Long-term Bowel and Stoma Function Following Colorectal Cancer Surgery

Sofia Sandberg

Department of Surgery

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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sofia.sandberg.2@gu.se

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The art of medicine consists of amusing the patient while nature cures the disease.

-Voltaire

To Matilda, Knut, Anders.

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Sofia Sandberg

Department of Surgery, Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Aim The aim of this thesis was to explore bowel and stoma function following colorectal cancer surgery, to investigate associated distress and identify possible risk factors.

Methods *Papers I, II*, and *IV* were based on two prospective, observational cohort studies focusing on rectal cancer (*I, II*) and colon cancer (*IV*). Paper *I* included patients who had an anastomosis, while *paper II* included patients with a permanent stoma. *Paper III* was a registry-based cross-sectional study.

Results *Paper I* found that more than half of the patients experienced significant bowel dysfunction, identifying a defunctioning stoma as a risk factor. Distress was common, decreasing over time. In *paper II,* most patients reported high stoma functionality and acceptance, only one-fifth experienced distress. *Paper III* demonstrated that the anastomotic configuration had equal impact on bowel dysfunction. P*aper IV* showed that most patients maintained intact bowel function after colon resection. After right-sided resections loose stools were common and associated with distress, as was incontinence.

Conclusion Providing preoperative information, managing expectations, and ensuring early detection and treatment of symptoms are important to achieve optimal function and minimise distress. For patients with minimal or no impairment, extensive follow-up may be unnecessary.

Keywords: Colorectal cancer, functional outcome, surgical technique
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SAMMANFATTNING PÅ SVENSKA

Bakgrund Tjock- och ändtarmscancer är en av de vanligaste cancerformerna i världen, även i Sverige. De senaste decennierna, framför allt de senaste åren, har behandlingsmetoderna förbättrats. Prognosen är i allmänhet relativt god, fler patienter kan botas eller leva längre med sin sjukdom.

Behandling av tjock- och ändtarmscancer innefattar ofta operation, där det tumörbärande tarmsegmentet tas bort följt av att kvarvarande tarm kopplas samman (anastomos) eller dras ut genom bukväggen till en påse på magen (stomi). Ibland ges tillägg av cellgifter. Vid ändtarmscancer kan även strålbehandling bli aktuellt, i syfte att krympa tumören inför operation och minska risk för återfall.

Följdsymptom efter behandling är dock ofta förekommande, framför allt vid ändtarmscancer. Påverkan på tarmfunktion, men även påverkan på urinfunktion och sexuell funktion, är vanligt då tarm, urinblåsa och inre könsorgan är placerade tätt intill varandra i lilla bäckenet. Orsaken och den exakta mekanismen bakom försämrad funktion är inte helt klarlagda. Vid behandling av tjocktarmscancer engageras inte organen i lilla bäckenet på samma sätt men däremot kan tarmfunktionen påverkas.

Det har inte kunnat klarläggas vilket alternativ som erbjuder bäst livskvalitet, anastomos eller stomi. Långtidsstudier av funktion efter tjock- och ändtarmscancer har saknats, i synnerhet efter operation av tjocktarmscancer.

Syfte Syftet med denna avhandling var att studera långsiktig tarm- och stomifunktion efter operation av tjock- och ändtarmscancer, patientens upplevelse av sin funktion samt riskfaktorer för försämrat utfall.

Metod *Delarbete I, II* och *IV* har baserats på två stora studier av patienter med ändtarms- respektive tjocktarmscancer, QoLiRECT- Quality of Life in RECTal cancer (*I, II*) och QoLiCOL- Quality of Life in COLon cancer (*IV*). I *delarbete I* inkluderades patienter med ändtarmscancer som hade opererats med anastomos, i *delarbete II* analyserades patienter som i stället hade erhållit permanent stomi. I *delarbete IV* inkluderades patienter med tjocktarmscancer och analyserades utifrån om de hade opererats med borttagande av antingen höger eller vänster sida av tjocktarmen.

Delarbete III utgjordes av en nationell registerbaserad studie baserad på data från Svenska Kolorektalcancerregistret.

Resultat I *delarbete I* fann vi att över hälften av patienterna hade uttalat försämrad tarmfunktion, utan förbättring under uppföljningstiden. Endast hälften av dessa patienter upplevde sig besvärade av sin tarmfunktion, med viss förbättring över tid. Justerat för störfaktorer, utgjorde tillfällig avlastade stomi en riskfaktor för dålig funktion.

Delarbete II visade att de flesta patienter som hade opererats med stomi hade en god funktion och hög acceptans för sin stomi. Ungefär en femtedel av patienterna upplevde sig besvärade av sin stomi. Denna grupp rapporterade en sämre funktion och en lägre stomiacceptans. Faktorer vid diagnos, som god fysisk hälsa och hög livskvalitet, påverkade den långsiktiga upplevelsen av en stomi men träffsäkerheten i vår statistiska modell var låg då så många olika kända och okända faktorer påverkar en patients upplevelse av en stomi.

