Early Closure of a Temporary Ileostomy after Rectal Resection for Cancer

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Gothenburg 2019

UNIVERSITY OF GOTHENBURG

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"A wonderful thing about true laughter is that it just destroys any kind of system of dividing people"

- John Cleese

To Colin

For your brilliant wittiness

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ABSTRACT

A temporary ileostomy may reduce symptoms of anastomotic leakage after rectal resection for cancer. However, the stoma itself is associated with morbidity and early closure may reduce these symptoms. The aim of this thesis, based on a multicentre randomized controlled trial (EASY trial), was to evaluate early closure (8-13 days) of a temporary ileostomy compared to late closure (>12 weeks), after rectal resection for cancer. Endpoints were complications, quality of life, healthcare costs and bowel function. The trial included 55 patients in the early closure group, and 57 patients in the late closure group.

Paper I evaluated number of postoperative complications up to 12 months following rectal resection. We found significantly fewer complications in the early closure group. Severe complications were uncommon in both groups.

Paper II included assessment of patient reported quality of life, by validated questionnaires at 3, 6 and 12 months. There were no significant differences between the two groups.

Paper III comprised a cost analysis, comparing direct costs from a healthcare perspective. Early closure was found to be significantly less costly at evaluation 12 months after surgery.

Paper IV was a cross-sectional study performed at median 4 years after rectal resection, comparing patient reported bowel function. The late closure group reported more problems with urgency, compared with the early closure group. There was no difference in prevalence of low anterior resection syndrome.

Overall, in selected patients without signs of postoperative complications, early closure of a temporary ileostomy after rectal resection for cancer was found to be safe and clinically advantageous in a randomized trial setting.

Keywords: temporary ileostomy, rectal cancer, surgery

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SAMMANFATTNING PÅ SVENSKA

Bakgrund

I Sverige diagnosticeras ca 2000 personer årligen med ändtarmscancer, och tjock- och ändtarmscancer är den tredje vanligaste cancerformen i västvärlden. Behandlingen utgörs av enbart eller en kombination av strålning, cellgifter och kirurgi. Vid botande kirurgisk behandling opererar man bort tumören med marginal, vilket medför att man även tar med större delen av ändtarmen. Man skapar då en s.k. anastomos, en förbindelse mellan nedre delen av ändtarmen och tjocktarmen. Denna anastomos är känslig på grund av sitt utsatta läge nära bäckenbotten. Därför anlägger man enligt rutin (efter tidigare studiers resultat) en temporär stomi på tunntarmsnivå, för att skydda anastomosen från tarminnehåll. Stomin i sig orsakar dock ofta besvär med höga flöden från tarmen, risk för intorkning och njursvikt samt är orsaken till flertalet inläggningar. Man brukar ha kvar sin stomi i minst 12 veckor innan man opererar tillbaka tarmen och återställer tarmkontinuiteten (nedläggning av stomin).

Syfte

Syftet med studien var att undersöka möjligheterna och säkerheten till tidig nedläggning av stomin, dvs. redan inom 8-13 dagar efter operationen för tumören i ändtarmen. Detta gjordes genom en randomiserad studie (EASY studien) där patienter blev lottade mellan tidig (8-13 dagar) och sen (minst 12 veckor) nedläggning av stomin. Studien undersökte också livskvalitet och tarmfunktion hos patienterna samt jämförde direkta sjukvårdskostnader för respektive grupp.

Metod

Vuxna patienter som genomgick operation för ändtarmscancer, och där återhämtningen gick bra, utan tecken till komplikationer, bjöds in till att medverka i studien. Röntgenundersökning med kontrast gjordes av anastomosen och om det inte fanns några tecken till läckage, lottades sedan patienterna antingen till tidig nedläggning (interventionsgruppen) eller sen nedläggning (kontrollgruppen). Interventionsgruppen lade ner sin stomi inom 8-13 dagar efter ändtarmsoperationen, medan kontrollgruppen fick sin stomi nedlagd efter minst

12 veckor (rutinsjukvård). Patienterna följdes i 12 månader för studie I-III, och även vid ca 4 år (studie IV).

Resultat

Studie I undersökte antal komplikationer som patienterna drabbades av upp till 12 månader efter ändtarmsoperationen. Vi fann att patienterna i den tidiga nedläggningsgruppen drabbades av färre komplikationer, men att allvarliga komplikationer, såsom reoperationer och organsvikt, var ovanliga i båda behandlingsgrupperna.

Studie II undersökte patientrapporterad livskvalitet vid 3, 6 och 12 månader efter ändtarmsoperationen. Detta mättes med hjälp av enkäter som patienterna fick svara på vid respektive uppföljningstillfälle. Vi såg ingen skillnad mellan behandlingsgrupperna, och resultaten var jämförbara med tidigare studiers resultat.

Studie III utgjorde en kostnadsanalys, där syftet var att jämföra direkta sjukvårdskostnader, vilka baserades på bland annat röntgenundersökningar, återbesök, återinläggningar och reoperationer. Resultaten visade att det var mindre kostsamt att lägga ner sin stomi tidigt, men också att det var hälften så vanligt att återinläggas på sjukhus under 12 månaders perioden efter ändtarmsoperationen, jämfört med sen nedläggning av stomin.

I **studie IV** jämfördes tarmfunktion hos patienterna i respektive grupp, med hjälp av två formulär. Det ena formuläret mätte förekomst av s.k. lågt främre resektionssyndrom, ett tillstånd där tarmfunktionen är försämrad vilket ger uttryck i bland annat inkontinens, täta trängningar och ofullständig tarmtömning. Studien gjordes under hösten 2017, vilket innebar en median uppföljningstid på ca 4 år efter ändtarmsoperationen. Trängningar och brådska till toaletten var vanligare i den sena nedläggningsgruppen, men det fanns ingen skillnad i förekomsten av lågt främre resektionssyndrom, även om förekomsten var generellt hög i båda behandlingsgrupperna.

Slutsats

Sammanfattningsvis har den randomiserade studien påvisat att hos utvalda patienter, utan tecken till komplikationer efter operation för ändtarmscancer, är det säkert och kliniskt gynnsamt att lägga ner en temporär stomi tidigt i förloppet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals (I-IV).

I. Danielsen AK, Park J, Jansen JE, Bock D, Skullman S, Wedin A, Correa-Marinez A, Haglind E, Angenete E, Rosenberg J.

Early closure of a temporary ileostomy in patients with rectal cancer: A multicenter randomized controlled trial

Ann Surg 2017;265(2):284-90

II. Park J, Danielsen AK, Angenete E, Bock D, Correa-Marinez A, Haglind E, Jansen JE, Skullman S, Wedin A, Rosenberg J.

Quality of life in a randomized trial of early closure of a temporary ileostomy after rectal resection for cancer (EASY trial)

Br J Surg 2018;105(3):244-251

III. Park J, Angenete E, Bock D, Correa-Marinez A, Danielsen AK, Gehrman J, Haglind E, Jansen JE, Skullman S, Wedin A, Rosenberg J.

Cost analysis in a randomized trial of early closure of a temporary ileostomy after rectal resection for cancer (EASY trial)

Submitted manuscript

IV. Keane C, Park J, Öberg S, Wedin A, Bock D, O'Grady G, Bissett I, Rosenberg J, Angenete E.

Functional outcome of early closure of temporary ileostomy after rectal resection for cancer: Secondary analysis of a randomized clinical trial

Manuscript accepted in Br J Surg

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ABBREVIATIONS

EASY	EArly closure of a temporary ileoStomY
TME	Total mesorectal excision
RCT	Randomized controlled trial
QoL	Quality of life
HRQoL	Health related quality of life
LARS	Low anterior resection syndrome
BMI	Body mass index
MSKCC BFI	Memorial Sloan Kettering cancer center bowel function instrument
EORTC	European organisation for research and treatment of cancer
SF-36®	Short form 36
CCI®	Comprehensive complication index
CRF	Clinical report form / case report form
CT	Computed tomography
ERAS	Enhanced recovery after surgery
WHO	World health organization
UICC	Union for international cancer control
CMA	Cost-minimization analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CBA	Cost-benefit analysis
QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio
PPP	Purchasing power parity

1 INTRODUCTION

1.1 RECTAL CANCER

Colorectal cancer is the third most common cancer disease in the western world. In Sweden the incidence is increasing (figure 1) and currently approximately 2000 individuals are diagnosed with rectal cancer each year[1, 2]. Since the 1980s there has been a change in surgical treatment strategy, where the previous method of blunt dissection of the rectum has been replaced by following the anatomical planes, total mesorectal excision (TME)[3]. Together with the initiation of preoperative (chemo)radiotherapy, the local recurrence rates have decreased substantially and oncological outcome has improved[4-6]. This has rendered an increase in five-year relative survival for rectal cancer, which is now in general approximately 60%[7-9]. A study based on data from the Swedish colorectal cancer registry including patients who had undergone rectal resection for cancer (where approximately 85% were with curative intent), reported a three year survival rate of approximately 75% and a 5-year local recurrence rate of 5%[10].

Evaluation of patients and treatment strategies (including neo-adjuvant chemo/radiotherapy, adjuvant chemotherapy and choice of surgical technique) are together with patients' comorbidity and general condition, based on tumour-specific characteristics. These include tumour node metastasis classification, height of tumour (distance from the anal verge), engagement of circumferential margin or mesorectal fascia and signs of extramural vascular invasion. The evidence for the different treatment options are of various levels and even though national guidelines exist, there is no international consensus for the treatment of rectal cancer and adherence to defined guidelines varies[11, 12].

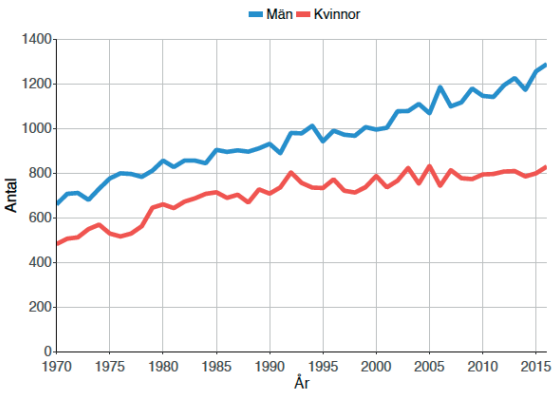


Figure 1. *Annual number of patients diagnosed with rectal cancer 1970-2016 in Sweden. Number of patients (y-axis) diagnosed each year (x-axis), where blue represents men and red women. Data and diagram presented with permission from the Swedish Cancer Society (available at www.cancercentrum.se)*

1.2 SURGICAL TREATMENT STRATEGIES

Low anterior resection

Low anterior resection with total mesorectal excision (TME) has increasingly been regarded as the optimal surgical treatment for potentially curable carcinoma in the mid rectum[3, 9, 13, 14]. The principles of TME surgery include sharp dissection under direct vision in the embryological avascular planes between the visceral and parietal pelvic fascia, removing the rectum with intact mesorectum[14]. Even though the introduction of training programs and centralization of rectal cancer surgery has led to decreased mortality and morbidity, rectal cancer surgery is still associated with complications, where anastomotic leakage is one of the most feared[15-17].

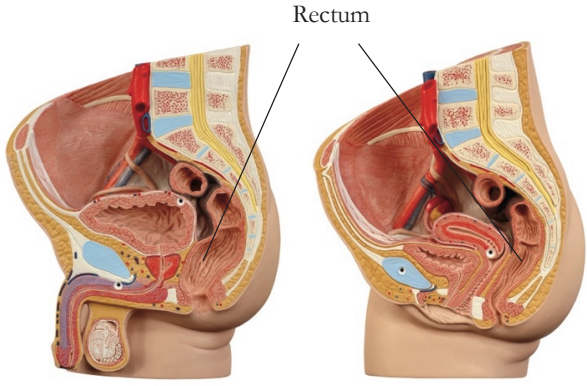


Figure 2. *Anatomy of the rectum in men and women respectively*

Anastomotic leakage

Anastomotic leakage in the colo-anal anastomosis is a complication with considerable consequences including mortality, delayed start of adjuvant chemotherapy, poor long-term outcome and decreased quality of life[18, 19]. Risk factors for anastomotic leakage are low tumour height, radiotherapy, male sex, smoking, obesity, immunosuppression and emergency resection[17, 20, 21]. The suspicion of an anastomotic leak may be obvious in a severely ill patient with

peritonitis, but may also be asymptomatic. The diagnostic tools suggested to investigate the anastomosis in a stable, less ill patient are computed tomography (CT), preferable with rectal contrast, and in selected cases flexible endoscopy (sigmoidoscopy). However the sensitivity and specificity varies[22, 23]. The following definition of anastomotic leakage after anterior resection has been suggested: 'a communication between the intra- and extraluminal compartments at the site of the anastomosis'. A grading system for severity has also been proposed with grade A: requiring no active therapeutic intervention, grade B: requiring active intervention (for example drainage) but manageable without re-laparotomy and grade C: requiring re-laparotomy[24]. Validation of the grading system in 746 patients with sphincter preserving rectal cancer surgery with a primary anastomosis, revealed an overall leakage rate of 7.5% and that grade A patients had an uneventful postoperative course (asymptomatic). Patients with grade C leakage (thus requiring re-laparotomy) comprised more than half of the leakage cases[25].

One approach to decrease the risk of anastomotic leakage is to optimize the conditions for the anastomosis to heal, by diverting the bowel contents away from the anastomosis. This can be done by the formation of a temporary ileostomy during the operation for the rectal tumour and requires a second operation for stoma closure.

Temporary ileostomy

In an attempt to reduce number of anastomotic leakages and their consequences, a Swedish randomized controlled trial investigated the role of the formation of a defunctioning stoma in conjunction with anterior resection for cancer. Results revealed significantly fewer symptomatic anastomotic leakages (10.3% vs 28%) and less need for urgent reoperation (8.6% vs 25.4%) in the group with a diverting stoma[26]. Other studies have reached similar conclusions[27-29], which have resulted in the routine use of a diverting stoma (often a temporary loop ileostomy) in patients undergoing TME surgery for mid rectal tumours, in many countries including Sweden.

Regardless the benefits of less symptoms if anastomotic leakage would occur, there is considerable morbidity related to the temporary ileostomy. Various complications occur with rates up to 50%[30-32], including readmissions, dehydration and chronic renal failure[33, 34]. The patients are also in need of a second operation (closure) with the inherent risk of postoperative complications, such as

wound infection and small bowel obstruction[34]. Most patients with a temporary ileostomy will keep their stoma for at least three months, but it is not unusual that the stoma is left in place much longer, and for a few patients it becomes permanent[35]. Because of this associated morbidity, studies have suggested a more selective use of diverting stoma[36]. There are however difficulties in identifying which patients who would benefit from a stoma, even though many risk factors for anastomotic leakage are known[20]. A nomogram has been suggested to preoperatively be able to predict the risk of anastomotic leakage after colon resections[37]. However, when tested on patients who had undergone rectal resection, the sensitivity was low[38].

Previous studies have shown that patients with a stoma may suffer from impaired health related quality of life (HRQoL)[39] where especially complications such as stoma leakage, parastomal skin irritation, retraction and prolapse of the stoma have significant impact on the patient's daily life[40].

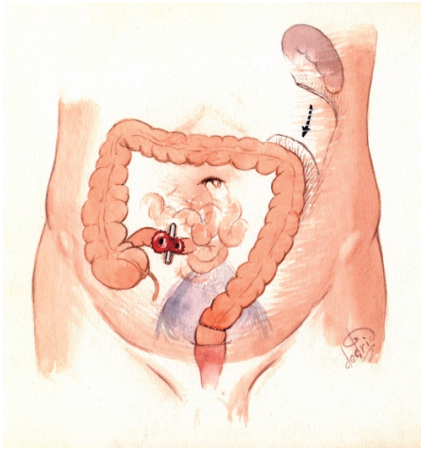
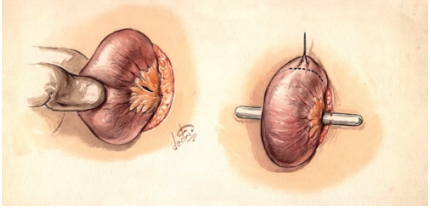


Figure 3. *Formation of a loop ileostomy (below) of the distal part of the ileum, through the abdominal wall (left) in the lower right quadrant. Copyright Diedrick*



Timing of stoma closure

Rather than omitting the stoma in preoperatively selected patients, with the risk of considerable consequences if an anastomotic leak occurs, early closure has been considered a potential option[41, 42]. The timing of stoma closure has previously been investigated in a few prospective studies that mainly focused on morbidity and mortality related to early closure of the stoma[41, 42]. These studies did not demonstrate any significant effect related to early closure, although wound

infection at the stoma sight seemed to be more common. In other studies, investigating the possibility of an early closure, the results have been promising, but were inconclusive[43, 44]. A recent meta-analysis, including results from three randomized controlled trials (RCTs) (one of which was the EASY trial), one prospective and two retrospective studies, proposed early closure for selected patients with the absence of anastomotic leakage and uneventful postoperative outcomes[45].

1.3 QUALITY OF LIFE AND FUNCTIONAL OUTCOME

According to the World Health Organization (WHO) the main ambition of cancer diagnosis and treatment programs are to cure or considerably prolong the life of patients and to ensure the best possible quality of life (QoL) for cancer survivors[46]. Improved multidisciplinary management has led to cure or prolonged survival of rectal cancer patients and the effects of treatments become more important for the individual. Quality of life is a multidimensional construct and health related quality of life (HRQoL) has in the context of healthcare been used to stress that it is the impact of health issues on quality of life that is of interest. It should be measured from the patient's perspective as QoL might be interpreted differently by patients and caregivers[47]. For example, patients might be willing to accept certain burdensome treatment for only small to modest potential benefits. Nevertheless HRQoL has become a more important outcome measure in clinical trials[48]. The need for including patient reported outcome measures as primary endpoints in randomized controlled trials, has been identified, although few prospective trials have been conducted[49, 50].

Recovery after rectal resection

Rectal cancer surgery has a negative effect on QoL[51]. Compared to surgery for colonic cancer, patients with rectal cancer appear to need longer time for recovery after surgery[51, 52] regardless the use of open or laparoscopic surgical technique. Postoperative conditions such as bowel disturbances and low anterior resection syndrome (LARS) are recognized complications. Patients may also suffer from sexual and urinary dysfunction, due to damage to pelvic autonomic nervous

structures by preoperative radiotherapy or by surgery[53, 54]. Since the rectal resection itself has such an impact on patients, it has, using standardized and validated questionnaires, been difficult to differentiate the actual effect of the temporary ileostomy and if closure has a positive influence on HRQoL or not[55, 56]. Even though reversal of a temporary ileostomy may lead to improved global QoL[57], other symptoms, such as anterior resection syndrome, might reveal themselves as soon as bowel continuity is restored.

Low anterior resection syndrome – LARS

Major defaecatory problems frequently occur after rectal surgery, including constipation, stool incontinence, urgency, abdominal pain and increased flatulence[58]. The presence of these types of symptoms is referred to as low anterior resection syndrome. Between 40% and 80% of patients undergoing low anterior resection report severe postoperative bowel dysfunction within the first 12 months[59-62]. According to a validated questionnaire the extent of LARS is divided into none-, minor- and major depending on the total score, using a scoring system[63-65]. Low anastomotic height, total mesorectal excision (in contrast to partial mesorectal excision), pre- and postoperative radiotherapy and a temporary stoma have been identified as risk factors for developing LARS or impaired anorectal function in the postoperative and long-term course[61, 62, 66-68]. As LARS is more frequently measured both pre- and postoperatively in patients in clinical practice, the prevalence is fairly well investigated[69]. Even though a longitudinal follow-up with LARS score is valuable, there is a lack of baseline information as patients' preoperative scores involve the presence of a rectal tumour, which might cause symptoms similar to LARS. A recent Danish study investigated the prevalence of LARS in a normal population, which may be more accurate for comparison. The study found that between 10-15% of the general population suffered from major LARS, with higher prevalence in the ages 50-79 years and among women (with up to 19% prevalence of major LARS)[70].

Identifying, informing and treating low anterior resection syndrome requires multidisciplinary management. Treatment is empirical and symptom-based and includes pelvic floor training, rectal irrigation, bio-feedback therapy and neuromodulation with sacral nerve stimulation[58, 71].

1.4 HEALTH ECONOMIC EVALUATION AND COST ANALYSIS

The role and use of evaluating economics in health care has increased substantially around the world. Economic evaluations alongside randomized clinical trials are important sources of information for decision makers[72]. Healthcare resources are limited and decisions regarding allocation of resources must be made. Economic evaluation requires comparison of two or more alternative courses of action, while considering both the inputs (costs) and outputs (consequences) associated with each[73]. This is done by comparing costs and health effects of at least two alternatives, and can be done in four different models. The main difference between them is the measure of the health effect (table 1).

Table 1. Measurements in different types of studies

Model	Description
Cost-minimization analysis (CMA)	Implies that two treatments achieve equivalent health effects and compares the incremental costs of two or more interventions.
Cost-effectiveness analysis (CEA)	Estimates incremental costs and health gains of alternative interventions. The clinical effectiveness is expressed in physical units; for example life years gained and can only compare interventions with the same specific measure of health effect.
Cost-utility analysis (CUA)	Takes into account the time spent in a health-state and the health related quality of life for that health-state. Expressed as quality-adjusted life years (QALYs).
Cost-benefit analysis (CBA)	Monetary value is assigned to the measure of health effect and the results can be compared to other interventions on different sectors of society.

Numerous guidelines recommend the use of cost-utility analysis with quality-adjusted life years (QALYs) as the measurement of benefit. QALY is an outcome measure that combines quality of life and "quantity" of life lived, and one QALY can be viewed as one year lived in the best possible health state. It is also the most widely published form of economic evaluation[73]. The cost-utility analysis commonly uses the incremental cost-effectiveness ratio (ICER), which is the incremental cost divided by the incremental effect, resulting in the increased cost of the added effect (figure 4). This can be defined as cost per QALY gained and enables comparisons between interventions in all areas of health care. To determine whether an intervention is cost-effective or not relies further on the threshold of the maximum accepted level of cost-effectiveness. Usually there are national guidelines for thresholds, depending on the type of treatment. The WHO has suggested a threshold range of between 1 and 3 times gross domestic product (GDP) per capita, although the willingness to pay per QALY also depends on type of treatment (intervention), indication (condition or disease) and what the alternative treatment is[74].

$$ICER = \frac{Cost_A - Cost_B}{Effectivness_A - Effectiveness_B}$$

Figure 4. *The ICER is calculated using the formula above, where A represents the intervention and B the control/ standard treatment.*

Cost-effectiveness plane

The ICER and willingness to pay threshold need to be carefully considered when an intervention is believed more effective and more costly. A way to explain this is through the cost-effective plane (figure 5). If the intervention is in quadrant B the choice of program is apparent, as it is more effective and less costly. The choice is also clear if the intervention is in quadrant D (less effective and more costly). In quadrants A and C the choice depends on the maximum cost-effectiveness ratio one is willing to accept.

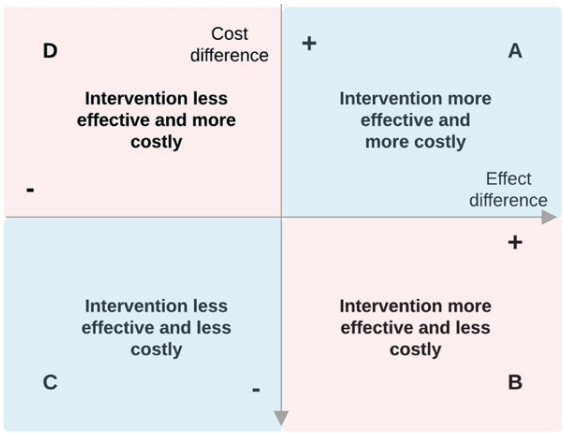


Figure 5. *Cost-effectiveness plane.*

In each quadrant (A-D), the intervention is:

A: *more effective, more costly*
B: *more effective, less costly*
C: *less effective, less costly*
D: *less effective, more costly*

Economic considerations within colorectal surgery

Hospital costs associated with treatment of colorectal cancer are considerable. Tumours in the rectum (compared to colon), formation of a stoma and more advanced tumour stages at diagnosis lead to higher costs[75, 76]. Overall costs from healthcare perspectives are increasing, partly due to more advanced technology (laparoscopic and robot-assisted laparoscopic surgery)[77, 78] but also due to improved survival including patients requiring palliative care[75]. From a societal perspective (including costs for sick-leave) there might however not be such a large difference between laparoscopic and open surgery[77]. A recent study including 7707 patients in routine Swedish care for colorectal cancer, found that laparoscopic surgery (compared to open) was favourable in terms of clinical effectiveness and costs, both from a societal and a health care perspective[79].

The formation of a temporary stoma is associated with costly events such as higher risk for readmission[80, 81] and a second operation (stoma closure)[75, 76]. However, as discussed earlier in this chapter, since previous studies have strongly indicated clinical benefits from the use of a defunctioning stoma[26, 29], this has been included in the standard surgical treatment. Furthermore as this strategy is associated with higher costs, despite cost savings due to less symptomatic anastomotic leaks[76], early closure may be a cost-effective alternative[82].

2 AIMS OF THE THESIS

The overall objective of this thesis and the EASY trial was to investigate the safety, feasibility and consequences of early closure of a temporary ileostomy after rectal resection for cancer.

The specific aims for each study were:

I. To compare early and late closure of a temporary ileostomy regarding surgical complications within 12 months after rectal resection.

II. To evaluate health related quality of life within 12 months after rectal resection, comparing early and late closure.

III. To perform a cost analysis 12 months after rectal resection, comparing early and late closure.

IV. To investigate and evaluate bowel function four years after rectal cancer surgery, comparing early and late closure.

3 PATIENTS AND METHODS

3.1 DESIGN OF THE EASY TRIAL

The EASY trial

The EASY trial was designed as a randomized, controlled multicentre trial[83]. It was set up in 2011 when early closure had only previously been studied in a randomized trial with several diagnoses[42] and a pilot study[41], both of which had identified the feasibility of early closure in selected patients with uneventful recovery after rectal resection. Eight centres from Denmark and Sweden participated in the EASY trial and patients were included from February 2011. Due to slower enrolment than anticipated, a recalculation of the sample size was performed, and with the revised sample size in mind the study was closed for inclusion in November 2014. Patients were randomized in computer generated blocks of six with a 1:1 ratio. All eligible patients were recorded in a screening log at the participating centres, reporting reasons for non-inclusion. A screening log including a representative sample of the target population at large is important in order to ensure external validity or generalizability in a study[84]. When inclusion of patients was complete, it emerged that three centres had inadequately reported the screening of all eligible patients. Before further analysis, the decision was made to exclude these centres, with the consequence that the intended number of patients was not reached, according to the sample size of 60 patients per group. A total of 112 patients were included, 55 in the early closure group and 57 in the late closure group.

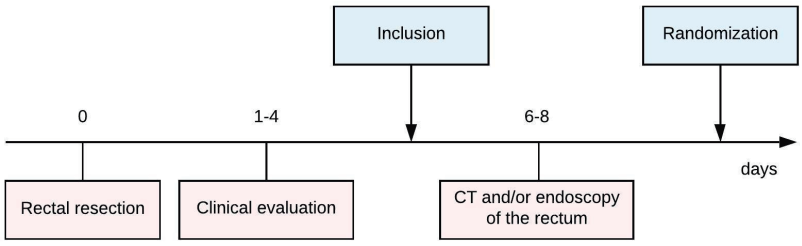


Figure 6. *Time line of postoperative evaluation and inclusion process from rectal resection (day 0) to randomization (8 days).*

Selection and inclusion of patients

Screening for and inclusion of participants was made after rectal resection (index surgery) with creation of a temporary loop ileostomy (figure 6). Inclusion criteria were rectal resection for cancer with formation of a temporary ileostomy and age ≥ 18 years. Exclusion criteria were diabetes mellitus, steroid treatment and signs of postoperative complications or anastomotic leakage. Patients who were unable to understand the written Danish or Swedish language respectively, were not enrolled in the study. Details of the inclusion process has been described in the study protocol[83].

Follow-up

Follow up of the different outcomes were up to 12 months for study I-III (figure 7) and approximately 4 years for study IV, after rectal resection. Analysis was conducted in line with the intention-to-treat approach, meaning that the patients were analysed according to the group they were assigned, regardless of what treatment they received.

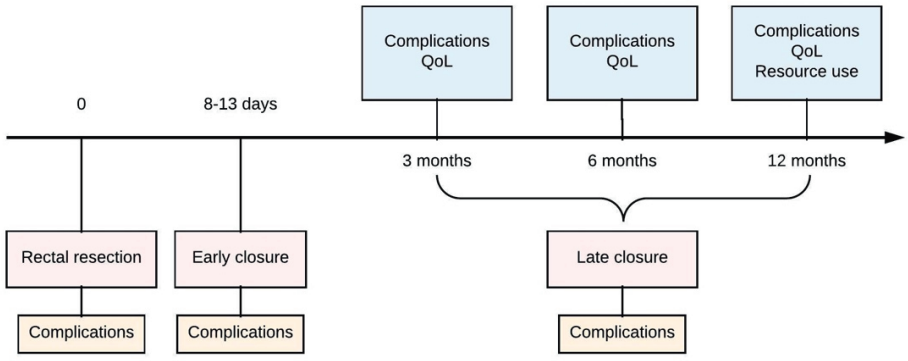


Figure 7. *Follow-up of outcomes up to 12 months after rectal resection (study I-III).*

3.2 OUTCOME MEASURES

The EASY trial explored three different outcome measures in the corresponding studies; morbidity and complications (primary endpoint), quality of life and cost analysis within 12 months after index surgery. Later, a separate study of functional outcome was added, including the surviving patients randomized in EASY, approximately four years after rectal resection (table 2).

Table 2. Outcomes, measurements and follow-up of the different studies

Study	Outcome	Measurement	Follow-up[a]
I	Complications	Clavien-Dindo classification, CCI®[b]	Baseline, closure, 3, 6, 12 months
II	Quality of life	EORTC QLQ-C30, CR29, SF-36®	3, 6, 12 months
III	Cost analysis	Resource use	12 months
IV	Functional outcome	LARS score, MSKCC BFI[c]	Median 50 months[d]

[a] follow-up specified as time from rectal resection (baseline)
[b] comprehensive complication index
[c] Memorial Sloan Kettering cancer center bowel function instrument
[d] follow-up in October 2017

3.2.1 MORBIDITY AND COMPLICATIONS (I)

The Clavien-Dindo classification of surgical complications

The Clavien-Dindo classification of surgical complications[85] is a system of grading postoperative complications based on the type of therapy that is required to treat the complication (table 3).

Table 3. Clavien-Dindo classification of surgical complications[a]

Grade I	Any deviation from normal postoperative course Antiemetics, analgetics, diuretics, electrolytes, superficial wound infection (opened at bedside)
Grade II	Additional pharmacological treatment other than grade I Blood transfusion, parenteral nutrition, antibiotics
Grade III	Requiring intervention (surgical, endoscopic, radiologic) IIIa: intervention not under general anaesthesia IIIb: intervention under general anaesthesia
Grade IV	Life-threatening complication IVa: single organ dysfunction (including dialysis) IVb: multiorgan dysfunction
Grade V	Death

[a] simplified from the classification of surgical complications[85, 86]

The classification has been used to grade complications after surgery since the publication of the original article in 2004 and the use of the classification system has increased over time. The classification grading system has further been evaluated using patient case examples, revealing some differences in interpretation of the grading of complications among and between patients, nurses and doctors[86]. There were for example differences in interpretation of medical complications that were sometimes recognized as being unrelated to the

surgical procedure. The overall recommendations are to classify all medical complications if they occur during hospital stay or within 30 days from surgery, even if they are considered being unrelated to the actual surgical procedure. If multiple complications occur, the recommendations are to only count the most severe one (if they are consequences from one another). However if the complications are independent, to grade them separately and take all into account[86].

Bearing this in mind, using the suggested recommendations, there are still difficulties in defining what a complication might be or when it is considered a "normal" postoperative course after extensive surgery, such as rectal resection. One example is the postoperative use of opioids. In the current study the complications were graded in the clinical report forms (CRFs) by the treating physician. All prospective data were also reviewed retrospectively in order to ensure that all complications were graded using similar definitions and not counted twice by mistake. Concerning the example of opioid use, if the patient had a prescription renewal, dosage increase at follow-up or if pain was described problematic for the patient, this was considered a complication in the present study. However there are no generally accepted strict definitions to follow.

The loop ileostomy complications were also graded in the same system. For the less severe complications (grade I) such as skin irritation, leakage and small bleeding at the stoma, they were considered complications only if they were brought up as problems at least twice by the patient or caregiver. In the trial, follow-up of stoma function was provided by stoma care nurses.

Comprehensive complication index

Quality of life and postoperative complications are often reported as separate outcome measures, where QoL is usually reported by the patients, and complications by the surgeon or caregiver. A suggestion of a correlation between patient reported QoL and grade of complications, both of which seem to recover within 12 months in elective colorectal surgical patients, has previously been made[51, 87]. The Clavien-Dindo classification grades reflect the magnitude of each complication. However the system may not represent the entire burden of postoperative morbidity, as often only the complication with the highest grade is reported. The effect on patients with more than one complication may therefore be underestimated[88]. Thus, comparisons of patients with more than one complication are difficult; for example when comparing the morbidity of a patient

with four grade I and II complications with another patient experiencing one grade IIIb complication, is not a simple task.

The comprehensive complication index (CCI®) was developed in order to overcome these problems and integrate all recorded complications weighted by severity[89]. It is based on the Clavien-Dindo classification and summarizes the morbidity burden in a scale ranging from 0 (no complication) to 100 (death) (figure 8).

$$CCI^{®} = \frac{\sqrt{(wC_1 + wC_2 \ldots + wC_x)}}{2}$$

wC = Weight of Complication

	wC	CCI® Single Value
Grade I	300	8.7
Grade II	1750	20.9
Grade IIIa	2750	26.2
Grade IIIb	4550	33.7
Grade IVa	7200	42.4
Grade IVb	8550	46.2

Clavien-Dindo grade V always results in CCI® 100.

Figure 8. *Formula for calculation of the CCI® and the weight of each corresponding Clavien-Dindo grade of complication.*

The CCI® single value corresponds to the CCI® of one complication with a certain Clavien-Dindo grade. If for example a patient has one grade IIIa complication, the comprehensive complication index would be 26.2.

When explored in randomized controlled trials, the CCI® has indicated better sensitivity to detect differences between treatment effects. Furthermore, this suggests that the use might allow smaller sample size in future studies, as well as enabling longitudinal assessment of complications over time. When used in clinical trials with overall morbidity as endpoint, it could be considered as the primary outcome measure[90].

The EASY trial was designed before the CCI® was in use. However, with regard to the added value of the comprehensive complication index as outcome measure, this was included as a supporting endpoint to the number of complications and their Clavien-Dindo classifications.

3.2.2 QUALITY OF LIFE (II)

The importance of evaluating quality of life, or patient reported outcome measures, has increased and in clinical trials it is more commonly recommended to include QoL evaluation. It may even be the primary outcome of choice for trials[47], especially in the palliative care setting. Measurements and instruments for assessing QoL should satisfy basic properties if they are to be clinically useful. These properties are validity, reliability, repeatability, sensitivity and responsiveness. *Validity* describes how well a measurement represents the attribute being measured. *Reliability* and *repeatability* concern the random variability associated with measurements, where ideally patients with no change in status, should give similar responses each time they are assessed. *Sensitivity* is the ability of detecting differences between patients/groups and *responsiveness* relates the to the capability of detecting changes when a patient experiences improvements or deteriorations[47]. The validation of instruments is based on the process of determining whether the instrument measures what it is intended to measure, and subsequently if it's useful for its intended purpose.

In the QoL evaluation in the EASY trial, three validated questionnaires were included; European organisation for research and treatment of cancer (EORTC) questionnaires QLQ-C30 and CR29 (colorectal module), and Short Form 36 (SF-36®) (see appendix). These questionnaires, divided into several items, give scores that make the longitudinal follow-up possible as well as comparison between groups of patients and to reference populations. However, often raised questions are: how large must a change or difference in QoL score be in order to be clinically important, and when is the difference between groups large enough to be noticeable? For example, regarding the EORTC QLQ C30, which is developed to assess QoL in patients with cancer, it has been suggested that 5-10 points difference should be considered as 'little change' and 10-20 points difference would represent a 'moderate change'[91]. As for the SF-36®, other values are suggested in a similar manner[92].

Baseline assessment

There should usually be a baseline/pre-treatment assessment for evaluation of change over time from when the treatment is introduced. This would also enable baseline comparison between the studied groups. The assessment should be made before the patients have been informed of group assignment in order to minimize

bias in questionnaire response[47] and it is desirable to assess the patients at the same points in time in all treatment arms.

Missing data

The largest challenge concerning patient reported outcomes in clinical trials is compliance, which depends on several factors, including timing of assessment, type and severity of disease and treatment.

Regarding QoL assessment, missing data is a recurring problem. At best, the pattern of missing data is not related to patient characteristics that influence the outcome. This is referred to as data missing at random, and the missing data would only render wider confidence intervals and reduced statistical power, but the estimated treatment effects would be unbiased. At worst, missing data would be related to factors influencing outcome. This is referred to as missing not at random. The missing data would then result in biased estimates of the treatment effect. It is important to understand the cause of missing data and if there is a pattern which could lead to biased results and incorrect conclusions. In general, if more than 50% of the data for a particular endpoint is missing, analysis is not recommended, while fewer missing answers can have minor to moderate impact on study findings. If there is less than 10% missing, a simple imputation may be sufficient[93]. A major problem regarding the EORTC QLQ-C30 occurred at 12-month follow-up in the trial, as a total of 36 patients were by mistake given an incomplete questionnaire lacking one page. This was equal to half of the questions. Due to the fact that data were missing at random, i.e. the missing values did not correlate to scores recorded in the QoL assessment (because of distribution of incomplete questionnaires), imputation was considered unnecessary[47]. Instead analysis of physical- and role functioning was performed and presented for the 12 month follow-up, as these functional scales were completely scored using the distributed questions (1-15), and were not affected by the missing page of the questionnaire.

Comparison of results

Ideally, comparisons are conducted within and between the treatment groups from baseline and over time. Because of the design of the EASY trial, patients were included after their rectal resection and therefor no baseline, preoperative evaluation was available. In order to evaluate and to guide interpretation of results, comparisons with reference scores of general populations were made, as suggested[47]. In the trial, reference populations from Sweden[94, 95] and Germany[96] were available and used for comparison, as supposedly these would be representative for the patients studied in Sweden and Denmark.

3.2.3 COST ANALYSIS (III)

The role and use of economics in healthcare has increased substantially around the world and economic evaluations alongside randomized clinical trials are important sources of information for decision makers[97]. Ideally, studies would be powered also for economic outcome measures, however this is rarely the case as sample sizes are usually based on primary outcomes alone. Consequently, the economic comparisons may be underpowered[97]. The costs can be analysed from the healthcare perspective and/or the societal perspective, the latter adding the cost of sick-leave to the direct healthcare costs. In Sweden data on sick-leave can be attained through the Swedish Social Insurance Agency. Since the EASY trial also included Danish patients (where sick-leave data were not available), the cost analysis it the study was only performed from the healthcare perspective.

Identification of cost variables

There are two ways of collecting and analysing data; either through micro costing, where all separate resource items are identified in great detail, or gross costing, where consumption of single resources is aggregated to meaningful resource units. Nevertheless, it is important to identify the potential key cost-driving events; usually those that either have a high unit cost or those with a small unit cost but occur at high frequency[97]. Furthermore it is also recommended to include costs that differ between treatment groups[73]. The cost analysis alongside the clinical trial had an intention to treat approach, as recommended[97]. Surgical treatment for rectal cancer is resource consuming. One might assume that it

would be less costly with an early closure of a temporary ileostomy, knowing that the presence of a stoma has a substantial influence on readmission rates and healthcare costs[75-77, 80]. The primary endpoint analysis showed significantly more complications, many of which were stoma related, in the late closure group. There was no difference in severe complications and/or number of reoperations[98]. Even though complications of all grades increase the costs of major surgical procedures, including colorectal surgery[99], the impact of less severe complications on healthcare costs were unknown in the present study. Actual frequencies of readmissions and investigations were not evaluated as a primary outcome measure. The key cost-driving resources that were identified prior to inclusion of patients and evaluation of data in the cost analysis are seen below (table 4).

Table 4. Identified key cost-driving resources from the healthcare perspective

Cost variable	Reason for inclusion
Rectal resection	High unit cost, low frequency
Stoma closure	High unit cost, low frequency
Reoperation	High unit cost, low frequency
Length of stay – readmission	Medium unit cost, unknown frequency[a]
Outpatient visit	Low unit cost, high frequency
Outpatient endoscopy	Medium[b] unit cost, unknown frequency[a]
Outpatient radiology	Medium[b] unit cost, unknown frequency[a]
Stoma appliances	Low unit cost, high frequency[c]

[a] expected to be high frequency
[b] varying cost depending on type of examination
[c] predominantly in the late closure group

Unit costs

The cost variables were derived from Swedish unit costs in order to eliminate bias in the sense that different countries apply different costs for equal treatment. Since complete data regarding all costs in association with procedures were not available through the clinical report forms, all inpatient surgical procedures were priced according to their corresponding diagnosis and performed procedure. The tariffs were based on national data covering approximately 85-90% of all inpatient procedures in Sweden (Swedish Association of Local Authorities and Regions). When available, national prices were used (surgical procedures), however for specific examinations, radiologic investigations, and outpatient visits, local unit costs from a university hospital were used.

The importance and use of quality adjusted life years (QALYs)

It is recommended that baseline data regarding HRQoL should be collected at point of enrolment, prior to the intervention in a study. QALY analysis should then be adjusted for any baseline imbalance. In the EASY trial, as mentioned previously, no baseline QoL data were obtained, which made adjustment impossible. Regarding the calculation of QALYs; the need of analysis of economic thresholds and the willingness to pay per QALY gained, is based on scenarios where either the intervention is more costly and more effective, or less effective and less costly. Concerning the results of the first and second study of the EASY trial, the intervention was found to be more effective (through the surrogate end point of complications up to 12 months after surgery) without any difference in QoL. If the intervention was believed to be more expensive, there would have been indication for calculation of QALYs and ICER (see chapter 1), but as there were no signs of increased resource use in the intervention group (early closure) a cost analysis was appropriate.

Protocol-driven costs

When conducting a cost analysis alongside a clinical trial there is a risk that the costs for the study population will be protocol-driven, by for example increasing the resource use through more surgical procedures, radiologic investigations or follow-up visits. This is particularly important if there is a difference between the intervention and the control group. In the cost analysis of the EASY trial we did not include the costs of the endoscopy and/or radiologic examination prior to

inclusion. However, patients allocated to the late closure group had in many cases undergone an extra endoscopy prior to stoma closure (since the former examination would've been carried out several months earlier). The consequence of this was that several patients in the late closure group had undergone two examinations of the anastomosis; prior to trial inclusion and prior to closure. This endoscopic examination was therefor considered protocol-driven and a decision was made to add the cost of an endoscopy in the intervention group as well as for the patients in the control group who had not undergone an extra examination, as a sensitivity analysis to address this problem.

The non-parametric bootstrap

Non-parametric bootstrapping is used when data are skewed and you need to describe the distribution of possible mean values. Through the use of resampling from the existing data with replacements, an empirical estimate of the sampling distribution of mean costs is generated[73]. In the cost analysis a non-parametric bootstrap analysis generating 2000 iterations was performed due to skewed data in order to assess robustness.

3.2.4 FUNCTIONAL OUTCOME (IV)

Four-year follow-up

The functional follow-up was a separate study including the surviving patients randomized in the EASY trial and comprised two questionnaires, the LARS score and the Memorial Sloan Kettering cancer center bowel function instrument (MSKCC BFI). The LARS score was developed in Denmark and published originally in 2012[63]. Inclusion of patients in the EASY trial took place between 2011-2014, hence started before the LARS score was fully developed and in use, and consequently not included in a functional follow-up at the initial stage. Since there have been suggestions that a temporary stoma increases the risk of low anterior resection syndrome[61, 67], it was considered out of interest to follow up the patients with regard to bowel function and investigate if there were signs of differences between the two groups, depending on timing of stoma closure. Questionnaires were therefor sent to all surviving patients in 2017, resulting in a mean follow-up time of 50 months after rectal resection.

Sample size

Since the study was based on the cohort from the EASY trial, which was not designed for the endpoint in study IV, a post hoc sample size calculation was performed. A previous study on bowel function after rectal resection reported a mean LARS score of 25, with a standard deviation of 12[100]. Corresponding value for the general population was approximately 15, with a standard deviation of 12[70]. This corresponds to a difference in LARS score of 10 units. With 25 patients per group we would have 80% power to detect a difference of 10 units, at a 5% significance level. If however we would anticipate smaller difference in LARS score (since both treatment groups have undergone rectal resection), we would have 80% power to detect a difference of 5 units with approximately 90 patients per group.

Questionnaires

The LARS score consists of five questions, where different questions have different weight based on the impact on QoL. Depending on score, the results are divided into no, minor or major LARS. The BFI is more detailed, containing 18 questions. Both questionnaires have been validated[63, 101]. The LARS score was available in Danish and Swedish, whilst the BFI was available in English and translated into Danish and Swedish through a forward and backward translation procedure, for study IV. A recent study has evaluated the prevalence of LARS in a normal Danish population[70], which enables comparison to a reference population, as described in the first chapter. Unlike the BFI, the LARS score has since publication been adapted widely into routine care of rectal cancer patients, as it is considered a simple instrument enabling longitudinal follow-up.

3.3 METHODOLOGICAL CONSIDERATIONS

The randomized controlled trial design

The first randomized controlled trial was conducted in the mid 1900s. This type of study has the last 20-30 years emerged to be considered providing the highest grade of evidence when evaluating a new therapy. Systematic reviews and, even better, meta-analyses of several RCTs[102] should show the new intervention to be superior compared to clinical routine, before systematic implementation of the new therapy is considered. In randomized controlled trials it is desirable to restrict participants to a near-homogenous group, which will reduce the outcome variability, consequently reducing the sample size needed in order to obtain statistically significant differences. A consequence is however that the trial might end up evaluating only small subsets of potential populations of interest hence questioning the external validity, generalizability and decreasing the applicability of the research results[103]. In contrast, observational studies might include broad populations and generalize well, however there are issues regarding internal validity and unknown quantity of confounders and their effects.

There are a few major sources of error in clinical research to consider[104].

Selection bias results from one or several non-random elements that influence the allocation of patients to exposures in a way that will influence the outcome. A randomized trial will minimize this problem. It is however vital to follow the randomization process and maintain a screening log, in order to reduce selection bias.

Confounding is when an apparent association between exposure and outcome actually results from their separate relationships with something else (confounder). The randomized design will randomly and evenly allocate the patients and hence the confounder. This will not only divide the influence of the confounder evenly, but also implies that you don't always have to identify all potential confounders. In practice, a situation can occur when the groups are not similar despite randomization. You can then perform sensitivity adjusted analyses for specific variables in order to minimize the effect of a confounder on the results. Block randomization can be performed in order to minimize the impact of site-related variations that are assumed to be a substantial potential confounder[103, 105].

Measurement bias results from non-random errors in assessing exposure and/or outcome (disease). Thoroughly designed study protocols and clinical report forms, where the objectives are to standardize data quality, can enhance the quality of the measurements. To minimize bias further, blinding is a possibility. Blinding can be difficult to achieve in surgical studies because of the nature of interventions. However some studies have achieved this by for example using standard surgical dressings in order to conceal laparoscopic or open approach in abdominal surgery, both to the patients and the investigators assessing the patients[106].

Overall the randomized study design minimizes selection bias and, in sufficiently large studies, ideally prevents confounding. To fully prevent measurement bias, however blinding would be required. Studies fulfilling these requirements, randomized, blinded clinical trials with sufficient number of patients provide the most valid clinical research results[103].

3.4 STATISTICAL ANALYSIS

Statistical models

A large body of empirical research, including clinical studies, involves the aim of explaining to what extent different factors (effects), including therapeutic interventions, can explain variability in outcome. This is done by statistical models that aim to quantify the contribution of each factor, as well as the part one can't explain (the residual term consisting of random variation). Assuming that the factors and the random variation contribute to the outcome according to a linear model, makes estimation and interpretation easier. One key component in parameter estimation is the specification of a probability distribution for the randomness in the data. A broad class of statistical models, referred to as generalized linear models[107], consist of two components; a probability distribution for the randomness in the data and a link function that specifies at what scale the effects contribute linearly. Generalized linear models allow a broad class of different probability distributions, including the normal, binomial and Poisson distribution. Different link-functions are suitable for the different distributions. The different link-functions do in turn mean that the contribution of the effects to the outcome on the linear form, are done at different scales than for the

outcome. For the normal distribution, the identity link is suitable, meaning that no change in scale is needed and the effects are quantified at the same scale as the original measurement. For the binomial distribution the logit or log links are suitable; for the effects to be interpretable on the original scale (risk or probability for an event) the results are presented as an odds ratio.

When a reasonable statistical distribution and a link-function are specified, a generalized linear model enables a unified framework for the estimation and interpretation of treatment effects. However, for a large body of data in clinical research the assumptions required for a generalized linear model may be questionable. This occurs for example when data have skewed or multimodal distribution (more than one mode) or extreme values, where determining a reasonable distribution is not possible. In these cases, a generalized linear model is not considered appropriate and a non-parametric method may be used. Non-parametric methods require less stringent assumption regarding the data. However the methods are mainly limited to hypothesis testing where only p-values are obtained with no interpretable quantification of treatment effects, for example the average difference between treatment groups. In the EASY trial, a generalized linear model was used for study I and III, but non-parametric methods were used in study II and IV, as data were skewed and included extreme values.

Sample size

When planning a study one needs to determine the number of patients required to reach a sufficient statistical power. If a difference, of a magnitude that is of interest, truly exists between treatments (intervention and control), sufficient amount of information (number of patients) is required in order to have a good chance of detecting it. In other words, sufficient statistical power is required to detect a clinically meaningful treatment effect (the chance of rejecting the null hypothesis when a certain alternative that we aim to detect, is true). Besides deciding a clinically meaningful difference, the sample size calculation also depends on the level of the anticipated variability (or the incidence rate) in the data and the risk of a type I error (risk of incorrectly rejecting a true null hypothesis) one is willing to take. The clinically relevant difference which one would like to detect (if it is present), can arise from previous published data, alongside clinical experience[105]. However, this becomes a challenge when there are no previous data available.

The trial was powered for the primary outcome (study I), but power calculation was also executed for QoL (study II), where previously described minimally clinically important differences were used, both for the SF-36® and the EORTC QLQ C30.

Multiple hypothesis testing

In the framework of statistical hypothesis testing, two types of errors can be made; type I (falsely rejecting a true null hypothesis) and type II (failing to reject the null hypothesis when the alternative hypothesis is true). The risk of type II error depends on the statistical power. The error rates are controlled by having a fixed risk of type I error, usually set to 5%, and the type II error is minimized by increasing the sample size. When performing several hypothesis tests the risk of making at least one erroneous decision will be larger than 5%. This error is called the familywise error[108]. The more tests that are made, the higher the familywise error rate will be. There are different strategies available for having the familywise error rate set to remain at 5% when several hypothesis tests are performed. The different strategies depend on whether all tests are of equal importance (referred to as parallel procedures) or if we have an order of priority (referred to as fixed sequence procedures), for example if some endpoints are of more interest than others. One strategy is to inflate the p-values, making it more difficult to reject the null hypothesis at the pre-specified significance level, e.g. 5%, by using methods for multiple testing. One parallel procedure is the Bonferroni correction, where each p-value is multiplied by the number of planned tests. One fixed sequence procedure is to only test a secondary hypothesis if the primary is rejected. In study I some of the hypotheses were of equal importance and some were of higher priority. The strategy used was a combination of parallel and fixed sequence procedures (referred to as gatekeeping procedures) where the two secondary hypotheses were only tested at 2.5% level if the primary hypothesis was rejected at the 5% level.

The seriousness of the increase in familywise error rate depends on the scientific objective. In early phases of the study of new therapies where the objective is characterized as explorative and hypothesis generating, or for secondary and tertiary endpoints in a clinical trial, correction for multiple testing may not be necessary. But for the primary objective of confirmatory studies, a correction for multiple testing may be needed.

3.5 ETHICAL CONSIDERATIONS

Safety

The trial included patients undergoing surgery with risk of complications, anastomotic leakage being one of them. Even though the integrity of the anastomosis was confirmed prior to inclusion in the trial, there was still a small risk for "late" leakage and consequently a risk that these patients would benefit from a stoma during a longer period, exceeding two weeks. The primary aim was to investigate safety of early closure, hence the narrow inclusion criteria with the consequence of only selecting patients without any signs of postoperative complications or considerable comorbidity. However, with regard to known complications and morbidity associated with a temporary ileostomy and the importance of an early closure, the potential benefits outweighed the risks, and the study was therefor designed accordingly.

Ethical approval and data security

The trial was approved by the Science Ethical Committee for the capital region in Denmark (protocol id: H-1-2010-113) and in Sweden the project was approved by the Regional Ethical Review Board in Gothenburg (Dnr 064-2011). For the functional follow-up (October 2017), ethical approval was achieved in Denmark and Sweden. The trial was approved by the Data Protection Agency in Denmark, and by the Personal Data Representative at the Sahlgrenska University Hospital, Göteborg, Sweden. Before inclusion, patients were informed about the study and all participating patients returned a signed consent form.

4 RESULTS

4.1 COMMON FINDINGS

During the inclusion period, 418 patients were identified and assessed for eligibility. Of these, 291 did not meet inclusion criteria, where 37 had a suspected anastomotic leakage. Randomization was performed in 127 patients but was followed by further exclusions (the larger part being due to exclusion of centres that failed to maintain a screening log, as described in chapter 3), and in the end 55 patients were allocated to early closure, and 57 to late closure. See figure 9 for details.

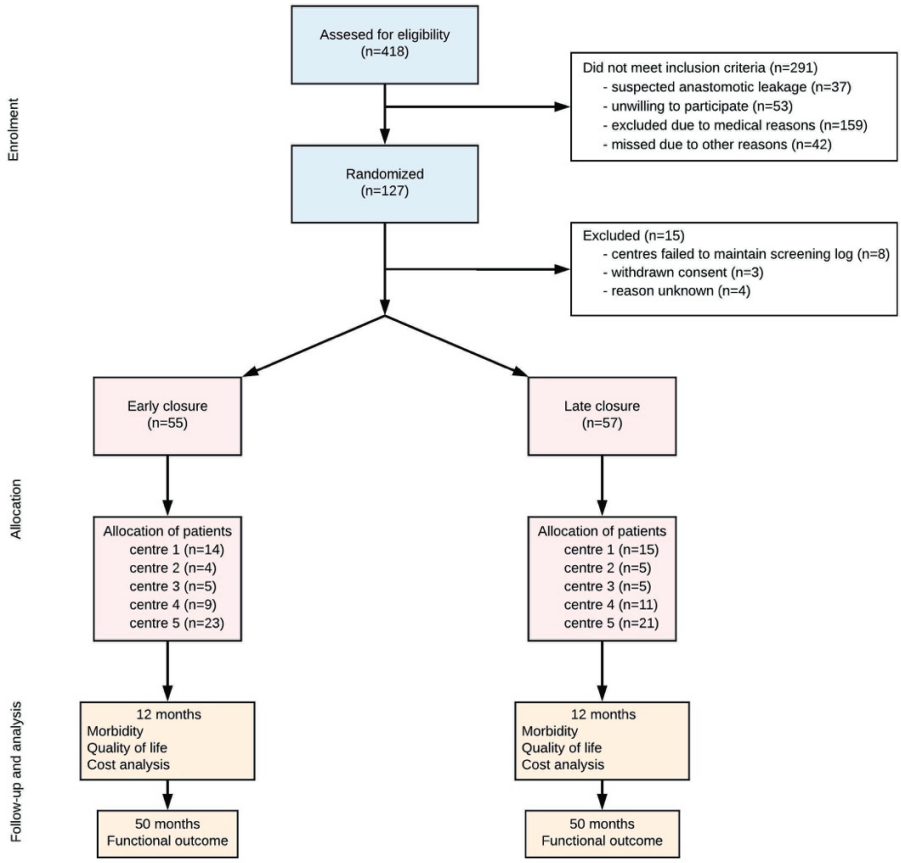


Figure 9. *Participant flow diagram showing enrolment, allocation, follow-up and analysis of patients*

Reasons for exclusion

Approximately 70% of the patients who were assessed for eligibility did not meet inclusion criteria (figure 9). Some of these were due to medical reasons (n=159). Patients who had undergone different types of surgery than rectal resection with the formation of a temporary ileostomy constituted a large proportion (28%). Postoperative complications such as paralytic ileus, infection and reoperations, as well as diabetes were other causes for non-inclusion (table 5).

Table 5. Medical reasons for non-inclusion

Medical cause	Number of patients
Permanent or no stoma (including Hartmann's procedure)	45 (28%)
Diabetes	28 (18%)
Paralytic ileus	24 (15%)
Delayed postoperative recovery	15 (9%)
Perioperative complications	7 (4%)
Reoperation	7 (4%)
Other infection	5 (3%)
High stoma output	5 (3%)
Language difficulties	5 (3%)
Extensive cancer disease	3 (2%)
Steroid treatment	3 (2%)
Cardiovascular disease & pulmonary embolism	3 (2%)
Ulcerative colitis	1 (1%)
Other	8 (5%)
Total	**159**

There were 37 patients with suspected anastomotic leakage (corresponding to approximately 9% of the 418 assessed patients) and some 53 patients (13%) were unwilling to participate, with further three patients withdrawing consent after randomization.

Response rates

Although the trial and the four studies in this thesis were based on the same patient population, sources of information (CRF data and questionnaires), outcome measures and follow-up times were different. The total number of patients analysed at each follow-up occasion varied (participant flow diagram presented in each study), but were overall high. Patients available for follow-up and response rates for patient reported outcome measures (study II and IV) are seen in table 6.

Table 6. Data source and response rates for each study[a]

Data source and study	Early closure (n=55)	Late closure (n=57)	Time of follow-up (from rectal resection)
CRF			
Study I	55/55 (100%)	57/57 (100%)	Closure, 3, 6, 12 months
Study III	55/55 (100%)	57/57 (100%)	12 months
Questionnaires			
Study II	52/55 (95%)	53/57 (93%)	3, 6, 12 months
Study IV	42/47[b] (89%)	40/46[c] (87%)	Median 50 months (range 34-77 months)

[a] response rates refer to the number of patients with data from at least one follow-up occasion for each study
[b] patients available for follow-up (n=47); deceased (n=7), permanent stoma (n=1)
[c] patients available for follow-up (n=46); deceased (n=5), permanent stoma (n=6)

Patient characteristics

Patient characteristics at baseline are presented in a table in each study. Overall the patients were comparable regarding age, body mass index (BMI), comorbidity, radiotherapy (including long-term), adjuvant chemotherapy, employment and educational level. The early closure group had more women (n=31) compared to the late closure group (n=21). Tumour height differed slightly with higher tumours in the late closure group. There were also somewhat more patients with clinical stage I of their cancer disease, according to the Union for international cancer control (UICC), in the late closure group. At the functional evaluation approximately four years after rectal resection, the difference in sex, tumour height and clinical stage of cancer disease persisted between the groups. At this follow-up there was a larger proportion of patients in the late closure group who had been treated with adjuvant chemotherapy, although the differences were small.

4.2 MORBIDITY AND COMPLICATIONS (I)

The main outcome for the first study in this thesis was the mean number of complications after rectal resection within 12 months. CRFs were collected at baseline (after inclusion), at stoma closure and at 3, 6 and 12 months respectively. All complications within 12 months were registered, including stoma related complications that were registered retrospectively by inspection of patient charts. The Clavien-Dindo classification of complications was used to grade all complications and the CCI® was applied as a supporting endpoint.

The mean number of complications per patient was 1.24 in the early closure group compared to 2.88 in the late closure group, with a mean ratio for intervention versus control of 0.42 (95% CI: 0.32-0.57). The difference was statistically significant with a p-value of <0.0001. Regarding CCI® level, there was a median difference of 15.7 units (8.7 and 24.4 for early and late closure group respectively)[98].

There was no difference regarding more severe complications (Clavien-Dindo grade IIIa or higher), including reoperations. There were more stoma related complications in the late closure group, and the median for the duration of the loop ileostomy was 11 days and 148 days in the early and late closure group respectively.

Sensitivity adjusted analyses were performed with sex, age, BMI, comorbidity and radiotherapy as covariates, and did not alter the results.

4.3 QUALITY OF LIFE (II)

In the second paper the aim was to compare QoL and disease-specific quality of life between the two groups, at 3, 6 and 12 months after index surgery[109]. The questionnaires included the SF-36®, EORTC QLQ-C30 and CR29 (the latter more specific for colorectal cancer).

An printing error lead to a low response rate regarding the EORTC QLQ C30 at 12 months (55%), whilst response rates were otherwise 82-95%.

SF-36® scores were similar with no difference in physical or mental component scores. All dimensions improved over time. At 3 months a majority of patients scored values below mean levels of the reference population[94] while at 12 months scoring higher than the reference population, with physical functioning yielding the highest scores among the dimensions.

EORTC QLQ C30 and CR29 scores were comparable between the early and late closure group.

The results indicated that global quality of life generally improved in the later part of the follow-up period (6-12 months), and at 12 months the results were comparable, not only between the two groups but also to age-matched reference populations as well as previous findings[56, 95, 96].

4.4 COST ANALYSIS (III)

The resource use analysis was carried out at 12 months after rectal resection. All data were collected through CRFs and for the analyses, unit costs were derived from Swedish sources and applied for all patients. All costs were adjusted to the price year of 2016 and analysed from the health care perspective.

The total difference in mean cost per patient was 4060 USD ($) in favour of early closure (95% CI: 1121-6999). The difference was found statistically significant with a p-value of <0.01.

Sensitivity analysis (as described in study III and in chapter 3) and adjustment for sex, comorbidity, BMI, age and radiotherapy did not alter the results. To test robustness a non-parametric bootstrap analysis based on 2000 iterations was performed, showing similar findings.

In summary, the predominant cost affecting factors were reoperations, readmissions and endoscopic examinations. Readmission rates had not previously been investigated in the EASY trial, and the present study showed that 24% of the patients in the early closure group were readmitted to hospital within 12 months after surgery while 49% of the patients in the late closure group were readmitted (excluding the readmission required for stoma closure).

4.5 FUNCTIONAL OUTCOME (IV)

Another secondary analysis of the trial was long-term functional outcome. Questionnaires LARS score and MSKCC BFI were sent to patients in the autumn of 2017, yielding a median follow-up time of four years.

Overall 54 patients (66%) reported major LARS and 16 (20%) reported no LARS. There was no difference in median LARS scores between the groups and the prevalence of LARS (minor and major) was 76% and 85% in the early and late closure group respectively (RR: 0.89, 95% CI: 0.72-1.11, p=0.29).

Median BFI scores did not differ between the groups. The patients in the early closure group reported less urgency with a median urgency subscale score of 17, compared to 14 for the late closure group (p=0.02).

There was an observed difference in permanent stoma occurrence at follow-up; one patient in the early closure group and six patients in the late closure group, however the difference was non-significant.

Tumour height and use of radiotherapy (known risk factors for LARS) were included as covariates in adjusted analysis, and did not alter the findings.

5 DISCUSSION

5.1 DISCUSSION ON FINDINGS

The randomized controlled trial found that early closure of a temporary ileostomy in selected patients was superior in terms of the primary outcome; number of complications up to 12 months after rectal resection. The null hypothesis could therefore be rejected.

Complications and cost analysis

Not only was the number of complications per patient fewer, but there were also fewer patients with any grade of complication in the early closure group, indicating an even distribution of complications among the patients. This difference persisted and there was a pattern of more severe complications in the latter part of the follow-up period, 6-12 months, in the late closure group[98]. Compared to a previous RCT[42], the 3-month morbidity was similar (complication rates approximately 30-45%), which is also comparable to reported rates on national level after resection of rectal tumours[110]. However in the EASY trial, it seemed as if the difference in complications/morbidity between the two groups was more pronounced at 3-12 months, which had not been studied previously. This could of course be the consequence of the presence of a loop ileostomy (median time with ileostomy in the late closure group was approximately 5 months). Further, in the cost analysis and the calculation of resource use, the readmission rate was found twice as high in the late closure group. Many readmissions were due to stoma related complications such as dehydration, and there was a difference already within 90 days from surgery with readmission rates of 24% and 35% in the early and late closure group respectively. This is slightly higher than previously reported[81]. Although severe complications did not differ between the groups, the burden of stoma related complications was evident in the median CCI® score with a difference of 15.7 units, which is considered clinically relevant [90].

Two meta-analyses have been published on the subject, one of which had overall postoperative morbidity as primary endpoint[45] whereas one[111] had anastomotic leakage. In the included RCTs[42, 98, 112] anastomotic leakage was one of the exclusion criteria and radiologic examination of the anastomosis was undertaken

before inclusion in the studies. In both meta-analyses, increased number of surgical wound infections at the stoma site have been reported following early closure. In the EASY trial, we did not see the same infection rates nor a difference between the groups, which perhaps is due to the fact that, by routine practice, most skin closures, in connection with stoma reversal, are executed with a purse string suture technique. This has previously been suggested to decrease surgical site infections after stoma closure[113].

The cost analysis identified reoperations, endoscopic examinations and readmissions as the predominant cost affecting factors. Even though a sensitivity analysis was performed, the difference still prevailed. Colorectal surgery is associated with rather high complication rates, and complications, as well as readmissions, are in turn linked with higher costs[80, 99]. Even though directs costs from a healthcare perspective were analysed, we lack information on indirect costs from a societal perspective. Considering the higher readmission rate, the costs for sick-leave could be believed to be higher in the late closure group, with approximately 45% of the study population being employed, even though the median age was 67 years. This was however not investigated in the trial.

Overall, with complications as a measurement of effectiveness, less complications lead to lower costs, and it is considered as an economically "dominant" strategy[114]. This is in line with the findings of the morbidity and cost analysis of the EASY trial.

Patient reported outcomes – QoL and functional outcome

Secondary analyses included assessment of QoL and functional outcome, the latter comprising a cross sectional prevalence study at median 4 years after rectal resection. The results indicated that global quality of life generally improved between 6 and 12 months, and at 12 months the results were comparable, not only between the two groups, but also to age-matched reference populations[94-96] as well as to previous findings[56]. The hypothesis of the QoL assessment; that there would be a difference in patient reported QoL with regard to the duration of the temporary stoma, was not proved in this study.

Thresholds for clinical importance of four domains in the EORTC QLQ C30 (including physical functioning and emotional functioning) have been suggested, based on a Dutch study including 548 patients with cancer[115]. In comparison, patients in the EASY trial had higher scores on the function scales. However when comparing the study populations, there were mixed cancer diagnoses and

more patients with advanced cancer stage (UICC III-IV) in the Dutch study, compared to the EASY population. One could also assume that the EASY population to greater extent were under curative treatment and this might affect both physical and emotional functioning. It has been difficult to detect clinically important differences as well in the QLQ C30 and the corresponding colorectal module (CR29 or the former CR38) with regard to stoma closure and stoma related complications[56, 91]. It has been suggested that patients with rectal cancer need longer time for recovery compared to patients with colon cancer[51, 57] and that baseline QoL (in particular physical functioning) is a strong predictor for both survival and recovery[57]. One of the most important weaknesses of the QoL assessment in the EASY trial is the lack of baseline data, which limits the analysis and interpretation of data. Furthermore, being a secondary endpoint, with regard to the power calculation performed for the QoL assessment[109], the study probably needed more patients for the relatively small differences one could expect between the groups, both of which had patients that had undergone major abdominal surgery for life-threatening disease.

In contrast to the QoL assessment questionnaires QLQ C30 and CR29, baseline measurement of LARS at the time of diagnosis is often a poor estimate of a patient's true function, as it may be severely affected by the rectal cancer[70]. Therefor comparison with normative data may be more beneficial. A recent Danish study evaluated the prevalence of LARS in a general population, with 1875 patients responding to the questionnaire[70], resulting in a general response rate of 54.5%, but considerably higher (70.5%) in the ages 50-79 years, corresponding to the median age in the EASY trial. There was no difference in participating number of men or women in this age span, and the study showed that almost 20% of the studied female population suffered from major LARS. Considering this, we performed a post hoc sensitivity analysis, adjusting for sex, which showed similar results and did not affect the outcome. The high prevalence of major LARS in a normal population reflects that there are other common problems/diagnoses that affect bowel function, including irritable bowel syndrome, neurological disorders and previous vaginal childbirth. A further analysis may have been possible in the EASY trial, if data regarding risk factors such as these would have been available.

The results of the functional outcome indicate that a substantial proportion of the patients suffered from severe bowel dysfunction many months after ileostomy reversal, and that there was a strong correlation between the patient reported outcome scales LARS and MSKCC bowel function instrument. Since the questionnaires regarding QoL (which offer a longitudinal assessment at 3, 6 and

12 months) and bowel function (cross sectional prevalence assessment) were conducted at different time points (1 year versus 4 years) it is not possible to correlate the patients' reported outcomes to one another. This would've been interesting, in order to assess if the relatively high major LARS prevalence does in fact reflect on patient reported QoL, or perhaps the QoL assessment is too blunt to pick up on bowel symptoms in a population size equivalent to the one of the EASY trial.

5.2 METHODOLOGICAL CONSIDERATIONS

Potential bias

The EASY trial, designed and conducted as a multicentre RCT, and with a study protocol[83] clearly stating inclusion criteria and requiring a screening log, are all considered as strengths with regard to risk for bias.

As mentioned previously in chapter 3, randomization is a method of ensuring that no bias is present in the allocation process. Further, this would ideally evenly distribute potential known and unknown confounders. In the EASY trial we came across the problem of an uneven distribution of sex, with more female patients in the early closure group. We did perform sensitivity adjusted analyses for specific variables, including sex, in order to compensate for unequal distribution. An option for future studies would be to stratify the randomization for sex and even for other factors of interest. With regard to the functional outcome, where women aged 50-79 years have reported worse function in a normative population[70], stratification may have led to a larger difference between the groups, as the early closure group had a tendency of lower LARS scores, fewer patients with major LARS and were also in the group with more women, i.e. more prone to higher LARS prevalence. As for the functional follow-up, there was also a difference in permanent stoma prevalence (higher in the late closure group). This could represent a selection bias, as these patients suffered from anastomotic leakage, stenosis and bowel dysfunction (table 1 in study IV). We were by nature not able to assess these patients with regard to bowel function and presence of LARS at the time of follow-up.

We made a decision, prior to analysis, to exclude patients from three centres based on the absence of complete screening logs, which was considered essential in

order to minimize selection bias. Being a trial with multicentre design, block randomization was performed in order to reduce the impact of site-related variations, considered as potential confounders[103].

Blinding was not possible for this trial, and there is therefore a risk of measurement bias. Even though there was a thoroughly designed study protocol prior to data acquisition, we still identified the need of adding a stoma specific CRF, after the patients were included in the study, but prior to analysis. This could be considered a weakness, as this data was retrospectively obtained, but was crucial in order to collect necessary data on stoma related complications. The fact that one author examined all coding of complications, in order to ensure that no complications were coded twice and that coding was consistent, is considered a strength with regard to internal validity of the trial and its primary outcome.

One might argue that our careful selection of patients was a bias and consequently affected the external validity. The inclusion criteria, strictly limiting study participation to patients with an uneventful postoperative course, most certainly contributed to reduced variability. However, given the risk and potential consequences of reversing a stoma in a patient with anastomotic leakage, as this could be potential life-threatening complication in a frail patient, narrow inclusion criteria were necessary. Thus early closure of a temporary ileostomy is suggested to only be relevant in these selected patients.

Representability and generalisability

When conducting a study it is important to consider the generalisability and representability of the included patients, with regard to the target population. If we look at the characteristics of the patients in the EASY trial, they were slightly younger than patients with newly diagnosed rectal cancer in Sweden (67 years compared to approximately 70 years)[116]. Regarding severity of the cancer disease (measured in percentage of patients undergoing adjuvant chemotherapy), this was fairly similar compared to the Swedish oncological registry (40% in the study population compared to 40-70% for patients <75 years of age with stage III rectal cancer disease)[117]. Thirty-day postoperative complications were lower in the Swedish colorectal cancer registry (although only Clavien-Dindo grade II and higher were registered), but readmissions within 30 days from surgery, corresponded quite well with the study population (31% in the registry vs 24% and 35% in the early and late closure group respectively). Supposedly if grade I complications were registered in the registry the complication rates would be

more similar. It is however important to acknowledge that the Swedish colorectal cancer registry records all operated patients, including the patients undergoing abdominoperineal excision, Hartmann's procedure and resection. One reason for lower age in the EASY trial is probably the strict inclusion criteria. The fact that only patients who had undergone an anterior resection with a primary anastomosis were included, compared to perhaps older and more frail patients where you do not consider an anastomosis because of the potential complications, represents a difference in the studied population. Additionally, patients with diabetes or delayed postoperative recovery may also represent more comorbid patients (table 5), and this represents a selection. Nevertheless, as described previously, the selection of patients was deliberate, with regard to patient safety.

The multicentre design and block randomization were important for the generalisability with regard to the participation of hospitals with different volumes of rectal cancer surgery, representing standard care.

Intention-to-treat analysis

The intention-to-treat approach means that the patients retain their group allocation, even though the clinical course departs from the assigned treatments. In other words, keeping the analysis to intention-to-treat protects against exaggeration of true treatment differences, at the expense of potentially underestimating treatment effects and diminishing study power[103]. The intention-to-treat analysis almost always would result in a conservative estimate of effects of the new and tested intervention. The alternative, per protocol analysis, would place the patient at analysis in the group with the actual treatment received. This may exaggerate the difference of the compared treatments in favour of the new intervention. In the EASY trial there was one patient in the early closure group who had a late closure, due to failed attempt at early closure. This patient was analysed according to intention-to-treat and consequently the failed closure attempt was considered a complication and a reoperation.

Measurement of treatment effects

The trial comprised three subsets of outcomes; complications, resource use and patient reported outcomes. The two former (complications and resource use, corresponding to study I and III), are based on completeness and accuracy of the clinical report forms and, especially complications, often comprise primary

outcomes in clinical studies. The methods used for these measurements have been described previously (chapter 3). Regarding the patient reported outcomes, QoL and bowel function assessment (study II and IV), the measurements are more complex. As described earlier, in QoL assessment, it is preferable to compare pre-treatment to post-treatment evaluations, particularly since this will reflect the changes in each patient more directly[47]. In EASY, pretreatment assessment was not included, and the remaining alternative was to compare to a normative reference population. This also limited the opportunity of baseline comparison between the treatment and control groups. Even though other characteristics such as age, cancer stage, adjuvant chemotherapy treatment and comorbidity were similar between the groups, this does not necessarily mean that patient reported QoL was.

Regarding LARS score, the lack of baseline assessment was not necessarily a disadvantage, as preoperative values are less prone to be representative of the patients true, pre-rectal cancer baseline, as described previously[70]. However, with regard to the progress in LARS after rectal resection, even though symptoms often improve over time, assessing the bowel function through LARS score would have been optimal on a yearly basis. This in order to pick up on severe symptoms that may lead to surgical intervention (permanent stoma), even fairly shortly after rectal resection. As the scoring system was originally published in 2012[63], there will certainly be more longitudinal follow-up studies on the prevalence of low anterior resection syndrome after rectal cancer surgery in the near future.

6 CONCLUSIONS

Early closure (8-13 days) of a temporary ileostomy after rectal resection for cancer resulted in a significantly lower mean number of complications compared to late closure (>12 weeks), with a follow-up of 12 months.

Early closure was safe and there were few severe complications in both treatment groups.

Costs from a health care perspective correlated with the burden of postoperative complications. Early closure was associated with less use of outpatient resources as well as fewer readmissions, resulting in significant cost reduction compared to late closure.

Quality of life generally improved up to 12 months after surgery, but did not seem to correlate with the clinical advantages of early closure, in comparison to late closure.

A substantial proportion of patients suffered from severe bowel dysfunction several months after ileostomy closure. There was no statistically difference in prevalence of low anterior resection syndrome between the groups.

Overall conclusion

In selected patients, without signs of postoperative complications and certain comorbidity, early closure of a temporary ileostomy after rectal resection for cancer is safe and clinically advantageous.

7 FUTURE PERSPECTIVES

The results of the trial have led to implementation of early closure in selected patients. A routine document has been established, with the strict inclusion criteria of the trial retained in practice. In order to follow up on results, assuring that the outcomes of the trial also translate into practice, ethical consent to follow-up on patients treated with early closure after rectal resection for cancer, has been approved by the Regional Ethical Review Board in Gothenburg (Dnr 834-17).

Since early closure has not been studied to the same extent on other patient categories that may benefit from the procedure, such as patients with inflammatory bowel disease who receive an ileo-anal pouch anastomosis with a temporary ileostomy, the procedure cannot be recommended more widely as of now. However, with growing experience of early closure, future studies may be designed also to include a wider group of patients (compared to the strict inclusion criteria of the trial), and more diagnoses. The optimal timing of stoma closure is still unknown and, in many countries, is not subject to national targets, unlike the cancer surgery itself. In the EASY trial the median time to closure was 5 months (bearing in mind that this is a trial population), which is still fairly short compared to other countries. A national audit report from the United Kingdom reported that within 18 months from surgery, 66% of patients with a stoma following anterior resection had undergone stoma reversal[118]. This has further led to a nationwide trial aiming to study the timing of stoma closure, identify causes for delay or non-closure and develop guidelines in order to reduce delays in closure[119].

In line with the importance of the enhanced recovery after surgery (ERAS) program, and the increased use of minimal invasive surgical techniques, early closure in selected patients may also in the future be a more common part of the surgical treatment of rectal cancer. A more precise follow-up on bowel function, using the LARS score in practice, will aid the identification and enable early management and treatment of patients with low anterior resection syndrome.

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10 APPENDIX

Questionnaires

SF-36®

EORTC QLQ-C30

EORTC QLQ-CR29

LARS score

Study I-IV

Your Health and Well-Being

HEALTH STATUS SURVEY SF-36

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

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3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

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6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

SPECIMEN

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EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

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Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

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Bowel function questionnaire

The aim of this questionnaire is to assess your bowel function.
Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patients symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

Do you ever have occasions when you cannot control your flatus (wind)?
□ No, never
□ Yes, less than once per week
□ Yes, at least once per week

Do you ever have any accidental leakage of liquid stool?
□ No, never
□ Yes, less than once per week
□ Yes, at least once per week

How often do you open your bowels?
□ More than 7 times per day (24 hours)
□ 4-7 times per day (24 hours)
□ 1-3 times per day (24 hours)
□ Less than once per day (24 hours)

Do you ever have to open your bowels again within one hour of the last bowel opening?
□ No, never
□ Yes, less than once per week
□ Yes, at least once per week

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?
□ No, never
□ Yes, less than once per week
□ Yes, at least once per week

Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg. 2012;255(5):922-8.*

Juul T, Battersby NJ, Christensen P, Janjua AZ, Branagan G, Laurberg S, et al. Validation of the English translation of the low anterior resection syndrome score. *Colorectal dis.* 2015;17(10):908-16.