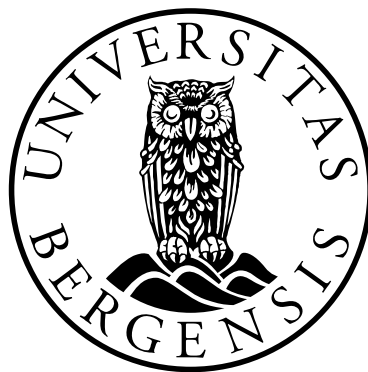


Enhanced recovery after colorectal surgery – a randomized study of optimized perioperative treatment with an emphasis on patient counselling

Håvard Mjørud Forsmo



Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

2017

Dissertation date: 17th October 2017

© Copyright Håvard Mjørud Forsmo

The material in this publication is protected by copyright law.

Year: 2017

Title: Enhanced recovery after colorectal surgery – a randomized study of optimized perioperative treatment with an emphasis on patient counselling

Author: Håvard Mjørud Forsmo

Print: AiT Bjerch AS / University of Bergen

Scientific environment



Department of Gastrointestinal and Emergency Surgery, Colorectal unit
Haukeland University Hospital, Bergen Norway



Department of Clinical Medicine, K1
University of Bergen, Norway

Contents

SCIENTIFIC ENVIRONMENT	3
ACKNOWLEDGEMENTS	7
LIST OF PUBLICATIONS	9
ABBREVIATIONS	10
ABSTRACT	12
1. INTRODUCTION	14
1.1 BACKGROUND.....	14
1.2 STANDARD TRADITIONAL CARE.....	14
1.3 ENHANCED RECOVERY AFTER SURGERY (ERAS).....	16
1.4 STOMA EDUCATION AND ERAS	19
1.5 ERAS CARE IN ELDERLY PATIENTS	19
1.6 ERAS INTERVENTIONS.....	21
1.6.1 Perioperative counselling	21
1.6.2 Preoperative optimisation / prehabilitation	22
1.6.3 Preoperative fasting and carbohydrate loading (CHL)	23
1.6.4 Preoperative bowel preparation	24
1.6.5 Thrombosis prophylaxis	24
1.6.6 Premedication	25
1.6.7 Antimicrobial prophylaxis.....	26
1.6.8 Anaesthetic protocol.....	26
1.6.9 Prevention of hypothermia	27
1.6.10 Perioperativ fluid management	27
1.6.11 Epidural anaesthesia (EDA) / Postoperative analgesia.....	28
1.6.12 Minimal invasive surgery.....	30

1.6.13	<i>Use of nasogastric (NG) tubes, abdominal drainage and urinary drainage</i>	30
1.6.14	<i>Enforced postoperative mobilisation</i>	31
1.6.15	<i>Enforced postoperative feeding</i>	32
1.6.16	<i>Periopertaiv glycaemic control</i>	32
1.6.17	<i>Prevention of postoperative ileus (POI)</i>	33
1.6.18	<i>Prevention of postoperative nausea and vomiting (PONV)</i>	33
1.7	RATIONAL FOR FURTHER ERAS CARE RESEARCH	35
2.	AIMS OF THE THESIS	37
3.	MATERIALS AND METHODS	39
3.1	PAPER I: ERAS CARE VS. STANDARD TRADITIONAL CARE	39
3.2	PAPER II: STOMA EDUCATION WITHIN AN ERAS PROGRAM.....	41
3.3	PAPER III: ERAS CARE IN ELDERLY PATIENTS	41
3.4	PAPER IV: COUNSELLING AS AN INDEPENDENT STRATEGY TO REDUCE HOSPITAL STAY.....	41
3.5	STATISTICAL ANALYSIS.....	42
3.6	ETHICS	43
4.	RESULTS AND SUMMARY OF PAPERS	44
4.1	PAPER I:	44
4.2	PAPER II:.....	45
4.3	PAPER III.....	46
4.4	PAPER IV	47
5.	GENERAL DISCUSSION	49
5.1	ERAS CARE VS STANDARD TRADITIONAL CARE.....	49
5.2	STOMA EDUCATION WITHIN AN ERAS PROGRAM.....	50
5.3	ERAS CARE IN ELDERLY PATIENTS	52
5.4	COUNSELLING AS AN INDEPENDENT STRATEGY TO REDUCE HOSPITAL STAY	53

5.5	STRENGTHS, LIMITATIONS AND METHODOLOGICAL CONSIDERATIONS	54
6.	CONCLUSIONS AND FUTURE PERSPECTIVES	58
7.	REFERENCES	60
8.	PAPERS I-IV	76

Acknowledgements

The study was carried out between 2011 and 2017 at Haukeland University Hospital, Department of gastrointestinal and emergency surgery and University of Bergen, Institute for Clinical Sciences. There are several people I want to thank for enabling me to complete this PhD thesis:

Co-supervisor PhD **Christian Erichsen**, you planned the study in 2010, which you early also welcomed me to take part in. You have done the main part of the outpatient clinic consultations and have put an enormous amount of work in order to complete the study. Without your commitment and knowledge, it would not have been possible to carry out the study. **Anne Nysted Rasdal**, our local ERAS champion. We show in this thesis that dedicated nurses like you make a huge difference in the post-operative course of the patients, especially with regard to length of hospital stay. You have organized and participated in all preoperative consultations and postoperative controls, and have done a lot of work with patient registration and data registration. You have a huge workforce with a lot of energy, and the patients love you, even if you drive them hard. Professor **Frank Pfeffer**, the chief of the colorectal unit, my main supervisor, a very good teacher in colorectal surgery, and my good friend. You are always a great discussion partner. I've greatly enjoyed our long scientific discussions and I am lucky to share my office with you. You have an enormous work capacity, both clinical and scientific. Together with our manager of the gastrointestinal surgical department, **Janiche Buanes Heltne**, you both have facilitated the conditions of the department so that the study could be completed. Professor **Hartwig Körner**, your support and help, especially while writing the articles has been very helpful. I have appreciated your clear, constructive and quick feedback.

My gratitude also goes to the persons who contributed substantially, some of whom are co-authors of the papers. PhD **Gro Østgard**, responsible for the preparation of the anaesthesiology part of the study, **Arne Christian Mohn**, for writing a part of the first draft of the study protocol, professor **Harry Sintonen**, without your help with

the HRQoL questionnaires and analysis this part of the study could not have been completed, **Jörg Assmus**, for all your help with statistics, and **Jon Meyer Tvinnereim** for taking care of a part of the outpatient clinic. I also want to thank all the other consultants in the colorectal unit during the study period; **Rune Svensen**, **Bjørg Furnes**, **Anne Karlizcek**, and especially **Aly Dicko** for learning me so much in the field of colorectal surgery. **Irene Æsøy**, **Øyvind Grytaas**, **Borghild Straume**, **Nina Rolland**, **Anita Anfinssen**, **staff at the surgical outpatient clinic** and **the stoma outpatient clinic**: you have all helped in different issues. My good friend **Øyvind Kommedal**, thank you for all constructive feedbacks and discussion when we have our regular running tours.

I would like to thank all the **patients** who have kindly agreed to be included in these trials.

Finally, I wish to thank my closest family. My father, **Trond**, who unfortunately died far too early, thank you for encouraging me to study medicine, and my mother **Marit** for your love and interest for me and my family. **Pål** and **Atle**, thank you for being the best of brothers and good friends. I would also like to thank my parent's in-law, **Nina** and **Gunnar**, for their support and help that my wife and I often need in a busy everyday life. At last, but not least, my wife **Marianne** for her unconditional love and support, although it's hard to be married to a surgeon. Even if you have the same busy work and also do your own PhD, you always encourage and come up with many good inputs. You do a fantastic job keeping our home on track and raising together our precious children **Ida**, **Ulrik** and **Martin**.

List of publications

- Paper I:** Forsmo HM, Pfeffer F, Rasdal A, Østgaard G, Mohn AC, Körner H, Erichsen C. **Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: results of a randomized controlled trial.** *Colorectal Dis.* 2016 Jun;18(6):603-11
- Paper II:** Forsmo HM, Pfeffer F, Rasdal A, Sintonen H, Körner H, Erichsen C. **Pre- and postoperative stoma education and guidance within an enhanced recovery after surgery (ERAS) programme reduces length of hospital stay in colorectal surgery.** *Int J Surg.* 2016 Oct 22;36(Pt A):121-126.
- Paper III:** Forsmo HM, Erichsen C, Rasdal A, Körner H, Pfeffer F. **Enhanced recovery after colorectal surgery (ERAS) in elderly patients is feasible and achieves similar results as in younger patients.** *Gerontology & geriatric medicine* 2017, 3:2333721417706299.
- Paper IV:** Forsmo HM, Erichsen C, Rasdal A, Tvinnereim JM, Körner H, Pfeffer F. **Randomized controlled trial of extended counselling in enhanced recovery after colorectal surgery.** *Diseases of the Colon and Rectum.* Accepted 09.07.17.

Abbreviations

ASA	American association of anaesthesiologists
BIS	Bispectral index
CGA	Comprehensive Geriatric Assessment
CHL	Carbohydrate loading
CRC	Colorectal cancer
CRP	C Reactive Protein
DM	Diabetes mellitus
DVT	Deep vein thrombosis
EDA	Epidural anaesthesia
ERAS	Enhanced recovery after surgery
EWS	Early warning scores
GDFT	Goal directed fluid therapy
HRQoL	Health related quality of life
IV	Intravenous
LAR	Low anterior resection
LMWH	Low molecular weight heparin
LOHS	Length of hospital stay
MBP	Mechanical bowel preparation
NG	Nasogastric
NMBA	Neuromuscular blockade agents
NPO	Nil per os

NSAID	Nonsteroidal anti-inflammatory drugs
OAMPB	Oral antibiotics and mechanical bowel preparation
ONS	Oral nutritional supplement
PE	Pulmonary embolism
PHS	Postoperative hospital stay
POI	Postoperative ileus
PONV	Postoperative nausea and vomiting
RCT	Randomized controlled trial
SDD	Selective Decontamination of the Digestive tract
SSI	Surgical site infection
SWI	Surgical wound infection
TED	Transoesophageal Doppler
THS	Total hospital stay
TIVA	Total intravenous anaesthesia
UFH	Unfractionated heparin
UTI	Urinary tract infection
VTE	Venous thromboembolism

Abstract

Background: Enhanced recovery after surgery (ERAS) is a perioperative multimodal approach with purpose to reduce surgical stress response and organ dysfunction, and thus to decrease the perioperative morbidity and length of hospital stay (LOHS). Randomized trials have shown that patients recover faster when traditions are altered, including extended information and guidance to patients, changes in analgesia and anaesthetic procedures, mobilisation procedures, and concerted effort by the department to reduce hospital stay. Although the benefits of ERAS on LOHS are recognized, the main causes for this reduction are not well understood.

Objectives of PhD-work/research questions:

1. We endeavoured to perform a controlled, randomized trial in which we compared patients treated by an ERAS approach with a special focus on counselling and guidance to patients treated in a standard traditional care pathway. The main objective of this study was to find whether we were able to decrease the total hospital stay (THS), primarily as a result of reduced morbidity (paper I).
2. A large part of patients with colorectal resections also need stoma. We wanted to examine whether pre- and postoperative stoma education within an ERAS programme can reduce the length of hospital stay, stoma-related complications, re-admissions and improve health-related quality of life (HRQoL) (PaperII).
3. Evaluate patients in various age groups in the ERAS care pathway, and examine whether elderly patients adhered to an ERAS program and achieved the same outcomes as younger patients (paper III).
4. Assess additional insights into the impact of perioperative counselling and guidance when groups of patients are otherwise the same with respect to ERAS criteria (paper IV).

Results: Paper I showed that THS was significantly shorter in patients randomized to the ERAS care group than in patients randomized to the standard care group, although the two treatment groups had similar outcomes regarding 30-day mortality, major and minor morbidity, rate of reoperation, and readmissions. There were also no differences in postoperative C-reactive protein (CRP) levels, reflecting the inflammatory response, or the patients' tolerance of enteral nutrition. From this first study we cannot determine that one ERAS element is more effective than other interventions, but it suggests that accurate pre- and postoperative information and continuous guidance are important for the reduction in hospital stay.

Paper II also showed a significantly shorter THS in the ERAS group with stoma education than in the standard care group. Regarding major and minor complications, stoma-related complications, re-admission rate, 30-day mortality and HRQoL, the two treatment groups had similar outcomes.

Paper III investigated whether elderly patients may comply with the implementation of this multidisciplinary program, and whether they have better or worse outcome in an ERAS program than younger patients. This sub analysis showed that the adherence to the ERAS protocol was equally good in elderly and in younger patients. There were also no significant differences in THS in the different age groups treated in an ERAS program.

Paper IV described a new randomized trial where we compared ERAS care plus extended counselling to ERAS care with standard counselling. The main result was that THS can be significantly reduced with extended pre- and postoperative counselling and guidance as an independent strategy.

Conclusion: ERAS reduces the length of hospital stay in younger and older patients, as well as in patients receiving a planned stoma. The main reason for this reduction is due to extended pre- and postoperative patient information, education and guidance.

1. INTRODUCTION

1.1 Background

The estimated numbers of surgical procedures performed world-wide each year are more than 320 million [1]. Operations on the colon and rectum, for both malignant and benign diseases, are among the most common operations performed in hospitals in the western world. Colorectal cancer (CRC) is the second most common cancer in females and third in males, with 1.4 million new cases and 693.900 deaths globally in 2012 [2]. European data from 2012 estimate 447 000 new cases and 215 000 deaths caused by CRC, which makes it the second most frequent and second most deadly cancer in Europe [3]. Data from the Norwegian cancer registry shows that also in Norway CRC is the second most common cancer with an incidence of 4200 new cases per year, with an expected increase of 20% over the next 20 years. Only breast and prostate cancer are more frequent in females and males, respectively. Treatment of CRC has also been estimated to be the most expensive cancer to treat, costing approximately 1.6 billion NOK/ year[4].

Colorectal surgery has the largest group of patients treated at gastro-surgical departments in Norway. The use of healthcare resources and costs of elective colorectal surgery are associated with the length of hospital stay (LOHS) and the extent of postoperative morbidity. LOHS after elective colorectal surgery is usually 6-12 days, and the complication rate varies between 10 and 50% [5-7]. Optimizing of health care is important especially in colorectal surgery where complications occur at a higher rate than most other surgical procedures, with a large impact on hospital costs [8].

1.2 Standard traditional care

Traditionally patients have been hospitalized after operations to observe and treat any surgical or anaesthetic complications that may occur, and in addition the patients should be back to a level of self-care before discharge [9]. Traditional perioperative

care and surgical training have been based on a master-trainee and hands-on experience, with surgeons-passed operative techniques and methods of perioperative care to residents [10]. These methods were generally accepted and considered successfully, although often not based on scientific evidence. Due to improved organizational structure within institutions and increased attention to surgical technique and performance, postoperative outcome improved [11-15]. However, patients were still suffering from morbidity, slow recovery and need for prolonged length of hospital stay. Standard elements in a traditional care pathway were fasting from midnight before surgery, preoperative bowel preparation, the use of nasogastric (NG) tubes and intra-abdominal drains, postoperative fasting, enforced bed rest and reduced mobilisation [10].

A surgical patient is often examined and treated in several different departments in a hospital with different professional competencies, such as medical and surgical outpatient clinic, preoperative unit, operating room, postoperative recovery unit, surgical ward, and when necessary in other departments, without having dedicated staff following the patient through the care pathway. Treatment in one unit affects the next [16]. An example is mechanical bowel preparation (MBP) which may lead to dehydration and electrolyte imbalance, which in turn causes that the anaesthetist must provide more intravenous (IV) fluids preoperatively. Fluid overload may in turn have negative postoperative effect on gut function and possibly increase the risk of postoperative complications [17]. Another example is traditional opiate based anaesthesia and analgesia that often preclude early mobilisation and enforced enteral nutrition, as this requires a cooperating and fully awake patient. Premedication with long acting sedatives may also have additional effects on postoperative feeding and mobilisation. Already in the 1980s and 1990s, data suggested beneficial effects when allowing early feeding postoperatively [18], without leading to approval or acceptance in surgical societies. Allowing nutrition postoperatively was also in conflict with two key cornerstones in traditional care; intestinal decompression via a NG suction and postoperative nil-by-mouth regimen. NG tubes were usually placed during surgery and kept in place until signs of postoperative ileus was gone, leading to significant patient discomfort [19]. The nil-by-mouth regimen, also

postoperatively, was probably adopted by surgeons trained in a tradition where aspiration was a feared complication [20]. Long lasting emesis and vomiting were common after former types of anaesthesia, especially chloroform and ether [21]. These factors, together with the use of intraabdominal drains and long lasting urinary catheterisation, also decreased the possibility of postoperative mobilisation.

1.3 Enhanced recovery after surgery (ERAS)

During the last two decades there has been an increased focus on optimal perioperative treatment and care. Different treatment modalities have been initiated with attempts to reduce postoperative LOHS, readmissions, reoperations and perioperative morbidity. The reasons for late recovery and discharge are complex. Organ dysfunction (surgical stress), postoperative pain, postoperative nausea and vomiting (PONV) and paralytic ileus are key elements, but many other factors, such as postoperative cognitive dysfunction, sleeping disorders, immobilisation and local hospital traditions like NG tubes, drains and urinary catheter postoperatively are also important.

In Norway the University Hospital of North Norway in Tromsø, early started to give patients solid food the same evening or the day after surgery. Kehlet's group at Hvidovre Hospital in Copenhagen has been a pioneer in systematic and controlled optimisation of the postoperative phase, by focusing on gut function, postoperative pain and mobility and combining interventions [22]. In a representative group of 60 patients with open colon resections, 50% were discharged on the second postoperative day and 75% the third postoperative day. Over half of the patients had passage of stool within 24 hours, urinary catheter was removed the first postoperative day, and only 11% had to be catheterized an extra time. Complication rates were not higher than in other studies [23]. This group has later published similar results [24-26]. An early prospective observational study, according to ERAS principles, from 2000 to 2003 with 98 patients has been performed at our own hospital together with Haugesund Hospital. This study showed that 80% of patients were discharged on day 5 with no differences in complication rates [27].

With increased recognition of the influence of perioperative practice and surgical trauma on the postoperative recovery, efforts were made to modify the surgical care pathway. ERAS or fast-track surgery is a multidisciplinary and multimodal perioperative approach that aims to reduce surgical stress response and organ dysfunction, thereby reducing morbidity and length of hospital stay [28]. ERAS includes standardized preoperative, intraoperative and postoperative elements. The purpose of the **preoperative ERAS elements** are to optimize the patient before surgery, and includes patient information and counselling, avoidance or selective use of mechanical bowel preparation, avoiding prolonged fasting, carbohydrate loading, thrombosis prophylaxis and antibiotic prophylaxis. **Intraoperative ERAS elements** include anaesthesia techniques including epidural anaesthesia, operative technique including minimal invasive surgery, goal directed fluid management, prevention of hypothermia, and none or selective use of intraabdominal drains. **Postoperative ERAS elements** aim to enhance patient recovery and rehabilitation and include prevention of PONV, no NG tube, early removal of catheters and eventually drains, opioid sparing analgesia, enforced enteral nutrition and enforced mobilisation [29, 30]. Examples of outcomes that are targeted and evaluated in an ERAS program are pain management, insulin resistance, return of gastrointestinal function, postoperative complications, length of hospital stay and return to normal daily routines [31]. There are 20 individual components described in consensus guidelines to the Enhanced Recovery After Surgery society[32], carried out by a multidisciplinary team of anaesthesiologists, surgeons, nurses and physical therapists. Guidelines in ERAS care were first described and published for colorectal resection and in recent times also for other procedures in gastrointestinal surgery, gynaecology and urology, and include around 20 perioperative elements.

Several prospective studies have shown shorter hospital stay and less morbidity in ERAS care, but no difference in mortality. Some of the randomized controlled trials (RCT) to date have shown no difference in the complication rate [7, 33-41], while others have reported a difference in minor complications [42-45] (Table 1). There have been several meta-analyses and reviews analysing these RCTs. A Cochrane

Review from 2011 stated, however, that the quantity and particularly the quality of the data are low [46].

First author (ref.)	Year	Patients (n)	Numbers of ERAS items	Reduced morbidity
Delany et al. [34]	2003	64	4	No
Anderson et al. [33]	2003	25	12	No
Gatt et al. [36]	2005	39	12	No
Khoo et al. [38]	2007	70	8	No
Ionescu et al. [37]	2009	96	10	No
Muller et al. [42]	2009	151	9	Non-surgical
Serclova et al. [43]	2009	103	10	Non-surgical
Garcia-Botello et al. [35]	2011	119	9	No
Vlug et al. [7]	2011	400	11	No
Ren et al. [40]	2011	507	11	No
Wang Q et al. [45]	2011	78	9	Non-surgical
Wang G et al [44]	2011	210	8	Non-surgical
Lee et al [39]	2011	100	5	No
Wang Q et al [41]	2012	99	8	No

Table 1: Randomised controlled trials comparing ERAS care to standard traditional care

In Norway, the University Hospital of North Norway has been a pioneer hospital with members in the ERAS study group since its inception in 2001. This group has worked to develop ERAS through different strategies and interventions, but the implementation across health care systems has been slow [16]. Also today the number of ERAS items used in clinical practice vary greatly between hospitals.

ERAS strategies are considered by most surgeons as “standard of care”, and surgeons believe they are adhering to ERAS principles, but in fact they are mostly only using a "light" version. Adoption of ERAS care outside clinical studies is probably variable. Compliance with an ERAS protocol has been shown to be lower outside of a clinical trial [47]. Today most surgical departments in Norway use an ERAS “light” version in different degrees, and no one uses “traditional care”. “The “Norwegian National Guidelines for diagnosis, treatment and follow-up of colon and rectal cancer” also declares ERAS as the standard of care in treatment of CRC [48].

1.4 Stoma education and ERAS

In Norway, about 14.000 people currently live with an entero- or colostomy, and about 1500 new stoma creations are carried out each year [49]. Delayed discharge after stoma formation is well-known in colorectal surgery [50-52]. The creation of a stoma will often be associated with both psychological and physical morbidity, which may be reduced by pre- and postoperative education of patients. It is recognized that a well-placed stoma improves independence in patient stoma care thus enabling the patients to earlier start up again with normal activities [53-55].

Although education of patients receiving a new stoma is widely recommended, little data exist on the effect of educational interventions on stoma related complications, length of stay, and readmissions. A systematic review of educational interventions for stoma patients found no consensus on the benefit of stoma education, although the grade of evidence was low [56]. The knowledge about patients with a planned stoma formation within an ERAS program is limited, since these patients mostly are not included in trials. In the literature there is only one randomised study with few patients evaluating stoma education as a part of an ERAS programme [34].

1.5 ERAS care in elderly patients

The average age of the population is increasing and the surgical management of elderly patients is complex due to more comorbidity and reduced functional capacity.

More than 55% of patients with colorectal cancer are older than 70 years and more than 26% are older than 80 years [4]. Age, comorbidities and poor nutritional status are identified causes of increased morbidity and delayed recovery after elective surgery [57-60]. Elderly patients are more often rejected for surgery, and in one report 21% of patients older than 85 years were not offered surgery, compared with 4% in patients younger than 65 years, probably because of increased comorbidity or the older patients were thought to be unfit [61]. There is, however, a great heterogeneity concerning comorbidity and degree of mobility in elderly patients. Biological characteristics and not chronological age should be decisive for treatment and the choice of surgical intervention. The term frailty has been introduced. Frailty includes decreased reserves in general and deterioration in organ systems, but is not equivalent with comorbidity. Frailty may not exist in patients with considerably comorbidity. On the other hand, some elderly patients with little or no disease show to be frail [62]. Evaluation of frailty is important to avoid under and over treatment, which is a well-known pitfall in geriatric oncology [63]. A simple test to predict postoperative outcome in frail elderly patients is not available. The best tool for preoperative evaluation in elderly patients is the Comprehensive Geriatric Assessment (CGA) [64, 65]. Even though the CGA is time-consuming, it seems to be reasonable to spend this extra time in identifying and correcting conditions in complex patients, which in turn may decrease surgical stress, length of hospital stay and postoperative complications.

Studies have shown that ERAS is safe and reduces hospital stay in younger patients [29, 66]. For older patients, this age group has often either been excluded or numbers have been too small for subgroup analysis [67]. There is uncertainty whether elderly patients can carry out such a multimodal program and whether they have worse or better outcomes than their younger counterparts. There has also been a fear that early postoperative feeding and enforced mobilisation is too hazardous for elderly patients [68]. However, patients at risk and elderly patients may especially benefit from this multimodal approach to avoid organ dysfunction, enhance recovery and reduce perioperative morbidity. A systematic review from 2014 [67] found that ERAS both

reduced hospital stay and the occurrence of complications in elderly patients in two randomized controlled trials [45, 69], and in the majority of the observational cohort studies no differences between younger and elderly patients were found. However, a considerably variation was found in the definitions of elderly in the studies included in the review, ranging from ages >65 to >80 years [67].

1.6 ERAS interventions

ERAS flow chart

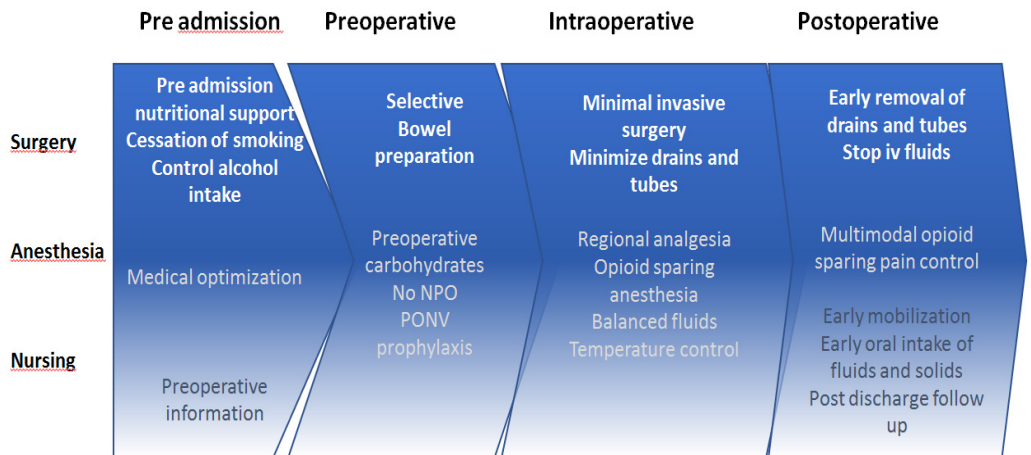


Figure 1 ERAS flow chart. Adopted from Ljungqvist, Scott, Fearon, JAMA Surgery, 2017. With permission from Olle Ljungqvist.

1.6.1 Perioperative counselling

Included in the term “counselling” are preoperative information and education, as well as postoperative guidance. Preadmission information and counselling are

considered as core factors in an ERAS protocol, even if the evidence levels are considered low [32, 70]. Patients should be informed preoperatively about the course of the operation, the postoperative care plan and expected hospital stay, and discharge criteria. Information regarding postoperative pain control, mobilisation and oral intake should be described. Detailed information about anaesthetic and surgical procedures may reduce anxiety and fear, and enhance postoperative recovery with reduced length of hospital stay [71-75]. Personal counselling or multimedia information including information of the course of the procedure with expectations and tasks to patients may improve pain control, early postoperative mobilisation, pre- and postoperative feeding, and respiratory physiotherapy, and thus reduce complications [76-79]. However, patient education and counselling as independent strategies for enhanced recovery and reduced length of hospital stay have received little attention and there are no randomised trials reported in the literature addressing counselling specifically in general or colorectal surgery as such.

1.6.2 Preoperative optimisation / prehabilitation

The preoperative medical evaluation with history-taking and physical examination is important in order to identify medical conditions and risk factors for perioperative morbidity and postoperative mortality. Ancillary studies should be performed for individual indications [80]. Excessive testing can cause delays in treatment and unnecessary and possible harmful treatments and also anxiety in patients, and routine testing should be abandoned and rather ordered selectively [81-83]. Factors like cigarette smoking, alcohol consumption (>3 units /day), anaemia (Hb <7 mmol/l), diabetes mellitus (DM), poor nutritional status and American association of anaesthesiologists (ASA) grade III are all shown to be independent risk factors for complications in colorectal surgery, and optimisation improves outcomes [84-88]. Four to eight weeks smoking cessation prior to surgery reduces postoperative complications and morbidity significantly [89]. Malnourished patients benefit from preoperative nutritional supplementation with fewer anastomotic leaks and infectious complications [70, 90]. The duration of supplementation will depend on the severity of malnutrition [91].

Even in the absence of postoperative complications, major surgery is associated with 20-40 % reduction in functional and physiologic capacity, which has been measured by energy expenditure, endurance time, workload, and heart rate during maximum exercise [92, 93]. Efforts to improve outcomes have primarily focused on the perioperative and postoperative period, but the preoperative period is probably a better time to make changes in patient's lifestyles and to enhance the functional capacity to enable the patients to withstand the surgical stress. The concept of prehabilitation is a multidisciplinary programme, which includes preoperative physical exercise, nutritional support and psychological support, to increase functional capacity in anticipation of the upcoming surgical stress. There seems to be a clear benefit of prehabilitation programmes on postoperative functional capacity, but it is still not demonstrated regarding other postoperative outcomes [94].

1.6.3 Preoperative fasting and carbohydrate loading (CHL)

Fasting from midnight was for many years standard practice and was intended to reduce aspiration at the induction of anaesthesia. There has, however, never been a scientific backup for this dogma [95]. A Cochrane review of 22 RCTs found no evidence of an increased risk of aspiration or related morbidity in patients who were allowed free intake of clear fluids until 2 hours before anaesthesia and surgery, compared with the standard fasting from midnight policy [96]. Most guidelines have also stated that clear fluids are safe to take up to 2 hours and solids up to 6 hours before elective surgery [97, 98].

Postoperative insulin resistance is an indirect expression of the metabolic response to surgical stress, resulting in reduced insulin stimulated glucose uptake, increased glucose release and hyperglycaemia [99, 100]. Hyperglycaemia may in turn lead to prolonged recovery and postoperative complications [101]. Preoperative carbohydrate loading has demonstrated reduced insulin resistance, and to maintain and improve whole-body protein balance and muscle functions [100, 102, 103]. There have been more than 30 RCT investigating the effect of CHL on improved postoperative outcomes, and these studies have been summarized in three meta- analyses [104-106]

and one Cochrane review [107]. Both the most recently published and the most robust meta-analysis found that CHL caused a small reduction in length of hospital stay compared to fasting, and no benefit on length of stay or complications when compared with water or placebo[104].

1.6.4 Preoperative bowel preparation

Mechanical bowel preparation (MBP) alone, prior to elective colorectal surgery, should be abandoned and the evidence is consistent and robust [108, 109]. MBP without oral antibiotics does not give any beneficial effects on outcomes and may even be harmful due to the risk of fluid and electrolyte disturbances [110-112]. Most national guidelines follow this advice recommending abandonment of MBP [113]. The Enhanced Recovery After Surgery Society also recommends either no or selective use of MBP [32, 70]. Nevertheless, MBP has been used extensively in colorectal surgery [114]. This may be due to other benefits as improved detection of smaller tumours and polyps, possibility for on table endoscopy and generally easier bowel handling [115]. However, previously several studies could demonstrate benefits of non-absorbable broad-spectrum oral antibiotics in combination with mechanical bowel preparation (OAMBP) in elective colorectal surgery. The use of OAMBP reduced the incidence of surgical site infections (SSI), non-SSI complications including anastomotic leak, postoperative ileus and also reduced the length of hospital stay[116-119]. The benefit or harm of MBP is a subject with great controversy in the literature, but the evidence today supports OAMBP in combination with IV antibiotics at induction of surgery [109].

1.6.5 Thrombosis prophylaxis

Major abdominal surgery implies a high risk of venous thromboembolism (VTE). VTE-prophylaxis is well established to reduce the incidence of deep vein thrombosis (DVT), pulmonary embolism (PE) and mortality [120]. Graduated compression stockings give additional reduction [121]. Meta-analyses have not found differences between perioperative thromboprophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) regarding mortality, major or minor

bleeding, or thromboembolic outcomes [122]. Controversies in recent years have been whether patients should have only in-hospital or extended 4 weeks antithrombotic prophylaxis. A Cochrane review from 2009 stated that prolonged thromboprophylaxis significantly reduced the risk of VTE compared to in-hospital prophylaxis only, in major abdominal and pelvic surgery without increased bleeding complications [123]. However, only 4 studies were found eligible for inclusion in this analysis. No randomized controlled trial has been able to demonstrate a reduction in clinical variables as symptomatic DVT, symptomatic PE or mortality in prolonged prophylaxis. They have only shown a reduction in asymptomatic screening detected DVT [124-126]. Current guidelines vary somewhat, but mostly they recommend 4 weeks prophylaxis, or state that it should be considered or recommended particularly in high risk patients (prior VTE, anaesthesia >2 hours, bed rest greater than 4 days, age >60 years, advanced stage cancer disease) [127, 128].

1.6.6 Premedication

Long acting sedatives have traditionally been used to reduce patient anxiety and calm down the patients before entering the operating room. To reduce anxiety, benzodiazepines are frequently used, but they also causes drowsiness, amnesia and cognitive impairment [129]. In a recently published RCT, patients with various elective surgeries were randomized to lorazepam, placebo or no premedication. Lorazepam did not improve patient satisfaction, and was associated with extended time to extubation and lower rate of early cognitive recovery [130]. Premedication with long acting sedatives may also have additional effects on postoperative feeding and mobilisation. A Cochrane review from 2009 evaluating premedication on anxiety in adult day-surgery under general anaesthesia found no evidence of different time to discharge in patients receiving premedication [131]. Other anxiolytics, such as clonidine and melatonin, have shown to have opioid sparing effects in addition to anxiolytic effect [132]. Clonidine is associated with sedation and hypotension, but melatonin offers an atoxic alternative to benzodiazepines, and in meta-analysis melatonin may be equally effective in reducing preoperative anxiety, compared to standard treatment with midazolam [133]. In summary, traditional long acting

sedatives delay immediate postoperative recovery and should not routinely be used before surgery.

1.6.7 Antimicrobial prophylaxis

Already in the 1960s and 70s firm evidence existed that prophylactic IV antibiotics reduced postoperative surgical wound infections (SWI) in colorectal surgery [134, 135]. Prophylactic IV antibiotics are now routinely used in colorectal operations within 60 minutes prior the operation, and should include both anaerobic and aerobic coverage. Repeated doses may be beneficial in prolonged procedures, but there is generally acceptance that continuation of treatment does not give any supplemental benefit [113]. The national guidelines in Norway today recommend oral antibiotics with high bioavailability alone, 2 hours before surgery, and acts as a systemic prophylaxis and not as a selective decontamination of the digestive tract (SDD) [136]. However, data on the use of oral antibiotics alone are lacking [113]. A meta-analysis from 2011 and a recent Cochrane Review from 2014 showed a significant reduction in SWI when oral and IV antibiotic prophylaxis were combined compared to IV alone [137, 138]. Oral antibiotics given as SDD should be broad spectrum and non-absorbable and optimally given as supplement to MBP.

1.6.8 Anaesthetic protocol

There is no good evidence to determine different general anaesthetic techniques. It is rationally wise to use short acting agents like propofol in combination with fentanyl or remifentanyl instead of long-acting IV opioids, to promote recovery. Most commonly, inhalational anaesthetics such as isoflurane, sevoflurane or desflurane are used in combination with propofol and fentanyl/remifentanyl. Total intravenous anaesthesia (TIVA) with propofol and remifentanyl without gas may be beneficial in patients when suspecting PONV [32]. In an experimental porcine model during cardiopulmonary bypass surgery, isoflurane significantly increased fluid shift from intravascular to interstitial space, in contrast to propofol. The resulting tissue/organ oedema may have negative effect on vital organ functions [139]. Depth of anaesthesia should be monitored by Bispectral Index (BIS) to titrate anaesthetics drugs to a

minimum, and avoid complications like cognitive dysfunction in elderly [140]. Long-acting neuromuscular blockade agents (NMBA) should be avoided, and always when using NMBA, neuromuscular function should be monitored [141].

1.6.9 Prevention of hypothermia

Perioperative hypothermia (body core temperature $<36^{\circ}\text{C}$) is common in patients undergoing surgery with incidence reported as high as 70% [142]. Risk factors are prolonged surgery, extremes of age (neonates and elderly), extensive burns, preoperative low body temperature and severe trauma [143]. A systematic review and meta-analysis found that clinically relevant hypothermia starts with body core temperature $<36^{\circ}\text{C}$, and hypotherm patients have shown to have increased SSI and morbid cardiac events. Hypothermia inhibits coagulation, impairs drug metabolism, extends post- anaesthesia recovery and prolongs hospitalization [144]. Skin surface pre-warming is effective in preventing hypothermia and pre-warmed patients often report less anxiety and greater comfort with their surgical experience [145, 146]. Maintaining normothermia during surgical procedures is necessary and can be achieved by forced air warming, resistive heating blankets or circulating water garments devices. Among these methods, forced-air warming is most effective and safest [143]. IV fluids should be warmed (37°C). Body temperature should be monitored perioperatively to titrate warming and also to prevent hyperpyrexia.

1.6.10 Perioperativ fluid management

Fluid therapy has been a controversial aspect of perioperative care over years. On the one hand too little fluid may cause hypovolaemia with possible hypo-perfusion of vital organs and the bowel. On the other hand too much fluid may lead to increased interstitial lung fluid and bowel oedema, which in turn also may lead to complications [32, 147]. Historically, practice in standard care has been providing IV fluids in volumes in excess of actual perioperative losses. Traditional regimens with volumes of 3.5 to 7 litres IV fluid on the day of surgery and more than 3 litres the following postoperative days can lead to 3-6 kg weight gain [148, 149]. Some randomized controlled trials have demonstrated that fluid restriction in colorectal surgery is

associated with reduction in morbidity and hospital stay [148, 150] while other studies have indicated no difference [17, 151]. Definitions of what is “restricted” and “liberal” have, however, varied substantially between the studies. In a meta-analysis Vardahan concluded that fluid volume delivered rather should be classified in “fluid balance” (between 1.75 and 2.75 litres/d) or “fluid imbalance” (restricted < 1.75 litres/d or liberal >2.75 litres/d fluid therapy). When “restricted” fluid regimens were compared to “standard” or “liberal” fluid regimen there were no differences in length of stay or complications, but when reclassified to fluid balance or imbalance there was a clear difference in favour of fluid balance [147]. To optimize and individualise the perioperative fluid therapy, a number of methods have in recent years been used, e.g. transoesophageal Doppler (TED), to measure intraoperative stroke volume and cardiac output in order to deliver an intraoperative goal-directed fluid therapy (GDFT). In a recent meta-analysis GDFT had no effect on mortality, morbidity or length of stay when considered in the settings of ERAS pathways, compared to controls. When considered in a traditional care pathway, there was however a reduction in morbidity and length of stay [152]. A randomized controlled study of patients undergoing open colorectal surgery in our hospital found similar morbidity in the group treated with Central Venous Oxygen Saturation (ScvO₂)-guided, restricted fluid therapy, as in the control group [153]. Individualised fluid therapy is, however, a main component of modern ERAS care. Intravenous fluid postoperatively should be minimised and a return to oral fluids the day of surgery or first postoperative day should be sought.

1.6.11 Epidural anaesthesia (EDA) / Postoperative analgesia

Postoperative pain management is recognized as a key factor in patient recovery after surgical procedures. It is not only important for pain relief, but also to ensure that patients can start with early mobilisation and feeding. Postoperative pain relief with EDA has been shown in open surgery to have a positive effect on bowel function, food intake and out-of-bed mobilisation, which results in improvement in quality of life [154]. EDA has shown to reduce the postoperative period of ileus, but only when opiate-free epidural was used [155]. There is, however, no evidence that EDA

improves outcomes such as reduced LOHS, postoperative morbidity or mortality in colorectal surgery [156]. The benefit of EDA is therefore controversial, especially in minimal invasive surgery, where it has not proven to be more effective than other analgesic techniques. A review article from 2012 stated that routine use of EDA in laparoscopic surgery cannot be recommended [157]. A recent RCT concluded that EDA after laparoscopic colorectal resections rather impeded recovery [158]. The optimal duration of EDA in open surgery is 2-3 days [32].

Other analgesic techniques described are the use of spinal analgesia, lidocaine infusion during and after surgery, intraperitoneal instillation of long acting anaesthetics and transversus abdominis plane (TAP) block. Most of these techniques are not routinely used, and due to lack of evidence, also not recommended [157]. Infiltration with local anaesthetic of the surgical wound can provide excellent analgesia and is recommended.

Non opioid analgesics as paracetamol and nonsteroidal anti-inflammatory drugs (NSAID) are important components to reduce opioid-related adverse effect on recovery [159, 160]. However, there is conflicting evidence regarding the adverse effect of NSAID use with anastomotic healing in colorectal surgery. The latest updated meta-analysis concluded that data strongly suggest a link between postoperative NSAID and anastomotic leak [161]. Subsequent studies have shown both an association with anastomotic leak [162, 163] (one study for diclofenac only) and no significant association with anastomotic leak [164, 165]. Whether NSAID use is a clinically relevant risk factor for anastomotic leakage still requires further studies, but some caution is certainly justified.

Glucocorticoids (dexamethasone or methylprednisolone) have shown to reduce postoperative pain and nausea, as well as length of stay with no increased complications [166, 167], and should be considered as a part of the multimodal analgesic strategy in both open and minimal invasive surgery.

1.6.12 Minimal invasive surgery

Large trials comparing open and laparoscopic surgery have demonstrated reduced length of hospital stay and postoperative pain for laparoscopic procedures [168-171]. The only randomised trial found in the literature comparing the four combinations of standard or ERAS care with laparoscopic or open surgery is the Dutch LAFA trial [7]. This study reported significantly shorter total hospital stay (THS) among patients randomized to the laparoscopic/ERAS group, but no differences between the four treatment groups regarding morbidity, readmission or quality of life. Laparoscopy was also found to be the only independent factor that significantly reduced THS. The EnROL trial, which also included rectal surgery, found a significantly reduction in length of stay in laparoscopic surgery and ERAS compared to open surgery and ERAS, but no differences in other outcomes [172]. Short term outcomes of robotic surgery are comparable to standard laparoscopy [173].

1.6.13 Use of nasogastric (NG) tubes, abdominal drainage and urinary drainage

Three meta-analyses in different time periods have all concluded that routine NG decompression should be avoided because the risk of atelectasis, pneumonia and fever is reduced in patients without NG tubes. No routine NG decompression improves bowel function and reduces discomfort and LOHS [174-176].

Intraperitoneal drains after colonic surgery do not reduce postoperative complications like anastomotic leakage or SWI, reoperation or mortality [177, 178] and should not be used routinely because it reduces mobilisation. In rectal surgery there is more controversy. A systematic review and meta-analysis from 2013 concluded that the presence of a pelvic drain reduces anastomotic leakages and the rate of reinterventions after low anterior resections (LAR) [179]. The results were, however, only supported by the data from 5 non RCTs. Subgroup analyses of 3 RCTs could not find any benefits for pelvic drainage. A recently published RCT with more than 460 patients could not show a decrease in neither the risk of pelvic sepsis, time to

diagnosis, nor the risk of reoperation in the patients with pelvic drain after LAR [180].

The duration of transurethral catheterisation should be as short as possible, as prolonged catheterisation is associated with increased risk of urinary tract infection (UTI). In one study early removal of bladder catheter the morning after thoracic or abdominal surgery significantly reduced the risk of UTI compared to prolonged catheterisation of 3-5 days until the EDA was discontinued [181]. The same study showed no difference in urinary retention. Urinary drainage is not necessary for the duration of EDA and can be removed the morning after surgery [182]. In rectal surgery it has been assumed that nerve damage due to pelvic dissection results in more urinary retention. Also after pelvic surgery there are no benefits of prolonged catheterisation compared to removal first postoperative day [183, 184]. One study, however, found an increased risk of retention in patients with low rectal carcinoma [183]. Suprapubic compared to transurethral catheterisation after abdominal surgery has been investigated in several trials, and a meta-analysis of these trials found significantly more bacteriuria and patient dissatisfaction in patients with transurethral catheterisation [185]. However, all patients had 4-7 days of urinary drainage and the urinary catheter was not removed the first or second postoperative day as recommended today. Routinely use of suprapubic catheterisation is not recommended, but could be used in patients with increased risk of postoperative urinary retention.

1.6.14 Enforced postoperative mobilisation

Bed rest and reduced mobilisation is believed to be an important factor for postoperative morbidity. The rationale is that enforced mobilisation reduces risk for thromboembolic complications, prevents cardiovascular and muscle deconditioning, and stimulates gastrointestinal recovery [186-188]. There are several studies supporting an association between early mobilisation and postoperative outcomes, but a systematic review found that the results of these studies are conflicting and the study quality was poor [189]. In a recently published RCT staff-directed facilitation

of early mobilisation in an ERAS program did not improve outcomes as recovery of walking capacity, recovery of gastrointestinal function, complications or readiness for discharge [190]. Both study groups were a part of an ERAS program, and indicated that further targeted mobilisation that already is a part of the program had no impact on outcomes. Although the evidence level is weak, the recommendation grade in the ERAS society guidelines are strong, due to reduced risk of pneumonia, muscle weakness and insulin resistance [32, 70].

1.6.15 Enforced postoperative feeding

Early oral nutrition after major gastrointestinal surgery is safe and a Cochrane review found indications that early postoperative feeding reduces the risk of postoperative complications [191]. There might be an increased risk of vomiting and other efforts to prevent postoperative paralytic ileus have to be taken into account. Also a newer meta-analysis comparing early oral feeding vs. traditional delayed feeding in colorectal surgery found that early oral feeding is safe and reduces LOHS and total complications [192]. Oral nutritional supplement (ONS) to achieve targeted intake of protein and energy may be used more extensively, but probably in more selected patient groups, e.g. patients with malnutrition or unplanned weight loss. It has been shown in malnourished patients that postoperative ONS improved nutritional status, quality of life, and morbidity [193]. Also in patients without malnutrition it could be demonstrated a reduction in postoperative weight loss and incidence of minor complications [194]. ONS from the day before surgery and at least the first four postoperative days is recommended in ERAS guidelines [32].

1.6.16 Perioperative glycaemic control

Hyperglycaemia is common after major surgery and is present in as many as 20% to 46% in non-diabetic patients and 24% to 72% in diabetic patients [195]. An association between perioperative hyperglycaemia and postoperative complications has been recognised in almost every surgical speciality. One study of patients with and without DM after general surgery found that perioperative hyperglycaemia increased the risks of adverse events. Non-diabetic patients had nearly twice the risk

of reoperative interventions, infections and of hospital deaths as patients with DM [196]. This was confirmed in another recent study. Non-diabetic patients with hyperglycaemia had more adverse events than patients with DM [197]. Kiran et al described a high incidence of postoperative hyperglycaemia in non-diabetic patients undergoing colorectal surgery. Even only a single episode of elevated glucose postoperatively was associated with complications and increased mortality, and the risk was related to the degree of elevated glucose [198]. They recommended monitoring of glucose postoperatively in order to take action for glycaemic control even in patients without DM. However, most of these studies were not done within an ERAS setting. Several ERAS elements affect glucose levels and insulin resistance, and thereby improve glycaemic control without giving insulin, which carries the risk of hypoglycaemia in a ward setting [32, 199].

1.6.17 Prevention of postoperative ileus (POI)

Prolonged postoperative ileus (POI) is a major problem after colorectal surgery, with a reported incidence between 10% and 30% [200, 201], and has been associated with a large increase in LOHS [202]. A number of the above listed measures help to reduce the incidence of POI such as thoracic EDA in open surgery, avoidance of nasogastric decompression, prevention of fluid overloading intra- and postoperatively, and minimal invasive surgery. Increased adherence to an ERAS protocol helps to prevent POI, but still almost 25% of patients needed a NG tube in a well-established ERAS pathway in one study [203]. No prokinetic drug has proven to be effective in treating POI, but the use of magnesium has been evaluated in two RCT after abdominal and colorectal surgery with effect on POI in one study [204] and no effect in the other [205]. Other interventions as chewing gum and coffee consumptions have in RCT shown to have positive effect on POI [206, 207].

1.6.18 Prevention of postoperative nausea and vomiting (PONV)

PONV is common and affects approximately 30% of patients after anaesthesia and surgery [208]. There are many risk factors for developing PONV, like patients related factors (previous history of PONV, non-smoking status and female gender),

anaesthetic related factors (inhalation agents, opioid use) and surgical factors (long duration of surgery) [209]. If more than two risk factors are present, a multimodal approach to reduce PONV should be conducted, which includes both pharmacological and no-pharmacological therapies [32]. Minimizing anxiety is important and can be achieved with information and counselling. Other factors like adequate preoperative hydration, minimal preoperative fasting and carbohydrate loading may also reduce the incidence of PONV. Preoperative dexamethasone has both positive effects on PONV and postoperative pain [210]. TIVA with propofol, compared to gas anaesthesia, reduces the incidence of PONV [209]. Increased use of opioids intra- and postoperatively are associated with higher incidence of PONV [211]. Antiemetic drugs act on at least four different receptor systems; cholinergic, dopaminergic (D2), histaminergic (H1), and serotonergic (5HT3) [208]. The most commonly used are metoclopramide (dopamine antagonist), ondansetron (serotonin antagonist), droperidol (dopamine antagonist) and meclizine (antihistamine). All of these different antiemetics have shown to be effective in reducing PONV [208, 212].

1.7 Rational for further ERAS care research

The hypothesis of an ERAS program is that the total sum of all implemented measures affects the surgical stress response. There are about 20 items included in an ERAS program. Many argue that only a rigid adherence to an ERAS program can provide the proposed benefits, citing studies showing that the more ERAS elements are implemented, the more frequently the postoperative course is improved [213, 214]. For several of these individual components it has been discussed whether they have effect alone. Some examples are omission of MBP compared to MBP in combination with oral antibiotics, individualized analgesic approach without EDA in laparoscopic surgery, preoperative carbohydrate loading, and different fluid protocols where the optimal approach still is unclear.

Several different outcome measures have been reported, like LOHS, return of gut function and morbidity. The LOHS when evaluating the effectiveness of ERAS is questionable, especially in elderly patients where discharge to home and return to baseline function is more unlikely. Postoperative complications are, from the surgeon's perspective, the most important outcome of recovery. Early discharge should not be a goal in itself. The main goal of ERAS should be to reduce morbidity and thereby reduce the length of stay. Shorter LOHS will though, have major financial consequences for the community in providing effective health care with high quality. One important question is why ERAS care reduces LOHS although most of the RCT's do not show reduced morbidity. Furthermore, none of the RCTs or meta-analysis have shown differences in major complications or mortality [46, 215]. Is the reduced LOHS due to improvement in postoperative functional status, or due to the patient's mental preparations and information about the course of the operation? Or is it related to changes in organization of care and not necessarily due to improved physiological recovery as proposed in a study by Maessen et al [216].

Haukeland University Hospital started early with the introduction of ERAS, where the Department of Gastrointestinal Surgery performed an observational study already from 2000-2003, comparing standard care to ERAS care. After this study, the plan

was to conduct an RCT, but was never completed before we took up this work in 2010. We endeavoured to conduct a controlled, randomized trial in which patients treated by the best possible multimodal approach (ERAS) were compared to patients treated in a conventional standard care pathway used at that time. The main goal of the first study was to determine whether we were able to decrease LOHS, mainly as a result of reduced morbidity [217].

A large proportion of the patients included in this RTC had a planned stoma as part of their surgical treatment. All patients with a planned stoma in the ERAS care arm of the RCT also had preoperative stoma education. There is little evidence that stoma education improves outcomes in these patients, especially within an ERAS program.

Elderly patients have in many ERAS studies either been excluded or the patients have been too few to perform subgroup analyses. There is uncertainty whether elderly patients can comply and adhere to this multidisciplinary program, and if they have equal outcomes in an ERAS program as younger patients.

2. Aims of the thesis

There are two main objectives of the study:

- 1) Determine if an ERAS care pathway can reduce the total length of hospital stay (THS), and reduce postoperative morbidity.
- 2) Evaluate the specific role of extended counselling on THS within an ERAS program.

Paper I:

The aim of this study was to evaluate patients receiving colorectal resection within an ERAS care pathway compared to standard traditional care. We wanted to determine whether THS can be reduced, primarily as a result of reduced postoperative morbidity.

Paper II:

In this sub-study we wanted to compare patients receiving a planned stoma within ERAS care and standard care. We wanted to evaluate whether stoma education within an ERAS program can reduce THS and stoma related complications, and improve health related quality of life (HRQoL), compared to traditional standard care and current stoma education.

Paper III:

In this sub-study, the aim was to evaluate patients in different age groups in the ERAS care and find out whether elderly patients attained the same outcome-results as younger patients. We also wanted to evaluate adherence to an ERAS program in elderly patients compared to younger patients.

Paper IV:

In this RCT patients who received ERAS care with extended pre- and postoperative counselling were compared to patients who received ERAS care with standard counselling. The aim was to evaluate whether counselling alone could decrease THS.

3. Materials and methods

3.1 Paper I: ERAS care vs. standard traditional care

The patients included in paper 1 to 3 derive from the same randomized controlled trial which was conducted at Haukeland University Hospital in the time period 5th January 2012 to 4th March 2015.

Adult patients, who were scheduled for elective open or laparoscopic colorectal surgery (malignant or benign diseases), with or without stoma, could be included in the study. After thorough information, both orally and in writing, written consent was obtained. Exclusion criteria were emergency operations, pregnancy, impaired mental capacities, inability to adapt to the ERAS criteria, ASA IV and if a multi-visceral resection was planned.

Randomization

Patients were block randomized to ERAS or standard care with an allocation ratio of 1:1, and an independent statistician prepared the sequence in advance. Due to the nature of the trial, neither the patient nor the physician were blinded to the treatment assignment.

Objectives and end points

THS was the primary outcome measure and was defined as postoperative hospital stay (PHS), plus additional readmission days within the first 30 days after surgery. Prior to study commencement discharge criteria were defined: (1) no complications requiring treatment in hospital, (2) postoperative pain adequately controlled with oral medication (VAS <4), (3) bowel function (faeces or repeated flatus) and (4) mobilized and out of bed more than 6 hours each day. Patients who received a stoma should be satisfied with their stoma care before discharge. Secondary end points were postoperative complications, PHS, postoperative C-reactive protein (CRP) levels, readmission rate, HRqoL (stoma patients) and mortality.

Perioperative care

The ERAS elements used in the two treatment groups in the study, appear in Table 1. The two treatment groups were admitted to separate wards during hospitalization. Patients who were randomized to the ERAS group were treated to the ward's best ability in accordance with ERAS consensus guidelines [32, 70]. Patients randomized to the standard treatment group were treated as they had been earlier after colorectal resections. As some ERAS items already were considered as standard of care, some items were included in this treatment group as well.

Table 1 Numbers of ERAS items used in both groups [217]

	ERAS care	Standard care
Preoperative		
Preoperative counselling	V	
Preoperative feeding	V	
Carbohydrate loading	V	
No bowel preparation		
No premedication	V	
Antimicrobial prophylaxis	V	V
Perioperative		
Fluid restriction	V	
Anaesthetic protocol	TIVA	Gas
Prevention of hypothermia	V	V
Epidural anaesthesia	V	V
Minimal invasive incisions		
Postoperative		
No routine use of nasogastric tubes	V	V
No use of drains in colon surgery	V	V
Enforced postoperative mobilisation	V	
Enforced postoperative feeding	V	
No systemic morphine use	V	
Standard laxative	V	
Early removal of urine catheter	V	
Total number	16	5

TIVA: total intravenous anaesthesia

3.2 Paper II: Stoma education within an ERAS program

In this sub-study, we examined patients who would receive a planned stoma as part of their surgical treatment and who would presumably manage their stoma before discharge. Stoma patients were also examined with regard to HRQoL, evaluated with the 15D instrument (<http://www.15d-instrument.net/15d>). This is a self-administered, standardized health state descriptive questionnaire, also validated and translated into Norwegian, and can be used both as a single index and a profile score measure [218].

All patients who were to have a planned stoma in the ERAS group had one or two consultations before surgery with the stoma and ERAS nurse specialist. They received thorough information about what stoma implies and were trained in stoma care preoperatively, while patients in the standard group received their first information about the stoma at admission the day before surgery. Postoperatively, patients in the ERAS group received daily education from a stoma nurse specialist, while the patients in the standard group were educated from colorectal ward nurses.

3.3 Paper III: ERAS care in elderly patients

This is also a sub-study from the above described RCT, where we focused only on patients in the intervention arm (ERAS group). Patients in the ERAS group were divided into 3 subgroups depending on age; ≤ 65 years ($n=79$), 66–79 years ($n=56$), and ≥ 80 years ($n=19$), and we investigated the influence of age on the ERAS program. We wanted to evaluate the adherence to an ERAS program in elderly patients compared to younger patient, and examine whether the elderly patients had the same outcomes as the younger ones.

3.4 Paper IV: Counselling as an independent strategy to reduce hospital stay

Based on our first RCT (paper I), the perioperative information and guidance to patients appear to be quite essential in order to achieve early discharge. This study

strongly suggests that trustworthy perioperative information with regard to each patient's expectations, and a continuous guidance in the ERAS elements is an important single factor for reducing THS. Further studies would still be necessary to understand the specific role and impact of patient-counselling in an ERAS program. We therefore enrolled our patients with colorectal resections into a new randomized trial in which both arms of the study included the same ERAS elements; the arms only differed in terms of perioperative counselling and guidance. Patients were randomized to ERAS with standard counselling or ERAS plus extended counselling. The patients in the study intervention arm with extended counselling had one or two additional outpatient clinic consultations with a dedicated ERAS nurse before surgery, whereas patients in the standard counselling group had the ordinary preoperative information the day before surgery, where they also were introduced to the ERAS criteria. Patients in the intervention and control arm of the study were admitted to two separate wards. In the extended counselling group the same nurse who gave the preoperative information, also monitored the postoperative course.

3.5 Statistical analysis

Paper I-III: A power analysis was carried out after first conducting a pilot study with 20 patients. In the pilot study the difference in the primary outcome THS was 2.5 days. In order to detect a difference in length of stay of 2.5 days, in a two-sided hypothesis test with a significance level of 5% and a statistical power of 0.8, we needed a total sample size of 300 randomized patients divided into an intervention and a control arm in both RCTs.

We used IBM SPSS, version 22 and 23 for statistical analyses, and descriptive statistical methods were used to characterize the sample. In all papers, data are presented as median and range, and we used chi-squared test to compare discrete variables, independent-sample t-test for continuous, normally distributed variables, and Mann–Whitney U test for continuous, non-normally distributed variables. Continuous outcomes in paper III were analysed with ANOVA or regression analysis. The reported p values are based on two-sided tests.

Paper II: To detect changes in the 15D score from baseline to 10 days and 30 days in both treatment groups, a paired sample t-test was applied, and to compare differences between the groups in the change in the 15D score from baseline to 30 days an ANOVA regression was used.

Paper IV: Also in this trial the total sample size was 300 patients, but we planned in advance an interim analysis when more than half of the necessary patients were included. After we had included and followed-up 164 patients we carried out the interim analysis with the statistical program R 3.3 and group sequential design with gsDesign 3.0. With a p-value <0.001 for the difference in primary outcome (THS) between the extended and standard counselling group, the criterion for ending the study was fulfilled.

3.6 Ethics

All patients received oral and written information about the study according to the Helsinki Declaration before they signed a consent form for participation. The study was approved by the Regional Committee for Medical and Health Research Ethics of Western Norway (reference number 2010/2079) and was registered with Clinical Trials.gov (number NCT01610726).

4. Results and summary of papers

4.1 Paper I:

During a time period of three years 324 patients were randomized and after some exclusions, 154 in the ERAS care group and 153 in the standard care group were included in the final analysis.

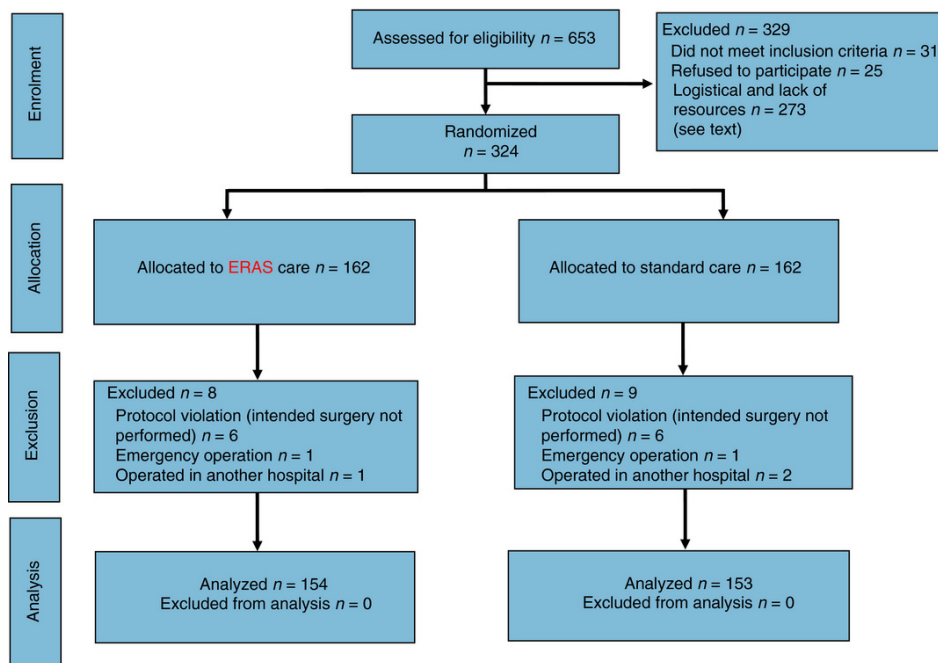


Figure 2 Consort diagram for the trial [217].

Patients randomized to ERAS care had a significantly shorter THS than in standard care (median 5 [range 2-50] vs. median 8 [range 2-48]; $p=0.001$). There were no differences in postoperative C - reactive protein (CRP) levels (which reflects the

inflammatory response) or toleration of enteral nutrition postoperatively. There were also no differences regarding overall, major, or minor morbidity; reoperation rate; readmission rate; and 30-day mortality.

Patients operated with laparoscopic surgery in both treatment groups had a significantly shorter THS than patients operated with open surgery (median 5 vs. 7 days; $p < 0.005$).

4.2 Paper II:

In patients receiving a planned stoma ($n=122$), the patients randomized to ERAS care and peri-operative stoma education had a significantly shorter THS than patients in the standard care group (median [range], 6 days [2- 21 days] vs. 9 days [5-45 days]; $p < 0.001$). Stoma related complications were common in both treatment groups, 38% in the ERAS group with stoma education and 51% in the standard group, but without significant differences. There was, however, significantly more complications with ileostomies compared to colostomies in both groups ($p < 0.001$).

Health-related quality of life (HRQoL)

There were no differences in the 15D score or in any dimension level value at baseline, 10 days, or 30 days. From baseline to 10 days postoperatively there was a significantly and clinically important worsening in the 15D score (ERAS: -0.0868, $p < 0.001$; standard care: -0.0910, $p < 0.001$) and from 10 days to 30 days a significant and important improvement in the 15D score (ERAS: 0.0273, $p = 0.001$; standard care: 0.0322, $p = 0.004$). We found no significant differences between the two treatment groups in HRQoL within the first 30 days.

4.3 Paper III

In this sub-study we analysed the interventional ERAS arm with regard to age of the patients. Figure 3 shows a flow chart of patients included in the analysis.

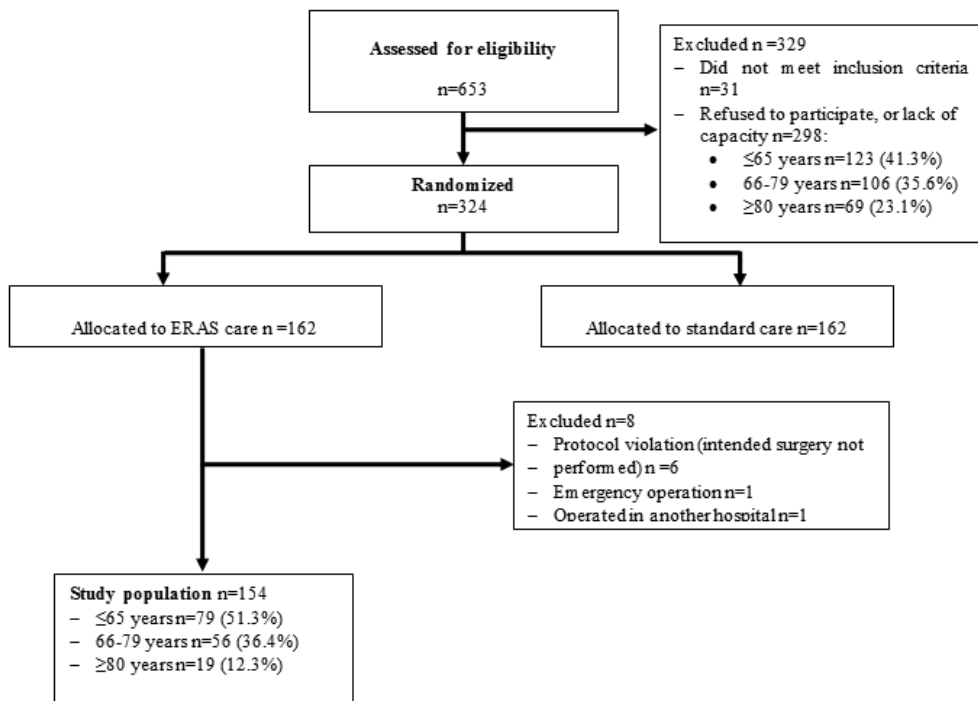


Figure 3 Flow chart of patients considered for inclusion [219].

Between the different age groups there were neither significant differences in THS (≤ 65 years, median 5 [range 2–47] days; 66–79 years, median 5.5 [range 2–36] days; ≥ 80 years, median 7 [range 3–50] days; $p=0.53$), nor among all secondary outcomes. There were no differences in postoperative tolerance of enteral nutrition in the different age group and the adherence to the different ERAS elements was just as good in the two oldest age groups as in the younger patients.

4.4 Paper IV

In the time period from 10th March 2015 to 5th December 2016, 179 patients were randomised to ERAS plus extended counselling or ERAS with standard counselling. We calculated that we needed at least 152 patients in the interim analysis. After 15 exclusions, we had 164 patients for the final analysis (figure 4)

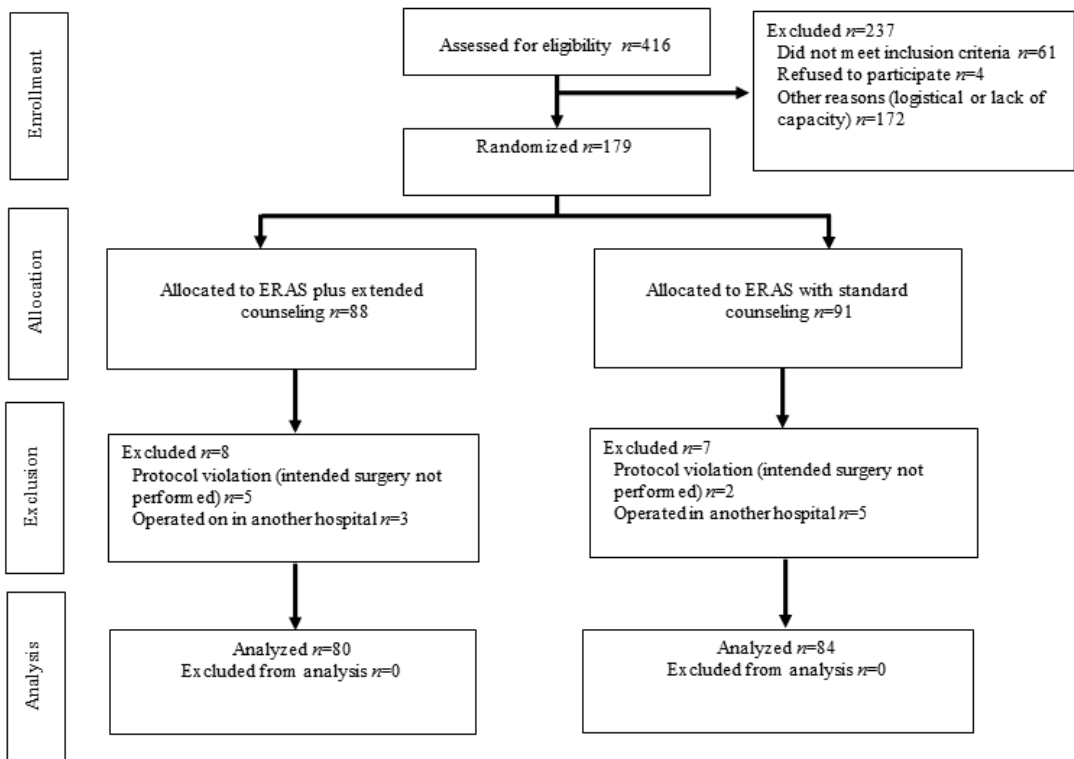


Figure 4 Consort diagram of the trial

A significantly shorter THS was found among patients randomized to ERAS plus extended counselling compared to ERAS with standard counselling (median 5 [range

2–29] days vs. 7 [range 2–39] days, $p < 0.001$). The adherence to the postoperative ERAS elements mobilisation and total oral intake differed between the two treatment groups. There were no differences in major or minor morbidity, reoperations, readmissions and 30-day mortality between the treatment groups.

5. General discussion

The major finding in this thesis is that ERAS reduces THS, both in younger and older patients, as well as in patients receiving a planned stoma. There were no differences in major or minor morbidity. The reduced THS is mainly due to extended pre- and postoperative patient information, education and guidance. We have shown a significantly shorter THS in patients treated with ERAS care plus extended counselling, which enables patients to comply especially with postoperative ERAS elements, compared to ERAS care with standard counselling after elective colorectal surgery.

5.1 ERAS care vs standard traditional care

This study showed a significant reduction in THS in the ERAS care compared to standard care, although there were no differences in postoperative mortality, reoperation, major or minor morbidity or readmission. In order to achieve early discharge, perioperative information, guidance and instructions to patients appear to be very important. Counselling and continuous repetition of details by trained nurses throughout the care pathway help patients to comply with the ERAS program and seem to be essential.

The ERAS approach combines multimodal interventions, rather than one specific strategy. Randomized controlled trials comparing ERAS care to standard care have demonstrated a significant reduction in hospital stay associated with ERAS pathways. However, the results of these studies did not enable us to conclude that one ERAS item is more effective than other interventions. The designs of all these studies were appropriate for evaluating the overall effect of ERAS interventions, but not various single interventions. Consequently, we could not expect that a multivariable model comparing the effects of single interventions would uncover meaningful and interpretable results. In a large prospective observational study, an association between increased protocol adherence and improved outcome was found [213]. There is, however, no clear evidence of whether all the elements are equally important and

whether all the elements must be conducted entirely strict in order to achieve a good result. It is also reasonable that patients who have better outcomes also have a higher compliance. Patients who receive a surgical complication will naturally not be able to carry out postoperative ERAS elements. It has also been suggested that it is likely that compliance with postoperative ERAS elements is of particular importance for accelerated postoperative recovery and good progress [220, 221]. A large systematic review and meta-analysis could however not show that programs with many ERAS elements were more successful than others with fewer components [222].

The assessment of ERAS vs. standard care is not new, but assessing the specific role of preoperative counselling and optimisation in a trial has not been investigated in particular. From the data in paper I it was however not possible to assert that counselling was more effective than other ERAS elements, such as fluid management or laxative use. Upon completion of the first study, we planned a new RCT where we wanted to generate more information and insights into the impact of perioperative counselling when both study arms were otherwise equal in terms of ERAS criteria (paper IV). From previously published literature, it is not possible to find RCT's that focus specifically on patient information and guidance in colorectal surgery.

Laparoscopic surgery was associated with a significant reduction in LOHS in both treatment groups in paper I, although this may be due to selection bias since the surgical procedure was not a part of the study protocol. In RCT's minimal invasive surgery has shown to reduce LOHS, but not complication rates [170, 223]. When minimal invasive surgery is combined with ERAS, postoperative morbidity is also reduced. Laparoscopy rather than ERAS seems, however, to be the reason for this reduction in morbidity, and offers independent advantages beyond ERAS [224].

5.2 Stoma education within an ERAS program

Patients, who were receiving a planned stoma and treated within an ERAS pathway with stoma education, had a significantly shorter THS than patients receiving

standard care after colorectal surgery. There were no differences between the two treatment groups in regard to secondary outcomes.

In patients receiving a planned stoma little research has been published that compares the relationship between stoma education and LOHS. In a recently published review article only five studies were found investigating the relationship between stoma training and LOHS. Two of the studies found a reduction, while three showed no difference [56]. In our opinion the main benefit of pre-operative stoma education is that these patients are more capable to start stoma training directly after surgery. During the pre-operative education, they have already received stoma training and are familiar with the stoma equipment. Comparing patients with and without stoma in the ERAS and standard care groups in the main study population (n = 308), the difference in THS was greater for those who received a stoma (median [range], 6 days [2- 21 days] vs. 9 days [5-45 days]; $p < 0.001$) than for those who did not receive a stoma (5 days [2-50 days] vs. 6 days [2-48 days]; $p = 0.35$). The difference in hospital stay reduction in stoma vs non stoma patients indicates that intensified stoma education is the main variable for this reduction, but it might also be that the ERAS protocol is more powerful in patients with a stoma.

Stoma related complications are frequent, but there are few available data in the literature. Peristomal dermatitis has been reported in 5-25% of patients with ileostomies, and significant fluid loss with dehydration in up to 20% [225]. In our study, all complications were registered prospectively and we found a large proportion of patients with stoma-related complications. There were fewer stoma-related complications in the ERAS group but the difference was not significant. As stoma-related complications were not the main focus in this trial, it might not have the sufficient power regarding this question, even though we had a large number of patients.

Significantly more complications were observed in ileostomies than colostomies. Peristomal dermatitis requiring treatment was observed in half of the patients with ileostomies, and 18% had high output with large fluid loss and dehydration which

resulted in decreased renal function and S-creatinine > 100 µmol/L. High output ileostomy in patients who recently have formed a ileostomy was a major problem and resulted in readmissions. Severe short-term complications in colostomies were rare.

5.3 ERAS care in elderly patients

Although THS was two days longer in the age group ≥ 80 years compared to the youngest age group, there were no significant differences in THS between the three different age groups. It was not possible to identify factors that caused the two days delayed discharge. Logistical challenges, such as the patient's own wishes, home care situation where elderly patients often live alone, and a situation where elderly often have to wait for nursing home placement, are likely causes. This has also been seen in other studies in which elderly patients are discharged 3-5 days after they met the discharge criteria [226]. We did, however, not measure days until readiness for discharge in our study.

Postoperative ERAS items are a reflection of the postoperative recovery. If a patient is feeling well, compared to a patient with nausea and vomiting, it is more likely that the patient will comply with the postoperative ERAS items. These items are markers of both protocol compliance and recovery and have been suggested to be of special importance for progress and accelerated recovery [220, 221]. Enforced mobilisation is a key factor in an ERAS protocol. In one study age >80 years and higher ASA score were identified as predictors of delayed mobilisation [58]. In our sub-study, the compliance to the different ERAS elements was equally good in the oldest age group as in the younger age groups, without particular difference in the level of mobilisation. A reason for this may be too strict inclusion among the very oldest patients, as some elderly patients were excluded if they could not implement the entire ERAS program. We think that especially elderly patients should carry out such a program with guidance and supervision of dedicated nurses, particularly in important postoperative elements. High risk- and elderly patients are probably those who would benefit most from ERAS care with augmented recovery.

5.4 Counselling as an independent strategy to reduce hospital stay

This RCT (paper IV) demonstrated a significantly shorter THS in ERAS care plus extended counselling compared to ERAS care with standard counselling in patients receiving elective colorectal surgery. From the results in paper I we could not conclude whether one specific ERAS strategy or the ERAS package as a whole were responsible for the beneficial effects, but the results from paper IV suggest that extended counselling alone reduces THS significantly. As far as we know this is the first randomized study which demonstrates that LOHS in patients undergoing colorectal resection in an ERAS setting can be decreased significantly by focusing especially on counselling.

In order to achieve early discharge, it appears to be essential that a dedicated nurse provides both the preoperative information and the postoperative supervision. Accurate pre- and postoperative information about the patients' expectations and continuous guidance and counselling were important elements for reduced THS. Detailed information preoperatively, as well as repetition and continuous counselling throughout the care pathway by dedicated nurses, is crucial to motivate patients to comply with the ERAS program. The results from this study show that counselled patients more strongly comply, especially with postoperative ERAS elements, which we think have an important impact on both postoperative recovery and LOHS.

Good leadership in the hospital and local champions (nurses, surgeons, anaesthesiologists) are important factors for a successful implementation of an ERAS program [227]. In our case the local champion was a dedicated nurse who followed up and supervised all the patients. Even though we cannot show reduced morbidity, this supervision and continuous guidance caused a significantly reduction in hospital stay. Early discharge from hospital should not be the goal itself, but rather the avoidance of particularly major complications. Patients are equally satisfied if they are discharged after 3 or 7 days. What matters to patients, is that they feel a safe treatment course and avoid complications. Nevertheless, LOHS has huge financial

consequences as one hospital day at the regular ward costs around 10000, - NOK. Good preoperative patient information and education, as well as continues follow up by a dedicated person, as in our case a dedicated nurse, can reduce hospital costs significantly.

5.5 Strengths, limitations and methodological considerations

The main strengths of the studies (**paper I and IV**) are the randomized controlled trial design. Besides that, we had two separated wards for patients allocated to the intervention and control arms of the studies. These wards had different nursing staff to reduce the possibility of introducing confounders. During the entire study period the department had a stable staff of seven senior surgeons in a separate colorectal unit. To minimize observer-related bias, all postoperative controls were carried out by one nurse and two surgeons. A high proportion of eligible patients were included in the studies. In the first RCT we included more than 300 patients over a 3-year period, and in the second RCT more than 150 patients were included in 1.5-year period. All data were registered prospectively by one nurse and one surgeon.

All studies have several limitations. The main limitation of both RCTs was the absence of blinding. Neither patients nor staffs were blinded with regard to treatment groups. In both RCTs the two treatment groups were admitted to different wards and a blinding would not be possible. At least the staff at the two wards could not have been blinded, but one could argue that the patients may have been blinded, although it would have been difficult. An externally audit system as the “ERAS Interactive Audit System”, was not performed. This is an on-line interactive software tool for implementation and monitoring compliance to the protocol, developed by the “ERAS Society”. Another limitation in **paper I** is the difficulty to define standard care. Some ERAS items are also implemented in modern standard care, and were therefore also implemented in the standard conventional group. This relates not only to the medical care provided, but also to the nursing and allied professional care provided (e.g. early enteral challenge, mobilization etc.). ERAS strategies, which are nowadays

considered as 'standard of care', may have affected the standard care group and made it more difficult to identify differences.

The rate of laparoscopic procedures was higher in the included cohort. It is well described that laparoscopic surgery plays an important role reducing surgical stress and postoperative length of stay. Some authors, supported by the LAFA trial, proposed that laparoscopy is an important item of ERAS protocols [7]. The lower rate of laparoscopic resection in the excluded cohort could be a selection bias.

One can also argue that one should not include both rectal- and colon surgery in the same RCT with the argument that these are very different operations and that it's hard to "ERAS/Fast-track" rectal cases. We have, however, included both rectum and colon resections in this study as we think it should be possible to use ERAS independently of the type of colorectal procedure. When the current study was designed, we perceived the literature and practical approach to ERAS as not being different with regard to colon and rectal resections, and thus, chose to include patients undergoing all types of colorectal resections.

The main limitation in **paper II** is, that the relative benefit of giving information and counselling to patients planned to have a stoma is difficult to isolate from other benefits of an ERAS pathway programme, including global information and counselling to all patients in this group. The main conclusion from this study is regarding the overall benefit of ERAS pathway on this specific population. The isolated effect of intensified stoma education may not be properly evaluated within the present design. One could argue that the methodology of this trial cannot answer the question about the benefit of information and counselling correctly. Two interventions - stoma education and ERAS were mixed and analysed as one intervention. To answer the question, patients randomised to ERAS or standard care should have been stratified further in stoma education vs. non education.

In the sub-study analysis in **paper III** the proportion of included patients in the oldest age group was smaller than in the younger age groups, which could be a selection bias where only the fittest patients in the oldest age group were included. There is a

great heterogeneity regarding comorbidities in elderly patients. What treatment older patients should be offered, should to a lesser extent, be based on chronological age and more on biological characteristics. A frailty evaluation or risk stratification with a tool like “Comprehensive Geriatric Assessment” has been recognized as a better test in elderly patients than the more traditional comorbidity scores [64, 65]. Such a stratification of frailty was not applied in our study.

Whether the design of the present study is adequate to find any differences between age groups is debatable. The initial sample size was not calculated to find difference in terms of outcome between elderly and younger within one arm. Therefore, the reason for why no difference was found may have been due to quite low number of patients, especially in the group aged more than 80 years (n=19). Based on these data it can be concluded, that there was no difference between elderly and younger patients.

A potential limitation in **paper IV** is that ERAS care took place for a longer period of time in the extended counselling group; it began in 2011 vs. 2015 in the standard counselling group. An earlier study that analysed adherence to ERAS items and length of hospital stay, revealed higher adherence rates in the first 2 years following implementation of ERAS compared to the subsequent 2 years [228]. Thus, the disparity in ERAS program commencement could have favoured the standard counselling group with better adherence to the protocol by nurses in the standard counselling arm since the program was new to that ward.

Although we see the use of separate wards as strength of the study, it could also be argued to be a limitation to the study design. In both groups, nurses experienced in colorectal surgery provided the care; in fact, the amount of experience of the nurses with colorectal patients was higher in the control group with ERAS and standard counselling. More experienced nursing staff in general can identify and "rescue" postoperative complications and prevent major morbidity and reduce THS. Major complications including anastomotic leak, multi-organ failure or respiratory failure requiring ICU admission are less a consequence of lack of extended counselling and

more a consequence of the system of care that supports the patients' postoperative recovery. Although there were more complications in the standard counselling group, the difference was not significant. In our first trial (paper I) the results were opposite, with more complications in the ERAS- compared to the standard- care group, also without statistical significance.

Though not significant, there was a higher rate of protective ileostomy following low anterior resection in the standard counselling group that may contribute to longer THS in this group.

6. Conclusions and future perspectives

After elective colorectal surgery ERAS care had a significantly shorter THS than standard care without any difference in surgical or general complications.

LOHS in patients with the need for stoma creation was reduced significantly by preoperative stoma education and postoperative guidance by dedicated nurses as part of an ERAS care pathway.

Elderly patients benefited from an ERAS program with reduced LOHS and adhered to the program similar to their younger counterparts.

Perioperative information and guidance were associated with a significantly reduction in LOHS and seem to be the most important factors for the reduced LOHS in an ERAS care pathway.

Future perspectives

Although ERAS enthusiasts' believe that a strict implementation of the entire program should be carried out, it is currently unknown which ERAS items have the greatest benefit for outcome, especially for older patients. Minimal invasive surgery is undoubtedly an important factor, but it has to be investigated which of the other ERAS items may be superfluous in the era of laparoscopy. ERAS trials have demonstrated reduced LOHS, but no reduction in serious complications or mortality. When evaluating ERAS studies LOHS as outcome seems reasonable for younger patients, but probably not for older patients. They often remain in hospital even if they are ready for discharge. Studies investigating the functional status before and after surgery should be performed in elderly patients. In our opinion, in frail patients the concept of prehabilitation will improve the functional capacity before surgery, and most likely play an important role in the future.

The ERAS approach is a dynamic protocol and not set in stone [229]. Further studies must be conducted looking at individual ERAS elements. Reducing the risk of surgery and morbidity, rather than focusing on LOHS as primary outcome should be focused. A number of areas within the ERAS protocol will most probably in some way be changed or at least be individualised in accordance with new evidence.