Delarbete III visade att sättet för att koppla samman tarmen vid operation av ändtarmscancer, anastomoskonfigurationen, inte påverkade tarmfunktionen tre år efter operation, värderat med ett validerat mätinstrument (LARS-score), och inte heller påverkade andelen komplikationer efter operation.

I delarbete IV fann vi att knappt en femtedel av patienterna upplevde försämrad tarmfunktion ett och tre år efter tjocktarmsoperation värderat med mätinstrumentet LARS-score. Av samtliga patienter upplevde sig en knapp femtedel besvärade av sin tarmfunktion. Efter tre år var den enda skillnaden mellan höger- och vänstersidig resektion av tarmen en hög förekomst av lös avföring efter högersidig resektion. De symptom som var främst associerade med upplevt besvär var lös avföring och inkontinens-symtom.

Slutsats Efter operation av tjock- och ändtarmscancer är långsiktigt försämrad tarmfunktion särskilt vanligt efter operation av ändtarmscancer med anastomos, oavsett på vilket sätt tarmen kopplas ihop. Hur patienter upplever tarm- och stomifunktion beror inte enbart på den faktiska funktionen. För att uppnå bästa möjliga upplevelse är bemötande av patientens förväntningar inför operation viktigt. Efter operation, är tidig upptäckt och behandling av symptom värdefullt för patienter som upplever sig besvärade medan extensiv uppföljning av patienter som är nöjda med sin funktion sannolikt är överflödig.

LIST OF PAPERS

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

I. Sandberg S, Asplund D, Bisgaard B, Bock D, Gonzalez E, Karlsson L, Matthiessen P, Ohlsson B, Park J, Rosenberg J, Skullman S, Sörensson M, Angenete E.

Low anterior resection syndrome in a Scandinavian population of patients with rectal cancer: a longitudinal follow-up within the QoLiRECT study.

*Colorectal Dis. 2020;**22**(10):1367-78.*

II. Sandberg S, Asplund D, Bock D, Ehrencrona C, Ohlsson B, Park J, Rosenberg J, Smedh K, Walming S, Angenete E.

Predicting life with a permanent end colostomy: A prospective study on function, bother and acceptance.

*Colorectal Dis. 2021;**23**(10):2681-9*

III. Sandberg S, Bock D, Lydrup ML, Park J, Rutegård M, Angenete E.

The impact of the anastomotic configuration on low anterior resection syndrome 3 years after total mesorectal excision for rectal cancer: a national cohort study.

*Colorectal Dis. 2023;**25**(6):1144-52*

IV. Sandberg S, Park J, Tasselius V, Angenete E.

Bowel Dysfunction after Colon Cancer Surgery: A Prospective Multicentre Study

Submitted manuscript.

CONTENTS

ABBREVIATIONS

ASA	American Society of Anaesthesiologists physical status classification
AUROC	Area Under the Receiver Operating Characteristic
C-index	Concordance Index
DAG	Directed Acyclic Graph
GLM	Generalised Linear Model
GLMM	Generalised Linear Mixed Model
HRQoL	Health-Related Quality of Life
LARS	Low Anterior Resection Syndrome
LASSO	Least Absolute Shrinkage and Selection Operator
PTNS	Percutaneous Tibial Nerve Stimulation
TAI	Transanal Irrigation
SCRCR	Swedish Colorectal Cancer Registry
SNS	Sacral Nerve Stimulation
SOC-29	Sense of Coherence scale
QoL	Quality of Life
UICC	Union for International Cancer Control

INTRODUCTION

INCIDENCE OF COLORECTAL CANCER

Colorectal cancer consists of cancers originating from the colon or the most distal part of the bowel, the rectum. With more than 1.9 million new colorectal cancers during 2020, colorectal cancer is one of the most frequently diagnosed cancer globally (after breast and lung cancer) and ranked as the second most lethal (after lung cancer).[1]

Globally, the incidence of colorectal cancer varies, with Europe, Australia/New Zealand, North America, and Eastern Asia experiencing the highest rates, whereas much lower rates are noted in most parts of Africa and South Central Asia.[1] This variation is largely attributed to socioeconomic factors. While the incidence is increasing in certain parts of the world, stabilising or decreasing trends have been observed in highly developed countries, possible due to factors such as increased screening and healthier lifestyles such as a decline in smoking.[2]

However, a concerning increase in early-onset colorectal cancer (diagnosis before age 50) has been observed in countries like the USA, Canada, Australia, and other high-income countries, including Sweden.[3, 4]

TREATMENT

Treatment strategies differ in certain aspects depending on localisation of the tumour.

For colon cancer, the primary approach typically involves surgery with removal of the affected segment of the bowel and, if feasible, reconnection of the remaining parts through an anastomosis. