgeons, anesthesiologists and surgical nurses (Polle et al. 2007). There is one report describing significant variability in the components of different fast track protocols (Polle et al 2007). In particular, it has been questioned whether all fast-track elements are of equal importance i.e. what are the key factors that determine short-term clinical outcome in the fast-track setting? (Vlug et al. 2012, Maessen et al. 2007).

Initially, combining the laparoscopy to the fast-track setting was considered controversial. One randomized trial revealed that laparoscopic colonic surgery within fast-track care resulted in faster recovery and a shorter hospital stay than open surgery (Vlug et al. 2011). However, it is still unresolved whether laparoscopic colonic surgery improves the economical efficiency of fast-track perioperative care in comparison to open surgery (Lee et al. 2014).
Effective analgesia is a prerequisite for fast-track care and continuous thoracic epidural analgesia is considered as fundamental, since it avoids the need to administer morphine systemically (Kehlet et al 2008, Lassen et al 2009). However, its value in the perioperative management of patients undergoing laparoscopic colorectal surgery is being increasingly questioned.
2 Review of Literature

2.1 EPIDEMIOLOGY OF COLORECTAL DISEASES

Patients undergo elective colon surgery for various conditions including colorectal cancer, diverticular disease, polyps and inflammatory bowel disease (Crohn’s disease and ulcerative colitis). The most common colorectal surgical disease is colorectal cancer.

Colorectal cancer (CRC) is the third most common cancer in the world; this cancer has a poor prognosis if it has metastasized to lymph nodes or distant organs (Ferlay 2013). After lung cancer, it is the most common cause of cancer death in Europe. In 2013, a total of 3007 cases of CRC were diagnosed in Finland and the incidence of CRC is 27.3/100 000 among men and 21.1/100 000 among women (Finnish Cancer Registry 2013). In the developed countries, the prevalence of CRC continues to increase in the general population, in particular in elderly patients (Kiran et al 2007). Nonetheless, since 1970, colorectal cancer mortality has been declining in most European countries. The largest reductions have been observed in western and northern Europe as a result of the combined contributions of better public awareness of the disease, greater participation in screening, and improved treatment and patient management protocols. From 1989 to 2011 CRC mortality decreased 20.2% in Finland whereas during the same period, CRC mortality increased by 15.4% in Estonia (Ouakrim et al. 2013).

Diverticular disease is the second most common gastrointestinal disorder requiring a surgical intervention. Diverticular disease has been considered a disease of Western society, caused by the low fiber content in the diet consumed in developed countries and its frequency increases with age. The prevalence of diverticulosis ranges from 5% at the age of 40 years and up to 65% at 80 years of age and it is estimated that 10% to 25% of individuals with diverticulosis will develop diverticulitis with an average age of 62 years (Parks et al 1975). In the last decade, there has been striking shift in our understanding and management of diverticular disease.

Adenomatous colorectal polyps are considered to be precursor lesions of colorectal cancer (Vogelstein et al. 1988). Most polyps can be safely removed by endoscopic polypectomy but if a polyp is not suitable for endoscopic removal, a formal surgical resection may be needed. Pokala et al. reported that after laparoscopic resection for endoscopically non-resectable polyps, there was an invasive malignancy in up to 20% of polyps which had displayed an initial benign histology (Pokala et al. 2007).

The incidence of inflammatory bowel disease (IBD) is highest in the westernized nations, with a reported incidence in Finland of 7.2 for Crohn’s disease per 100 000 and 16.5 for ulcerative colitis per 100 000 inhabitants. The incidence of IBD is increasing with time and in different regions around the word (Molodecky et al 2012).

Pelvic organ prolapse is common, occurring in up to 40% of parous women (Wu et al. 2014). Laparoscopic ventral rectopexy is increasingly be applied in the treatment of rectal prolapse and for symptomatic high-grade (Oxford Grade 3-4) internal rectal prolapse (Figure 1).
Figure 1. The Oxford Prolapse Grade for proctographic grading of internal and external rectal prolapse. With permission of Elsevier.

2.2 LAPAROSCOPIC SURGERY FOR COLORECTAL DISEASES

2.2.1 History of laparoscopic surgery
George Kelling, a surgeon from Dresden (1901), performed the first true laparoscopic procedure. He introduced a cystoscope into a living dog through a small abdomen wall incision and examined the peritoneal cavity; in order to achieve better view, a pneumoperitoneum was created (Davis et al. 1995). Hans Christian Jacobaeus (1879-1937), a Swedish surgeon, developed a technique, which he termed laparoscopy and in 1910 he published the first report of laparoscopy in 17 patients (Jacobaus et al. 1910). In the following decades, laparoscopy became an accepted procedure for diagnostic purposes but its therapeutic use was limited (Andreas et al. 2001).

In 1929, the German hepatologist, Heinz Kalk, developed the 45 degree angle endoscopic lens system and performed liver biopsies under direct visual control. During the 1930s, gynecologists started to perform laparoscopic adhesiolysis and tubal ligations (Andreas et al 2001). The first laparoscopic cholecystectomy was performed by Senn and Muhe in 1985 and the major breakthrough in laparoscopy occurred when computer chip television camera was invented in 1985. Philippe Mouret was the first surgeon who performed a
video-laparoscopic cholecystectomy (1987) and Dubois published the first series of laparoscopic cholecystectomy, followed by numerous reports around the world during the next years.

2.2.2 Laparoscopic surgery for colorectal diseases.
The benefits of laparoscopy in colorectal surgery have always not been so obvious. The success of laparoscopic cholecystectomy has led naturally to the exploitation of this minimally invasive technique to colorectal surgery. Conceptually, the laparoscopic approach is intended to minimise post-operative pain, speed up recovery and improve cosmetic appearance, while maintaining an enhanced visual field for surgeons. The first report of laparoscopic sigmoidectomy for cancer dates from 1991 by Jacobs et al. Reports of port-site metastases after laparoscopic removal of colon cancer and other malignant neoplasms raised serious concerns among surgeons and halted the rapid adoption of minimally invasive surgery for colon cancer (Berends et al. 1994, Nduka et al. 1997). Consequently, randomized trials comparing laparoscopic versus open colon resection for colon cancer were simultaneously initiated in Europe and in North America to evaluate the oncological safety of laparoscopic colectomy.

The greatest advantage of laparoscopic surgery in comparison with open surgery is the reduction in the extent of tissue trauma. Access to the peritoneal cavity is established through small incisions, manual retraction of viscera is avoided, and blood loss can be minimized because of meticulous dissection facilitated by videoscopic magnification (Bonjer et al 2007).

In 2002, Lacy et al. reported improved survival after laparoscopic colectomy in patients with stage III colon cancer after a median follow-up of 43 months. However, the outcome of this study was criticized because the number of patients was small and the study was carried out in a single high-quality laparoscopic center (Lehnert et al 2003). In 2004, the Clinical Outcomes of Surgical Therapy (COST) study group reported similar disease-free survival after laparoscopically assisted or open colectomy for cancer after a median follow-up of 4.4 years (Nelson et al. 2004). The COST study was a multicenter trial; therefore its outcome reflected better general surgical practice in North America. In 2008, the COlon cancer Laparoscopic or Open Resection (COLOR) trial randomized 1248 patients in order to compare 3-years’ disease-free and overall survival after laparoscopic and open colon resection for colon cancer and their results were consistent with COST study (J Bonjer et al. 2008). The Australian Laparoscopic Colon Cancer Surgical (ALC CaS) trial reported significant improvements in recovery of gastrointestinal function and reductions in length of stay for laparoscopic colonic resection, with an increased operative time and no difference in the postoperative complication rate (Hewett et al 2008). In 2010 the Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer MRC CLASSIC trial confirmed the oncological safety of laparoscopic surgery for both colonic and rectal cancer in the 5-year analyses (Jayne et al 2010).

Several randomized trials comparing laparoscopic versus open resection for colon cancer have revealed that the laparoscopic method can provide an equivalent oncologic outcome, a similar rate of complications, and a faster short-term recovery than the open method (Table 1, Table 2).
Table 1. Hospital stay, 30-d morbidity and mortality of the COST, CLASSIC, COLOR and ALCCaSS studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Assigned Group</th>
<th>N. of patients</th>
<th>Hospital Stay</th>
<th>30-d Morbidity(%)</th>
<th>30-d Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>LAP</td>
<td>437</td>
<td>5</td>
<td>21</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>OPEN</td>
<td>435</td>
<td>6</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>CLASSIC</td>
<td>LAP</td>
<td>429</td>
<td>9</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>OPEN</td>
<td>212</td>
<td>9</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>COLOR</td>
<td>LAP</td>
<td>621</td>
<td>8</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>OPEN</td>
<td>627</td>
<td>9</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>ALCCaSS</td>
<td>LAP</td>
<td>294</td>
<td>10</td>
<td>38</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>OPEN</td>
<td>298</td>
<td>11</td>
<td>45</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 2. Oncologic outcome of the COST, CLASSIC, COLOR and ALCCaSS studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Assigned Group</th>
<th>N. of patients</th>
<th>Recurrence (%)</th>
<th>Wound/Port-Side Recurrence (N)</th>
<th>DFS (%)</th>
<th>OS(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>LAP</td>
<td>437</td>
<td>19</td>
<td>0.9</td>
<td>69</td>
<td>74</td>
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<tr>
<td></td>
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<td>435</td>
<td>22</td>
<td>0.5</td>
<td>68</td>
<td>76</td>
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<tr>
<td>CLASSIC</td>
<td>LAP</td>
<td>429</td>
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<td>2.4</td>
<td>58</td>
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<td>OPEN</td>
<td>212</td>
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<tr>
<td>COLOR</td>
<td>LAP</td>
<td>621</td>
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Based on meta-analysis of major randomized trials level 1, evidence now exists to show that laparoscopic-assisted surgery for colon cancer is as effective as open surgery and produces similar long-term outcomes. Laparoscopic colon surgery results in less bleeding, faster recovery, less stress reaction and better preservation of immunity. There is no difference in long-term survival and quality of life in favour of laparoscopy.

Laparoscopic resection for rectal cancer has remained controversial because of the long learning curve, technical challenges related to the anatomical circumstances, high conversion rate, and the lack of level 1 evidence regarding the oncologic safety and long-term survival. Despite these initial concerns, the 5-year follow-up data from the MRC CLASICC trial together with other smaller studies (Kellokumppu et al. 2012, Braga et al. 2007) and meta-analyses, (Poon et al. 2009) indicating also some short-term benefits, have
confirmed the oncologic safety of the laparoscopic approach and have helped to convince surgeons that laparoscopic surgery can be considered as an alternative method for the treatment of rectal carcinoma.

The COLOR II trial 2015 reported similar 3-year survival outcome and found that laparoscopic surgery in patients with rectal cancer was associated with similar rates of locoregional recurrence and disease-free and overall survival to those patients undergoing open surgery and these results were consistent with COREAN (the Comparison of Open versus laparoscopic surgery for mid or low REctal cancer After Neoadjuvant chemotherapy) randomized controlled trial (Bonjer et al. 2015, Jeong et al. 2014).

Laparoscopic resection for rectal cancer results in several benefits such as less bleeding, faster recovery (oral nutrition, bowel function, pain, mobilization) and shorter hospital stay. In addition, mortality, morbidity and quality of life are similar in patients subjected to either laparoscopic or open surgery for rectal cancer. Nonetheless, Level 1 evidence remains to be proven by European Color II, US ACSOG-Z6051 and Japanese JCOG 0404 trials.

2.2.3 Complete mesocolic excision for colon cancer

The surgical technique to resect colon cancer has undergone significant changes in the past decades (Bonjer et al. 2007). In the late 1960s, Turnbull et al. advocated no-touch techniques involving early ligation of the mesocolic vessels and bowel and atraumatic manipulation of the tumor to avoid spreading tumor cells. The introduction of total mesorectal excision (TME) for the surgical treatment of rectal cancer has been shown to significantly improve outcomes (Heald et al. 1986). While a relationship between the quality of rectal cancer surgery and local recurrence has been established, (Quirke et al 2009) the evidence for a similar effect in colon cancer is lacking, apart from the Medical Research Council CLASICC trial (Quirke et al 2008). Earlier studies have indicated that the oncologic outcome of open colon cancer surgery is directly related to the extent and completeness of mesenteric excision (Hohenberger et al. 2003, Bokey et al. 2003).

There are three essential components to successful complete mesocolon excision. The most important component involves a wide mesenteric excision according to the embryological planes in order to remove mesenteric lymph nodes. The second component is central vascular ligation to remove central lymph nodes and the third component is resection of an adequate length of bowel to remove any involved pericolic lymph nodes in longitudinal direction (Hohenberger et al. 2009) (Figure 2). In 2008, West et al. demonstrated that intact mesocolic plane surgery is associated with a 15% greater 5-year overall survival compared with cases where defects in the mesocolon extended down into the muscularis propria. At present, there are no randomized controlled trials comparing CME with standard colon surgery (Killeen et al. 2014). In the most recent retrospective study, the authors found that CME surgery was associated with better disease-free survival than conventional colon cancer resection for patients with stage I-III colon adenocarcinoma (Bertelsen et al 2015).

The value of reducing surgical trauma in cancer surgery was highlighted by Eggermont et al in an experimental study which observed that tumor recurrence rates were proportional to the extent of laparotomy wounds (Eggermont et al 1987).

Laparoscopic colectomy has become a standard procedure for colon cancer. However, exact details about the surgical technique have been lacking (Bagshaw 2012, Kuwabara et al. 2010.). Earlier, questions were raised about whether a good oncological clearance could be achieved by laparoscopic surgery in patients high BMI, transverse colon tumors and large bulky T4 tumors (Bagshaw 2012). There has been a debate about whether there is pneumoperitoneum related dissemination of cancer cells if the tumor has penetrated the serosal surface (Temesi et al. 2012). On the other hand, there are some studies showing that laparoscopy seems to offer specimens of similar quality and excellent 3-year overall survival after CME surgery for colon cancer compared to the open approach (Gouvas et al. 2012, Adamina et al 2012). According to a consensus conference held in 2014, laparoscopic
resection appears to be equally well suited for CME resection as for open surgery (Søndenaa 2014).

2.2.4 Survival of patients with colon cancer

In recent years, there has been a trend towards better survival in patients diagnosed with colorectal cancer. For example, the overall 5-year survival of patients with colon cancer was 41% between 1950 and 1952, but it has now increased steadily to 63.8% between 1993 and 2000 (Maingot Abdominal Operations 2007). When analysed separately for each stage graded by American Joint Committee on Cancer fifth edition system, the 5-year cancer specific survival was 93.2% for stage I, 82.5% for stage II, 59.5% for stage III and 8.1 for stage IV (O’Connell et al 2004). In 2008, West et al estimated that there was a 15% overall survival advantage at 5 years with the CME approach compared with surgery in the muscularis propria plane. In a systematic review investigating 5246 patients, there was a survival advantage for CME surgery with an overall survival rate of 58.7% vs 53.5% and disease-free survival rate of 77.4% vs 66.7% (Killeen et al. 2014).

There is increasing evidence indicating that colorectal cancer is a biologically heterogeneous disease that can develop via number of distinct pathways and should be subdivided into different prognostic groups (Phipps et al 2015). In their large population based study, Phipps et al. concluded that colorectal cancer subtypes are associated with marked differences in survival. MSS and BRAF mutated tumors had a poor prognosis (overall 5 year survival 46.2%) while MSI tumors had better prognosis (overall 5 year survival 80.5% and 84.1%). A recent large population based cohort study also described similar results although they did not find any prognostic significance of BRAF mutation within the MSI group (Seppälä et al 2015).
2.3 Fast-track care for colorectal surgery

Fast-track care is a method of patient management aiming at optimising the perioperative care by adopting various techniques such as minimally invasive surgery and optimal pain control (Wilmore et al. 2001). This method has been shown to improve patient recovery after surgery, reduce morbidity and shorten hospital stays (Delaney et al. 2001). Kehlet and colleagues conducted the first fast-track studies in elective large bowel surgery (Kehlet et al. 1999, Basse et al. 2000). They reported a median hospital stay of two days and reduced mortality for patients in the fast-track programmes (Kehlet et al. 1999, Basse et al. 2000). Similar benefits of fast-track care have also been described in other studies (Anderson et al 2003; Delaney et al. 2003). This approach has been shown to be feasible in elderly patients with high co-morbidity, as well as for patients undergoing major abdominal and pelvic surgery (Scharfenberg et al. 2007, Delaney et al 2001).

Initially the role of laparoscopic colorectal surgery in the fast-track setting was controversial. However, randomized trials and meta-analysis have revealed a statistically reduced overall hospital stay for laparoscopic colorectal surgery in patients receiving fast-track care (Basse et al. 2005, Vlug et al. 2011, Li et al 2012).

Although fast-track surgery seems to be beneficial in colorectal surgery, there might be some difficulties in implementing this method into daily practice. For example, it has been argued that fast track surgery could lead to an increased readmission rate (Basse et al. 2004, Wind et al. 2006). However, in their trial, Andersen et al. proved that readmission rate could be reduced to half by planning patient discharge at 3 days instead of 2 days after colorectal surgery within fast-track care (Andersen et al. 2007). It should also be noted that the success of the fast-track protocol requires seamless multidisciplinary collaboration between surgeons, anaesthesiologists and surgical nurses (Wilmore et al. 2001).

2.3.2 Fast-track care implementation.

Previous studies have included different fast track elements with the numbers of predefined FT elements varying widely between studies. In their systematic review, Wind et al. described 17 FT elements based on meta-analyses and randomized trials (Wind et al. 2006).

In 2009, the Enhanced Recovery After Surgery (ERAS) Group outlined the recommendations for clinical perioperative care of patients undergoing elective colorectal surgery, based on the best available evidence and in 2012, the same group described a consensus of optimal perioperative care with 20 elements. The quality of evidence and recommendations were evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines (Guyatt et al. 2008). Their recommendation indicates that the desirable outcomes outweigh the undesirable effects and the ERAS authors are confident in their conclusions. It should be noted that their recommendations are based not only on quality of evidence but also on the balance between desirable and undesirable effects (Table 3) (Gustafsson et al. 2013).

Preadmission patient information and counselling.

The patient should receive detailed oral and written information before the surgical procedure. Information regarding what will happen during hospitalization and what they should expect may diminish fears and anxiety and enhance the recovery process (Kiecolt-Glaser et al. 1998, Kahokehr et al 2012 Broadbent et al 2012). A concise awareness about patient specific tasks, including early postoperative food intake, mobilization during hospitalization allows early recovery and discharge.
Preoperative bowel preparation.
During the past two decades, criticisms have been raised against the need for preoperative mechanical bowel preparation in elective colorectal surgery. Mechanical bowel preparation can cause dehydration and electrolyte abnormalities, especially in elderly patients (Holte et al. 2004). RCTs have confirmed that mechanical bowel preparation prolongs postoperative ileus and increases morbidity (Bucher et al. 2005, Ram et al. 2005). In a Cochrane review, the authors could not find any statistically significant evidence that patients undergoing elective colorectal surgery benefited from mechanical bowel preparation, or the use of rectal enemas (Guenaga et al 2011). However, a recent study of 8442 patients concluded that combined preoperative MBP with oral antibiotics reduced surgical site infections compared to systemic antibiotic alone in elective colorectal surgery and the recent meta-analysis of RCTs conducted by Chen et al. support these results (Chen et al. 2016, Kiran et al. 2015).

Preanesthetic medication
It is recommended that the patient should not routinely receive long-acting sedative medication before surgery.
In 2009, a Cochrane review revealed that premedication for anxiolysis impaired psychomotor function postoperatively, which reduced patient mobilization and ability to eat. (Walker et al 2009). If necessary, a short-acting medication given to facilitate insertion of an epidural catheter or spinal analgesia, is acceptable.

Prophylaxis against thromboembolism
Patients undergoing colorectal surgery have considerable risk of developing venous thrombosis and pulmonary embolism, which can lead to life-threatening complications. According to the Cochrane review, the most effective prophylaxis in colorectal surgery is achieved with the combination of graduated compression stockings and low-dose unfractionated heparin (LMWH) (Wille-Jorgensen 2003). Prophylactic doses of LMWH should be given no later than 12 hours before insertion and removal of epidural catheter to avoid epidural hematoma (Vandermeulen 1994).

Antimicrobial prophylaxis
In a Cochrane review, the authors demonstrated that antimicrobial prophylaxis for patients undergoing colorectal surgery could reduce the risk of surgical site infection (Nelson 2009). The optimal time for intravenous antibiotic administration is 30-60 min before incision with further doses being given in prolonged procedures (>3 hours) (Steinberg et al 2009).

Standard anesthetic protocol
A standard anesthetic protocol allowing rapid awakening should be adopted. It is preferable that long-acting opioids should be avoided in patients undergoing anesthesia. Intravenous anesthesia (TIVA) using target controlled infusion pumps can be beneficial in patients with a susceptibility to postoperative nausea and vomiting (Gustafsson et al. 2013).

Preventing and treating postoperative nausea and vomiting
Almost 25-35% of surgical patients suffer from postoperative nausea and vomiting (PONV) which is the leading reason for prolonging their postoperative stay. In their review article, Chatterjee et al. divided the etiology of PONV into three categories: patient-, anesthesia- and surgery-related. Female gender, non-smokers, history of PONV and body mass index (BMI) over 30 were claimed to be risk factors for PONV. In adults, the incidence of PONV declines with higher age. Anesthesia-related independent predictors of PONV are the use of opioids and inhalation anesthetics as well as the duration of anesthesia. It was stated that major abdominal surgery for colorectal disease increases the prevalence of PONV (Chatterjee et al. 2011).
Many international guidelines suggest the use of a PONV scoring system and all patients with >2 risk factors should receive PONV prophylaxis. Combination therapy for PONV prophylaxis is preferable instead of using single drugs alone (Gan et al. 2014). The concept of adopting a multimodal approach to avoid PONV consists of avoidance of inhalation anaesthesia and increased use of propofol for induction of anesthesia. Minimal preoperative fasting, carbohydrate loading and adequate hydration of patients, also ensuring a perioperative high O2 concentration have been considered beneficial in avoiding PONV. Epidural and spinal analgesia have been proven to reduce postoperative opiate use, and this can influence the prevalence of PONV (Gustafsson et al. 2013).

Laparoscopy-assisted surgery
One multicenter RCT reported (LAFA-study) that laparoscopy in combination with fast track multimodal management was the best perioperative strategy in patients undergoing colonic surgery. Regression analysis revealed that laparoscopy was the only independent predictive factor which could reduce hospital stay and morbidity (Vlug et al. 2011). One meta-analysis evaluating laparoscopic versus open colorectal surgery within fast track care supported the results of LAFA-study (LI et al. 2012).

Surgical incision
If laparoscopic surgery is not possible (e.g. if there are large bulky tumors, intra-abdominal adhesions), the transverse abdominal access is preferable. The authors of a Cochrane review concluded that transverse abdominal access appears to affect pulmonary function less than midline access and entails less analgesia use and may also reduce the likelihood of wound dehiscence and incisional hernia (Brown et al. 2005). The choice of incision for abdominal surgery still remains the decision of the operating surgeons.

Nasogastric intubation
The Cochrane review of 37 trials indicated that routine use of a nasogastric tube may slow recovery and increase the risk of postoperative symptoms such as pulmonary complications (Verma et al 2007). The only reason to use a nasogastric tube during elective colorectal surgery is to evacuate air that may have entered into the stomach with ventilation during endotracheal intubation and the nasogastric tube should be removed before the reversal of anesthesia.

Preventing intraoperative hypothermia
Several RCTs have proved that hypothermic patients have higher rates of wound infections, cardiac complications and bleeding (Scott et al.2006, Frank et al. 1997). Ensuring the maintenance of the patient’s normal body temperature (>36°C) during the procedure can be achieved by using routine warming devices and warmed intravenous fluids. The temperature of patients needs to be monitored to avoid hyperpyrexia.

Perioperative fluid managment
The main aim is to achieve optimum peri-operative fluid balance. The most common side effect of epidural or spinal anesthesia is hypotension, which is traditionally combatted with fluid loading but would better be treated with vasopressors (Holte et al. 2004). Intraoperative hypovolemia can be a cause of hypoperfusion of the bowel, which can lead to complications. However, hyperperfusion can trigger bowel oedema, which can also evoke complications (Varadhan et al. 2010). The best way to avoid fluid overload is to refrain from bowel preparation, to provide an oral carbohydrate preload 2h before the operation and return to oral feeding as soon as possible. The optimal type of fluid to be used has not yet been discovered. Several studies have shown that balanced crystalloids should be preferred over 0.9 % saline (Kimberger et
al. 2009). There is no evidence that colloids exert any beneficial effect over crystalloids (Yates et al 2014).

Goal-directed fluid management with minimal invasive cardiac output monitoring should be considered on an individual basis (Senagore et al. 2009).

Drainage of peritoneal cavity
Prophylactic drains have been traditionally used to remove intraperitoneal collections and to detect early complications, such as postoperative hemorrhage and leakage. Nonetheless, neither several meta-analyses nor a Cochrane review have been able to demonstrate any benefit conferred by peritoneal drainage in elective colorectal surgery (Jesus et al. 2004, Karliczek et al. 2005). Therefore, drains are not indicated following routine colonic resection. Nonetheless, short-term use of drains after low rectal resections is supported by the Duch total mesorectal trial (Peeters et al. 2005).

Urinary drainage
A urinary catheter is routinely used in colorectal patients in FT care to monitor urine output in the perioperative period and to prevent urinary retention in patients receiving epidural analgesia (Lassen et al. 2009). The urinary catheter was traditionally removed after withdrawal of the epidural catheter to avoid the risk of urinary retention (Tammela et al. 1986). On the other hand, postoperative urinary catheters have been routinely kept in place for longer than 2 days but this has been associated with a twofold elevated incidence of urinary tract infections and delayed mobilisations (Wald et al. 2008). It has been proposed that urinary catheter should be removed by 48 h after surgery in all female patients after colorectal resections and in all male patients after colon resections, even though the patients may still be receiving epidural analgesia (Coyle et al. 2015).

One meta-analysis has shown that the suprapubic route for bladder drainage in abdominal surgery is associated with a lower rate of urinary tract infections (McPhail et al. 2006). However, the advantage of suprapubic over urethral catheterizations is uncertain in colorectal surgery and routine transurethral bladder drainage is recommended (Gustafsson et al. 2013).

Prevention of postoperative ileus
After pain and PONV, postoperative ileus is a major cause of delayed patient discharge. According to one meta-analysis of trials, epidural analgesia significantly reduced the duration of ileus when compared with parenteral opioids (Marret et al 2007). Avoiding fluid overloading during perioperative period and laparoscopic assisted colon resection also leads to faster recovery of bowel functions (Nisanevich et al 2005). Oral magnesium oxide has been reported to enhance the recovery of gastrointestinal function (Basse et al. 2001). However, the findings of a small RCT (49 patients) did not support these previous results (Andersen et al. 2011).

The results of a systematic review indicated that the perioperative use of chewing gum could reduce postoperative ileus after elective colorectal resection (Chan et al. 2007, Shum et al. 2016).

Postoperative analgesia
Optimal analgesia is a key element in FT care. The most important part of pain relief is multimodal analgesia combining regional analgesia or local anaesthetic techniques and striving to avoid parenteral opioids with their inherent side effects (Gustafsson et al. 2013). The different types of regional anesthesia will be discussed in chapter 2.4.

Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are also a vital part of postoperative multimodal analgesia. Some clinical studies reported an association between non-selective NSAIDs and anastomotic leakage but the evidence has not been sufficiently
convincing to stop the use of NSAIDs as a component of pain management in the postoperative period (Gorissen et al. 2012).

**Enhanced oral nutrition**

In Western societies, the population’s average body mass index (BMI) is often in the overweight or obese range. Even in colorectal cancer patients with a high BMI value, consumption of energy and protein is often low. In a multicentric prospective study with 3193 patients, the authors reported that a low serum total protein level was associated with a higher risk of anastomotic leakage (Frasson et al. 2015). Therefore, careful nutritional status should be assessed and for malnourished patients, preoperative supplementation should be started at least 7-10 days before surgery to reduce postoperative morbidity. In gastrointestinal surgery, anastomotic leaks were 46% less prevalent after optimal preoperative nutrition treatment (Waitzberg et al. 2006). However, for all patients undergoing colorectal resection in fast-track care, oral nutrient supplements have been used on the day of surgery and continued for at least until normal food intake is achieved (Gustafsson et al. 2013).

The RCT and meta-analysis reported that early enteral feeding did not prolong postoperative ileus after elective gastrointestinal resection and a normal diet was tolerated after median of 2 days (Hans-Guerts et al 2007, Lewis et al. 2001).

**Early mobilisation**

Enhanced mobilization is one cornerstone in FT care and failure to mobilize patients after colorectal surgery has been associated with a prolonged hospital stay. In the LAFA trial, multivariate linear regression analysis showed that successful mobilization was associated with enhanced recovery, a result confirmed in a later review (Vlug et al 2011). The presence of abdominal drains, urinary catheters, PONV and sub-optimal analgesia are all factors that may hinder mobilization and should be avoided. A prescheduled care plan with daily goals for mobilization should be explained to the patient during preadmission counselling.

**Audit**

Measuring outcomes of the FT programme is mandatory in high-quality healthcare. According to the ERAS society recommendation, the following domains should be assessed: clinical outcomes of fast-track via postoperative stay, readmission rates and complications, compliance of fast-track protocol, functional recovery and patient satisfaction.

**Table 3. ERAS consensus guidelines quality assessment for perioperative care 2012**

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Recommendation</th>
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<tr>
<td>Preoperative information and counselling</td>
<td>Low</td>
</tr>
<tr>
<td>Preoperative bowel preparation</td>
<td>High</td>
</tr>
<tr>
<td>Preoperative carbohydrate loading</td>
<td>Low</td>
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<tr>
<td>Preanesthetic medication</td>
<td>High</td>
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<tr>
<td>Prophylaxis against thromboembolism</td>
<td>High</td>
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<tr>
<td>Antimicrobial prophylaxis</td>
<td>High</td>
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<tr>
<td>Standard anesthetic protocol</td>
<td>Low</td>
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<tr>
<td>Preventing and treating postoperative nausea and vomiting</td>
<td>Low</td>
</tr>
<tr>
<td>Laparoscopy-assisted surgery</td>
<td>High</td>
</tr>
<tr>
<td>Surgical incision</td>
<td>Low</td>
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<tr>
<td>Nasogastric intubation</td>
<td>High</td>
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<tr>
<td>Preventing intraoperative hypothermia</td>
<td>High</td>
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<tr>
<td>Perioperative fluid management</td>
<td>High</td>
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</table>
2.4 ANALGESIC REGIMENS

Optimal analgesia is a crucial factor for the success of FT care since effective analgesia is essential in reducing the surgical stress response and speeding up the time to patient mobilization. Continuous thoracic epidural analgesia was once considered the gold standard; it was thought to be beneficial in major open abdominal procedures for controlling pain and decreasing catabolism, paralytic ileus, nausea, and vomiting (Lassen 2009). Nonetheless, several trials comparing thoracic epidural analgesia with patient-controlled analgesia (PCA) could not detect any significant advantages over PCA (Senagore et al. 2003). Another study demonstrated a detrimental effect of epidural analgesia on recovery after laparoscopic colorectal surgery when compared with spinal analgesia or PCA (Levy et al. 2011). The use of spinal analgesia has traditionally been limited in cases where the postoperative analgesia requirements are moderate (Levy et al. 2011). Single dose intrathecal morphine may provide effective analgesia and permit rapid mobilization on the first day after laparoscopic surgery. The initial reports of intravenous lidocaine to treat postoperative pain control have been promising and transversus abdominal plane block (TAP) as a regional anaesthesia technique has also been shown to reduce postoperative pain (Keller et al 2014, Joshi et al. 2012). The optimal postoperative analgesia for patients undergoing laparoscopic colorectal surgery is still a matter for debate.

2.5 IN-HOSPITAL COSTS

Healthcare costs have been continuously rising. In the current economic circumstances, all means of curtailing clinical costs are increasingly attractive. However, cost-cutting should not be achieved at the expense of lowering the quality of care. Therefore, it is encouraging that randomized studies and meta-analysis have revealed that laparoscopic colorectal surgery within fast-track multimodal management has decreased postoperative and overall hospital stay compared with open surgery within fast-track care (Li et al. 2012, Vlug et al 2012). In their systematic review, Lee et al. reported that fast-track care was cost-effective compared with traditional care for patients undergoing colorectal surgery (Lee et al. 2015). A systematic review of the costs of laparoscopic colorectal surgery within traditional perioperative care reported similar total costs for laparoscopic surgery than open surgery despite greater operating room costs (Dowson et al 2007). However, strong evidence is lacking for any cost minimization effects associated with the laparoscopic technique and fast-track care.
3 Aims of the study

The aims of the present study were to evaluate the contemporary surgical management and perioperative care of patients with benign and malignant colorectal diseases.

The aims of the individual investigations were:

1. To evaluate the feasibility and quality of a FT care pathway for elective colorectal surgery, and to assess its impact on postoperative recovery (Study I)

2. To compare laparoscopic and open colonic resection within fast-track and traditional perioperative care pathways focusing on clinical outcomes and in-hospital costs. (Study II)

3. To determine the effect of the laparoscopic CME technique for colon cancer on clinical and oncological outcomes in a multimodal setting (Study III)

4. To compare the impact of epidural versus spinal analgesic regimens on postoperative outcomes of patients undergoing laparoscopic ventral rectopexy within a fast-track care pathway (Study IV).
4 Patients and Methods

4.1 PATIENTS (I-IV)

Study I consisted of 180 patients who underwent laparoscopic or open bowel resection (n=138) or sacrocolporectopexy (n=42). The data was gathered prospectively between 2007 and 2009.

Study II consisted of 116 patients who underwent laparoscopic or open colonic resection for benign or malignant disease within the fast-track care pathway from 2007 to 2009. The control group consisted of 116 age-, sex-, comorbidity-, type of surgery-, and diagnosis-matched patients who received traditional perioperative care in the time period from 2000 to 2007. Data of patients who underwent open or laparoscopic surgery in the fast-track setting were collected prospectively and control group data of open surgery were collected retrospectively, whereas laparoscopic data were retrieved from a prospective colorectal database.

Study III consisted of 222 patients who underwent laparoscopic colonic resection for cancer using wide mesocolic excision and central vascular ligation techniques (table 4). Study IV investigated 38 consecutive patients who underwent LVR within the fast-track care pathway and epidural analgesia. These patients were compared with the spinal analgesia group consisting of 42 consecutive patients who underwent LVR during 2013 - 2014.

All studies included patients with a good mental and physical performance status and the American Society of Anesthesiologists (ASA) score I-III. Elderly patients fulfilling the predefined criteria were also included. Patients were excluded if they had undergone emergency surgery or a major multiorgan resection or palliative surgery for cancer. Data was collected from a prospectively maintained, institutionally approved and password protected electronic colorectal database in the Central Hospital of Central Finland. All studies were approved by the ethics committee of the Central Hospital of Central Finland.

4.2 SURGICAL TECHNIQUE

4.2.1 Laparoscopic colon surgery

Laparoscopic bowel resection was performed using the 5-trocar technique for right and left hemicolecotomies and rectal cancer surgery. Specimens were extracted through a Pfannenstiel incision (left hemicolecotomy, rectal cancer surgery) or a peri-umbilical horizontal incision (small bowel and ileo-colic resection, right hemicolecotomy).

Ventral rectopexy was performed using the four-trocar technique. An autonomic nervesparing anterior rectal mobilization was performed at the level of the anal canal. Polypropylene or polyester mesh was sutured distally on both sides of the levator muscles. The mesh was attached to the rectum with four to six interrupted sutures and to the vagina with two stitches. The proximal end of the mesh was anchored to the sacral promontory using non-absorbable tackers.

The operations were performed by senior staff surgeons with the participation of the residents.
4.2.2 Complete mesocolic excision
Right colon cancers were managed with medial to lateral mobilization along the right side of the superior mesenteric vein and central ligation of ileocolic artery and right colic artery, when present, and with preservation of the trunk of the middle colic artery. Carcinomas of the hepatic flexure and right transverse colon were managed by extended right hemicolectomy and central transection of ileocolic, right colic artery, when present and the trunk of the middle colic artery. Gastroepiploic lymph nodes and lymph nodes over the pancreatic head were not routinely dissected. Tumors of the middle transverse colon were treated either with extended right hemicolectomy or with transverse colon resection and central ligation of the middle colic artery.

Carcinomas of the left transverse colon or splenic flexure were treated with extended left hemicolectomy and central ligation of the middle colic artery and inferior mesenteric artery. Division of the inferior mesenteric vein and transverse mesocolon was conducted at the lower edge of the pancreas.

Carcinomas of the descending colon were managed with left hemicolectomy and a central ligation of the inferior mesenteric artery with distal limit in the upper third of rectum and division of inferior mesenteric vein at the lower border of the pancreas. Sigmoid and rectosigmoid tumors were treated with sigmoid resections with central ligation of inferior mesenteric artery and bowel transection in the upper rectum. Because lymphogenous spread of colon carcinoma to the pericolic nodes at most extends for a distance of 10 cm, the aim was to achieve proximal and distal margins of 10 cm from the tumor. A 5-cm rule was accepted, if the anastomosis was made in the upper rectum. Ileocolic anastomoses were made side-by-side using linear staplers and left-side anastomoses were double-stapled using linear and circular staplers. The operation was considered non-curative if the patient had synchronous distant metastases and/or the resection margins were involved.

4.3 FAST-TRACK PROTOCOL
In accordance with an international consensus review, the fast-track protocol included 20 evidence-based fast-track elements (Lassen et al. 2009). Preoperatively patients received extensive counselling, oral carbohydrates until two hours before surgery, and no mechanical bowel preparation. All patients received antimicrobial prophylaxis before surgery. Total intravenous anesthesia (TIVA) with short-acting anesthetics (propofol-remifentanil and cis-atracurium for muscle relaxation) was used for all patients in the FT setting and traditional inhalation anesthesia (oxygen-sevoflurane and cis-atracurium for muscle relaxation) was used in the traditional care group in study II.

Short duration of postoperative opioid-sparing analgesia (ropivacaine 1.23 – 1.29 mg/ml and fentanyl 3.07 – 3.23 µg/ml) with epidural catheter (level Th9-11) and a single-use pump was scheduled to be removed on the second postoperative day. Oral paracetamol and NSAID were initiated two days after surgery, and opioids used only for breakthrough pain; these were the main differences between FT and traditional care. Ondansetron for postoperative nausea was used, if necessary.

In study IV, spinal analgesia involved a single intrathecal injection of anesthetic before induction of general anesthesia. This was performed at the L2-3 or L3-4 interspace using a combination of bupivacaine (5 mg), fentanyl (10-20 µg) and morphine (100-160 µg). All patients in the spinal group received preoperatively ondansetron 4 mg and betamethasone 4 – 8 mg perorally.

Furthermore, fast-track recovery was protocol driven with discontinuation of iv-fluids as soon as possible, early postoperative feeding, removal of the urinary catheter on the first
postoperative day and early mobilization. Patients were discharged when they were 1) able to consume a normal diet, 2) afebrile, 3) flatus, 4) fully mobilized, 5) had adequate pain control with oral analgesics and 6) had adequate home support.

4.4 STATISTICAL ANALYSIS

Results are given as mean (SD) or median (interquartile range, IQR). The comparison between groups was made using t-test, ANOVA, Mann-Whitney, Kruskall-Wallis (continuous variables) or chi-square test (categorical variables). All statistical tests were two sided, p<0.05 considered as statistically significant. Statistical analysis was conducted using SPSS (version 22.0 for Window; SPSS Inc., Chicago, IL, United States) software.

In studies I and II, analysis of patient-related, treatment-related, and protocol compliance–related determinants affecting postoperative hospital stay was done using univariate and multivariate zero-truncated Poisson regression models with robust standard errors or negative binomial regression (zero-truncated) models, when overdispersion was present. Only those fast-track elements with an adherence rate less than 100% were entered in the uni- and multivariate models. In study II, because the cost data in this study were highly skewed, a bootstrap-type analysis (10,000 repetitions) was used.

In study III, survival times were calculated from the date of surgery until the time of death or the end of follow-up. Analysis of prognostic factors for disease-free survival was done using univariate and multivariate Cox proportional hazards regression model in stage I-III patients. Only variables with p<0.20 in the univariate analysis were entered into the multivariate analysis.

4.5 DEFINITIONS

Patients were considered functionally recovered when they were pain-free (visual analogue scale (VAS) 4 on oral analgesics, fully mobilized and able to eat normal food. Conversion to open surgery was defined as the necessity to interrupt the laparoscopic procedure and proceed using conventional techniques. Postoperative hospital stay during index admission was defined as the number of days spent in the hospital after surgery. Length of total hospital stay included preoperative, postoperative and readmission-related days spent in the hospital.

In study II, all costs were calculated according to the year 2010 prices (€). Costs of operating room resources (basic costs, anesthesia and services of nurses, surgical team, instrument use) and recovery room services were calculated according to the time spent in the operating and recovery rooms, duration of surgery, and the level of training required. The costs of disposable instruments including circular and linear staplers for open and laparoscopic surgery, trocars, laparoscopic diathermy scissors, harmonic scissors, and bipolar vessel sealers were calculated according to their use. It was decided to exclude capital costs of reusable instruments and standard laparoscopic equipment, administrative and traveling costs, as well as the costs of different adjuvant chemotherapy treatments for stage III colon cancer.
Table 4. Demographic data of patients in study I-III

<table>
<thead>
<tr>
<th></th>
<th>STUDY I</th>
<th>STUDY II</th>
<th>STUDY III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bowel resection</td>
<td>SCRP</td>
<td>Fast-Track Lap</td>
</tr>
<tr>
<td></td>
<td>N=138</td>
<td>N=42</td>
<td>N=73</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>6.1(12.6)</td>
<td>61.9(14.6)</td>
<td>62.8(12.2)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>58(42.6)</td>
<td>0</td>
<td>27(37.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.6(4.4)</td>
<td>26.2(4.1)</td>
<td>25.9(3.5)</td>
</tr>
<tr>
<td>ASA I-II, n (%)</td>
<td>99(71.7)</td>
<td>31(73.8)</td>
<td>55(75.3)</td>
</tr>
<tr>
<td>Malignant disease, n (%)</td>
<td>72(52.2)</td>
<td>0</td>
<td>40(54.8)</td>
</tr>
<tr>
<td>Type of resection, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileo-colic resection</td>
<td>15(8.3)</td>
<td>-</td>
<td>6(8.2)</td>
</tr>
<tr>
<td>Right/transverse colon</td>
<td>49(27.7)</td>
<td>-</td>
<td>32(43.8)</td>
</tr>
<tr>
<td>Left/sigmoid colon</td>
<td>59(32.7)</td>
<td>-</td>
<td>33(45.2)</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>2(1.1)</td>
<td>-</td>
<td>2(2.7)</td>
</tr>
</tbody>
</table>
Table 5. Operative data and surgical outcome study I-III

<table>
<thead>
<tr>
<th></th>
<th>STUDY I</th>
<th>STUDY II</th>
<th>STUDY III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bowel resection N=138</td>
<td>SCRP N=42</td>
<td>Fast-Track Lap N=73</td>
</tr>
<tr>
<td>OP time, median(IQR) min</td>
<td>139(100-165)</td>
<td>114(95-128)</td>
<td>135(102-165)</td>
</tr>
<tr>
<td>Bleeding, median (IQR) ml</td>
<td>50(20-150)</td>
<td>5(1-10)</td>
<td>50(10-100)</td>
</tr>
<tr>
<td>Conversion rate (%)</td>
<td>5.3</td>
<td>0</td>
<td>6.8</td>
</tr>
<tr>
<td>Mortality (30 d), n (%)</td>
<td>_</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morbidity (30 d), n (%)</td>
<td>0</td>
<td>0</td>
<td>7(9.5)</td>
</tr>
<tr>
<td>Surgical morbidity, n (%)</td>
<td>17(12.3)</td>
<td>0</td>
<td>4(5.5)</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>5(3.6)</td>
<td>0</td>
<td>3(4.1)</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>6</td>
<td>0</td>
<td>1(1.4)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General morbidity, n (%)</td>
<td>3(2.2)</td>
<td>0</td>
<td>4(5.5)</td>
</tr>
<tr>
<td>Reoperations (%)</td>
<td>5(3.6)</td>
<td>0</td>
<td>2(2.7)</td>
</tr>
<tr>
<td>Readmissions, n (%)</td>
<td>12(8.7)</td>
<td>1(2.9)</td>
<td>5(6.8)</td>
</tr>
<tr>
<td>Postop stay, median (IQR)</td>
<td>4(3-6)</td>
<td>3(2-6)</td>
<td>3(3-4)</td>
</tr>
</tbody>
</table>

\(^a\) Figures in the columns are not additive, because some patients had more than one complication

\(^b\) P<0.001 in study II
5 Results

5.1 BASELINE CLINICAL CHARACTERISTICS, INTRAOPERATIVE DATA AND SURGICAL OUTCOME

5.1.1 Studies I-III
Baseline demographic characteristics did not differ significantly between the studies (table 3). Most patients were older than 60 years, and conversion to open surgery occurred in between 5.3% to 12.1% of the cases. Operative data and surgical outcome in studies I-III are shown in Table 4. There was no mortality in studies I-II; in study III, postoperative 30 day mortality was 1.3%. Postoperative hospital stay was shorter in the fast-track setting than in the traditional care group. Anastomotic leakage occurred in five (3.6%) patients who underwent bowel resection in study I. In study II, the anastomotic leakage rate was lower in the fast track group than in the traditional group, but the difference was not statistically significant. In study III, the anastomotic leakage rate was 9.5% (21 patients) (table 5).

5.1.1 Study IV
Baseline clinical and treatment characteristics did not differ significantly between the study groups (Table 5). Complete rectal prolapse and internal rectal prolapse were evenly distributed in the study groups. The median duration of epidural analgesia was 2 (IQR2-2) days. Postoperative hospital stay was shorter after spinal than epidural analgesia [median 2 (IQR 1-3) days versus 3 (IQR2-3) days (p<0.001)] (table 6). Fifteen out of the 42 patients (35.7%) in the spinal group were discharged on postoperative day one versus none in the epidural group.

Table 6. Baseline clinical characteristics, intraoperative data and surgical outcome in study IV.

<table>
<thead>
<tr>
<th></th>
<th>Epidural N=38</th>
<th>Spinal N=42</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>61.4(15.2)</td>
<td>64(14.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>38(100)</td>
<td>40(95.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.1(4.1)</td>
<td>25.7(3.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>ASA I-II, n (%)</td>
<td>31(73.8)</td>
<td>28(66.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Intussusceptio</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Operation time, median(IQR)</td>
<td>114(98.5-130.0)</td>
<td>105(76.5-127.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Bleeding, median(IQR)</td>
<td>5(0.8-10)</td>
<td>20(10-50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conversion rate, n(%)</td>
<td>0</td>
<td>1(2.4)</td>
<td></td>
</tr>
<tr>
<td>Mortality (30d), n(%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Morbidity (30d), n(%)</td>
<td>0</td>
<td>1(2.4)</td>
<td></td>
</tr>
<tr>
<td>LOS, median(IQR)</td>
<td>3(2-3)</td>
<td>2(1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Readmission, n(%)</td>
<td>1(2.6)</td>
<td>4(9.5)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
5.2 EVALUATION OF FAST-TRACK PROTOCOL (STUDIES I-II)

In study I, time to functional recovery was median 2 (IQR 2–3) days after sacrocolporectopexy, small bowel, ileocolic, and colonic resection, and 4 (IQR 2–5) days after rectal resection and subtotal colectomy. The multivariate model conducted in study I revealed that the patient-related characteristics increasing the length of postoperative hospital stay were body mass index > 30 kg/m2 (LOS ratio 1.37 (95% CI 1.14–1.66), P = 0.031) and malignant disease (1.30 (1.12–1.51), P = 0.001). The treatment-related determinants were complexity of surgery (rectal resection and subtotal colectomy 1.61 (1.19–2.17), P = 0.003), recovery of bowel function later than 2 days after surgery (1.49 (1.21–1.85), P < 0.001), time to functional recovery > 2 days (1.34 (1.10–1.62), P = 0.003), general (1.54 (1.00–2.38), P = 0.050), and surgical (2.59 (2.12–3.17), P < 0.001) complications. Protocol compliance–related determinants increasing postoperative hospital stay were removal of urinary catheter later than 1 day after surgery (1.51 (1.24–1.83), P < 0.001), intake of normal food (1.47 (1.16–1.86), P = 0.001), and mobilization ≥ 6 h/day (1.47 (1.07–2.01), P = 0.003) later than 2 days after surgery. Adherence to the protocol elements was high during the preoperative period (89.1-100%) but slightly lower during the postoperative phase (table 7).

According to the univariate and multivariate regression analysis, traditional perioperative care (LOS ratio 1.56 (95% CI: 1.39–1.74), p < 0.001), open surgery (1.17 (1.04–1.33), p = 0.009), general (1.73 (1.38–2.15), p < 0.001), surgical complications (1.85 (1.52–2.25), p < 0.001) complications, and severity of complications (Clavien-Dindo grade 3a-5 1.89 (1.55–2.31), p < 0.001) were factors increasing the LOS in study II.
Table 7. Compliance with fast-track protocol

<table>
<thead>
<tr>
<th></th>
<th>Bowel resection N=138(%)</th>
<th>Sacrocolporectopexy N=42(%)</th>
<th>All N=180</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative elements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative information and counseling</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Fasting guidelines/carbohydrate loading</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>No mechanical bowel preparation</td>
<td>123(89.1)</td>
<td>42(100)</td>
<td>165(91.7)</td>
</tr>
<tr>
<td>No sedative preanesthetic medication</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Prophylaxis against thromboembolism</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td><strong>Intraoperative elements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized intravenous anesthesia</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Prevention of hypothermia</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Laparoscopic surgery</td>
<td>89(64.5)</td>
<td>42(100)</td>
<td>131(72.8)</td>
</tr>
<tr>
<td>Restriction to moderate perioperative fluid regimen (40mL/kg/first 24h)</td>
<td>83(60.1)</td>
<td>26(61.9)</td>
<td>109(60.6)</td>
</tr>
<tr>
<td><strong>Postoperative elements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance of nasogastric tubes</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Perioperative high O2 concentrations</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Avoidance of abdominal drains</td>
<td>125(90.6)</td>
<td>42(100)</td>
<td>167(92.8)</td>
</tr>
<tr>
<td>Epidural catheter removed POD2</td>
<td>120/132(90.9)</td>
<td>38/38(100)</td>
<td>158/170(92.9)</td>
</tr>
<tr>
<td>Paracetamol and NSAID</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Use antiemetics on demand</td>
<td>48(34.8)</td>
<td>20(47.4)</td>
<td>68(37.8)</td>
</tr>
<tr>
<td>Use laxatives (Milk of Magnesia)</td>
<td>138(100)</td>
<td>42(100)</td>
<td>180(100)</td>
</tr>
<tr>
<td>Urinary catheter removed POD1</td>
<td>114(82.6)</td>
<td>38(90.5)</td>
<td>152(84.4)</td>
</tr>
<tr>
<td><strong>Enhanced mobilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobilized 2h POD 0</td>
<td>87(63)</td>
<td>28(66.7)</td>
<td>115(63.9)</td>
</tr>
<tr>
<td>Mobilized 6h POD 2</td>
<td>105(76.1)</td>
<td>36(85.7)</td>
<td>141(78.3)</td>
</tr>
<tr>
<td><strong>Enhanced oral nutrition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral intake of liquids POD 0</td>
<td>127(92.0)</td>
<td>35(83.3)</td>
<td>162(90)</td>
</tr>
<tr>
<td>Liquid food/protein drinks &amp;&amp; POD1</td>
<td>132(95.7)</td>
<td>42(100)</td>
<td>174(96.7)</td>
</tr>
<tr>
<td>Normal food POD 2</td>
<td>110(79.7)</td>
<td>40(95.2)</td>
<td>150(83.3)</td>
</tr>
</tbody>
</table>

5.3 IN-HOSPITAL COSTS (STUDY II)

Preoperative costs between the study groups were similar because the fast-track group included only one extra additional preoperative visit for information and counseling. The per patient operating room costs were higher in the laparoscopic than in the open surgery group mainly due to an increased use of disposable instruments (mean difference €678 (95% CI: €598–€722), p = 0.001). The per-patient postoperative expenses were lower in the laparoscopic than in the open group, the main reason being attributable to their shorter stay in the elective abdominal ward (mean difference €−922 (€−1576 to €−329), p = 0.0043)(table 8).
Table 8. In-hospital costs

<table>
<thead>
<tr>
<th></th>
<th>Fast-track Laparoscopy N=73</th>
<th>Fast-track Open N=43</th>
<th>Traditional Laparoscopy N=73</th>
<th>Traditional Open N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total costs, €</strong></td>
<td>9029 (7980-10912)</td>
<td>8098 (7450-8845)</td>
<td>9836 (8872-11228)</td>
<td>10273 (8763-12569)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preoperative costs, €</strong></td>
<td>2162 (2142-2177)</td>
<td>2130 (2104-2155)</td>
<td>1920 (1905-1937)</td>
<td>1888 (1862-1913)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operative costs, €</strong></td>
<td>3397 (3259-3539)</td>
<td>2737 (2542-2930)</td>
<td>3335 (3197-3495)</td>
<td>21845 (2044-2337)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative costs, €</strong></td>
<td>3469 (2459-5289)</td>
<td>3231 (2735-3967)</td>
<td>4580 (3614-6058)</td>
<td>6200 (4659-8483)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.4 LAPAROSCOPIC COMPLETE MESOCOLIC EXCISION (STUDY III)

The 5-year overall survival (OS) for all 222 patients was 80.2% (95%CI: 74.0 to 85.1) and disease-specific survival (DSS) 87.5% (81.9 to 91.4 ), and for those 210 R0-patients with stage I-III disease 83.9% (77.7 to 88.4) and 91.3% (86.0 to 94.6), respectively. The 5-year DSS was 97.3% (82.3 to 99.6) for stage I, 95.6% (86.8 to 98.6) for stage II and 83.5% (71.9 to 90.1) for stage III , p =0.02. The 5-year disease-free survival (DFS) was 85.8% (80.1 to 90.0): stage I 94.7% (80.6 to 98.7), stage II 90.8% (82.3 to 95.3) and stage III 75.6% (64.0 to 83.9), p=0.004 (Fig. 2)(table 9). An increasing lymph node ratio significantly decreased the 5-year DFS rate: 91.7% (85.8 to 95.2) for LN ratio <10%, 77.1% (59.5 to 87.9) for LN ratio 10%-25% and 56.1% (30.5 to 75.5) for LN ratio >25%, p<0.001 (Fig. 3). Tumor site [right-sided 86.3% (78.2 to 91.5) vs. left-sided 85.3% (76.0 to 91.2, p=0.69] had no impact on the 5-year DFS rate.

Univariate and multivariate analyses for disease-free survival were performed in 210 patients with stage I-III disease. Of all patient-, tumor- and treatment-related factors, it was found that UICC stage (p=0.007), LN ratio (p<0.001) and adjuvant chemotherapy (p=0.003) were prognostic factors for DFS in the univariate analysis. In the multivariate analysis, LN ratio (p=0.04) was the only independent prognostic factor for disease-free survival whereas other variables included in the multivariate model failed to achieve statistical significance (Figure 3,4).
Figure 3. Overall survival according to the tumor stage I-IV. Cum OS – cumulative overall survival and FU - follow-up years.

Figure 4. 5-year DSS (%) in CHCF versus in Erlangen hospital.
Table 9. 5-year overall, disease-specific and disease-free survival subdivided according to disease stage.

<table>
<thead>
<tr>
<th>Stage</th>
<th>OS</th>
<th>DSS (%)</th>
<th>DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>94.9</td>
<td>97.3</td>
<td>94.7</td>
</tr>
<tr>
<td>Stage II</td>
<td>87.5</td>
<td>95.6</td>
<td>90.8</td>
</tr>
<tr>
<td>Stage III</td>
<td>74.4</td>
<td>83.8</td>
<td>75.6</td>
</tr>
<tr>
<td>Stage IV</td>
<td>16.7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

5.5 COMPARISON OF EPIDURAL AND SPINAL ANALGESIA (STUDY IV)

The mean pain scores were similar in both study groups on the day of surgery but significantly higher in the epidural group on postoperative day one (Table 10). Mean systemic opioid consumption was higher in the spinal group on postoperative day one but on postoperative day two, the epidural catheter was removed and the opioid consumption was higher in the epidural group. Inadequate mobilization during the first and second postoperative days was more frequently observed in the epidural group. Surgery- and anesthesia-related side effects, such as PONV, dizziness and hypotonia were infrequent.

Table 10. Postoperative data and pain scores during basic ward care.

<table>
<thead>
<tr>
<th></th>
<th>Epidural N=38</th>
<th>Spinal N=42</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pain score, mean VAS score (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>0.68 (1.05)</td>
<td>0.74 (1.15)</td>
<td>0.66</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.67 (1.09)</td>
<td>0.16 (0.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Opioid consumption, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>0.03 (0.16)</td>
<td>0.07 (0.26)</td>
<td>0.3</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.26 (1.03)</td>
<td>0.93 (1.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.13 (1.54)</td>
<td>0.43 (1.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>PONV, n of patients (%)</td>
<td>6 (15.8)</td>
<td>6 (14.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mobilized &lt;6 hrs/day POD 1-2</td>
<td>11 (28.9)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysuria, n of patients (%)</td>
<td>0</td>
<td>2 (4.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Dizziness, n of patients (%)</td>
<td>1 (2.6)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypotonia n of patients (%)</td>
<td>1 (2.6)</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>
6 Discussion

6.1 LAPAROSCOPIC COLORECTAL SURGERY

6.1.1 Laparoscopic colon cancer surgery
During the last decade, laparoscopic colon surgery has proved to be a major technical advance in abdominal surgery. At first, the laparoscopic approach was associated with concerns about oncologic safety, based on case reports of port-site metastases (Berends et al. 1994). Subsequently, several large multicenter randomized trials have confirmed the oncologic safety of laparoscopic colon resection providing similar patient survival than in those undergoing open colon resection (Jayne et al 2010, Fleshmann et al 2007). The COST and CLASSIC studies reported port site recurrence of 0.9-2.4% and overall survival of 56-76%; in our study III, the port-site recurrence rate was 0.5% and overall survival 80% after laparoscopic wide mesocolic resection. A Cochrane review concluded that the laparoscopic approach increased operating time but reduced intraoperative blood loss compared to open surgery (Schwenk et al. 2005). The results of our study II did not detect any significant differences in operating times, but we did observe a reduction in intraoperative blood loss. Conversion rates in our studies varied from 5.3% to 12.2%, which is in line with other reports (15-21%) (Hewett et al 2008, Fleshman et al. 2007). A number of reviews have shown short-term benefits for laparoscopic colonic resection, such as reduced postoperative pain, shorter duration of postoperative ileus, improved pulmonary function, shorter length of stay and reduced wound infection rate (Shwenk et al. 2005, Hewett et al. 2008). The variability of postoperative hospital stay is relatively high, ranging from 3.9 to 10.4 days (Schwenk et al. 2005). In our study, median postoperative stay varied from 3 to 5 days after laparoscopic colorectal resection, and was 1-2 days shorter after laparoscopic than open surgery (study II). At present, laparoscopic colon resection is the method of choice in our clinical unit, and our positive views of this technique are in agreement with previous studies. Our clinical practice is also in line with the Cochrane review concluding that laparoscopic technique should be preferred in colorectal surgery, because it has an equivalent long term outcome and a better short-term outcome (Kuhry et al. 2008).

6.1.2. Laparoscopic complete mesocolic excision in colon cancer surgery
The concept of total mesorectal excision, first published by Heald, is based on the theory that the mesorectum is composed of visceral and parietal planes covering the rectal vessels and lymph nodes like an envelope. The adoption of the technique was reported to improve significantly the survival of patients with rectal cancer (Heald et al. 1986). Hohenberger et al. introduced the concept of the mesocolic envelope to colon cancer surgery, including dissection following embryologic tissue planes along the entire regional mesocolon, a high arterial ligation and resection of an adequate length of bowel. They proved that the CME technique in open surgery achieved low recurrence rates and good overall survival (Hohenberger et al. 2003, West and al. 2008, West and al. 2010). In our hospital, when starting laparoscopic colon cancer surgery in 2003, we aimed to standardize laparoscopic colon cancer surgery according to principles described by Hohenberg et al. in 2003. In our study III, we demonstrated that laparoscopic CME and central vascular ligation for colon cancer achieved comparable oncological results as the open surgery performed by the Erlangen and Danish groups (Hohenberg et al 2009, Bertelsen et al 2015) (Figure 3).
The number of lymph nodes excised and evaluated after colon carcinoma resection may affect patient prognosis. A minimum of 12 excised nodes has been proposed in an international guideline (Willaert et al. 2014, Nelson et al. 2000). In our study, the median number of lymph nodes excised was 14. We also found that an increasing lymph node ratio was associated with reduced disease-free survival. Along with the introduction of CME, West et al. proposed a new pathologic quality grading of the surgical specimen and demonstrated its association with survival (West et al. 2008). The specimen grading system was initially developed for the MRC-CLASSIC trial, and classified surgery as being muscular propria plane (poor), intramesocolic plane (moderate) and mesocolic plane (good). This grading system was not applied in our study III, because data had been gathered since 2003. Our oncological results are consistent with other CME studies suggesting that the quality of surgery has been reasonably good. The median length of proximal and distal margins as well as the number of lymph nodes harvested were considered to be adequate. In 2014, we implemented the principle of quality grading of surgical specimens into our clinical practice according to the proposal of West et al.

The postoperative mortality (Study III) was low in our study (1.3%) and was comparable with the reported range of 2-5% from other European countries (Bertelsen et al. 2015, Hohenberger et al. 2009). In addition, the 30-day morbidity was in line with other reports. Anastomotic leakage is a serious complication and may have a long-term impact on survival. The anastomotic leak rate varies widely between studies. There is some large prospective data reporting anastomotic leak rates as high as 8.7%-9.4% (Fransson et al. 2015, Nachiappan et al. 2014). Another study reported anastomotic leaks as low as 3.0% in patients (Kube et al. 2009). In our study, the anastomotic leak was 9.2%. One reason may be the high tie, central vascular ligations which cause hypoperfusion in the proximal bowel limb. In some prospective studies, anastomotic leak has probably been underestimated in the computer tomographic assessment.

Laparoscopic complete mesocolic excision is a feasible technique for colon surgery and results in a good oncologic outcome. However, more randomized trials are needed to demonstrate the benefits of the laparoscopic CME technique before it can become standard care of colon cancer surgery.

6.2 FAST-TRACK PROTOCOL

6.2.1 Evaluation of fast-track protocol

Fast-track programs integrate a range of perioperative interventions to enhance postoperative recovery. Although the fast-track approach was introduced many years ago, implementation into daily clinical practice has been slow (Gustafsson et al. 2011). In our hospital, implementation of the fast-track protocol started in January 2007 after a pilot project. Selected multidisciplinary team members developed management instructions and after the initial follow-up, guidelines were modified several times. Finally, the current fast-track protocol included 20 evidence-based elements in accordance with international consensus review (Lassen 2012). After implementing the evidence-based elements in daily clinical practice, we could show that fast-track significantly reduced the postoperative stay without causing any increase in complication rates. Adherence to the protocol elements was high during the preoperative period (89.1-100%) but slightly lower during the postoperative phase. Time to functional recovery was a median of 2 days after bowel resection in line with previous studies, indicating that functional recovery can be achieved within 2 to 3 days. In study II, we compared laparoscopic and open colonic resection within fast-track and traditional care pathways. In the fast-track group, the postoperative hospital stay was shorter than in the control group: laparoscopic resection median 3 vs 5 days, and open resection 4 vs 7 days. Andersen et al. observed that the readmission rate was around 10% instead of 20% by planning discharge at 3 days instead of 2 days after surgery within
fast-track care (Anderson et al. 2007). Accordingly, our readmission rate in the fast-track settings was well below 10%. A multicenter randomized trial including 427 patients reported rather similar results: median postoperative stay in the laparoscopic/fast-track group was 5 days and in the open/fast-track group 7 days. In the laparoscopic/standard care group, it was 6 days and one day longer in the open/standard (Vlug et al. 2011).

In our study, fast-track care and laparoscopic surgery were independent determinants reducing the length of the postoperative stay in line with the results of the LaFa study (Vlug et al. 2011). They also found that female sex was an independent determinant of early recovery, a result that we could not confirm.

6.2.2 In-hospital costs
One of the reasons for delaying the implementation of laparoscopic surgery has been the increased costs associated with this type of surgery. However, a systematic review has demonstrated that although the operative costs of laparoscopic colorectal surgery are greater than open surgery, overall hospital costs are similar due to the reduced time that patients need to stay in the hospital (Dowson et al. 2007).

The results of study II show that open surgery within fast-track care was the least costly option compared to laparoscopic surgery combined with fast-track care, but the difference was not statistically significant. The most expensive combination was open colon surgery within traditional care. Our results are consistent with a randomized study reporting lower costs after open surgery with fast-track care than with traditional care (Vlug et al 2011, Ren et al. 2012.). The length of hospital stay is a significant cost element for overall in-hospital costs. Recent studies have shown that laparoscopic colorectal surgery within fast-track care results in a shorter postoperative hospital stay than open surgery in line with our results (Vlug et al. 2011). In study II, multivariate regression analysis demonstrated that traditional perioperative care, open surgery, general and surgical complications were factors increasing the length of hospital stay. High quality surgical care is therefore important not only to reduce complications but also to minimize in-hospital costs.

In summary, according to our results, laparoscopic colonic resection combined with fast-track care resulted in a shorter hospital stay and a lower complication rate than open surgery without significantly increasing in-hospital costs. Therefore, the combination of laparoscopic surgery and fast-track care seems to be the method of choice for elective colonic surgery, as proposed also by the LAFA trial.

6.2.3 Analgesia in fast-track laparoscopic colorectal surgery
Epidural analgesia has been the method of choice to provide optimal pain relief and in order to enhance mobilization in colorectal surgery. Epidural analgesia has been adopted from open colorectal surgery, but in fact, recent studies suggest that routine epidural analgesia is unnecessary during laparoscopic colon resection (Zafar et al. 2008, Turunen et al. 2009). Levy et al. compared epidural, spinal and PCA analgesia for patients undergoing laparoscopic colorectal surgery and noted that the outcomes in the epidural analgesia group were significantly worse (Levy et al 2011). There is no consensus about what represents the best analgesic technique for patients undergoing laparoscopic ventral rectopexy nor is it known whether one form of analgesia is especially suited for fast-track perioperative care (Mercer-Jones et al 2014). For patients undergoing laparoscopic ventral rectopexy, the main analgesic method used so far has been epidural analgesia. This kind of analgesic delivery resulted in a relatively long hospital stay (study I). Therefore, we compared epidural and spinal analgesia for patients undergoing laparoscopic ventral rectopexy within fast-track care (study IV).

In our study, postoperative stay was shorter in the spinal than in the epidural group (median 2 versus 3 days). Our results are consistent with those of Levy et al. and Virlos et al. suggesting that spinal analgesia is not only a safe analgesic regimen but it also improves mobilization and shortens postoperative stay when compared to epidural analgesia (Virlos
et al 2010). Spinal analgesia seemed to provide good early pain relief during the first 24 hours (study IV). On postoperative day one, mean opioid consumption was higher in the spinal group than in the epidural group in contrast to the results of Virlos and Levy.

Spinal analgesia with high dose morphine (10-20mg) has been associated with severe central neurologic and respiratory side effects (Bailey et al. 2000). In our study, we used low dose intrathecal morphine according to the recommendation of American Society of Anesthesiologists (ASA) and no morphine related signs of respiratory depression or hemodynamic effects were observed.

According to the guidelines for Perioperative Care in Elective Colonic Surgery ERAS society, epidural analgesia should be considered for open surgery. In laparoscopic colorectal surgery, spinal analgesia or PCA can be considered as an alternative to epidural analgesia (Gustafsson et al. 2013). Optimal pain management for colorectal patients is still a matter for debate. Wongyingsin from Montreal compared a spinal mixture of bupivacaine and morphine and patient-controlled analgesia for laparoscopic colonic resection within an ERAS-protocol, and demonstrated that spinal analgesia was associated with less postoperative opioid consumption, but conferred no other advantages (Wongyungsin et al 2012). Joshi et al. in their procedure-specific postoperative pain management (PROSPECT) collaboration claimed that neuraxial blocks (i.e. epidural analgesia and spinal morphine) were not advantageous based on high risk and low benefit ratio, and recommended infiltration of surgical incisions with local anaesthetic at the end of surgery, systemic administration of steroids as well as conventional nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-selective inhibitors in combination with paracetamol with opioid being used as rescue medication (Josh et al. 2013). However, the finding of the current study demonstrated that spinal analgesia is a safe analgetic regimen for patients undergoing laparoscopic ventral rectopexy, and shortens postoperative stay compared with epidural analgesia. Future studies will be needed to define the optimal pain management protocol for colorectal surgery.

**7 FUTURE PROSPECTIVES**

**7.1 Robotic surgery**

At present, the Da Vinci Robot is most widely used in prostatectomy. It has many advantages such three dimensional vision, 7 wrist-like motion, tremor filtering, motion scaling, better ergonomics and less fatigue. These advantages make it possible to operate in restricted sites and demanding conditions, such as in the narrow pelvis. Robotic prostatectomy is now being assessed as the primary treatment for localized prostate cancer achieving comparable oncological outcome and fewer complication rates as open prostatectomy (Finkelstein et al 2010). The Robotic vs Laparoscopic Resection for Rectal cancer multi-center randomized trial including 471 patients detected no statistically significant difference in oncological clearance, patient outcome or conversion to open surgery between laparoscopic and robotic TME. These results have been presented at the European Society of Coloproctology, September 2015. At present, the long operation time and high costs are the major limitations associated with robotic surgery.

In colon surgery, robotic-assisted ileocolic anastomosis allows a faster recovery compared with extracorporeal anastomosis but it has not been demonstrated that robotic surgery confers any benefits over laparoscopic colonic surgery which could justify the greater cost (Morpurgo et al 2013, Park et al 2012).

The overall conclusion regarding robotics in gastrointestinal surgery is that there are no proven advantages in upper or lower GI-surgery.
7.2 Development of the fast-track care protocol.
Transversus abdominal plane (TAP) blocks is a potentially valuable pain management technique, and over the last 6 years, several clinical trials have demonstrated the efficacy of TAP blockade after laparoscopic colon surgery. Firstly, non-randomized trials indicated that TAP blockade with an enhanced recovery pathway contribute to a shorter length of stay after laparoscopic colectomy without increasing either complication or readmission rates (Zafar et al. 2010, Favuzza et al. 2012). Subsequently, randomized trials have shown that TAP blocks in patients undergoing laparoscopic colorectal resection reduced opioid use during the first postoperative day (Walter et al. 2012, Keller et al. 2014). Later, a randomized trial investigating 226 patients demonstrated that TAP blockade appeared to be a safe intervention but conferred no specific advantage following laparoscopic colorectal surgery (Smith and al. 2015).

Perioperative intravenous lidocaine has also been shown to reduce postoperative pain, opioid requirements, and to shorten the length of the operative stay after laparoscopic colorectal surgery (McCarthy et al. 2010). Large randomized clinical trials are needed to reveal the utility of perioperative intravenous lidocaine in routine use (Joshi et al. 2012).

Minor new findings are that laparoscopic colonic resection without urinary drainage is safe and feasible (Alyami et al. 2016). Kiran et al. showed that combined preoperative mechanical bowel preparation with oral antibiotics reduces surgical site infections compared with systemic antibiotic alone in elective colorectal surgery and these findings were supported in a meta-analysis conducted by Chen et al. (Kiran et al. 2015, Chen et al. 2016). Oral magnesium oxide has now been abandoned as Andersen et al. proved that magnesium oxide did not enhance recovery of gastrointestinal function (Andersen et al. 2012).

Early peroral nutrition and postoperative mobilization are still the cornerstones of enhanced recovery pathways.

Despite the benefits of the fast-track programme, the sustainability of the fast-track protocol after its initial implementation remains a challenge. The Dutch team reported their follow-up at 3-5 years in the 10 selected successful hospitals (Gillissen et al. 2014). According to their study, fast-track protocol adherence had declined from 75% to 67%. In particular, adherence to postoperative care elements had decreased considerably. A systematic audit of quality of fast-track elements is essential if one wishes to maintain adherence of clinical pathway and continuous re-evaluation of evidence is mandatory (Martin et al. 2016).
7 Conclusions

1. The effectiveness of fast-track colorectal surgery, as reflected by a relatively good adherence to predefined fast-track elements, low morbidity, reduced reoperation and readmission rates, short postoperative hospital stay, and good patient satisfaction, indicated that our fast-track protocol had been successfully implemented and should form the mainstay of elective colorectal surgery.

2. Compared with open surgery, laparoscopic colonic resection within fast-track perioperative care was found to be safe, improved postoperative recovery with lower surgical morbidity, without significantly increasing in-hospital costs.

3. Laparoscopic wide mesocolic excision and central vascular ligation for colon cancer was proved to be a feasible technique for colon cancer surgery and achieved a good long-term oncologic outcome.

4. Spinal anesthesia for laparoscopic ventral rectopexy within fast-track perioperative care was proven to be safe, speeding up postoperative recovery and resulting in shorter hospital stay thereby improving the efficiency of fast-track perioperative care.
8 References


Chen M, Song X, Chen LZ, Lin ZD, Zhang XL. Comparing Mechanical Bowel Preparation With Both Oral and Systemic Antibiotics Versus Mechanical Bowel Preparation and Systemic Antibiotics Alone for the Prevention of Surgical Site Infection After Elective


ORIGINAL PUBLICATIONS (I-IV)
Comparison of epidural and spinal analgesia for patients undergoing laparoscopic ventral rectopexy within fast-track care

Ehrlich A, Kairaluoma M, Wagner B and Kellokumpu I.

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Comparison of epidural and spinal analgesia for patients undergoing laparoscopic ventral rectopexy within fast-track care

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Abstract

Background: To compare the effects of epidural and spinal analgesic regimens on outcomes for patients undergoing laparoscopic ventral rectopexy (LVR) within a fast-track care pathway.

Material and methods: This study is a retrospective analysis of prospectively collected data from two time periods. From 2007 to 2009, a total of 38 consecutive patients underwent a standardized LVR within fast-track care pathway and epidural analgesia. The spinal analgesia group consisted of 42 consecutive patients who received similar LVR from 2013 to 2014. Totally intravenous anesthesia regimen and fast-track care pathway were similar during both study periods. The main measures of outcome were postoperative hospital stay, pain scores, and postoperative opioid consumption with 30-day morbidity and readmission rates as secondary outcomes.

Results: The study groups were well balanced for baseline characteristics. Postoperative hospital stay was shorter in the spinal than in the epidural group (median 2 versus 3 days, p<0.02). Fifteen of the 42 patients (35.7%) in the spinal group were discharged on postoperative day one versus none in the epidural group. Pain scores were higher in the epidural group on postoperative day one. There were no deaths and only one complication and one conversion to open surgery in the spinal group. Conclusion: Spinal analgesia is a safe analgesic regimen for patients undergoing LVR, and improves mobilization and shortens postoperative stay compared with epidural analgesia in the fast-track setting.

Key words

spinal analgesia, fast track care, laparoscopic ventral rectopexy

Introduction

Pelvic organ prolapse is common occurring in up to 40% of parous women [1]. Laparoscopic ventral rectopexy (LVR) is increasingly used for the treatment of rectal prolapse and for symptomatic high-grade (Oxford Grade 3-4) internal rectal prolapse [2].

Randomized trials and meta-analyses have now demonstrated the safety and efficacy of fast-track perioperative care in colorectal surgery, not only in reducing postoperative hospital stay and morbidity, but also in improving patient
convalescence and satisfaction when compared with traditional care [3-6]. The role of fast-track perioperative care after LVR is not well known [2].

Optimal analgesia is an essential component of the fast-track program as it would facilitate earlier mobilization and oral intake, thus leading to shorter length of hospital stay [4-6]. For patient undergoing laparoscopic colorectal surgery the main analgesic method used so far has been epidural analgesia, which has been adopted from open colorectal surgery [7-8]. A recent randomized trial, however, showed that many of the outcomes in the epidural analgesia groups were significantly worse than those in the spinal analgesia and patient-controlled anesthesia (PCA) groups [9].

While rationalizing the perioperative care for colorectal surgery the aim of this study was to examine the impact of epidural versus spinal analgesic regimen on outcomes for patients undergoing standardized LVR within a fast-track care pathway.

Methods

Patients and study design

This study is a retrospective analysis of prospectively collected data from two time periods. From 2007 to 2009, a total of 38 consecutive patients underwent a standardized LVR within fast-track care pathway and epidural analgesia. The spinal analgesia group consisted of 42 consecutive patients who received similar LVR from 2013 to 2014. Totally intravenous anesthesia and similar fast-track care pathways were used during both study periods. The main measures of outcome were postoperative hospital stay, pain scores, and postoperative opioid consumption with 30-day morbidity and readmission rates as secondary outcomes. The study was approved by the ethics committee of the Central Hospital of Central Finland.

Indications for surgery were complete rectal prolapse or symptomatic internal rectal prolapse (Oxford grade III-IV) accompanied with large rectocele or enterocele and no response to conservative therapy. Patients having the American Society of Anesthesiologists (ASA) score I-III, a good mental and physical performance status and having an attending person at home were included. Elderly patients fulfilling the predefined criteria were also included.

Preoperatively all patients underwent a complete history and physical examination and dynamic fluoroscopic defaecography with vaginal contrast agent or MRI proctography to detect intussusception and other concomitant pelvic floor disorders. Colonoscopy was performed selectively when clinically indicated. All patients were followed up for 30 days to assess morbidity and readmissions. Data was collected from a prospectively maintained, institutionally approved and password protected electronic colorectal database.

Surgical technique

The operation was standardized LVR using the four-trocar technique, and performed by two senior staff surgeons with the participation of residents in training [10]. An autonomic nerve-sparing anterior rectal mobilization was performed to levator level. Polypropylene or polyester mesh was sutured distally to the both sides of levator muscles, and attached to the rectum with four to six interrupted sutures and to the vagina with tow stiches. The proximal end of mesh was anchored to the sacral promontory using non-absorbable tackers.

Fast-track protocol
In accordance with a recent international consensus review the fast-track protocol included 20 evidence-based fast-track elements [11,12]. Preoperatively patients received extensive counseling, oral carbohydrates until two hours before surgery, and no mechanical bowel preparation. All patients received antimicrobial and thrombosis prophylaxis. The intraoperative protocol during both study periods consisted of standardized totally intravenous anesthesia (TIVA) using short-acting anesthetics ((induction with Propofol 1.0-2.5 mg/kg, Remifentanil 0.5-1.5 µg/kg and Cis-atracurium 0.1-0.15 mg/kg as bolus iv injection, maintenance with Propofol 2-4 mg/kg/h and Remifentanil 0.1-0.5 µg/kg/min and bolus injections of Cis-atracurium 0.02-0.03 mg/kg for muscle relaxation), intraoperative epidural analgesia with Ropivacain 0.2% 18 ml and Fentanyl 100 ug as bolus (5-10 ml preoperatively, followed by 2-5 ml every 60-90 minutes), restrictive to moderate administration of crystalloid solutions intra-operatively and crystalloid solution postoperatively on the day of surgery until next morning.

In the epidural group postoperative opioid-sparing analgesia (ropivacaine 1.23 – 1.29 mg/ml and fentanyl 3.07 – 3.23 µg/ml) with epidural catheter (level Th9-11) and a single-use pump was scheduled to be removed on the second postoperative day. Oral paracetamol was started on the first postoperative day and NSAID-medication 2 days after surgery. Opioids were used for breakthrough pain. Ondansetron for postoperative nausea was used, if necessary.

In the spinal group analgesia involved injection of intrathecal anaesthetic before induction of general anaesthesia. This was performed at the L2-3 or L3-4 interspace using a combination of bupivacaine (5 mg), fentanyl (10-20 µg) and morphine (100-160 µg). All patients in the spinal group received preoperatively ondansetron 4 mg and betamethasone 4 – 8 mg per orally.

Furthermore, fast-track recovery was protocol driven with discontinuation of iv-fluids as soon as possible, early oral intake of fluids and postoperative feeding, removal of urinary catheter on the first postoperative day and early mobilization. In both study groups patients were discharged when they were afebrile, fully mobilized, tolerated three meals per day, had adequate pain control on oral analgesics and adequate home support.

Postoperative follow-up

Patients were viewed 3-5 times daily by operating surgeons and staff nurses. Dysuria, dizziness, hypotonia, cessation of nausea, vomiting and tolerance of full diet was recorded. If patient was out of bed less than six hours per day, the aim of early mobilization was not fulfilled. Pain scores were recorded 3-5 times daily by a specific nurse for pain management using a ten point visual analogue scale and a mean daily pain score was calculated. Mean number of systemic daily opioid doses (one opioid dose is oral oxynorm 5-10 mg or intramuscular oxanest 8-10 mg) was calculated.

Statistical analysis

Results are given as mean (SD) or median (interquartile range, IQR). The comparison between groups was made using t-test, Mann-Whitney, Kruskall-Wallis or chi-square test. All statistical tests were two sided, p<0,05 considered as statistically significant. Statistical analysis were conducted using SPSS (version 22.0 for Window; SPPS Inc., Chicago, IL, United States) software.

Results

Baseline clinical and treatment characteristics did not differ significantly between the study groups (Table 1). Complete rectal prolapse and internal rectal prolapse were evenly distributed in the study groups. The median duration of epidural analgesia was 2 (IQR2-2) days.
Table 1. Baseline clinical characteristics, intraoperative data and surgical outcome

<table>
<thead>
<tr>
<th></th>
<th>Epidural (N=38)</th>
<th>Spinal (N=42)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>61.4(15.2)</td>
<td>64(14.3)</td>
<td>0.42</td>
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<td>Female sex, n (%)</td>
<td>38(100)</td>
<td>40(95.2)</td>
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<td>BMI, mean (SD)</td>
<td>26.1(4.1)</td>
<td>25.7(3.5)</td>
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</tr>
<tr>
<td>ASA I-II, n (%)</td>
<td>31(73.8)</td>
<td>28(66.7)</td>
<td>0.5</td>
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<td>Comorbidity, n of patients (%)</td>
<td>17(44.7)</td>
<td>25(59.5)</td>
<td>0.45</td>
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<td>Cardiac</td>
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</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Pulmonary</td>
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<td>3</td>
<td></td>
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<td>Diabetes</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypothyreosis</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Intussusceptio</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Operation time, median(IQR)</td>
<td>114(98.5-130.0)</td>
<td>105(76.5-127.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Bleeding, median(IQR)</td>
<td>5(0.8-10)</td>
<td>20(10-50)</td>
<td>&lt;0.001</td>
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<td>Conversion rate, n(%)</td>
<td>0</td>
<td>1(2.4)</td>
<td>-</td>
</tr>
<tr>
<td>Mortality (30d), n(%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>LOS, median(IQR)</td>
<td>3(2-3)</td>
<td>2(1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Readmission, n(%)</td>
<td>1(2.6)</td>
<td>4(9.5)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

a Figures in the columns are not additive because some patients had more than one comorbid condition

Postoperative hospital stay was shorter in the spinal group than in the epidural group [median 2 (IQR 1-3) days versus 3 (IQR2-3) days (p<0.001)] (Table 1). Fifteen of the 42 patients (35.7%) patients in the spinal group were discharged on postoperative day one versus none in the epidural group. Mean pain scores were similar in both study groups on the day of surgery but significantly higher in the epidural group on postoperative day one (Table 2). More than four pain score value was in 4 patients from epidural group and only in one patient from spinal group on postoperative day one. Mean systemic opioid consumption (one dose 5-10 mg) was higher in the spinal group than in the epidural group on postoperative day one. However, on postoperative day two after removal of epidural catheter the opioid consumption was higher in epidural group. Inadequate mobilization during first and second postoperative days was more frequently observed in the epidural group. Surgery and anesthesia-related side effects, such as postoperative nausea and vomiting (PONV), dizziness and hypotonia were infrequent in both study groups.

Table 2. Postoperative data and pain scores during basic ward care.

<table>
<thead>
<tr>
<th></th>
<th>Epidural (N=38)</th>
<th>Spinal (N=42)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Mean pain score, mean VAS score (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>0.68(1.05)</td>
<td>0.74(1.15)</td>
<td>0.66</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.67(1.09)</td>
<td>0.16(0.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Opioid consumption, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>0.03(0.16)</td>
<td>0.07(0.26)</td>
<td>0.3</td>
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</tbody>
</table>
Conversion to open surgery occurred in one patient in the spinal group due to severe adhesions from previous open surgeries. There were no deaths. One patient had a small presacral haematoma (Table 1). Readmission rates did not differ significantly between epidural or spinal study groups (2.6% versus 9.5%, P=0.36).

**Discussion**

Effective analgesia is a prerequisite to decrease surgical stress response and to enhance mobilization. For patient undergoing LVR the main anesthetic method used so far has been epidural anesthesia, which has been adopted from open colorectal surgery. This study indicates that spinal analgesia instead of epidural analgesia for LVR within fast-track care is effective in reducing the length of hospital stay, pain scores on postoperative days one, and improving early mobilization.

The postoperative length of stay following LVR usually ranges from 3 to 6 days instead of 2 to 3 days in our study [13]. Fifteen of the 42 patients (35.7%) patients in the spinal group were discharged on postoperative day one versus none in the epidural group. Powar et al. reported the efficacy and safety of same-day discharge after LVR in selected patients with pelvic floor disorder. In their study 67% of the patients were discharged on postoperative day one and early discharge was associated with younger age and private insurance status [14].

In our study spinal analgesia seemed to provide a good early pain relief during the first 24 hours but was associated with a higher mean systemic opioid consumption on postoperative day one compared to epidural analgesia. In contrast, postoperative opioid consumption was higher in the epidural group on day 2 when epidural catheter was removed. Multimodal analgesia avoiding routine use of systemic opioids is considered crucial within enhanced recovery pathways to reduce the use of opioids. Consequently oral paracetamol and NSAID were routinely used here in both study groups.

Continuous thoracic epidural analgesia has been considered beneficial in major open abdominal procedures to control pain and to decrease catabolism, paralytic ileus, nausea, and vomiting [11]. However, recent randomized studies reported no advantage of thoracic epidural analgesia over patient-controlled anesthesia and another study demonstrated a detrimental effect of epidural analgesia on recovery after laparoscopic colorectal surgery when compared with spinal analgesia or patient-controlled analgesia [7,9,15,16]. In our study single-dose spinal analgesia resulted in faster mobilization and seemed to provide a good early pain relief compared to epidural analgesia.

The role of epidural analgesia in laparoscopic surgery is increasingly being questioned because of increased time to mobilization, higher hospital costs, and longer length of hospital stay and higher incidence of urinary tract infections [9,17]. For open surgery, the recommendation is that the epidural should be left in situ for 48h. In our study the median duration of epidural analgesia was two days thereby potentially hindering the early discharge of patients. Of note,

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>0.26(1.03)</td>
<td>0.93(1.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>PONV, n of patients (%)</td>
<td>6(15.8)</td>
<td>6(14.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mobilized &lt;6 hrs/day POD 1-2</td>
<td>6(28.9)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysuria, n of patients (%)</td>
<td>0</td>
<td>2(4.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Dizziness, n of patients (%)</td>
<td>1(2.6)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypotonia n of patients (%)</td>
<td>1(2.6)</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>
recently published guidelines from UK do no longer recommend epidural analgesia as standard therapy for pain control after laparoscopic colorectal surgery [17,18].

Intrathecal analgesia with high dose morphine (10-20 mg) has been associated an analgesic effect lasting up to more than 48 hours. However, this may cause severe central neurologic and respiratory side effects [19]. Some authors have injected up to 0.3 mg of intrathecal morphine in elderly patients undergoing open colorectal surgery and did not report either respiratory depression or excessive sedation [19]. Today, the intrathecal dosage of morphine rarely exceeds 0.3 mg, which provides a significant reduction of dangerous, respiratory depression, even in elderly patients [20]. In line with the recommendation of American Society of Anesthesiologists (ASA) [21] using low dose intrathecal morphine in our study no morphine-related respiratory depression or haemodynamic side effects were observed.

The transversus abdominal 1plane (TAP) bloc is a regional anesthesia technique that provides analgesia of the parietal peritoneum, the anterior abdominal wall and the skin, and has only recently been implemented in laparoscopic abdominal surgery [22]. This technique has been shown to reduce postoperative pain and to reduce short-term opioid use after laparoscopic colorectal surgery [22,23].

A major challenge with this study was the lack of randomization which may have caused some selection bias. Another limitation was that the research was conducted in one hospital. However, patient demographics, technique of laparoscopic ventral rectopexy, TIVA-anesthesia, fast-track protocol, and discharge criteria were similar during the two study periods. Furthermore, senior surgeons had a large experience in laparoscopic colorectal surgery, and the quality of surgery was good as reflected by the short-term surgical outcome. Currently there are several analgesic methods in colorectal surgery. The optimal pain management for patients undergoing LVR and laparoscopic colorectal surgery remains to be determined in future randomized clinical trials.

**Conclusions**

Spinal analgesia for LVR within fast-track perioperative care is safe, improves postoperative recovery and results in shorter hospital stay thereby improving the efficiency of fast-track perioperative care.

**Acknowledgements**

The authors have no conflicts of interest to declare.

This study was approved by the ethics committee of the hospital.

**References**


During the past 20 years, fast-track care and the laparoscopic technique have been recognized as two major revolutions in colorectal surgery. The aims of this study were to investigate short and long term clinical outcomes of laparoscopic surgery and the impact of fast track care pathway on the recovery of patients undergoing elective colorectal surgery. In addition, this study examined survival of patients who underwent laparoscopic complete mesocolic excision for colon cancer.