From a surgical perspective, the most important issue is to reduce mortality and major complications. Large studies have shown similar complication rates in hospitals, but very different rates in postoperative mortality. Timely recognition and management of complications seem to be the main reasons [230, 231]. A very important question is how this can be improved. Early warning scores (EWS) with single bedside parameters have not shown to reduce mortality [232]. There are also currently no good accurate biochemical markers that indicate serious complications. Finding good clinical and biochemical markers that map the patients' recovery and thus also indicate complications will be of great importance in the future.

7. References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR *et al*: **Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes.** *Lancet* 2015, **385** Suppl 2:S11.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A: **Global cancer statistics, 2012.** *CA: a cancer journal for clinicians* 2015, **65**(2):87-108.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F: **Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.** *European journal of cancer (Oxford, England : 1990)* 2013, **49**(6):1374-1403.
4. **Cancer Registry of Norway. Cancer in Norway 2015 - Cancer incidence, mortality, survival and prevalence in Norway.** In.; 2016.
5. Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, Newland RC: **Postoperative morbidity and mortality following resection of the colon and rectum for cancer.** *DisColon Rectum* 1995, **38**(5):480-486.
6. Schoetz DJ, Jr., Bockler M, Rosenblatt MS, Malhotra S, Roberts PL, Murray JJ, Collier JA, Rusin LC: **"Ideal" length of stay after colectomy: whose ideal?** *DisColon Rectum* 1997, **40**(7):806-810.
7. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagenveld BA, van der Zaag ES, van Geloven AA *et al*: **Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study).** *AnnSurg* 2011, **254**(6):868-875.
8. Eappen S, Lane BH, Rosenberg B, Lipsitz SA, Sadoff D, Matheson D, Berry WR, Lester M, Gawande AA: **Relationship between occurrence of surgical complications and hospital finances.** *Jama* 2013, **309**(15):1599-1606.
9. Kehlet H, Wilmore DW: **Multimodal strategies to improve surgical outcome.** *American journal of surgery* 2002, **183**(6):630-641.
10. Kehlet H, Wilmore DW: **Evidence-based surgical care and the evolution of fast-track surgery.** *Annals of surgery* 2008, **248**(2):189-198.
11. Khuri SF, Henderson WG, Daley J, Jonasson O, Jones RS, Campbell DA, Jr., Fink AS, Mentzer RM, Jr., Steeger JE: **The patient safety in surgery study: background, study design, and patient populations.** *Journal of the American College of Surgeons* 2007, **204**(6):1089-1102.
12. Main DS, Cavender TA, Nowels CT, Henderson WG, Fink AS, Khuri SF: **Relationship of processes and structures of care in general surgery to postoperative outcomes: a qualitative analysis.** *Journal of the American College of Surgeons* 2007, **204**(6):1147-1156.
13. Main DS, Henderson WG, Pratte K, Cavender TA, Schiffnert TL, Kinney A, Stoner T, Steiner JF, Fink AS, Khuri SF: **Relationship of processes and structures of care in general surgery to postoperative outcomes: a descriptive analysis.** *Journal of the American College of Surgeons* 2007, **204**(6):1157-1165.
14. Rowell KS, Turrentine FE, Hutter MM, Khuri SF, Henderson WG: **Use of national surgical quality improvement program data as a catalyst for quality**

-
- improvement. *Journal of the American College of Surgeons* 2007, **204**(6):1293-1300.
15. Schiffner TL, Grunwald GK, Henderson WG, Main D, Khuri SF: **Relationship of processes and structures of care in general surgery to postoperative outcomes: a hierarchical analysis.** *Journal of the American College of Surgeons* 2007, **204**(6):1166-1177.
 16. Ljungqvist O, Scott M, Fearon KC: **Enhanced Recovery After Surgery: A Review.** *JAMA surgery* 2017, **152**(3):292-298.
 17. Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U: **Randomized clinical trial of fluid restriction in colorectal surgery.** *BrJSurg* 2012, **99**(2):186-191.
 18. Wara P, Hesson I: **Nutritional intake after colorectal surgery: a comparison of a traditional and a new post-operative regimen.** *Clinical nutrition (Edinburgh, Scotland)* 1985, **4**(4):225-228.
 19. Bauer JJ, Gelernt IM, Salky BA, Kreel I: **Is routine postoperative nasogastric decompression really necessary?** *Annals of surgery* 1985, **201**(2):233-236.
 20. Lassen K: **Challenging nil-by-mouth in digestive surgery: attitudes and evidence.** 2007.
 21. Raeder J: **History of postoperative nausea and vomiting.** *International anesthesiology clinics* 2003, **41**(4):1-12.
 22. Kehlet H: **Multimodal approach to control postoperative pathophysiology and rehabilitation.** *British journal of anaesthesia* 1997, **78**(5):606-617.
 23. Basse L, Hjort JD, Billesbolle P, Werner M, Kehlet H: **A clinical pathway to accelerate recovery after colonic resection.** *AnnSurg* 2000, **232**(1):51-57.
 24. Basse L, Jacobsen DH, Billesbolle P, Kehlet H: **Colostomy closure after Hartmann's procedure with fast-track rehabilitation.** *DisColon Rectum* 2002, **45**(12):1661-1664.
 25. Basse L, Thorbol JE, Lossl K, Kehlet H: **Colonic surgery with accelerated rehabilitation or conventional care.** *DisColon Rectum* 2004, **47**(3):271-277.
 26. Jakobsen DH, Sonne E, Andreasen J, Kehlet H: **Convalescence after colonic surgery with fast-track vs conventional care.** *Colorectal Dis* 2006, **8**(8):683-687.
 27. Mohn AC, Bernardshaw SV, Ristesund SM, Hovde Hansen PE, Rokke O: **Enhanced recovery after colorectal surgery. Results from a prospective observational two-centre study.** *ScandJSurg* 2009, **98**(3):155-159.
 28. Kehlet H: **Fast-track colorectal surgery.** *Lancet* 2008, **371**(9615):791-793.
 29. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP: **Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery.** *Surgery* 2011, **149**(6):830-840.
 30. Nanavati AJ, Prabhakar S: **Fast-track surgery: Toward comprehensive peri-operative care.** *Anesthesia, essays and researches* 2014, **8**(2):127-133.
 31. Lau CS, Chamberlain RS: **Enhanced Recovery After Surgery Programs Improve Patient Outcomes and Recovery: A Meta-analysis.** *World journal of surgery* 2017, **41**(4):899-913.
 32. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, McNaught CE, MacFie J, Liberman AS, Soop M *et al*: **Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations.** *World JSurg* 2013, **37**(2):259-284.

33. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ: **Randomized clinical trial of multimodal optimization and standard perioperative surgical care.** *BrJSurg* 2003, **90**(12):1497-1504.
34. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW: **Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection.** *DisColon Rectum* 2003, **46**(7):851-859.
35. Garcia-Botello S, Canovas de LR, Tornero C, Escamilla B, Espi-Macias A, Esclapez-Valero P, Flor-Lorente B, Garcia-Granero E: **[Implementation of a perioperative multimodal rehabilitation protocol in elective colorectal surgery. A prospective randomised controlled study].** *CirEsp* 2011, **89**(3):159-166.
36. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J: **Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection.** *BrJSurg* 2005, **92**(11):1354-1362.
37. Ionescu D, Iancu C, Ion D, Al-Hajjar N, Margarit S, Mocan L, Mocan T, Deac D, Bodea R, Vasian H: **Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial.** *World JSurg* 2009, **33**(11):2433-2438.
38. Khoo CK, Vickery CJ, Forsyth N, Vinnall NS, Eyre-Brook IA: **A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer.** *AnnSurg* 2007, **245**(6):867-872.
39. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ: **Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial.** *Diseases of the colon and rectum* 2011, **54**(1):21-28.
40. Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J, Zhong Y, Xue Z, Jin L, Zhan S *et al*: **Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial.** *World JSurg* 2012, **36**(2):407-414.
41. Wang G, Jiang ZW, Zhao K, Gao Y, Liu FT, Pan HF, Li JS: **Fast track rehabilitation programme enhances functional recovery after laparoscopic colonic resection.** *Hepatology* 2012, **59**(119):2158-2163.
42. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N: **A fast-track program reduces complications and length of hospital stay after open colonic surgery.** *Gastroenterology* 2009, **136**(3):842-847.
43. Serclova Z, Dytrych P, Marvan J, Nova K, Hankeova Z, Ryska O, Slegrova Z, Buresova L, Travnikova L, Antos F: **Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456).** *ClinNutr* 2009, **28**(6):618-624.
44. Wang G, Jiang ZW, Zhao K, Gao Y, Liu FT, Pan HF, Li JS: **Fast track rehabilitation programme enhances functional recovery after laparoscopic colonic resection.** *Hepatology* 2012, **59**(119):2158-2163.
45. Wang Q, Suo J, Jiang J, Wang C, Zhao YQ, Cao X: **Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial.** *Colorectal Dis* 2012, **14**(8):1009-1013.
46. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ: **Fast track surgery versus conventional recovery strategies for colorectal surgery.** *CochraneDatabaseSystRev* 2011(2):CD007635.

-
47. Ahmed J, Khan S, Gatt M, Kallam R, MacFie J: **Compliance with enhanced recovery programmes in elective colorectal surgery.** *The British journal of surgery* 2010, **97**(5):754-758.
 48. Helsedirektoratet: **Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm.** In.; 2015.
 49. Norwegian Health Economic Administrations HELFO. **Blåreseptforskriften §§ 5 og 6. Forvaltning av produkt- og prislisen. Delrapport 3 Stomi.** In.; 2015.
 50. Cartmell MT, Jones OM, Moran BJ, Cecil TD: **A defunctioning stoma significantly prolongs the length of stay in laparoscopic colorectal resection.** *SurgEndosc* 2008, **22**(12):2643-2647.
 51. Chaudhri S, Brown L, Hassan I, Horgan AF: **Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial.** *DisColon Rectum* 2005, **48**(3):504-509.
 52. Younis J, Salerno G, Fanto D, Hadjipavlou M, Chellar D, Trickett JP: **Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme.** *IntJColorectal Dis* 2012, **27**(1):43-47.
 53. Bass EM, Del PA, Tan A, Pearl RK, Orsay CP, Abcarian H: **Does preoperative stoma marking and education by the enterostomal therapist affect outcome?** *DisColon Rectum* 1997, **40**(4):440-442.
 54. Erwin-Toth P, Barrett P: **Stoma site marking: a primer.** *OstomyWoundManage* 1997, **43**(4):18-15.
 55. Person B, Ifargan R, Lachter J, Duek SD, Kluger Y, Assalia A: **The impact of preoperative stoma site marking on the incidence of complications, quality of life, and patient's independence.** *DisColon Rectum* 2012, **55**(7):783-787.
 56. Phatak UR, Li LT, Karanjawala B, Chang GJ, Kao LS: **Systematic review of educational interventions for ostomates.** *DisColon Rectum* 2014, **57**(4):529-537.
 57. Lohsiriwat V: **The influence of preoperative nutritional status on the outcomes of an enhanced recovery after surgery (ERAS) programme for colorectal cancer surgery.** *Techniques in coloproctology* 2014, **18**(11):1075-1080.
 58. Hendry PO, Hausel J, Nygren J, Lassen K, Dejong CH, Ljungqvist O, Fearon KC: **Determinants of outcome after colorectal resection within an enhanced recovery programme.** *BrJSurg* 2009, **96**(2):197-205.
 59. Fazio VW, Tekkis PP, Remzi F, Lavery IC: **Assessment of operative risk in colorectal cancer surgery: the Cleveland Clinic Foundation colorectal cancer model.** *Diseases of the colon and rectum* 2004, **47**(12):2015-2024.
 60. Heriot AG, Tekkis PP, Smith JJ, Cohen CR, Montgomery A, Audisio RA, Thompson MR, Stamatakis JD: **Prediction of postoperative mortality in elderly patients with colorectal cancer.** *Diseases of the colon and rectum* 2006, **49**(6):816-824.
 61. **Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group.** *Lancet (London, England)* 2000, **356**(9234):968-974.
 62. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G *et al*: **Frailty in older adults: evidence for a phenotype.** *The journals of gerontology Series A, Biological sciences and medical sciences* 2001, **56**(3):M146-156.
 63. Ommundsen N, Wyller TB, Nesbakken A, Jordhoy MS, Bakka A, Skovlund E, Rostoft S: **Frailty is an independent predictor of survival in older patients with colorectal cancer.** *The oncologist* 2014, **19**(12):1268-1275.

64. Feng MA, McMillan DT, Crowell K, Muss H, Nielsen ME, Smith AB: **Geriatric assessment in surgical oncology: a systematic review.** *The Journal of surgical research* 2015, **193**(1):265-272.
65. Kristjansson SR, Nesbakken A, Jordhoy MS, Skovlund E, Audisio RA, Johannessen HO, Bakka A, Wyller TB: **Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study.** *Critical reviews in oncology/hematology* 2010, **76**(3):208-217.
66. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN: **The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials.** *Clin Nutr* 2010, **29**(4):434-440.
67. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A: **A systematic review of enhanced recovery care after colorectal surgery in elderly patients.** *Colorectal Dis* 2014, **16**(12):947-956.
68. Scharfenberg M, Raue W, Junghans T, Schwenk W: **"Fast-track" rehabilitation after colonic surgery in elderly patients--is it feasible?** *Int J Colorectal Dis* 2007, **22**(12):1469-1474.
69. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, Li Z: **Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma.** *Langenbecks Arch Surg* 2014, **399**(1):77-84.
70. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, Ljungqvist O, Soop M, Ramirez J: **Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations.** *World JSurg* 2013, **37**(2):285-305.
71. Carli F, Charlebois P, Baldini G, Cachero O, Stein B: **An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery.** *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2009, **56**(11):837-842.
72. Egbert LD, Battit GE, Welch CE, Bartlett MK: **Reduction of Postoperative Pain by Encouragement and Instruction of Patients. A Study of Doctor-Patient Rapport.** *The New England journal of medicine* 1964, **270**:825-827.
73. Halaszynski TM, Juda R, Silverman DG: **Optimizing postoperative outcomes with efficient preoperative assessment and management.** *Crit Care Med* 2004, **32**(4 Suppl):S76-S86.
74. Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R: **Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology.** *The American psychologist* 1998, **53**(11):1209-1218.
75. Stergiopoulou A, Birbas K, Katostaras T, Mantas J: **The effect of interactive multimedia on preoperative knowledge and postoperative recovery of patients undergoing laparoscopic cholecystectomy.** *Methods of information in medicine* 2007, **46**(4):406-409.
76. Clarke HD, Timm VL, Goldberg BR, Hattrup SJ: **Preoperative patient education reduces in-hospital falls after total knee arthroplasty.** *Clinical orthopaedics and related research* 2012, **470**(1):244-249.
77. Edward GM, v d Naald N, Oort FJ, de Haes HC, Biervliet JD, Hollmann MW, Preckel B: **Information gain in patients using a multimedia website with tailored information on anaesthesia.** *British journal of anaesthesia* 2011, **106**(3):319-324.
78. Forster AJ, Clark HD, Menard A, Dupuis N, Chernish R, Chandok N, Khan A, Letourneau M, van Walraven C: **Effect of a nurse team coordinator on outcomes**

- for hospitalized medicine patients.** *The American journal of medicine* 2005, **118**(10):1148-1153.
79. Haines TP, Hill AM, Hill KD, McPhail S, Oliver D, Brauer S, Hoffmann T, Beer C: **Patient education to prevent falls among older hospital inpatients: a randomized controlled trial.** *Archives of internal medicine* 2011, **171**(6):516-524.
80. Bohmer AB, Wappler F, Zwissler B: **Preoperative risk assessment--from routine tests to individualized investigation.** *Deutsches Arzteblatt international* 2014, **111**(25):437-445; quiz 446.
81. **National Institute for Health and Care Excellence: Clinical Guidelines.** In: *Preoperative Tests (Update): Routine Preoperative Tests for Elective Surgery.* edn. London: National Institute for Health and Care Excellence (UK); 2016.
82. Fritsch G, Flamm M, Hepner DL, Panisch S, Seer J, Soennichsen A: **Abnormal preoperative tests, pathologic findings of medical history, and their predictive value for perioperative complications.** *Acta anaesthesiologica Scandinavica* 2012, **56**(3):339-350.
83. O'Neill F, Carter E, Pink N, Smith I: **Routine preoperative tests for elective surgery: summary of updated NICE guidance.** *Bmj* 2016, **354**:i3292.
84. Thompson BM, Stearns JD, Apsey HA, Schlinkert RT, Cook CB: **Perioperative Management of Patients with Diabetes and Hyperglycemia Undergoing Elective Surgery.** *Current diabetes reports* 2016, **16**(1):2.
85. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Liberman AS, Stein B, Charlebois P, Feldman LS *et al*: **Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer.** *Anesthesiology* 2014, **121**(5):937-947.
86. Shaffer VO, Baptiste CD, Liu Y, Srinivasan JK, Galloway JR, Sullivan PS, Staley CA, Sweeney JF, Sharma J, Gillespie TW: **Improving quality of surgical care and outcomes: factors impacting surgical site infection after colorectal resection.** *The American surgeon* 2014, **80**(8):759-763.
87. Sorensen LT, Jorgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jorgensen P: **Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery.** *The British journal of surgery* 1999, **86**(7):927-931.
88. van Rooijen S, Carli F, Dalton SO, Johansen C, Dieleman J, Roumen R, Slooter G: **Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation.** *Acta oncologica (Stockholm, Sweden)* 2017, **56**(2):329-334.
89. Thomsen T, Villebro N, Moller AM: **Interventions for preoperative smoking cessation.** *The Cochrane database of systematic reviews* 2014(3):Cd002294.
90. Gustafsson UO, Ljungqvist O: **Perioperative nutritional management in digestive tract surgery.** *Current opinion in clinical nutrition and metabolic care* 2011, **14**(5):504-509.
91. Goere D, Cunha AS: **Parenteral and enteral nutritional support (excluding immunonutrition).** *Journal of visceral surgery* 2015, **152** Suppl 1:S8-s13.
92. Christensen T, Kehlet H: **Postoperative fatigue.** *World journal of surgery* 1993, **17**(2):220-225.
93. Lawrence VA, Hazuda HP, Cornell JE, Pederson T, Bradshaw PT, Mulrow CD, Page CP: **Functional independence after major abdominal surgery in the elderly.** *Journal of the American College of Surgeons* 2004, **199**(5):762-772.
94. Le Roy B, Selvy M, Slim K: **The concept of prehabilitation: What the surgeon needs to know?** *Journal of visceral surgery* 2016, **153**(2):109-112.

95. Steenhagen E: **Enhanced Recovery After Surgery: It's Time to Change Practice!** *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition* 2016, **31**(1):18-29.
96. Brady M, Kinn S, Stuart P: **Preoperative fasting for adults to prevent perioperative complications.** *The Cochrane database of systematic reviews* 2003(4):Cd004423.
97. **Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration.** *Anesthesiology* 2017, **126**(3):376-393.
98. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Soreide E, Spies C, in't Veld B: **Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology.** *European journal of anaesthesiology* 2011, **28**(8):556-569.
99. Ljungqvist O, Soreide E: **Preoperative fasting.** *The British journal of surgery* 2003, **90**(4):400-406.
100. Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, Ljungqvist O: **Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics.** *The British journal of surgery* 2007, **94**(11):1342-1350.
101. Nygren J: **The metabolic effects of fasting and surgery.** *Best practice & research Clinical anaesthesiology* 2006, **20**(3):429-438.
102. Ljungqvist O, Nygren J, Thorell A: **Modulation of post-operative insulin resistance by pre-operative carbohydrate loading.** *Proc Nutr Soc* 2002, **61**(3):329-336.
103. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW: **The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial.** *Clinical nutrition (Edinburgh, Scotland)* 2005, **24**(1):32-37.
104. Amer MA, Smith MD, Herbison GP, Plank LD, McCall JL: **Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery.** *The British journal of surgery* 2017, **104**(3):187-197.
105. Awad S, Varadhan KK, Ljungqvist O, Lobo DN: **A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery.** *Clinical nutrition (Edinburgh, Scotland)* 2013, **32**(1):34-44.
106. Li L, Wang Z, Ying X, Tian J, Sun T, Yi K, Zhang P, Jing Z, Yang K: **Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis.** *Surgery today* 2012, **42**(7):613-624.
107. Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J: **Preoperative carbohydrate treatment for enhancing recovery after elective surgery.** *The Cochrane database of systematic reviews* 2014(8):Cd009161.
108. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT: **Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery.** *Annals of surgery* 2015, **261**(6):1034-1040.

109. Murray AC, Kiran RP: **Benefit of mechanical bowel preparation prior to elective colorectal surgery: current insights.** *Langenbeck's archives of surgery* 2016, **401**(5):573-580.
110. Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P: **Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery.** *The British journal of surgery* 2005, **92**(4):409-414.
111. Guenaga KF, Matos D, Wille-Jorgensen P: **Mechanical bowel preparation for elective colorectal surgery.** *The Cochrane database of systematic reviews* 2011(9):Cd001544.
112. Jung B, Pahlman L, Nystrom PO, Nilsson E: **Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection.** *The British journal of surgery* 2007, **94**(6):689-695.
113. Murray AC, Kiran RP: **Bowel Preparation: Are Antibiotics Necessary for Colorectal Surgery?** *Advances in surgery* 2016, **50**(1):49-66.
114. Zmora O, Pikarsky AJ, Wexner SD: **Bowel preparation for colorectal surgery.** *Diseases of the colon and rectum* 2001, **44**(10):1537-1549.
115. Rovera F, Dionigi G, Boni L, Ferrari A, Bianchi V, Diurni M, Carcano G, Dionigi R: **Mechanical bowel preparation for colorectal surgery.** *Surgical infections* 2006, **7** Suppl 2:S61-63.
116. Althumairi AA, Canner JK, Pawlik TM, Schneider E, Nagarajan N, Safar B, Efron JE: **Benefits of Bowel Preparation Beyond Surgical Site Infection: A Retrospective Study.** *Annals of surgery* 2016, **264**(6):1051-1057.
117. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K: **Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery.** *Annals of surgery* 2015, **262**(3):416-425; discussion 423-415.
118. Murphy MM, Tevis SE, Kennedy GD: **Independent risk factors for prolonged postoperative ileus development.** *The Journal of surgical research* 2016, **201**(2):279-285.
119. 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 Colorectal Surgery: A Meta-Analysis of Randomized Controlled Clinical Trials.** *Diseases of the colon and rectum* 2016, **59**(1):70-78.
120. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H: **Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery.** *The British journal of surgery* 2001, **88**(7):913-930.
121. Sachdeva A, Dalton M, Amaragiri SV, Lees T: **Graduated compression stockings for prevention of deep vein thrombosis.** *The Cochrane database of systematic reviews* 2014(12):Cd001484.
122. Akl EA, Kahale L, Sperati F, Neumann I, Labedi N, Terrenato I, Barba M, Sempos EV, Muti P, Cook D *et al*: **Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer.** *The Cochrane database of systematic reviews* 2014(6):Cd009447.
123. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P: **Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery.** *The Cochrane database of systematic reviews* 2009(1):Cd004318.
124. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, Dietrich-Neto F: **Duration of prophylaxis against venous thromboembolism with**

- enoxaparin after surgery for cancer.** *The New England journal of medicine* 2002, **346**(13):975-980.
125. Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P: **Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study.** *Journal of thrombosis and haemostasis* : *JTH* 2010, **8**(6):1223-1229.
 126. Vedovati MC, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, Mariani E, Flamini O, Pucciarelli S, Donini A *et al*: **A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer.** *Annals of surgery* 2014, **259**(4):665-669.
 127. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM: **Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.** *Chest* 2012, **141**(2 Suppl):e227S-277S.
 128. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW *et al*: **Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014.** *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015, **33**(6):654-656.
 129. Rogers JF, Morrison AL, Nafziger AN, Jones CL, Rocci ML, Jr., Bertino JS, Jr.: **Flumazenil reduces midazolam-induced cognitive impairment without altering pharmacokinetics.** *Clinical pharmacology and therapeutics* 2002, **72**(6):711-717.
 130. Maurice-Szamburski A, Auquier P, Viarre-Oreal V, Cuvillon P, Carles M, Ripart J, Honore S, Triglia T, Loundou A, Leone M *et al*: **Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial.** *Jama* 2015, **313**(9):916-925.
 131. Walker KJ, Smith AF: **Premedication for anxiety in adult day surgery.** *The Cochrane database of systematic reviews* 2009(4):Cd002192.
 132. Caumo W, Levandovski R, Hidalgo MP: **Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study.** *The journal of pain : official journal of the American Pain Society* 2009, **10**(1):100-108.
 133. Hansen MV, Halladin NL, Rosenberg J, Gogenur I, Moller AM: **Melatonin for pre- and postoperative anxiety in adults.** *The Cochrane database of systematic reviews* 2015(4):Cd009861.
 134. Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H, Jr., Fagerstrom RM: **A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls.** *The New England journal of medicine* 1981, **305**(14):795-799.
 135. Evans C, Pollock AV: **The reduction of surgical wound infections by prophylactic parenteral cephaloridine. A controlled clinical trial.** *The British journal of surgery* 1973, **60**(6):434-437.
 136. Helsedirektoratet: **Nasjonal faglig retningslinje for antibiotikabruk i sykehus 2014.** 2014.
 137. Bellows CF, Mills KT, Kelly TN, Gagliardi G: **Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infections after colorectal surgery: a meta-**

- analysis of randomized controlled trials.** *Techniques in coloproctology* 2011, **15**(4):385-395.
138. Nelson RL, Gladman E, Barbateskovic M: **Antimicrobial prophylaxis for colorectal surgery.** *The Cochrane database of systematic reviews* 2014(5):Cd001181.
139. Brekke HK, Hammersborg SM, Lundemoen S, Mongstad A, Kvalheim VL, Haugen O, Husby P: **Isoflurane in contrast to propofol promotes fluid extravasation during cardiopulmonary bypass in pigs.** *Anesthesiology* 2013, **119**(4):861-870.
140. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N: **Bispectral index for improving anaesthetic delivery and postoperative recovery.** *The Cochrane database of systematic reviews* 2014(6):Cd003843.
141. Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, Gan TJ, Kennedy RH, Ljungqvist O, Lobo DN *et al*: **Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice.** *Acta anaesthesiologica Scandinavica* 2016, **60**(3):289-334.
142. Torossian A: **Survey on intraoperative temperature management in Europe.** *European journal of anaesthesiology* 2007, **24**(8):668-675.
143. Torossian A: **Thermal management during anaesthesia and thermoregulation standards for the prevention of inadvertent perioperative hypothermia.** *Best practice & research Clinical anaesthesiology* 2008, **22**(4):659-668.
144. Scott EM, Buckland R: **A systematic review of intraoperative warming to prevent postoperative complications.** *AORN journal* 2006, **83**(5):1090-1104, 1107-1013.
145. Andrzejowski J, Hoyle J, Eapen G, Turnbull D: **Effect of prewarming on post-induction core temperature and the incidence of inadvertent perioperative hypothermia in patients undergoing general anaesthesia.** *British journal of anaesthesia* 2008, **101**(5):627-631.
146. Hooper VD, Chard R, Clifford T, Fetzer S, Fossum S, Godden B, Martinez EA, Noble KA, O'Brien D, Odom-Forren J *et al*: **ASPAN's evidence-based clinical practice guideline for the promotion of perioperative normothermia: second edition.** *Journal of perianesthesia nursing : official journal of the American Society of PeriAnesthesia Nurses* 2010, **25**(6):346-365.
147. Varadhan KK, Lobo DN: **A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right.** *The Proceedings of the Nutrition Society* 2010, **69**(4):488-498.
148. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: **Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial.** *Lancet* 2002, **359**(9320):1812-1818.
149. Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC: **Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection.** *World journal of surgery* 2004, **28**(10):1046-1051; discussion 1051-1042.
150. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lannig C, Wallin L, Iversen LH *et al*: **Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial.** *AnnSurg* 2003, **238**(5):641-648.
151. Mackay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ: **Randomized clinical trial of the effect of postoperative intravenous fluid**

- restriction on recovery after elective colorectal surgery. *BrJSurg* 2006, **93**(12):1469-1474.
152. Rollins KE, Lobo DN: **Intraoperative Goal-directed Fluid Therapy in Elective Major Abdominal Surgery: A Meta-analysis of Randomized Controlled Trials.** *Annals of surgery* 2016, **263**(3):465-476.
153. Jammer I, Ulvik A, Erichsen C, Lodemel O, Ostgaard G: **Does central venous oxygen saturation-directed fluid therapy affect postoperative morbidity after colorectal surgery? A randomized assessor-blinded controlled trial.** *Anesthesiology* 2010, **113**(5):1072-1080.
154. Carli F, Mayo N, Klubien K, Schrickler T, Trudel J, Belliveau P: **Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial.** *Anesthesiology* 2002, **97**(3):540-549.
155. Marret E, Remy C, Bonnet F: **Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery.** *The British journal of surgery* 2007, **94**(6):665-673.
156. Bonnet F, Marret E: **Postoperative pain management and outcome after surgery.** *Best practice & research Clinical anaesthesiology* 2007, **21**(1):99-107.
157. Joshi GP, Bonnet F, Kehlet H: **Evidence-based postoperative pain management after laparoscopic colorectal surgery.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2013, **15**(2):146-155.
158. Hubner M, Blanc C, Roulin D, Winiker M, Gander S, Demartines N: **Randomized clinical trial on epidural versus patient-controlled analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway.** *Annals of surgery* 2015, **261**(4):648-653.
159. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N: **Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review.** *British journal of anaesthesia* 2011, **106**(3):292-297.
160. McNicol ED, Tzortzopoulou A, Cepeda MS, Francia MB, Farhat T, Schumann R: **Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis.** *British journal of anaesthesia* 2011, **106**(6):764-775.
161. Bhangu A, Singh P, Fitzgerald JE, Slessor A, Tekkis P: **Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies.** *World journal of surgery* 2014, **38**(9):2247-2257.
162. Bakker N, Deelder JD, Richir MC, Cakir H, Doodeman HJ, Schreurs WH, Houdijk AP: **Risk of anastomotic leakage with nonsteroidal anti-inflammatory drugs within an enhanced recovery program.** *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2016, **20**(4):776-782.
163. Subendran J, Siddiqui N, Victor JC, McLeod RS, Govindarajan A: **NSAID use and anastomotic leaks following elective colorectal surgery: a matched case-control study.** *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014, **18**(8):1391-1397.
164. Paulasir S, Kaoutzanic C, Welch KB, Vandewarker JF, Krapohl G, Lampman RM, Franz MG, Cleary RK: **Nonsteroidal Anti-inflammatory Drugs: Do They Increase the Risk of Anastomotic Leaks Following Colorectal Operations?** *Diseases of the colon and rectum* 2015, **58**(9):870-877.

-
165. Saleh F, Jackson TD, Ambrosini L, Gnanasegaram JJ, Kwong J, Quereshy F, Okrainec A: **Perioperative nonselective non-steroidal anti-inflammatory drugs are not associated with anastomotic leakage after colorectal surgery.** *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014, **18**(8):1398-1404.
 166. Henzi I, Walder B, Tramer MR: **Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review.** *Anesthesia and analgesia* 2000, **90**(1):186-194.
 167. Srinivasa S, Kahokehr AA, Yu TC, Hill AG: **Preoperative glucocorticoid use in major abdominal surgery: systematic review and meta-analysis of randomized trials.** *Annals of surgery* 2011, **254**(2):183-191.
 168. **A comparison of laparoscopically assisted and open colectomy for colon cancer.** *NEnglJMed* 2004, **350**(20):2050-2059.
 169. Kennedy GD, Heise C, Rajamanickam V, Harms B, Foley EF: **Laparoscopy decreases postoperative complication rates after abdominal colectomy: results from the national surgical quality improvement program.** *Annals of surgery* 2009, **249**(4):596-601.
 170. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, Bonjer HJ: **Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial.** *The Lancet Oncology* 2013, **14**(3):210-218.
 171. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S *et al*: **Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial.** *Lancet Oncol* 2005, **6**(7):477-484.
 172. Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, Dutton SJ: **Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL.** *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014, **32**(17):1804-1811.
 173. Kim CW, Kim CH, Baik SH: **Outcomes of robotic-assisted colorectal surgery compared with laparoscopic and open surgery: a systematic review.** *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014, **18**(4):816-830.
 174. Cheatham ML, Chapman WC, Key SP, Sawyers JL: **A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy.** *Annals of surgery* 1995, **221**(5):469-476; discussion 476-468.
 175. Nelson R, Tse B, Edwards S: **Systematic review of prophylactic nasogastric decompression after abdominal operations.** *The British journal of surgery* 2005, **92**(6):673-680.
 176. Rao W, Zhang X, Zhang J, Yan R, Hu Z, Wang Q: **The role of nasogastric tube in decompression after elective colon and rectum surgery: a meta-analysis.** *International journal of colorectal disease* 2011, **26**(4):423-429.
 177. Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T: **Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2006, **8**(4):259-265.
 178. Petrowsky H, Demartines N, Rousson V, Clavien PA: **Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses.** *Annals of surgery* 2004, **240**(6):1074-1084; discussion 1084-1075.

179. Rondelli F, Bugiantella W, Vedovati MC, Balzarotti R, Avenia N, Mariani E, Agnelli G, Becattini C: **To drain or not to drain extraperitoneal colorectal anastomosis? A systematic review and meta-analysis.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2014, **16**(2):O35-42.
180. Denost Q, Rouanet P, Faucheron JL, Panis Y, Meunier B, Cotte E, Meurette G, Kirzin S, Sabbagh C, Loriau J *et al*: **To Drain or Not to Drain Infraperitoneal Anastomosis After Rectal Excision for Cancer: The GRECCAR 5 Randomized Trial.** *Annals of surgery* 2017, **265**(3):474-480.
181. Zaouter C, Kaneva P, Carli F: **Less urinary tract infection by earlier removal of bladder catheter in surgical patients receiving thoracic epidural analgesia.** *Regional anesthesia and pain medicine* 2009, **34**(6):542-548.
182. Basse L, Werner M, Kehlet H: **Is urinary drainage necessary during continuous epidural analgesia after colonic resection?** *Regional anesthesia and pain medicine* 2000, **25**(5):498-501.
183. Benoist S, Panis Y, Denet C, Mauvais F, Mariani P, Valleur P: **Optimal duration of urinary drainage after rectal resection: a randomized controlled trial.** *Surgery* 1999, **125**(2):135-141.
184. Zmora O, Madbouly K, Tulchinsky H, Hussein A, Khaikin M: **Urinary bladder catheter drainage following pelvic surgery--is it necessary for that long?** *Diseases of the colon and rectum* 2010, **53**(3):321-326.
185. McPhail MJ, Abu-Hilal M, Johnson CD: **A meta-analysis comparing suprapubic and transurethral catheterization for bladder drainage after abdominal surgery.** *The British journal of surgery* 2006, **93**(9):1038-1044.
186. Allen C, Glasziou P, Del Mar C: **Bed rest: a potentially harmful treatment needing more careful evaluation.** *Lancet* 1999, **354**(9186):1229-1233.
187. Killewich LA: **Strategies to minimize postoperative deconditioning in elderly surgical patients.** *Journal of the American College of Surgeons* 2006, **203**(5):735-745.
188. Story SK, Chamberlain RS: **A comprehensive review of evidence-based strategies to prevent and treat postoperative ileus.** *Digestive surgery* 2009, **26**(4):265-275.
189. Castelino T, Fiore JF, Jr., Niculiseanu P, Landry T, Augustin B, Feldman LS: **The effect of early mobilization protocols on postoperative outcomes following abdominal and thoracic surgery: A systematic review.** *Surgery* 2016, **159**(4):991-1003.
190. Fiore JF, Jr., Castelino T, Pecorelli N, Niculiseanu P, Balvardi S, Hershorn O, Liberman S, Charlebois P, Stein B, Carli F *et al*: **Ensuring Early Mobilization Within an Enhanced Recovery Program for Colorectal Surgery: A Randomized Controlled Trial.** *Annals of surgery* 2016.
191. Andersen HK, Lewis SJ, Thomas S: **Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications.** *The Cochrane database of systematic reviews* 2006(4):Cd004080.
192. Zhuang CL, Ye XZ, Zhang CJ, Dong QT, Chen BC, Yu Z: **Early versus traditional postoperative oral feeding in patients undergoing elective colorectal surgery: a meta-analysis of randomized clinical trials.** *Digestive surgery* 2013, **30**(3):225-232.
193. Beattie AH, Prach AT, Baxter JP, Pennington CR: **A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients.** *Gut* 2000, **46**(6):813-818.
194. Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, Oldale C, Jones P, Silk D: **Randomized clinical trial of the effects of preoperative and**

- postoperative oral nutritional supplements on clinical course and cost of care.** *The British journal of surgery* 2004, **91**(8):983-990.
195. Jackson RS, Amdur RL, White JC, Macsata RA: **Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer.** *Journal of the American College of Surgeons* 2012, **214**(1):68-80.
196. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohi E, Flum D: **Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program.** *Annals of surgery* 2013, **257**(1):8-14.
197. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, Flum DR: **Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes.** *Annals of surgery* 2015, **261**(1):97-103.
198. Kiran RP, Turina M, Hammel J, Fazio V: **The clinical significance of an elevated postoperative glucose value in nondiabetic patients after colorectal surgery: evidence for the need for tight glucose control?** *Annals of surgery* 2013, **258**(4):599-604; discussion 604-595.
199. Ljungqvist O: **Insulin resistance and outcomes in surgery.** *The Journal of clinical endocrinology and metabolism* 2010, **95**(9):4217-4219.
200. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, Meurette G: **Postoperative ileus: Pathophysiology, incidence, and prevention.** *Journal of visceral surgery* 2016, **153**(6):439-446.
201. Wolthuis AM, Bislenghi G, Fieuws S, de Buck van Overstraeten A, Boeckxstaens G, D'Hoore A: **Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016, **18**(1):O1-9.
202. Ahmed Ali U, Dunne T, Gurland B, Vogel JD, Kiran RP: **Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation?** *American journal of surgery* 2014, **208**(4):663-669.
203. Grass F, Slieker J, Jurt J, Kummer A, Sola J, Hahnloser D, Demartines N, Hubner M: **Postoperative ileus in an enhanced recovery pathway-a retrospective cohort study.** *International journal of colorectal disease* 2017.
204. Shariat Moharari R, Motalebi M, Najafi A, Zamani MM, Imani F, Etezadi F, Pourfakhr P, Khajavi MR: **Magnesium Can Decrease Postoperative Physiological Ileus and Postoperative Pain in Major non Laparoscopic Gastrointestinal Surgeries: A Randomized Controlled Trial.** *Anesthesiology and pain medicine* 2014, **4**(1):e12750.
205. Andersen J, Christensen H, Pachler JH, Hallin M, Thaysen HV, Kehlet H: **Effect of the laxative magnesium oxide on gastrointestinal functional recovery in fast-track colonic resection: a double-blind, placebo-controlled randomized study.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2012, **14**(6):776-782.
206. Muller SA, Rahbari NN, Schneider F, Warschkow R, Simon T, von Frankenberg M, Bork U, Weitz J, Schmied BM, Buchler MW: **Randomized clinical trial on the effect of coffee on postoperative ileus following elective colectomy.** *The British journal of surgery* 2012, **99**(11):1530-1538.
207. Shum NF, Choi HK, Mak JC, Foo DC, Li WC, Law WL: **Randomized clinical trial of chewing gum after laparoscopic colorectal resection.** *The British journal of surgery* 2016, **103**(11):1447-1452.
208. Chatterjee S, Rudra A, Sengupta S: **Current concepts in the management of postoperative nausea and vomiting.** *Anesthesiology research and practice* 2011, **2011**:748031.

-
209. Chandrakantan A, Glass PS: **Multimodal therapies for postoperative nausea and vomiting, and pain.** *British journal of anaesthesia* 2011, **107** Suppl 1:i27-40.
 210. Karanicolas PJ, Smith SE, Kanbur B, Davies E, Guyatt GH: **The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis.** *Annals of surgery* 2008, **248**(5):751-762.
 211. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF: **Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner.** *Anesthesia and analgesia* 2005, **101**(5):1343-1348.
 212. Carlisle JB, Stevenson CA: **Drugs for preventing postoperative nausea and vomiting.** *The Cochrane database of systematic reviews* 2006(3):Cd004125.
 213. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J, Enhanced Recovery After Surgery Study G: **Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery.** *Archives of surgery* 2011, **146**(5):571-577.
 214. Group EC: **The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry.** *Annals of surgery* 2015, **261**(6):1153-1159.
 215. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M: **Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials.** *World JSurg* 2014, **38**(6):1531-1541.
 216. Maessen JM, Dejong CH, Kessels AG, von Meyenfeldt MF: **Length of stay: an inappropriate readout of the success of enhanced recovery programs.** *World journal of surgery* 2008, **32**(6):971-975.
 217. Forsmo HM, Pfeffer F, Rasdal A, Ostgaard G, Mohn AC, Korner H, Erichsen C: **Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: results of a randomized controlled trial.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016, **18**(6):603-611.
 218. Sintonen H: **The 15D instrument of health-related quality of life: properties and applications.** *AnnMed* 2001, **33**(5):328-336.
 219. Forsmo HM, Erichsen C, Rasdal A, Korner H, Pfeffer F: **Enhanced Recovery After Colorectal Surgery (ERAS) in Elderly Patients Is Feasible and Achieves Similar Results as in Younger Patients.** *Gerontology & geriatric medicine* 2017, **3**:2333721417706299.
 220. Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, Kessels AG, Revhaug A, Kehlet H, Ljungqvist O *et al*: **A protocol is not enough to implement an enhanced recovery programme for colorectal resection.** *The British journal of surgery* 2007, **94**(2):224-231.
 221. Thorn CC, White I, Burch J, Malietzis G, Kennedy R, Jenkins JT: **Active and passive compliance in an enhanced recovery programme.** *International journal of colorectal disease* 2016, **31**(7):1329-1339.
 222. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF: **Systematic review and meta-analysis of enhanced recovery programmes in surgical patients.** *BrJSurg* 2014, **101**(3):172-188.
 223. Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, Beart RW, Jr., Hellinger M, Flanagan R, Jr., Peters W *et al*: **A comparison of laparoscopically assisted and open colectomy for colon cancer.** *The New England journal of medicine* 2004, **350**(20):2050-2059.

-
224. Spanjersberg WR, van Sambeek JD, Bremers A, Rosman C, van Laarhoven CJ: **Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme.** *Surgical endoscopy* 2015, **29**(12):3443-3453.
 225. Shabbir J, Britton DC: **Stoma complications: a literature overview.** *Colorectal Dis* 2010, **12**(10):958-964.
 226. Rumstadt B, Guenther N, Wendling P, Engemann R, Germer CT, Schmid M, Kipfmueller K, Walz MK, Schwenk W: **Multimodal perioperative rehabilitation for colonic surgery in the elderly.** *World JSurg* 2009, **33**(8):1757-1763.
 227. Gotlib Conn L, McKenzie M, Pearsall EA, McLeod RS: **Successful implementation of an enhanced recovery after surgery programme for elective colorectal surgery: a process evaluation of champions' experiences.** *Implementation science : IS* 2015, **10**:99.
 228. Cakir H, van Stijn MF, Lopes Cardozo AM, Langenhorst BL, Schreurs WH, van der Ploeg TJ, Bemelman WA, Houdijk AP: **Adherence to Enhanced Recovery After Surgery and length of stay after colonic resection.** *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2013, **15**(8):1019-1025.
 229. Kehlet H, Slim K: **The future of fast-track surgery.** *The British journal of surgery* 2012, **99**(8):1025-1026.
 230. Ghaferi AA, Birkmeyer JD, Dimick JB: **Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients.** *Annals of surgery* 2009, **250**(6):1029-1034.
 231. Ghaferi AA, Birkmeyer JD, Dimick JB: **Variation in hospital mortality associated with inpatient surgery.** *The New England journal of medicine* 2009, **361**(14):1368-1375.
 232. McGaughey J, Alderdice F, Fowler R, Kapila A, Mayhew A, Moutray M: **Outreach and Early Warning Systems (EWS) for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards.** *The Cochrane database of systematic reviews* 2007(3):Cd005529.

8. Papers I-IV

Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: results of a randomized controlled trial

H. M. Forsmo*, F. Pfeffer*†, A. Rasdal*, G. Østgaard‡, A. C. Mohn§, H. Körner¶ and C. Erichsen*

*Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway, †Department of Clinical Medicine, University of Bergen, Bergen, Norway, ‡Department of Anesthesiology, Haukeland University Hospital, Bergen, Norway, §Department of Gastrointestinal Surgery, Haugesund Hospital, Haugesund, Norway and ¶Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway

Received 18 September 2015; accepted 11 November 2015; Accepted Article online 6 January 2016

Abstract

Aim The aim of this randomized clinical trial was to compare patients treated using a multimodal approach [enhanced recovery after surgery (ERAS)], with a special focus on counselling, to patients treated in a standard conventional care pathway, who underwent elective colorectal resection.

Method In a single-centre trial, adult patients eligible for open or laparoscopic colorectal resection were randomized to an ERAS programme or standard care. The primary end-point was postoperative total hospital stay. Identical discharge criteria were defined for both treatment groups. Secondary end-points included postoperative complications, postoperative C-reactive protein levels, postoperative hospital stay, readmission rate and mortality. All parameters were recorded before operation, on the day of surgery and daily thereafter until discharge.

Results Total hospital stay was significantly shorter among patients randomized to ERAS than among the standard group [median 5 days (range 2–50 days) *vs* median 8 days (range 2–48 days); $P = 0.001$]. The two treatment groups exhibited similar outcomes regarding overall major and minor morbidity, reoperation rate,

readmission rate and 30-day mortality. There were also no differences in tolerance of enteral nutrition or in the inflammatory response, as reflected by postoperative C-reactive protein levels.

Conclusion ERAS care was associated with a significantly shorter length of hospital stay. Without any difference in surgical or general complications, tolerance of enteral nutrition or postoperative C-reactive protein levels, peri-operative information and guidance for ensuring that patients comply with the ERAS approach appear to be important factors to reduce the length of hospital stay.

Keywords Colorectal surgery, ERAS, complication, counselling

What does this paper add to the literature?

Although the benefits of enhanced recovery after surgery on length of stay are widely recognized, the main reasons for the reduction in hospital stay are not well understood. This study suggests that accurate peri-operative information and continuous guidance are important for this reduction.

Introduction

Enhanced recovery after surgery (ERAS) is a multimodal peri-operative approach that aims to reduce organ dysfunction and surgical stress response and thus

to reduce postoperative morbidity and length of hospital stay [1]. Several prospective studies have demonstrated associations between ERAS and shorter hospital stay and reduced morbidity, without a difference in mortality [2–4]. To date, randomized trials have shown that patients recover faster when traditions are amended, including changes in analgesia and anaesthetic procedures, mobilization procedures, better information

Correspondence to: Håvard Mjørud Forsmo, MD, Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, 5021 Bergen, Norway.

E-mail: havard.forsmo@helse-bergen.no

to patients and determined effort by the department to reduce hospital stay. Some randomized trials have reported no difference in the complication rate [5–10], while others show a difference in minor complications [11–14]. A 2011 Cochrane Review, however, stated that the quantity and especially the quality of published data are low [15].

An early prospective observational study of 98 patients was conducted from 2000 until 2003 at our own hospital and Haugesund Hospital, according to the ERAS principles. This study reported that 80% of patients were discharged on day 5 with a tendency toward a lower complication rate [16]. The length of the postoperative hospital stay varies broadly with geography. Most continental countries traditionally have a longer postoperative hospital stay than the Nordic countries, and it can also be difficult to generalize findings from Asia to Nordic and Norwegian conditions. We conducted a controlled, randomized study in which we compared patients treated by the best possible multimodal approach (ERAS) with a special focus on counselling to patients treated in a standard care pathway. The main goal of this study was to determine whether we were able to decrease the total length of hospital stay, mainly as a result of reduced morbidity.

Method

This prospective randomized clinical trial was undertaken at the Haukeland University Hospital in Bergen, Norway. It was registered with ClinicalTrials.gov (number NCT01610726). Adult patients older than 18 years scheduled for elective open or laparoscopic colorectal surgery for malignant or benign diseases, with or without stoma, were eligible for inclusion. Patients with rectal cancer who had had pelvic radiation were also included. Patients were informed both orally and in writing 1–3 weeks before surgery, and written consent was obtained. Patients were excluded if a multivisceral resection was planned or if the patient was scored American Society of Anesthesiologists grade IV. Additional exclusion criteria were pregnancy, emergency operations, difficulty to give informed consent because of impaired mental capacity, or inability to adapt to the ERAS criteria. Randomized patients were excluded if the intended colonic or rectal surgery was not performed. The regional ethics committee in Western Norway approved the trial (reference number 2010/2079).

Randomization

Patients fulfilling the inclusion criteria and consenting to participate in the study were randomized to ERAS or

standard care. A randomization list for 324 patients with an allocation ratio of 1:1 was generated with block randomization. An independent statistician prepared the sequence in advance. Allocation assignments were deposited in consecutively numbered and sealed letters and stored locked in the study office. Patients were informed about their treatment group at the time of information, 1–3 weeks before surgery. Neither the patient nor the physician was blinded to the treatment assignment.

Objectives and end-points

The primary end-point was total hospital stay (THS) measured in days. This was defined as postoperative hospital stay plus additional days if readmission was necessary within the first 30 days after surgery. Discharge criteria were defined and were similar for both treatment groups. These included (i) postoperative pain adequately controlled with oral medication (Visual Analog Scale <4), (ii) mobilized and out of bed more than 6 h each day, (iii) bowel function (faeces or repeated flatus) and (iv) no complications requiring treatment in hospital. All patients with a stoma were comfortable with stoma care before discharge.

Secondary end-points were postoperative complications, postoperative C-reactive protein (CRP) levels, postoperative hospital stay, readmission rate and mortality. Definitions for complications were established prior to study commencement and the incidence of complications was also recorded in accordance with the Clavien–Dindo classification [17].

All parameters were recorded before operation, on the day of surgery and daily thereafter until discharge. All patients had an outpatient control on postoperative days 10 and 30. An early postoperative control at day 10 was performed to record possible postoperative complications occurring after discharge and to refer the cancer patients for adjuvant treatment if indicated. To minimize observer-related bias, one dedicated nurse and the same two surgeons carried out all controls.

Peri-operative care and surgical technique

Patients randomized to ERAS had one to two consultations before surgery with the ERAS nurse. They were informed about the principles of ERAS care and the goal of the project. They were told about their own role in retraining so that they understood the importance of their own efforts, that they would eat the same day as the operation, the importance of mobilization and drinking and that they should preferably do without intravenous fluids. Patients were also informed

about nutritional drinks, the day of removal of any urinary catheter, drain and epidural analgesia, the expected length of stay and the discharge criteria. In both groups, patients operated with colon resection had no drain, while all patients with rectal resections received a pelvic drain.

Patients allocated to the ERAS group were treated according to the ERAS protocol described in the consensus guidelines [18,19]. The ERAS items used in the study are listed in Table 1. Patients randomized to standard care were treated according to traditional peri-operative care. Some ERAS items are also included in modern standard care that is currently practised in Norway and therefore were also implemented in that group.

Patients randomized to ERAS recovery during hospitalization were admitted to a separate ward from the standard group. Nurses who worked with the ERAS group had special training and education in the principles of ERAS. All operations were performed by or under the supervision of a colorectal surgeon. Five surgeons performed both laparoscopic and open surgery and two surgeons performed open surgery only. The operating surgeon decided which surgical approach

should be selected. Open resections were performed through a midline incision.

In both groups, patients were allowed to drink clear liquids up to 2 h before surgery. Bowel preparation was standard for rectal surgery, while the main surgeon pre-operatively determined the appropriate bowel preparation on an individual basis for patients undergoing colon surgery. Bowel preparation did not include enema. All patients received thromboembolic prophylaxis, preoperative antibiotics and prevention of hypothermia. All patients in both groups were encouraged to mobilize early starting immediately after surgery and were allowed to start drinking and eating immediately after surgery if they wanted. In the ERAS group only, we enforced patient mobilization and oral feeding postoperatively. In the ERAS group, patients had a carbohydrate-loaded drink (ProvideXtra®, 200 ml) the evening before surgery and 2 h before surgery. Routine preoperative glucocorticoid as part of peri-operative management was not used.

Thoracic epidural anaesthetic agents were inserted at Th9-11 with a continuous dose of bupivacaine 1 mg/ml, fentanyl 0.002 mg/ml and adrenalin 0.002 mg/ml. Epidural anaesthesia was used only in open surgery, in both the ERAS and standard care groups. General anaesthesia in the ERAS patients was total intravenous anaesthesia with propofol and remifentanyl. In the control group, the general anaesthesia was gas with propofol or thiopental, fentanyl, and isofluran or sevofluran. Nasogastric tubes were removed immediately after extubation in both groups.

Table 1 Numbers of ERAS items used in both groups.

	ERAS care	Standard care
Preoperative		
Preoperative counselling	✓	
Preoperative feeding	✓	
Carbohydrate loading	✓	
No bowel preparation		
No premedication	✓	
Antimicrobial prophylaxis	✓	✓
Peri-operative		
Fluid restriction	✓	
Anaesthetic protocol	TIVA	Gas
Prevention of hypothermia	✓	✓
Epidural anaesthesia	✓	✓
Minimal invasive incisions		
Postoperative		
No routine use of nasogastric tubes	✓	✓
No use of drains in colon surgery	✓	✓
Enforced postoperative mobilization	✓	
Enforced postoperative feeding	✓	
No systemic morphine use	✓	
Standard laxative	✓	
Early removal of urine catheter	✓	
Total number	16	5

TIVA, total intravenous anaesthesia.

Statistical analysis

THS was the primary outcome measure of the intervention. First, a pilot study with 20 patients was conducted. In this, the median difference in total length of stay was 2.5 days. Based on a power analysis for a power of 0.8 and significance level of 0.05, a total sample size of 300 patients was needed to detect a minimum reduction in THS of 2.5 days between the ERAS and conventional groups. The 20 patients previously analysed in the pilot study were not included in the current study.

Statistical analysis was performed on an intention-to-treat basis using IBM SPSS Statistics software, version 22. Descriptive statistical methods were used to characterize the sample. Data are presented as median and range. We used the chi-squared test to compare discrete variables. The Mann-Whitney *U* test was used for continuous, non-normally distributed variables, and an independent-sample *t* test was used for continuous, normally distributed data.

Results

Between 5 January 2012 and 4 March 2015, 324 patients were randomly assigned to the ERAS programme or standard care. Of 653 eligible patients, 329 were not included, mainly for logistical reasons and a lack of capacity in the ERAS outpatient clinic (Fig. 1). Patients who underwent surgery in July and August were not included due to the summer vacation of the responsible study nurse and surgeons. Among patients who met the inclusion criteria ($n = 298$) but were not included in the study, there were no differences in age (median 68 years) or the male/female ratio (151/147) compared with the included patients. There were fewer laparoscopies in patients not included in the study [81/298 (29.2%) *vs* 122/307 (39.7%)] and a smaller proportion of rectal operations [125/298 (41.9%) *vs* 167/307 (54.4%)], including proctocolectomy. The patient characteristics and surgical details for the included patients are summarized in Table 2. Baseline characteristics between the two treatment groups did not differ significantly.

THS was significantly shorter among patients randomized to the ERAS group than the standard group

[median 5 (range 2–50) days *vs* median 8 (range 2–48) days ($P = 0.001$)] (Table 2). All discharge criteria, such as passage of first flatus, passage of first stool and pain control with oral medication, were achieved earlier in the ERAS group. The interval to the toleration of solid food without nausea did not differ between the two groups (Table 3). Postoperative CRP levels were lower on postoperative day 2 in the standard than in the ERAS group; otherwise there were no differences between the groups. In both groups (ERAS and standard), patients operated by laparoscopic surgery exhibited a significantly shorter THS than patients operated openly (median 5 *vs* 7 days; $P < 0.005$).

The two treatment groups exhibited similar outcomes regarding overall, major and minor morbidity, reoperation rate, readmission rate and 30-day mortality (Tables 4 and 5). Complications did not differ significantly between the groups (Clavien–Dindo ≥ 3 b).

Adherence to ERAS and standard care protocols is summarized in Table 6. Although there were no differences in intra-operative fluid load, significantly less intravenous water was administered to the ERAS group than the standard care group during the first 24 postoperative hours and the first seven postoperative days

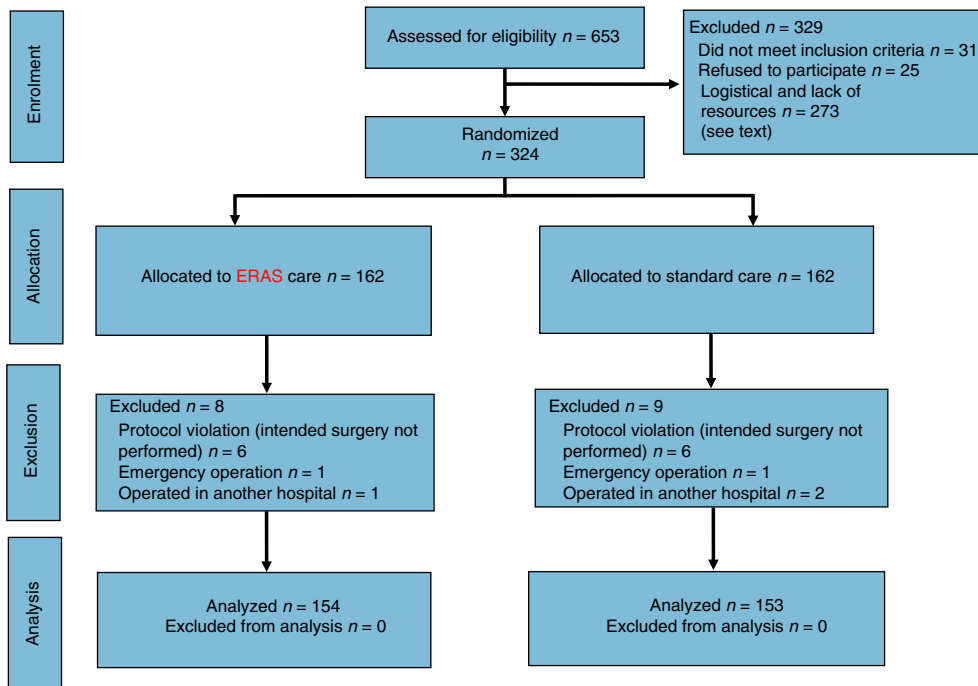


Figure 1 CONSORT diagram for the trial.

Table 2 Patient characteristics and surgical details.

	ERAS care	Standard care	<i>P</i>
Included patients	154	153	
Median age, years (range)	65 (23–89)	66 (19–93)	0.810*
Male/female ratio	83/71	82/71	0.960†
Malignant/benign	124/30	117/36	0.404†
ASA grade			0.394†
I	38	28	
II	93	101	
III	23	24	
Type of colorectal surgery			0.087†
Right-sided	35	41	
Left-sided or sigmoid	28	36	
Low anterior resection	53	40	
Protective ileostomy or colostomy	24	25	
Abdominoperineal resection (Procto) colectomy	6	8	
Laparoscopy	62	60	0.849†
Open surgery	92	93	
Conversion (%)	13	10	
Duration of surgery, median (range), min	168 (76–432)	161 (46–393)	0.420‡
Blood loss, median (range), ml	150 (0–1500)	150 (0–1700)	0.196‡

ASA, American Society of Anesthesiologists.

**t* test.

† χ^2 test.

‡Mann–Whitney *U* test.

(*P* = 0.001). Ninety-one patients in both groups received thoracic epidural analgesia, but significantly more patients in the ERAS group experienced removal of the epidural catheter on day 2 (*P* < 0.001). Significant differences were also observed in a large number of other ERAS elements, such as type of anaesthesia, intake of carbohydrate drinks, use of laxatives and oral opiates, total oral intake after surgery, postoperative mobilization and early removal of the urinary catheter.

Discussion

The study demonstrated a significantly shorter THS in patients treated with ERAS care compared with stan-

Table 3 Postoperative data.

	ERAS care (n = 154)	Standard care (n = 153)	<i>P</i>
Total hospital stay, median (range), days	5 (2–50)	8 (2–48)	0.001*
Postoperative hospital stay, median (range), days	5 (2–50)	7 (2–48)	<0.001*
Days to fulfil discharge criteria, median (range)			
Passage of first flatus	1 (0–4)	1 (1–14)	<0.001*
Passage of first stool	1 (1–6)	2 (1–14)	<0.001*
Ability to tolerate solid food without nausea	2 (0–9)	1 (0–12)	0.612*
Pain control with oral medication	2 (0–9)	4 (0–16)	<0.001*
CRP levels, median (range), mg/l			
Preoperative	2 (1–42)	2 (1–152)	0.926*
Day 2 postoperative	121 (19–499)	96 (7–454)	0.008*
Day 10 postoperative	10 (1–216)	12 (1–298)	0.921*
Day 30 postoperative	3 (1–119)	4 (1–257)	0.178*

CRP, C-reactive protein.

*Mann–Whitney *U* test.

dard care after colorectal surgery. Earlier discharge from hospital alone should not, however, be the primary object of surgical care. The main focus should be to improve care by decreasing morbidity. This study revealed no differences between the two treatment groups regarding mortality, major or minor morbidity, reoperations or readmissions.

The trial was initiated to compare an ERAS programme with standard peri-operative care in an everyday practice of open and laparoscopic colorectal surgery. Previously published cohort studies and randomized controlled trials have shown that the ERAS imparts benefits regarding hospital stay and bowel function. While a few randomized trials have indicated less morbidity [11–14], others have indicated no difference [5–10]. Most of these studies have included few patients or have included patients over a long time period, without reporting the total number of eligible patients who were assessed. In our study, there were relatively many complications. We have prospectively registered complications very carefully, and the largest proportion included minor complications.

The main strengths of our study, besides the randomized controlled trial design, are the high proportion of eligible patients included in the study and the use of

Table 4 Surgical and non-surgical complications.

	ERAS care (<i>n</i> = 154)	Standard care (<i>n</i> = 153)	<i>P</i> *
Overall morbidity < 30 days, <i>n</i> (%)	65 (42.2)	68 (44.4)	0.693
Patients with one or more major complications, <i>n</i> (%)	17 (11.1)	12 (7.8)	0.329
Total major complications, <i>n</i> (%)			
Anastomotic leakage/patients with an anastomosis	10/117 (8.5)	4/122 (3.3)	0.084
Colon	3/59 (5.1)	2/77 (2.6)	0.447
Rectum	7/58 (12.1)	2/45 (4.4)	0.174
Abdominal wall dehiscence	5 (3.2)	5 (3.3)	0.992
Mechanical ileus requiring reoperation	0 (0)	1 (0.7)	0.315
Other complications requiring reoperation [†]	2 (1.3)	2 (1.3)	0.995
Respiratory complications requiring ICU	2 (1.3)	0 (0)	0.156
Other major complication [‡]	4 (2.6)	1 (0.7)	0.178
Patient with one or more minor complications, <i>n</i> (%)	53 (34.4)	63 (41.2)	0.257
Wound infection, abdominal	10 (6.5)	13 (8.5)	0.505
Wound infection, perineal	8 (25.0)	9 (32.1)	0.803
Intra-abdominal infection, antibiotic treated or drainage	11 (7.1)	6 (3.9)	0.217
Prolonged postoperative ileus	4 (2.6)	7 (4.6)	0.351
Pneumonia	7 (4.5)	8 (5.2)	0.791
Pleural effusion requiring drainage	5 (3.2)	3 (2.0)	0.474
Pulmonary embolism (PE)	2 (1.3)	0 (0)	0.156
Cardiac arrhythmia	2 (1.3)	3 (2.0)	0.652
Urinary infection	11 (7.1)	16 (10.4)	0.305
Urine retention	9 (5.8)	15 (9.8)	0.202
Gastrointestinal bleeding not requiring intervention	1 (0.6)	1 (0.6)	0.995
Renal failure (S-Creatinine > 100 µmol/l)	8 (5.2)	7 (4.8)	0.791
Hyponatremia (S-Sodium < 130 mmol/l)	1 (0.06)	3 (2.0)	0.314
Postoperative confusion	3 (1.9)	3 (1.9)	0.994
Other minor complication [§]	8 (5.2)	4 (2.6)	0.243
Reoperations, <i>n</i> (%)	17 (11.0)	11 (7.2)	0.241
Readmission < 30 days, <i>n</i> (%)	29 (18.8)	21 (13.4)	0.226
Mortality < 30 days, <i>n</i> (%)	3 (1.9)	0 (0)	0.084

* χ^2 -test.

†Other complications requiring reoperation: postoperative bleeding, deep abdominal infection, iatrogenic bowel perforation.

‡Other major complication: Cerebral vascular accident, gastrointestinal bleeding requiring endoscopic intervention, sepsis.

§Other minor complication: paraesthesia of arm after laparoscopy, port site bleeding, pleuritis, subcutaneous infections, antibiotic treated infection unknown cause, transient ischemic attack with normal MRI.

two completely separate wards for patients allocated to the different study arms. These wards were staffed by different nurses to minimize the possibility of introducing confounders into treatment effects. The nurses in the ERAS department had received special training in the principles of ERAS and all patients were monitored daily by a dedicated nurse. In addition, the department had a separate colorectal unit with a stable staff of seven senior surgeons during the entire study period. To minimize observer-related bias, all checks at days 10 and 30 were conducted by the same dedicated nurse and the same two surgeons. All prospective data registration was performed by one nurse and one surgeon. We included more than 300 patients over a 3-year period. Main causes of not including patients were logistical reasons.

Due to a lack of capacity in the ERAS outpatient clinic, the staff secretary arbitrarily bypassed patients into the non-ERAS outpatient clinics, and during the summer vacation no patients were included in the study. Compared with patients not included in the study, more included patients underwent a laparoscopic procedure and a higher proportion underwent rectal resection. Although these differences may reflect a selection bias, patient randomization and inclusion was a continuous process, except during the summer vacation. Both colon and rectum resections have been included in this controlled randomized study as in our opinion it should be possible to apply ERAS criteria to surgical patients in a randomized controlled study design independent of the type of surgical procedure.

Table 5 Incidence of complications (Clavien–Dindo classification).

	ERAS care (n = 154)	Standard care (n = 153)	P*
Grade I	26	31	
Grade II	18	18	
Grade IIIa	3	7	
Grade IIIb	15	10	≥ Grade IIIb 0.088
Grade IVa	1	1	
Grade IVb	0	0	
Grade V	3	0	

* χ^2 test.

As with many other trials, the main limitation of this study is that it has become increasingly difficult to define standard care. Some ERAS strategies are considered the current ‘standard of care’, while the omission of elements of those strategies, such as antimicrobial prophylaxis, prevention of hypothermia and thoracic epidural anaesthesia during open surgery, may be considered unethical. This may have affected the results from the standard group and made it more difficult to identify significant differences. As the experience of staff surgeons, nurses and paramedical staff with ERAS recovery has increased, it has not been possible to exclude all ERAS items to obtain a true traditional care pathway as a control group,

Table 6 Adherence to the study protocol.

	ERAS care (n = 154)	Standard care (n = 153)	P
Preoperative phase – yes, n (%)			
Extended preoperative counselling	154 (100)	2 (1)	<0.001*
Omission of bowel preparation	38 (25)	39 (25)	0.21*
Intake of CHL evening before surgery, median (range), ml	200 (20–200)	0 (0–0)	<0.001‡
Day of surgery – yes, n (%)			
No preoperative fasting	154 (100)	153 (100)	1*
Intake of CHL 2 h before surgery, median (range), ml	200 (20–200)	0 (0–0)	<0.001*
No premedication	103 (67)	92 (60)	0.258*
Laxative (lactulose 10 ml)	154 (100)	0 (0–0)	<0.001*
Antimicrobial prophylaxis (doxycycline, metronidazole)	154 (100)	153 (100)	1*
Thoracic epidural analgesia	91 (59)	90 (59)	0.962*
Type of anaesthesia – gas/TIVA, n	1/153	151/2	<0.001*
Prevention of hypothermia	154 (100)	153 (100)	1*
Intra-operative fluid loading, median (range), l	2.8 (0.9–5.7)	2.6 (1.4–6.5)	0.282†
Total oral intake after surgery, median (range), l	0.6 (0–3.0)	0.2 (0–1.4)	<0.001†
Mobilization 24 h after surgery, median (range), min	180 (0–420)	5 (0–300)	<0.001‡
Intravenous fluid, median (range), l			
First 24 h, included intra-operative	3.9 (1.9–9.9)	4.4 (1.8–9.5)	0.001†
First 7 days, included intra-operative	5.6 (1.9–19.2)	7.8 (2.8–30.1)	<0.001†
Total oral intake, median (range), l			
POD 1	1.6 (0.3–3.2)	1.0 (0.1–2.5)	<0.001†
POD 2	1.6 (0.5–3.5)	1.3 (0.1–2.5)	<0.001†
Start laxative POD 1 – yes, n (%)	123 (80)	5 (3)	<0.001*
Use of oral opiates – yes, n (%)	63 (40)	83 (54)	0.02*
Nasogastric tube postoperatively – yes, n (%)	5 (3)	18 (12)	0.004*
Removal of urine catheter, median (range), days	2 (1–21)	4 (1–28)	<0.001*
Removal of thoracic epidural analgesia, median (range), days	2 (0–5)	4 (0–6)	<0.001†
Mobilization, median (range), min			
POD 2	240 (15–540)	65 (0–630)	<0.001‡
POD 3	250 (30–660)	140 (10–720)	<0.001‡

CHL, carbohydrate-loaded drink (ProvideXtra®); gas, gas anaesthesia with isoflurane or sevoflurane; TIVA, total intravenous anaesthesia; POD, postoperative day. Intra-operative fluid loading included 800 ml antibiotics.

* χ^2 test.

†t test.

‡Mann–Whitney U test.

but in our study significant differences were observed for a large number of ERAS elements. Another limitation of our study was the absence of blinding of the treatment. Neither the patient nor the physician or nurses were blinded to the treatment assignment. As patients were admitted to two separate wards it would not be possible to blind patients or staff.

A widely accepted intention of ERAS is to enhance patient recovery by more quickly restoring normal physiological function and attenuating the surgical stress response. The length of time required to regain bowel function was shorter in patients who received the ERAS protocol, although this is difficult to objectify. It is likely that bowel function is better assessed by the tolerance of enteral challenge than by excretory function. The discharge criteria of passage of first flatus, passage of first stool and adequate pain control with oral medication were all achieved earlier in the ERAS group. What we regard as the most important criterion, however, the ability to tolerate solid food without nausea, did not differ between the two groups (Table 2). Moreover, there was no difference in postoperative CRP levels between groups, indicating the lack of differential inflammatory response, and on the second postoperative day CRP levels were lower in the standard than in the ERAS group.

An important factor is the increasing use of minimal invasive colorectal surgery. Large randomized controlled trials comparing open and laparoscopic colon surgery demonstrated significantly reduced length of hospital stay for laparoscopic procedures [20,21]. The total length of hospital stay was significantly shorter in laparoscopically operated patients. As the surgical approach was not part of the trial protocol, we cannot exclude the possibility of selection bias, but the number of patients who underwent laparoscopic surgery did not differ between study arms, suggesting that selection bias is unlikely to have influenced the results.

Like many of the other randomized controlled trials [5–10], the present study revealed no differences in mortality, major or minor morbidity, reoperation or readmission, which may explain the shorter THS in the ERAS group. There were also no between-group differences in bowel function in the tolerance of enteral nutrition or surgical stress (according to postoperative CRP levels). In most studies the length of stay is the primary outcome, but the reasons for delay in discharge are mostly not given. Even with established discharge criteria, not all patients are discharged in everyday practice when they meet the criteria. This may be due to logistical difficulty or the patient's own wishes. The peri-operative information and instructions to patients are essential to achieve early discharge, but this is not a goal in itself. Patients are equally satisfied if they are dis-

charged after 5 or 7 days [10]. What matters for the patient is the experience of a safe treatment course with a minimum of complications. It has been shown that the more ERAS items are implemented, the more the postoperative course is improved [22], but the evidence is far from clear whether all elements are equally important. The results of this study do not allow the conclusion that one ERAS item is more effective than another. The ERAS approach consisted of a package of interventions that were implemented differently between groups but equally within each group. Thus, the groups had very little or no variation with respect to single interventions. This design is appropriate for evaluating the entire package of interventions, but not for comparing interventions. Consequently, it cannot be expected that a multivariate model comparing the effects of single interventions will lead to meaningful and interpretable results. Given the similar morbidity, postoperative CRP levels and the tolerance of enteral nutrition in both groups, the present study suggests that accurate peri-operative information about each patient's expectations and continuous guidance for ERAS elements is a highly important factor for reduced THS. Continuous counselling and repetition of details by trained personnel throughout the care pathway seem to be important for motivating the patient to comply with their ERAS programme and it is our clear impression that counselled patients more strongly comply with the ERAS criteria. We believe that patient commitment to the programme has an important impact on recovery and the time to discharge from the hospital.

Further studies will be necessary to assess the impact of counselling when groups of patients are otherwise equal in terms of ERAS criteria. We are therefore enrolling our colorectal patients into a new randomized study in which both study arms contain the same ERAS items and only differ in peri-operative information and follow-up by dedicated nurses.

Acknowledgements

This study was supported and facilitated by the Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway. The authors declare no conflicts of interest.

References

- 1 Kehlet H. Fast-track colorectal surgery. *Lancet* 2008; **371**: 791–3.
- 2 Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum* 2004; **47**: 271–7.

- 3 Polle SW, Wind J, Fuhring JW *et al.* Implementation of a fast-track perioperative care program: what are the difficulties? *Dig Surg* 2007; **24**: 441–9.
- 4 Stephen AE, Berger DL. Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. *Surgery* 2003; **133**: 277–82.
- 5 Anderson AD, McNaught CE, MacFie J *et al.* Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; **90**: 1497–504.
- 6 Delaney CP, Zutshi M, Senagore AJ *et al.* Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* 2003; **46**: 851–9.
- 7 Gatt M, Anderson AD, Reddy BS *et al.* Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005; **92**: 1354–62.
- 8 Khoo CK, Vickery CJ, Forsyth N, Vinal NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* 2007; **245**: 867–72.
- 9 Ren L, Zhu D, Wei Y *et al.* Enhanced recovery after surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. *World J Surg* 2012; **36**: 407–14.
- 10 Flug MS, Wind J, Hollmann MW *et al.* Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA study). *Ann Surg* 2011; **254**: 868–75.
- 11 Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology* 2009; **136**: 842–7.
- 12 Serclova Z, Dytrych P, Marvan J *et al.* Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). *Clin Nutr* 2009; **28**: 618–24.
- 13 Wang G, Jiang ZW, Xu J *et al.* Fast-track rehabilitation program vs conventional care after colorectal resection: a randomized clinical trial. *World J Gastroenterol* 2011; **17**: 671–6.
- 14 Wang Q, Suo J, Jiang J *et al.* Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial. *Colorectal Dis* 2012; **14**: 1009–13.
- 15 Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev* 2011; (2): CD007635.
- 16 Mohn AC, Bernardshaw SV, Ristesund SM, Hovde Hansen PE, Rokke O. Enhanced recovery after colorectal surgery. Results from a prospective observational two-centre study. *Scand J Surg* 2009; **98**: 155–9.
- 17 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13.
- 18 Gustafsson UO, Scott MJ, Schwenk W *et al.* Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS[®]) Society recommendations. *World J Surg* 2013; **37**: 259–84.
- 19 Nygren J, Thacker J, Carli F *et al.* Guidelines for perioperative care in elective rectal/pelvic surgery: enhanced Recovery After Surgery (ERAS[®]) Society recommendations. *World J Surg* 2013; **37**: 285–305.
- 20 Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; **350**: 2050–9.
- 21 Veldkamp R, Kuhry E, Hop WC *et al.* Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477–84.
- 22 Gustafsson UO, Hausel J, Thorell A *et al.* Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg* 2011; **146**: 571–7.



Original Research

Pre- and postoperative stoma education and guidance within an enhanced recovery after surgery (ERAS) programme reduces length of hospital stay in colorectal surgery



H.M. Forsmo^{a, b, *}, F. Pfeffer^{a, b}, A. Rasdal^a, H. Sintonen^c, H. Körner^{b, d}, C. Erichsen^a

^a Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway

^b Department of Clinical Medicine, University of Bergen, Norway

^c Department of Public Health, University of Helsinki, Helsinki, Finland

^d Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway

HIGHLIGHTS

- Patients with stoma formation in colorectal surgery benefits from an ERAS programme.
- Hospital stay can be reduced significantly by stoma education and counselling.
- Stoma formation is associated with high frequency of stoma related complications.

ARTICLE INFO

Article history:

Received 19 August 2016

Accepted 21 October 2016

Available online 22 October 2016

Keywords:

Colorectal surgery

Stoma

Education

ERAS

Complications

ABSTRACT

Introduction: Stoma formation delays discharge after colorectal surgery. Stoma education is widely recommended, but little data are available regarding whether educational interventions are effective. The aim of this prospective study was to investigate whether an enhanced recovery after surgery (ERAS) programme with dedicated ERAS and stoma nurse specialists focusing on counselling and stoma education can reduce the length of hospital stay, re-admission, and stoma-related complications and improve health-related quality of life (HRQoL) compared to current stoma education in a traditional standard care pathway.

Methods: In a single-center study 122 adult patients eligible for laparoscopic or open colorectal resection who received a planned stoma were treated in either the ERAS program with extended stoma education (n = 61) or standard care with current stoma education (n = 61). The primary endpoint was total postoperative hospital stay. Secondary endpoints were postoperative hospital stay, major or minor morbidity, early stoma-related complications, health-related quality of life, re-admission rate, and mortality. HRQoL was measured by the generic 15D instrument.

Results: Total hospital stay was significantly shorter in the ERAS group with education than the standard care group (median [range], 6 days [2–21 days] vs. 9 days [5–45 days]; $p < 0.001$). Regarding overall major and minor morbidity, re-admission rate, HRQoL, stoma-related complications and 30-day mortality, the two treatment groups exhibited similar outcomes.

Conclusion: Patients receiving a planned stoma can be included in an ERAS program. Pre-operative and postoperative stoma education in an enhanced recovery programme is associated with a significantly shorter hospital stay without any difference in re-admission rate or early stoma-related complications.

© 2016 IJS Publishing Group Ltd. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Stoma formation is a well-known cause of delayed discharge

after colorectal surgery [1–3]. Although education is widely recommended for patients receiving a new stoma, few data are available on the effect of educational interventions on decreased

* Corresponding author. Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, 5021, Bergen, Norway.

E-mail address: havard.forsmo@helse-bergen.no (H.M. Forsmo).

length of stay, re-admissions, and stoma complications. A recently published systematic review of educational interventions for stoma patients concluded that no consensus exists on the benefit of stoma education, though the grade of evidence was low [4]. Enhanced recovery after surgery (ERAS) is a multimodal peri-operative approach that aims to reduce organ dysfunction and the surgical stress response, reducing morbidity and length of hospital stay [5]. One important aspect of an enhanced recovery programme is the peri-operative information and patient education, which appears to be essential in achieving early discharge [6,7].

We carried out a controlled, randomized trial in which we compared patients treated by an ERAS approach to patients treated in a standard care pathway [6]. The main objective of the present sub-study was to evaluate patients receiving a planned stoma. We wanted to investigate whether an ERAS programme with dedicated ERAS and stoma nurse specialists focusing on counselling and stoma education can reduce the length of hospital stay, re-admission, and stoma-related complications and improve health-related quality of life (HRQoL) compared to current stoma education in a traditional standard care pathway.

2. Material and methods

2.1. Study design

The current study was part of a randomized controlled trial at Haukeland University Hospital in Bergen, Norway [6]. The aim was to determine whether an ERAS care pathway can reduce the total postoperative hospital stay (THS) compared to standard care, mainly as a result of reduced morbidity. Patients who were to receive a stoma were randomly divided in ERAS care with extended stoma education, and standard care with conventional stoma education. Patients older than 18 years of age scheduled for elective open or laparoscopic colorectal surgery for benign or malignant disease and planned stoma were eligible for inclusion. Patients with rectal cancer and pre-operative pelvic radiation were also included. Patients were informed about the study both in writing and orally, and written consent was obtained from those who accepted to participate. Patients were informed about the treatment group 1–3 weeks before surgery. Due to the nature of the study, neither the physician nor the patient was blinded to the treatment assignment. The trial was approved by the regional committee of ethics in Western Norway (reference number 2010/2079).

In the current sub-study, we wanted to focus on patients who were planning to have a stoma as part of their surgical treatment and were likely to be self-sufficient in managing their stoma. Patients who already had a stoma before the operation were not included.

2.2. Objectives and endpoints

The primary endpoint was the THS which was defined as the postoperative hospital stay (PHS), in days, and any additional days if re-admission was necessary within the first 30 days after surgery. The discharge criteria were similar for both treatment groups: (1) postoperative pain adequately controlled with per oral medication (VAS <4), (2) mobilized and out of bed more than 6 h/day, (3) bowel function and ability to tolerate solid food without nausea, and (4) no complications requiring treatment in hospital. Furthermore, all patients had to be comfortable with the stoma care based on an agreement between the ward nurse, the stoma nurse specialist, and the patients themselves that they were proficient enough.

Secondary endpoints were PHS, major or minor morbidity, mortality, early stoma-related complications, re-admission rate,

and HRQoL. Data were recorded before the operation, on the day of surgery, and daily after surgery until discharge. Definitions of complications were established prior to commencing the study. HRQoL was assessed using the 15D instrument (<http://www.15d-instrument.net/15d>), which is a standardized, self-administered health state descriptive questionnaire that has been validated and translated into Norwegian and can be used both as a profile and a single index score measure [8]. The 15D includes dimensions of mobility, vision, hearing, breathing, sleeping, eating, speech/communication, excretion, usual activities, mental functioning, discomfort and symptoms, depression, distress, vitality, and sexual activity, with five levels on each. The single index score (15D score) representing the overall HRQoL on a scale of 0–1 (1 = full health, 0 = being dead) and the dimension level values of 0–1 (1 = no problems on the dimension, 0 = being dead) are calculated from the health state descriptive system using a set of population-based preferences or utility weights. The minimum clinically important change/difference in the 15D score is 0.015 [9].

All patients visited an outpatient clinic on days 10 and 30, following up with the same stoma nurse specialist and the same two surgeons to minimize observer-related bias. The occurrences of previously undescribed stoma-related complications were noted during regular outpatient follow-up by the stoma nurse specialists after 12 weeks.

2.3. Peri-operative education and care

Patients in the ERAS group had one or two consultations 45–60 min in duration before surgery with the ERAS nurse and stoma nurse specialist. The patients were told about their own role in retraining so that they understood the importance of their own efforts and received thorough information about stoma surgery and training in stoma care. The explanation provided to the patients included the part of the intestine that was to be removed and the consequences it may have, they were shown pictures of a stoma, and the function of stoma care equipment was explained. Pre-operative stoma education included the possible impact of stoma creation on relationships and sexuality and various activities of daily life, such as bathing and showering. The routines after surgery were explained, the first shift being on the first postoperative day with daily changes in order to get used to and build up skills and confidence. Patients were also shown how to and practised changing a stoma, told where to buy stoma care equipment, and informed about the Norwegian patient association for stoma patients, Norilco. They received stoma care equipment to take home for practice and received an information brochure to read.

Patients in the standard group received their first information about the stoma from nurses with varying experience in stoma care on the day of admission, which was the day before surgery. Patients were told the part of the intestine to be removed and informed about the shift routines, life with a stoma, bathing and showering with a stoma, and Norilco.

In both groups, the stoma site was marked the day before surgery. After surgery, the patients in the standard care group received daily education from ward nurses, supervised sporadically by a stoma nurse specialist. In the ERAS group the patients received daily education from a stoma nurse specialist.

Patients in the ERAS group were treated according to the ERAS protocol, whereas patients allocated to standard care were treated according to standard peri-operative care in Norway [6]. The numbers of ERAS items used in both groups are shown in Table 1. During hospitalization, the patients in the ERAS group were admitted to a ward separate from the standard group. The responsible nurse in the ERAS group was a stoma nurse specialist who also provided pre-operative education. Nurses in the standard

care group were nurses experienced in the care of patients undergoing colorectal surgery, including stoma care.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22. Descriptive statistical methods were used to characterize the sample and data were presented as median and range. To compare discrete variables the chi-square test was used. The independent sample *t*-test was used for continuous, normally distributed outcomes and the Mann-Whitney *U* test for continuous, non-normally distributed outcomes. Paired sample *t*-test was used to detect significant changes in the 15D score from baseline to 10 days and 30 days in the two groups and an ANOVA regression was applied to compare differences in the change in the 15D score from baseline to 30 days between the groups.

This study was registered with ClinicalTrials.gov, no. NCT01610726.

3. Results

Between January 5, 2012, and March 4, 2015, 122 patients who received a planned stoma were included. The relevant patient characteristics and surgical details of patients who received a planned stoma are provided in Table 2. Baseline characteristics were similar in both treatment groups. The types of stoma are provided in Table 3.

3.1. Hospital stay and complications

The THS for patients receiving a stoma was significantly shorter in the group randomized to ERAS and peri-operative stoma education than the standard group (median [range], 6 days [2–21 days] vs. 9 days [5–45 days]; $p < 0.001$; Table 4). Regarding overall, major, and minor morbidity, re-operation rate, re-admission rate, and 30-day mortality, the two treatment groups exhibited similar outcomes (Table 5). A considerable proportion of patients experienced stoma complications, 38% in the ERAS group and 51% in the standard care group (Table 6, $p = 0.15$). Peristomal

Table 1
Numbers of ERAS items used in both groups [6].

	ERAS care	Standard care
Preoperative		
Preoperative counselling	V	
Preoperative feeding	V	
Carbohydrate loading	V	
No bowel preparation		
No premedication	V	
Antimicrobial prophylaxis	V	V
Perioperative		
Fluid restriction	V	
Anaesthetic protocol	TIVA	Gas
Prevention of hypothermia	V	V
Epidural anesthesia	V	V
Minimal invasive incisions		
Postoperative		
No routine use of nasogastric tubes	V	V
No use of drains in colon surgery	V	V
Enforced postoperative mobilisation	V	
Enforced postoperative feeding	V	
No systemic morphine use	V	
Standard laxative	V	
Early removal of urine catheter	V	
Total number	16	5

TIVA: total intravenous anesthesia.

Table 2

Patient characteristics and surgical details for patients who received a planned stoma.

	ERAS care	Standard care	p-value
Included patients	61	61	
Median age (range), years	64 (23–88)	66 (19–89)	0.68 ^a
Male/female, n/n	34/27	41/20	0.19 ^b
Malignant/benign, n/n	56/5	57/4	0.73 ^b
ASA, n (%)			0.84 ^b
I	10 (16.4)	12 (19.7)	
II	42 (68.8)	39 (63.9)	
III	9 (14.8)	10 (16.4)	
Type of colon-rectum surgery, n (%)			0.30 ^b
Left-sided or sigmoid	6 (9.8)	3 (4.9)	
Low anterior resection	23 (37.7)	25 (41.0)	
Abdominoperineal resection (APR)	28 (45.9)	26 (42.6)	
(Procto)-colectomy	4 (6.6)	7 (11.5)	
Laparoscopy, n (%)	19 (31.1)	13 (21.3)	0.22 ^b
Open surgery, n (%)	42 (68.9)	48 (78.9)	
Conversion, n (%)	2 (10.5)	0 (0)	
Median duration of surgery (range), minutes	193 (111–432)	197 (102–367)	0.87 ^a
Median blood loss (range), mL	200 (0–1500)	200 (0–1000)	0.74 ^a

^a *t*-test.

^b χ^2 test.

Table 3

Types of stoma used in each patient group.

	ERAS care (n = 61)	Standard care (n = 61)
Protective loop ileostomy after LAR (or IPAA), n	24 (2)	27 (3)
Protective loop colostomy after LAR, n	1	1
End ileostomy, n	2	4
End colostomy, n	34	29

LAR: low anterior resection; IPAA: ileal pouch-anal anastomosis.

Table 4

Postoperative data.

	ERAS care	Standard care	p-value ^a
Total hospital stay for planned stoma, median days (range)	6 (2–21)	9 (5–45)	<0.001
Postoperative hospital stay for planned stoma, median days (range)	5 (2–12)	9 (5–24)	<0.001

^a Mann-Whitney *U* test.

dermatitis was the most common complication, but more severe complications such as high output stomas with dehydration and renal failure (S-creatinine > 100 $\mu\text{mol/L}$) were frequent. Comparing ileostomies and colostomies in both groups, significantly more complications occurred with ileostomies (Table 7, $p < 0.001$).

3.2. Health-related quality of life

The mean 15D score at baseline was 0.871 in the ERAS group and 0.870 in the standard care group. No significant difference was found between the groups in any dimension level value or the 15D score at baseline, 10 days, or 30 days. Both groups had significant and clinically important deterioration in the 15D score from baseline to 10 days (ERAS: -0.0868, $p < 0.001$; standard care: -0.0910, $p < 0.001$) and significant and clinically important improvement in the 15D score from 10 days to 30 days (ERAS: 0.0273, $p = 0.001$;

Table 5
Surgical and non-surgical complications in patients who received a planned stoma.

	ERAS care (n = 61)	Standard care (n = 61)	p-value ^a
Overall morbidity < 30 days	29 (50.8)	37 (60.7)	0.15
Patients with one or more major complications	2 (3.3)	1 (1.6)	0.55
Major complications			
Anastomotic leakage/patients with an anastomosis	0/28 (0)	0/30 (0)	1.00
Abdominal wall dehiscence	1 (1.6)	0 (0)	0.32
Other complications requiring re-operation ^b	1 (1.6)	1 (1.6)	1.00
Other major complication ^c	1 (1.6)	0 (0)	0.32
One or more minor complications	29 (47.5)	36 (59.1)	0.20
Wound infection, abdominal	1 (1.6)	4 (6.6)	0.17
Wound infection, perineal	7 (25)	9 (34.6)	0.44
Intra-abdominal infection, antibiotic treated or drainage	2 (3.3)	1 (1.6)	0.55
Prolonged postoperative ileus	1 (1.6)	5 (8.2)	0.09
Pneumonia	1 (1.6)	3 (4.9)	0.31
Cardiac arrhythmia	0 (0)	2 (3.3)	0.15
Urinary infection	7 (11.5)	9 (14.8)	0.59
Urine retention	7 (11.5)	13 (21.3)	0.14
Gastrointestinal bleeding not requiring intervention	1 (1.3)	0 (0)	0.32
Renal failure (S-creatinine > 100 µmol/L)	5 (8.2)	5 (8.2)	1.00
Hyponatraemia (S-sodium < 130 mmol/L)	0 (0)	2 (3.3)	0.16
Postoperative confusion	1 (1.6)	0 (0)	0.32
Other minor complication ^d	3 (4.9)	0 (0)	0.08
Re-operation	2 (3.3)	1 (1.6)	0.56
Re-admission < 30 days	13 (21.3)	11 (18.0)	0.62
Mortality < 30 days	1 (1.6)	0 (0)	0.32

^a χ^2 test.

^b Postoperative bleeding, deep abdominal infection.

^c Sepsis.

^d Paraesthesia in arm after laparoscopy, antibiotic treated infection of unknown cause, transient ischaemic attack with normal MRI. Data are presented as n (%).

Table 6
Distribution of stoma-related complications.

	ERAS care (n = 61)	Standard care (n = 61)	p-value ^a
Patients with one or more stoma complications, n (%)	23 (37.7)	31 (50.8)	0.15
High output with dehydration and S-creatinine > 100 µmol/L, n	4	6	
Stoma necrosis, n	0	1	
Prolonged ileus due to stoma, n	1	0	
Peristomal dermatitis, n	9	11	
Peristomal dermatitis due to high output, n	5	7	
Peristomal dermatitis due to stoma leakage, n	3	5	
Stoma separation, n	2	3	

^a χ^2 test.

Table 7
Distribution of stoma-related complications according to stoma type.

	Ileostomy (n = 57)	Colostomy (n = 65)	p-value ^a
Patients with one or more stoma complications (%)	39 (68.4)	15 (23.1)	<0.001
High output with dehydration and S-creatinine > 100 µmol/L	10	0	
Stoma necrosis	1	0	
Prolonged ileus due to stoma	0	1	
Peristomal dermatitis	15	5	
Peristomal dermatitis due to high output	10	2	
Peristomal dermatitis due to stoma leakage	4	4	
Stoma separation	2	3	

^a χ^2 test.

standard care: 0.0322, $p = 0.004$). According to an ANOVA regression analysis, with age, gender, and baseline 15D score standardized, there was no difference between the groups regarding the change in 15D score from baseline to 30 days.

4. Discussion

This prospective study revealed a significantly shorter hospital stay for patients treated with ERAS care and stoma education than patients receiving standard care for stoma after colorectal surgery. The two treatment groups did not differ in regards to mortality, major or minor morbidity, stoma complications, re-operations, re-admissions, or HRQoL within the first 30 days. To minimize the possibility of confounding the treatment effect, patients in the two treatment groups were located in two different wards that were completely separated with different nursing personnel. All patients in the ERAS group were monitored daily by a dedicated stoma nurse specialist. To minimize observer-related bias, all outpatient visits on days 10 and 30 were carried out by the same stoma nurse specialist and the same two surgeons. They also performed all prospective data registration.

4.1. Hospital stay

This sub-study analysis was done to evaluate the effect of pre- and postoperative education for stoma patients within an ERAS programme. Very little published research has analyzed the relationship between pre-operative education and length of hospital stay for patients receiving a planned stoma in colorectal surgery. A recently published systematic review of educational interventions for stomas found only five studies evaluating the length of hospital stay [4]. Of the five studies, two reported a reduction [2,10] and three found no difference in length of stay [3,11,12]. Only two of the studies were randomized controlled trials with few patients [2,11], and one of them evaluated education as part of an enhanced recovery programme [11]. Three studies reported rates of re-admission, and none found a significant difference in re-admission rates between groups [3,11,12]. Thus, our knowledge of the effect of educational efforts in stoma patients combined with ERAS on hospital stay is limited and we think that our study makes an important contribution to the knowledge in this field.

4.2. Stoma related complications

Some retrospective and prospective studies, have reported a reduction in stoma-related complications among patients who underwent pre-operative stoma site marking and education [13–16]. Two prospective studies did not find a significant difference in complications [3,11]. Only one of these studies was randomized and few patients were included [11]. In our study, a high number of stoma-related complications were observed. We carefully registered complications prospectively. Although there was a tendency for fewer stoma-related complications in the ERAS group, the difference was not significant. The fact that stoma sites were marked by a stoma nurse specialist the day before surgery in both patient groups may have influenced the results, but we think it would be unethical to risk suboptimal stoma placement. Even if this study included a large number of patients, it might not be sufficiently powered with regard to the study question, as this was not the main focus.

Half of the patients with ileostomy had peristomal dermatitis that required treatment with crystal violet or local steroids, and 18% had high output with dehydration and S-creatinine > 100 µmol/L. Few data are available in the literature, but one review article from 2009 reported peristomal dermatitis in 5–25% of patients with

ileostomies, and significant dehydration in up to 20% [17]. In our study ileostomies had significantly more complications than colostomies, and severe complications (e.g., high output with dehydration and S-creatinine > 100 µmol/L) in colostomies were rare. Readmission due to high output ileostomy remains a significant concern in patients who have a newly formed ileostomy. Specific education around this issue was not provided but will be part of future improvement.

4.3. Health related quality of life

In this study no significant differences were observed between the two treatment groups in HRQoL within the first 30 days. To the best of our knowledge, only two studies have evaluated stoma education and HRQoL [18,19]. In a systematic review from 2012, only these two studies were found and only one was in English [20]. Both of these studies reported an improvement in HRQoL, but patients admitted for education had a previous stoma for several months. Therefore, it may be hard to decide whether the improvement is due to education or simply time. We noted a significant and clinically important improvement in the 15D score from 10 days to 30 days, indicating adoption of the stoma by the patient. The current study also demonstrates that patients have equal HRQoL if they are discharged after 5 or 9 days (PHS). In the important properties (reliability, validity, discriminatory power, and responsiveness to change), the 15D compares at least equally, often favourably, to the other preference-based generic instruments such as EQ-5D, HUI3, and SF-6D [8,21–23]. In contrast to disease-specific instruments, such as EORTC, comparisons of HRQoL are possible across different diseases and conditions.

4.4. Stoma education and counselling

One important component of ERAS care is pre-admission information and counselling. This study evaluated stoma education as part of an ERAS care pathway, which can make it difficult to identify education as an independent effect. We cannot determine how much of the reduced hospital length is due to ERAS care and how much is due to stoma care education and the extended counselling in general. It might be that the ERAS protocol is more powerful in those with a stoma. To answer this question a 2 × 2 factorial design would be necessary and substantial more patients would be required. The main benefit of extended pre-operative counselling and stoma education was that the patients were more responsive and capable of being taught directly after the operation. However, the results of this study do not enable us to conclude that counselling and stoma education or one other ERAS item is more effective than other interventions. The ERAS approach consisted of a package of interventions implemented differently between the ERAS and standard care groups but equally within each of them with very little or no variation with respect to single interventions. This study design is appropriate for evaluating the package of interventions but not to compare interventions. Consequently, we cannot expect that a multivariate model comparing the effects of single interventions will lead to meaningful and interpretable results.

4.5. Study limitations

A limitation of this study was that we did not measure days to stoma independence and proficiency. The study had predefined discharge criteria, and the patients should be considered proficient in managing their stoma. A randomized trial studying the effects of intensive community-based pre-operative stoma education found

proficiency in management of the stoma after a median 5.5 days, whereas the PHS was a median 8 days [2]. The reason for this large difference between the date of stoma proficiency and the date of discharge was not given. In our opinion, insufficient proficiency and lack of comfort with managing the stoma prolongs hospital stay among stoma patients when there are otherwise no complications requiring treatment in the hospital. In our study, patients with surgical complications resulting in a longer hospital stay were not excluded.

5. Conclusions

In summary, this prospective trial revealed a high frequency of stoma-related complications, but the length of stay after elective colorectal surgery with the need for stoma creation can be reduced significantly with peri-operative education and guidance by dedicated stoma nurses as part of an ERAS care pathway.

Ethical approval

The trial was approved by the regional committee of ethics in Western Norway (reference number 2010/2079).

Sources of funding

This study was supported and facilitated by the Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway.

Author contribution

HMF, CE, and FP initiated the study and were the principle investigators. HMF, CE, and AR coordinated the study activities. AR and HMF collected all data. HMF analyzed all data and designed the figures. HMF, CE, FP, AR, HS and HK were actively involved in the study design. HMF, CE, FP, AR, HS and HK as the writing team were responsible for the interpretation of data and the writing of the manuscript. All authors reviewed and commented on a draft version of the final report and gave the approval for publication.

Conflict of interest

None.

Research registration unique identifying number (UIN)

This study was registered with ClinicalTrials.gov, no. NCT01610726.

Guarantor

Håvard Mjørud Forsmo.

Acknowledgements


This study was supported and facilitated by the Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway.

References

- [1] M.T. Cartmell, O.M. Jones, B.J. Moran, T.D. Cecil, A defunctioning stoma significantly prolongs the length of stay in laparoscopic colorectal resection, *Surg. Endosc.* 22 (2008) 2643–2647.
- [2] S. Chaudhri, L. Brown, I. Hassan, A.F. Horgan, Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial, *Dis. Colon Rectum* 48 (2005) 504–509.

- [3] J. Younis, G. Salerno, D. Fanto, M. Hadjipavlou, D. Chellar, J.P. Trickett, Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme, *Int. J. Colorectal Dis.* 27 (2012) 43–47.
- [4] U.R. Phatak, L.T. Li, B. Karanjawala, G.J. Chang, L.S. Kao, Systematic review of educational interventions for ostomates, *Dis. Colon Rectum* 57 (2014) 529–537.
- [5] H. Kehlet, Fast-track colorectal surgery, *Lancet* 371 (2008) 791–793.
- [6] H.M. Forsmo, F. Pfeffer, A. Rasdal, G. Ostgaard, A.C. Mohn, H. Korner, et al., Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: results of a randomized controlled trial, *Colorectal Dis. Off. J. Assoc. Coloproctology G. B. Irel.* 18 (2016) 603–611.
- [7] T.M. Halaszynski, R. Juda, D.G. Silverman, Optimizing postoperative outcomes with efficient preoperative assessment and management, *Crit. Care Med.* 32 (2004) S76–S86.
- [8] H. Sintonen, The 15D instrument of health-related quality of life: properties and applications, *AnnMed* 33 (2001) 328–336.
- [9] S. Alanne, R.P. Roine, P. Rasanen, T. Vainiola, H. Sintonen, Estimating the minimum important change in the 15D scores, *QualLife Res.* 24 (2015) 599–606.
- [10] S. Bryan, S. Dukes, The Enhanced Recovery Programme for stoma patients: an audit, *Br. J. Nurs.* 19 (2010) 831–834.
- [11] C.P. Delaney, M. Zutshi, A.J. Senagore, F.H. Remzi, J. Hammel, V.W. Fazio, Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection, *Dis. Colon Rectum* 46 (2003) 851–859.
- [12] D. Nagle, T. Pare, E. Keenan, K. Marcet, S. Tizio, V. Poylin, Ileostomy pathway virtually eliminates readmissions for dehydration in new ostomates, *Dis. Colon Rectum* 55 (2012) 1266–1272.
- [13] E.M. Bass, P.A. Del, A. Tan, R.K. Pearl, C.P. Orsay, H. Abcarian, Does preoperative stoma marking and education by the enterostomal therapist affect outcome? *Dis. Colon Rectum* 40 (1997) 440–442.
- [14] B. Person, R. Ifargan, J. Lachter, S.D. Duek, Y. Kluger, A. Assalia, The impact of preoperative stoma site marking on the incidence of complications, quality of life, and patient's independence, *Dis. Colon Rectum* 55 (2012) 783–787.
- [15] J.C. Colwell, M. Gray, Does preoperative teaching and stoma site marking affect surgical outcomes in patients undergoing ostomy surgery? *J. Wound Ostomy Continence Nurs.* 34 (2007) 492–496.
- [16] M. Millan, M. Tegido, S. Biondo, E. Garcia-Granero, Preoperative stoma siting and education by stomatherapists of colorectal cancer patients: a descriptive study in twelve Spanish colorectal surgical units, *Colorectal Dis.* 12 (2010) e88–e92.
- [17] J. Shabbir, D.C. Britton, Stoma complications: a literature overview, *Colorectal Dis.* 12 (2010) 958–964.
- [18] A.G. Olsen, Stoma education provides a new life [Stomiskole giver nyt liv], *Sygeplejersken* 21 (2011) 78–81.
- [19] Y.E. Altuntas, M. Kement, C. Gezen, H.H. Eker, H. Aydin, F. Sahin, et al., The role of group education on quality of life in patients with a stoma, *Eur. J. Cancer Care Engl.* 21 (2012) 776–781.
- [20] A.K. Danielsen, J. Burcharth, J. Rosenberg, Patient education has a positive effect in patients with a stoma: a systematic review, *Colorectal Dis.* 15 (2013) e276–e283.
- [21] G. Hawthorne, J. Richardson, N.A. Day, A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments, *Ann Med.* 33 (2001) 358–370.
- [22] J. Moock, T. Kohlmann, Comparing preference-based quality-of-life measures: results from rehabilitation patients with musculoskeletal, cardiovascular, or psychosomatic disorders, *Qual. Life Res.* 17 (2008) 485–495.
- [23] K. Stavem, Reliability, validity and responsiveness of two multiattribute utility measures in patients with chronic obstructive pulmonary disease, *Qual. Life Res.* 8 (1999) 45–54.

Enhanced Recovery After Colorectal Surgery (ERAS) in Elderly Patients Is Feasible and Achieves Similar Results as in Younger Patients

Gerontology & Geriatric Medicine
Volume 3: 1–8
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2333721417706299
journals.sagepub.com/home/ggm


Håvard Mjørud Forsmo, MD^{1,2}, Christian Erichsen, MD, PhD¹,
Anne Rasdal, RN¹, Hartwig Körner, MD, PhD^{2,3},
and Frank Pfeffer, MD, PhD^{1,2}

Abstract

Aim: Enhanced recovery after surgery (ERAS) is a multimodal approach that aims to optimize perioperative treatment. Whether elderly patients receiving colorectal surgery can adhere to and benefit from an ERAS approach is uncertain. The aim of this study was to compare patients in different age groups participating in an ERAS program. **Method:** In this substudy of a randomized controlled trial, we analyzed the interventional ERAS arm of adult patients eligible for laparoscopic or open colorectal resection with regard to the importance of age. Patients were divided into three groups based on age: ≤ 65 years ($n = 79$), 66–79 years ($n = 56$), and ≥ 80 years ($n = 19$). The primary end point was total postoperative hospital stay (THS). Secondary end points were postoperative hospital stay, postoperative complications, postoperative C-reactive protein levels, readmission rate, mortality, and patient adherence to the different ERAS elements. All parameters and measuring the adherence to the ERAS protocol were recorded before surgery, on the day of the operation, and daily until discharge. **Results:** There were no significant differences in length of THS between age groups (≤ 65 years, median 5 [range 2–47] days; 66–79 years, median 5.5 [range 2–36] days; ≥ 80 years, median 7 [range 3–50] days; $p = .53$). All secondary outcomes were similar between age groups. Patient adherence to the ERAS protocol was as good in the elderly as it was in the younger patients. **Conclusion:** Elderly patients adhered to and benefited from an ERAS program, similar to their younger counterparts.

Keywords

ERAS, colorectal surgery, age groups, complications

Manuscript received: August 10, 2016; **final revision received:** March 22, 2017; **accepted:** March 27, 2017.

Introduction

Standard elective colorectal resection is usually associated with a postoperative length of hospital stay of 6 to 12 days, and complication rate varies between 10% and 50% (Bokey et al., 1995; Schoetz et al., 1997; Vlug et al., 2011). Important factors for late recovery and discharge are postoperative pain, paralytic ileus, and organ dysfunction related to surgical stress, but many other factors also play a role, such as immobilization, postoperative cognitive dysfunction, and local hospital traditions such as nasogastric tubes, drain, and urinary catheter postoperatively. Perioperative care has been improved in the last 20 years with development of minimally invasive surgery, newer anesthetic and analgesic techniques, and other factors to reduce the surgical stress (Kehlet & Dahl, 2003; White et al., 2007). Enhanced recovery after surgery (ERAS) is a multimodal approach that aims to optimize perioperative

management (Fearon et al., 2005). The ERAS program is a package of evidence-based changes in preoperative, intraoperative, and postoperative care to reduce organ dysfunction and surgical stress response to promote rapid recovery (Kehlet, 2008; Ren et al., 2012). ERAS guidelines were first published for colorectal surgery and in recent years also for other major procedures in gastrointestinal surgery, urology, and gynecology, and include mostly around 15 to 20 perioperative elements. The key elements

¹Haukeland University Hospital, Bergen, Norway

²University of Bergen, Norway

³Stavanger University Hospital, Norway

Corresponding Author:

Håvard Mjørud Forsmo, Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, 5021 Bergen, Norway.

Email: havard.forsmo@helse-bergen.no



of an enhanced recovery pathway are (a) extended patient information, (b) preservation of gastrointestinal function (carbohydrate solution before surgery, early enteral feeding), (c) minimizing organ dysfunction (omission of mechanical bowel preparation, goal-directed fluid therapy, avoidance of drains and nasogastric tube, minimally invasive surgery), (d) active pain control (opioid-sparing anesthesia and analgesia, local anesthetic infiltration of incisions), and (e) promotion of patient autonomy with early mobilization (Adamina, Kehlet, Tomlinson, Senagore, & Delaney, 2011). The more ERAS elements are implemented, the more frequently the postoperative course is improved (Gustafsson et al., 2011). Studies have demonstrated that ERAS is safe and shortens the length of the hospital stay (Adamina et al., 2011; Varadhan et al., 2010). However, elderly patients have either been excluded or the sample size has been too small to perform subgroup analyses (Bagnall et al., 2014). There is also uncertainty as to whether elderly patients can comply with the implementation of this multidisciplinary program and whether they have better or worse outcomes in such a program than younger patients.

We have earlier conducted a controlled, randomized trial in which we compared patients treated with an ERAS approach with patients treated with a standard of care pathway (Forsmo et al., 2016). In this substudy of this prospective trial, the main objective was to evaluate patients in different age groups in the ERAS care pathway and to see whether elderly patients achieved the same outcomes as younger patients. We also wanted to evaluate elderly patients' adherence to an ERAS program compared with younger patients.

Method

Study Design

The present study was based on data from a prospective clinical trial, which was undertaken at Haukeland University Hospital in Bergen, Norway, between January 5, 2012, and March 4, 2015. The aim of the study was to assess whether it was possible to decrease the length of total hospital stay (THS), mainly as a result of reduced morbidity. Detailed information regarding the study design and perioperative care is described elsewhere (Forsmo et al., 2016). In brief, patients aged ≥ 18 years who were scheduled for elective laparoscopic or open colorectal surgery for malignant or benign disease, with or without stoma, were eligible for inclusion in the study. One to 3 weeks before surgery, patients were informed about the study both orally and in writing, and written consent was obtained. Patients undergoing a planned multivisceral resection or with American Association of Anesthesiologist (ASA) score IV were excluded. Additional exclusion criteria were emergency operations, impaired mental capacity with difficulty providing informed consent, or inability to adapt to the ERAS criteria as evaluated by

Table 1. Numbers of ERAS Items.

	ERAS care
Preoperative	
Preoperative counseling	✓
Preoperative feeding	✓
Carbohydrate loading	✓
No bowel preparation	
No premedication	✓
Antimicrobial prophylaxis	✓
Perioperative	
Fluid restriction	✓
Anesthetic protocol	TIVA
Prevention of hypothermia	✓
Epidural anesthesia	✓
Minimal invasive incisions	
Postoperative	
No routine use of nasogastric tubes	✓
No use of drains in colon surgery	✓
Enforced postoperative mobilization	✓
Enforced postoperative feeding	✓
No systemic morphine use	✓
Standard laxative	✓
Early removal of urine catheter	✓
Total number	16

Note. ERAS = enhanced recovery after surgery; TIVA = total intravenous anesthesia; ✓ = ERAS item completed.

the study surgeons. If the intended colonic or rectal surgery was not performed for any reason, the randomized patients were excluded from the analysis. Patients were randomized to ERAS or standard of care, and a randomization list with an allocation ratio of 1:1 was generated with block randomization.

In this substudy, we focus on patients in the intervention arm (ERAS group) of this randomized, controlled trial and the influence of age on the ERAS program. Patients were divided into three groups based on age: ≤ 65 years ($n = 79$), 66-79 years ($n = 56$), and ≥ 80 years ($n = 19$). The numbers of ERAS items used are shown in Table 1. Adherence to all these items is dependent on physicians (surgeons, anesthesiologists), nurses, physical therapists, and the patients themselves. The ERAS pathway intends to provide all ERAS elements to all patients as far as possible. The same physicians and nurses treated all patients, and thus, provider-dependent differences between the age groups are highly unlikely.

Objectives and Endpoints

THS, measured in days, was the primary end point of this analysis. THS was defined as postoperative hospital stay (PHS) plus any additional days of readmission within the first 30 days after surgery. Equivalent discharge criteria were applied to all age groups. These included bowel function (feces or repeated flatus), mobilized and out of bed more than 6 hr each day, postoperative pain

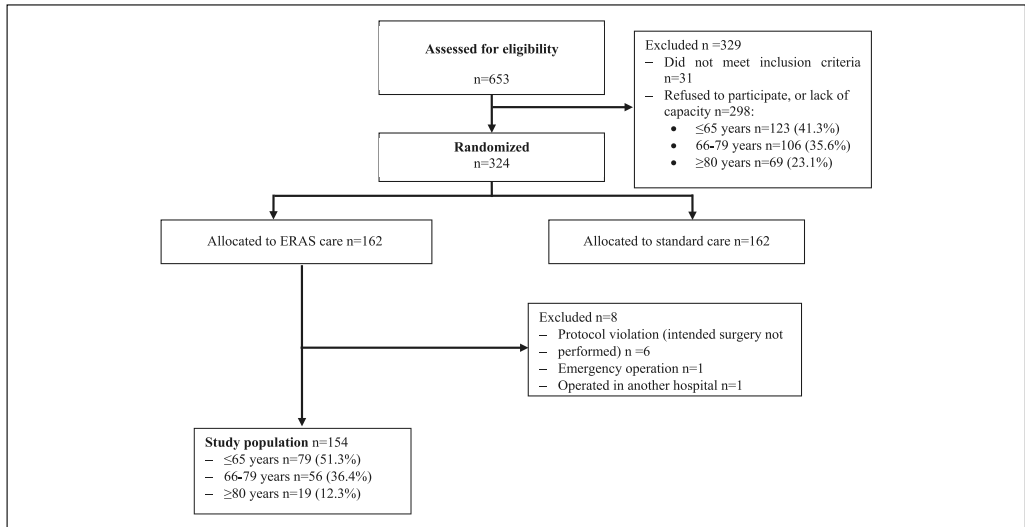


Figure 1. Flow chart of patients considered for inclusion.
Note. ERAS = enhanced recovery after surgery.

adequately controlled with oral medication (Visual Analog Scale < 4), and no complications requiring treatment in hospital. Secondary end points were postoperative complications, PHS, readmission rate, postoperative C-reactive protein (CRP) levels, mortality, and patient adherence to the different ERAS elements. CRP levels reflect the postoperative inflammatory response. Prior to study commencement, the definitions for complications were established and the incidences of complications were recorded in accordance with the Clavien–Dindo classification (Dindo, Demartines, & Clavien, 2004).

All parameters and measurements of adherence to the ERAS protocol were recorded by one study nurse and one surgeon before surgery, on the day of the operation, and daily until discharge. All patients had an outpatient clinic visit on Postoperative Days 10 and 30, which were all performed by one dedicated nurse and the same two surgeons.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software, version 22. The different age groups in the ERAS care pathway were analyzed using descriptive statistical methods, and the results of continuous variables were presented as the median and range. Discrete variables were compared with the chi-square test. For continuous outcomes, ANOVA and regression analysis (linear, quadratic, cubic, and exponential) were performed.

This study was registered with ClinicalTrials.gov (No. NCT01610726), and the local regional committee of ethics approved this trial (reference no. 2010/2079).

Results

In the main study, 329 of 653 eligible patients were not included, mainly because of a lack of capacity at the ERAS outpatient clinic, and 324 patients were randomly assigned to the ERAS program or standard of care. Among 298 patients not included in the study (Figure 1), the percentage of patients over the age of 80 was higher than those included in the study (23.1% vs. 12.3%, respectively). In the patient group younger than 65 years, this percentage was lower (41.3% vs. 51.3%, respectively) (Figure 1). The patient characteristics and surgical details for patients included in this analysis are summarized in Table 2. A greater proportion of patients in the two oldest age groups had ASA 3, and the proportion of patients with malignancy was higher. In patients aged <65 years, more rectal operations were performed.

There were no significant differences in THS between age groups treated in the ERAS program (Table 3). The ability to tolerate solid food without nausea did not differ between the groups. There were no differences between groups regarding postoperative CRP levels. Regression analysis with age as a continuous variable did not show any correlation between age and the outcomes variables either.

The age groups exhibited similar outcomes regarding overall, major, and minor morbidity; reoperation rate; readmission rate; and 30-day mortality (Table 4). Complications according to Clavien–Dindo $\geq 3b$ did not differ significantly between the groups.

Adherence to the ERAS protocol is summarized in Table 5. Although total oral intake on the day of surgery was somewhat lower in patients aged ≥ 80 years, there

Table 2. Characteristics and Surgical Details of Patients Assigned to ERAS Care in the Different Age Groups.

	Age group			p value
	≤65 years	66-79 years	≥80 years	
Included patients, n	79	56	19	
Median age (range), years	58 (23-65)	72 (66-78)	83 (80-89)	
Male/female, n/n	47/32	25/31	11/8	.22 ^a
Malignant/benign, n/n	58/21	47/9	19/0	.02 ^a
ASA, n (%)				<.001 ^a
I	27 (34.2)	11 (19.6)	0 (0)	
II	48 (60.8)	35 (62.5)	10 (52.6)	
III	4 (5.0)	10 (17.9)	9 (47.4)	
Type of colorectal surgery, n (%)				.04 ^a
Right-sided	12 (15.2)	20 (35.7)	3 (15.8)	
Left-sided or sigmoid	13 (16.5)	10 (17.8)	5 (26.3)	
Low anterior resection	31 (39.2)	17 (30.4)	5 (26.3)	
Protective ileostomy or colostomy	17	5	2	
Abdominoperineal resection	17 (21.5)	9 (16.1)	6 (31.6)	
(Procto)-colectomy	6 (7.6)	0 (0)	0 (0)	
Laparoscopy, n (%)	35 (44.3)	18 (32.1)	9 (47.4)	.37 ^a
Open surgery, n (%)	44 (55.7)	38 (67.9)	10 (52.6)	
Conversion, n (%)	3 (8.6)	4 (22.2)	1 (11.1)	
Median duration of surgery (range), minutes	177 (96-380)	154 (76-292)	172 (104-432)	.14 ^b
Median blood loss (range), mL	200 (0-1500)	150 (0-1050)	200 (0-700)	.80 ^b

Note. ERAS = enhanced recovery after surgery; ASA = American society of anesthesiologists.

^aχ² test.

^bANOVA test.

Table 3. Postoperative Data in Patients Receiving ERAS Care in the Different Age Groups.

	≤65 years (n = 79)	66-79 years (n = 56)	≥80 years (n = 19)	p value ^a
Total hospital stay, days	5 (2-47)	5.5 (2-36)	7 (3-50)	.53
Postoperative hospital stay, days	5 (2-30)	5 (2-21)	6.5 (3-50)	.22
Tolerated solid food without nausea, days	2 (0-8)	2 (0-9)	1 (0-6)	.13
Median CRP levels, mg/L				
Preoperative	2 (1-42)	3 (1-18)	3 (1-35)	.44
Day 2 postoperative	110 (19-400)	137 (25-284)	154 (75-499)	.30
Day 10 postoperative	8 (1-136)	13 (1-216)	16 (4-206)	.054

Note. Data are presented as median (range). ERAS = enhanced recovery after surgery; CRP = C- reactive protein.

^aANOVA test.

were no significant differences in intraoperative fluid load, intravenous fluid, total oral intake, or mobilization after surgery. Furthermore, there were no differences in the number of patients with preoperative counseling, omission of bowel preparation, intake of carbohydrate-loaded drinks before surgery, omission of preoperative fasting and premedication, postoperative laxative, thoracic epidural analgesia, type of anesthesia, prevention of hypothermia, and days to removal of the urinary tract catheter.

Discussion

The goal of this substudy was to evaluate the short-term outcomes of elderly and younger patients undergoing

open and laparoscopic colorectal surgery using an ERAS protocol, and to see whether elderly patients could adhere to an ERAS program. Our main findings were that elderly patients equally adhered well to and benefited from an ERAS program as younger patients according to the main outcome of reduced length of hospital stay. As the original study was a randomized trial, we believe that our results are based on a representative selection of patients who met the inclusion criteria.

A number of prospective and retrospective studies have demonstrated a similar length of stay when older and younger cohorts are compared (Baek et al., 2013; Kahokehr, Sammour, Sahakian, Zargar-Shoshtari, & Hill, 2011; Keller, Lawrence, Nobel, & Delaney, 2013;

Table 4. Surgical and Nonsurgical Complications in Patients Receiving ERAS Care in the Different Age Groups.

	≤65 years (n = 79)	66-79 years (n = 56)	≥80 years (n = 19)	p value ^a
Overall morbidity <30 days, n (%)	32 (40.5)	23 (41.2)	10 (52.6)	.62
Patients with one or more major complications, n (%)	7 (8.9)	9 (16.1)	2 (10.5)	.30
Major complications, n (%)				
Anastomotic leakage/patients with an anastomosis	4/61 (6.6)	5/46 (10.9)	1/10 (10.0)	.65
Colon	2/25 (8.0)	1/29 (3.4)	0/5 (0)	.65
Rectum	2/36 (5.6)	4/17 (23.5)	1/5 (20)	.15
Abdominal wall dehiscence	1 (1.3)	3 (5.4)	1 (5.2)	.36
Other complications requiring reoperation ^b	2 (2.5)	0 (0)	0 (0)	.39
Other major complication ^c	3 (3.8)	2 (3.6)	1 (5.3)	.59
Patient with one or more minor complications, n (%) ^d	26 (32.9)	19 (33.9)	8 (42.1)	.65
Reoperations, n (%)	7 (8.8)	8 (14.3)	2 (10.5)	.61
Readmission <30 days, n (%)	12 (15.2)	14 (25.0)	4 (21.1)	.33
Mortality <30 days, n (%)	0 (0)	2 (3.6)	1 (5.3)	.18
Clavien–Dindo ≤ Grade 3b, n (%)	25 (31.6)	14 (25.0)	8 (42.1)	.36
Clavien–Dindo ≥ Grade 3b, n (%)	7 (8.9)	9 (16.1)	2 (10.5)	.40

Note. ERAS = enhanced recovery after surgery; ICU = intensive care unit.

^aχ²-test.

^bOther complications requiring reoperation: postoperative bleeding, deep abdominal infection, iatrogenic bowel perforation, mechanical ileus requiring reoperation.

^cOther major complication: cerebral vascular accident, gastrointestinal bleeding requiring endoscopic intervention, respiratory complications requiring ICU, sepsis.

^dMinor complications: Wound infection (abdominal), wound infection (perineal), intraabdominal infection (antibiotic treated or drainage), prolonged postoperative ileus, pneumonia, pleural effusion requiring drainage, pulmonary embolism, cardiac arrhythmia, urinary infection, urine retention, gastrointestinal bleeding not requiring intervention, renal failure (S-creatinine >100 μmol/L), hyponatremia (s-Sodium <130 mmol/L), postoperative confusion, paresthesia of arm after laparoscopy, port site bleeding, pleuritis, subcutaneous infections, antibiotic treated infection unknown cause, early stoma related complications, transient ischemic attack with normal MRI. There were no significant differences in the subgroups of minor complications in the three groups of age.

Table 5. Adherence to the ERAS Study Protocol in the Different Age Groups.

	≤65 years (n = 79)	66-79 years (n = 56)	≥80 years (n = 19)	p value ^a
Day of surgery				
Intraoperative fluid loading, liters ^b	2.9 (1.2-5.7)	2.7 (0.9-5.5)	3.1 (1.8-4.6)	.28
Total oral intake after surgery, liters	0.6 (0-3.0)	0.6 (0-1.7)	0.4 (0-1.9)	.07
Mobilization 24 hr after surgery, minutes	180 (0-360)	180 (5-420)	120 (0-360)	.30
Intravenous fluid, liters				
First 24 hours, included intraoperative	3.8 (1.9-7.6)	3.9 (2.3-9.5)	4.8 (2.6-6.4)	.59
First 7 days, included intraoperative	5.2 (1.9-16.4)	4.9 (2.6-19.2)	6.4 (3.6-11.9)	.80
Total oral intake, liters				
POD 1	1.6 (0.5-3.2)	1.6 (0.8-3.1)	1.4 (0.3-3.0)	.23
POD 2	1.6 (0.5-3.3)	1.5 (0.5-3.5)	1.7 (0.9-2.9)	.39
Removal of urine catheter, days	3 (1-14)	2 (1-21)	3 (1-6)	.98
Removal of thoracic epidural analgesia, days	2.5 (0-5)	2 (0-4)	3 (1-4)	.72
Mobilization, minutes				
POD 2	240 (15-540)	225 (30-420)	240 (30-360)	.72
POD 3	300 (30-660)	240 (60-540)	240 (60-360)	.76

Note. Data are presented as median (range). ERAS = enhanced recovery after surgery; POD = postoperative day.

^aANOVA test.

^bIntraoperative fluid loading included 800 ml antibiotics.

Pawa, Cathcart, Arulampalam, Tutton, & Motson, 2012; Senagore et al., 2003; Verheijen, vd Ven, Davids, Vd Wall, & Pronk, 2012; Walter et al., 2011), while other studies found longer length of stay in older patients (Feroci et al., 2013; Hendry et al., 2009; Rumstadt et al.,

2009). Two randomized controlled trials comparing ERAS with standard of care in elderly patients found significantly reduced length of hospital stay in patients allocated to ERAS care (Jia et al., 2014; Wang et al., 2012). However, the definition of various age groups

differed widely in all these studies. In our study, there were no significant differences in THS between the age groups. However, THS in the age group ≥ 80 years was 2 days longer than in the age group < 65 years. There were no differences in morbidity or 30-day mortality which could explain this difference. It was not possible to determine other factors contributing to this difference. This may be due to logistical challenges, such as home care situation, or the patient's own wishes. Elderly patients are often living alone which implies that they have to be fit enough to manage their home situation by themselves. Even if discharge criteria are fulfilled, elderly patients may not be fit enough and have to wait for nursing home placement. This is in line with others who found that older patients remained in hospital for further 3 to 5 days after they met the criteria for safe discharge (Rumstadt et al., 2009). It might be a limitation of our study that we did not measure days until discharge criteria were fulfilled, but only THS.

As expected, patients in the oldest cohort in our study had more comorbidities and a higher proportion of malignancies than the younger age groups. Age is the single highest risk factor for developing cancer, and older patients are more likely to have malignant than benign tumors (Parks, Rostoft, Ommundsen, & Cheung, 2015). Decision making regarding surgery in elderly patients is challenging because these patients have more comorbidities as well as functional and cognitive impairments. The proportion of patients aged ≥ 80 years not included in the study was higher compared with the other age groups. This could represent a selection bias toward inclusion of more fit patients in the oldest age group, and exclusion of those who were considered frail and unable to adapt to the ERAS criteria as assessed by the study surgeons. This might reflect that a subgroup of elderly patients is not suitable for an ERAS program, although this may also be the case in younger frail patients. Interestingly, however, frailty does not necessarily exist in patients with many comorbidities, and some elderly patients with little or no concomitant disease appear to be frail (Fried et al., 2001). We did not apply frailty risk stratification in our analysis, for example, by "Comprehensive Geriatric Assessment" or "Fried criteria," and therefore, we cannot state the proportion of frail patients in the different age groups. The length of stay in the oldest age group may have been favorably influenced by the significantly increased proportion of patients undergoing hemicolectomies and the reduced proportion undergoing rectal resections compared with younger patients (Table 2).

No differences in morbidity and 30-day mortality were found between the age groups. A recently published systematic review of ERAS care after colorectal surgery in elderly patients found 11 studies comparing older and younger cohorts (Bagnall et al., 2014). Seven out of the 11 studies found no difference in mortality (Baek et al., 2013; Hendry et al., 2009; Keller et al., 2013; Naef, Kasemodel, Mouton, & Wagner, 2010;

Rumstadt et al., 2009; Senagore et al., 2003; Walter et al., 2011). Two studies did not report on mortality, and two found higher 30-day mortality in patients aged > 80 years (Feroci et al., 2013; Pawa et al., 2012). In five studies, the complication rates were similar (Baek et al., 2013; Hendry et al., 2009; Keller et al., 2013; Senagore et al., 2003; Walter et al., 2011); two studies did not report complications; and four studies found more complications in older patients (Feroci et al., 2013; Naef et al., 2010; Pawa et al., 2012; Rumstadt et al., 2009). However, the definitions of the elderly age groups in the studies included in the review varied considerably, ranging from ages > 65 to 80 years. We divided the patients into three age groups to see whether there were differences between those aged 65 to 79 years and those aged ≥ 80 years compared with younger patients. Considering the low number of patients aged ≥ 80 years, we could have divided the patients in two age groups instead of three. However, we think it would not be appropriate to dichotomize the patients into age groups above or below 65 years, which often is done. On the contrary, we think that our grouping reflects the various age groups who undergo colorectal resections properly with regard to their physical characteristics and different stages of life. This view is supported by regression analysis with age as a continuous variable that did not reveal any correlation between age and the outcomes variables. In elderly patients, there is greater heterogeneity regarding comorbidities and the degree of mobility. Treatment decisions and the choice of surgical intervention should therefore be based on biological characteristics rather than chronological age. Thus, chronological age should not be a determinant in itself. The term *frailty*, which includes decreased reserves in general and deterioration in multiple organ systems, has been introduced. The frailty evaluation is important to avoid over- and undertreatment, which is a well-known pitfall in geriatric oncology (Ommundsen et al., 2014). Currently, there are no simple tests available to predict postoperative outcome for frail elderly patients. The Comprehensive Geriatric Assessment is recognized as the best tool for evaluating elderly patients preoperatively (Feng et al., 2015; Kristjansson et al., 2010). Unfortunately, it is time-consuming and might be difficult to use in a busy surgical clinical practice (Ugolini et al., 2015). It seems, however, reasonable that this extra time spent in identifying and treating correctable conditions in complex patients may decrease postoperative complications and length of hospital stay. As a consequence of this study, in collaboration with our anesthesiologists, we will implement a tool for evaluating frailty in patients.

Adherence to the ERAS approach means to which extent the patients are able to implement the ERAS program. Conducting an ERAS program depends on both the provider (surgeons and nurses) and the patient. Staff must facilitate that patients can implement the program. Adherence is measured by the extent of individual ERAS elements carried out. Previous studies have demonstrated

good compliance with preoperative and intraoperative ERAS elements, but reduced adherence during the postoperative phase (Hendry et al., 2009; Maessen et al., 2007). However, it has been suggested that compliance with postoperative rather than preoperative ERAS elements is likely to be of particular importance for good progress and accelerated postoperative recovery (Maessen et al., 2007). Postoperative variables are markers of recovery and protocol compliance. Early mobilization is central in an enhanced recovery protocol. In a multivariate analysis, Hendry et al. (2009) identified age >80 years and higher ASA score as independent predictors of prolonged mobilization. In our study, we found no differences in compliance to the various ERAS elements between the different age groups. Also, no difference was found in the level of mobilization in contrast to other studies that have reported differences in levels of mobilization (Hendry et al., 2009; Pawa et al., 2012; Rumstadt et al., 2009). This may be related to the strict inclusion criteria among the oldest patients. We feel that it is highly likely that more elderly patients would benefit from special supervision and the guidance of specialist nurses in ERAS, particularly the postoperative ERAS elements, even if it is not possible to implement the entire program.

As expected, the elderly cohort in our study had more comorbidity and more malignancies than the younger age group. Elderly patients with more comorbidities might be expected to have higher rates of mortality and complications and experience longer hospital stays than younger patients. Our results show the safety of the ERAS program in elderly patients who are able to adapt to the ERAS criteria. We believe that more elderly patients should receive such perioperative treatment, and it is highly likely that they will have similar length of stay and the same rate of postoperative readmissions and complications as the younger patients.

Declaration of Conflicting Interests

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

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported and facilitated by the Department of Gastrointestinal and Emergency Surgery, Haukeland University Hospital, Bergen, Norway.

References

- Adamina, M., Kehlet, H., Tomlinson, G. A., Senagore, A. J., & Delaney, C. P. (2011). Enhanced recovery pathways optimize health outcomes and resource utilization: A meta-analysis of randomized controlled trials in colorectal surgery. *Surgery, 149*, 830-840. doi:10.1016/j.surg.2010.11.003
- Baek, S. J., Kim, S. H., Kim, S. Y., Shin, J. W., Kwak, J. M., & Kim, J. (2013). The safety of a "fast-track" program after laparoscopic colorectal surgery is comparable in older patients as in younger patients. *Surgical Endoscopy, 27*, 1225-1232. doi:10.1007/s00464-012-2579-7
- Bagnall, N. M., Malietzis, G., Kennedy, R. H., Athanasiou, T., Faiz, O., & Darzi, A. (2014). A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Disease, 16*, 947-956. doi:10.1111/codi.12718
- Bokey, E. L., Chapuis, P. H., Fung, C., Hughes, W. J., Koorey, S. G., Brewer, D., & Newland, R. C. (1995). Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Diseases of the Colon & Rectum, 38*, 480-486.
- Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery, 240*, 205-213.
- Fearon, K. C., Ljungqvist, O., Von Meyenfeldt, M., Revhaug, A., Dejong, C. H., Lassen, K., . . . Kehlet, H. (2005). Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. *Clinical Nutrition, 24*, 466-477. doi:10.1016/j.clnu.2005.02.002
- Feng, M. A., McMillan, D. T., Crowell, K., Muss, H., Nielsen, M. E., & Smith, A. B. (2015). Geriatric assessment in surgical oncology: A systematic review. *Journal of Surgical Research, 193*, 265-272. doi:10.1016/j.jss.2014.07.004
- Feroci, F., Lenzi, E., Baraghini, M., Garzi, A., Vannucchi, A., Cantafio, S., & Scatizzi, M. (2013). Fast-track surgery in real life: How patient factors influence outcomes and compliance with an enhanced recovery clinical pathway after colorectal surgery. *Surgical Laparoscopy Endoscopy & Percutaneous Techniques, 23*, 259-265. doi:10.1097/SLE.0b013e31828ba16f
- Forsmo, H.M., Pfeffer, F., Roldal, A., Østgaard, G., Mohn, A.C., Körner, H., . . . Erichsen, C. (2016). Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: Results of a randomized controlled trial. *Colorectal Disease, 18*(6), 603-11. doi: 10.1111/codi.13253
- Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology, Series A: Biological Sciences & Medical Sciences, 56*, M146-M156.
- Gustafsson, U. O., Hausel, J., Thorell, A., Ljungqvist, O., Soop, M., & Nygren, J. (2011). Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Archives of Surgery, 146*, 571-577. doi:10.1001/archsurg.2010.309
- Hendry, P. O., Hausel, J., Nygren, J., Lassen, K., Dejong, C. H., Ljungqvist, O., & Fearon, K. C. (2009). Determinants of outcome after colorectal resection within an enhanced recovery programme. *British Journal of Surgery, 96*, 197-205. doi:10.1002/bjs.6445
- Jia, Y., Jin, G., Guo, S., Gu, B., Jin, Z., Gao, X., & Li, Z. (2014). Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. *Langenbeck's Archives of Surgery, 399*, 77-84. doi:10.1007/s00423-013-1151-9
- Kahokehr, A. A., Sannour, T., Sahakian, V., Zargar-Shoshtari, K., & Hill, A. G. (2011). Influences on length

- of stay in an enhanced recovery programme after colonic surgery. *Colorectal Disease*, *13*, 594-599. doi:10.1111/j.1463-1318.2010.02228.x
- Kehlet, H. (2008). Fast-track colorectal surgery. *The Lancet*, *371*, 791-793. doi:10.1016/S0140-6736(08)60357-8
- Kehlet, H., & Dahl, J. B. (2003). Anaesthesia, surgery, and challenges in postoperative recovery. *The Lancet*, *362*, 1921-1928. doi:10.1016/s0140-6736(03)14966-5
- Keller, D. S., Lawrence, J. K., Nobel, T., & Delaney, C. P. (2013). Optimizing cost and short-term outcomes for elderly patients in laparoscopic colonic surgery. *Surgical Endoscopy*, *27*, 4463-4468. doi:10.1007/s00464-013-3088-z
- Kristjansson, S. R., Nesbakken, A., Jordhoy, M. S., Skovlund, E., Audisio, R. A., Johannessen, H. O., . . . Wyller, T. B. (2010). Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Critical Reviews in Oncology Hematology*, *76*, 208-217. doi:10.1016/j.critrevonc.2009.11.002
- Maessen, J., Dejong, C. H., Hausel, J., Nygren, J., Lassen, K., Andersen, J., . . . von Meyenfeldt, M. F. (2007). A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *British Journal of Surgery*, *94*, 224-231. doi:10.1002/bjs.5468
- Naef, M., Kasemodel, G. K., Mouton, W. G., & Wagner, H. E. (2010). Outcome of colorectal cancer surgery in the early fast-track era with special regard to elderly patients. *International Surgery*, *95*, 153-159.
- Ommundsen, N., Wyller, T. B., Nesbakken, A., Jordhoy, M. S., Bakka, A., Skovlund, E., & Rostoft, S. (2014). Frailty is an independent predictor of survival in older patients with colorectal cancer. *The Oncologist*, *19*, 1268-1275. doi:10.1634/theoncologist.2014-0237
- Parks, R. M., Rostoft, S., Ommundsen, N., & Cheung, K. L. (2015). Peri-operative management of older adults with cancer—The roles of the surgeon and geriatrician. *Cancers*, *7*, 1605-1621. doi:10.3390/cancers7030853
- Pawa, N., Cathcart, P. L., Arulampalam, T. H., Tutton, M. G., & Motson, R. W. (2012). Enhanced recovery program following colorectal resection in the elderly patient. *World Journal of Surgery*, *36*, 415-423. doi:10.1007/s00268-011-1328-8
- Ren, L., Zhu, D., Wei, Y., Pan, X., Liang, L., Xu, J., . . . Wu, Z. (2012). Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: A prospective randomized controlled trial. *World Journal of Surgery*, *36*, 407-414. doi:10.1007/s00268-011-1348-4
- Rumstadt, B., Guenther, N., Wendling, P., Engemann, R., Germer, C. T., Schmid, M., . . . Schwenk, W. (2009). Multimodal perioperative rehabilitation for colonic surgery in the elderly. *World Journal of Surgery*, *33*, 1757-1763. doi:10.1007/s00268-009-0018-2
- Schoetz, D. J., Jr., Bockler, M., Rosenblatt, M. S., Malhotra, S., Roberts, P. L., Murray, J. J., . . . Rusin, L. C. (1997). "Ideal" length of stay after colectomy: Whose ideal? *Diseases of the Colon & Rectum*, *40*, 806-810.
- Senagore, A. J., Madbouly, K. M., Fazio, V. W., Duepre, H. J., Brady, K. M., & Delaney, C. P. (2003). Advantages of laparoscopic colectomy in older patients. *Archives of Surgery*, *138*, 252-256.
- Ugolini, G., Pasini, F., Ghignone, F., Zattoni, D., Bacchi Reggiani, M. L., Parlanti, D., & Montroni, I. (2015). How to select elderly colorectal cancer patients for surgery: A pilot study in an Italian academic medical center. *Cancer Biology & Medicine*, *12*, 302-307. doi:10.7497/j.issn.2095-3941.2015.0084
- Varadhan, K. K., Neal, K. R., Dejong, C. H., Fearon, K. C., Ljungqvist, O., & Lobo, D. N. (2010). The Enhanced Recovery After Surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. *Clinical Nutrition*, *29*, 434-440. doi:10.1016/j.clnu.2010.01.004
- Verheijen, P. M., vd Ven, A. W., Davids, P. H., Vd Wall, B. J., & Pronk, A. (2012). Feasibility of enhanced recovery programme in various patient groups. *International Journal of Colorectal Disease*, *27*, 507-511. doi:10.1007/s00384-011-1336-z
- Vlug, M. S., Wind, J., Hollmann, M. W., Ubbink, D. T., Cense, H. A., Engel, A. F., . . . Bemelman, W. A. (2011). Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: A randomized clinical trial (LFAFA-study). *Annals of Surgery*, *254*, 868-875. doi:10.1097/SLA.0b013e31821fd1ce
- Walter, C. J., Watson, J. T., Pullan, R. D., Kenefick, N. J., Mitchell, S. J., & Defriend, D. J. (2011). Enhanced recovery in major colorectal surgery: Safety and efficacy in an unselected surgical population at a UK district general hospital. *The Surgeon*, *9*, 259-264. doi:10.1016/j.surge.2010.10.003
- Wang, Q., Suo, J., Jiang, J., Wang, C., Zhao, Y. Q., & Cao, X. (2012). Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: A randomized trial. *Colorectal Disease*, *14*, 1009-1013. doi:10.1111/j.1463-1318.2011.02855.x
- White, P. F., Kehlet, H., Neal, J. M., Schricker, T., Carr, D. B., & Carli, F. (2007). The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. *Anesthesia & Analgesia*, *104*, 1380-1396. doi:10.1213/01.ane.0000263034.96885.e1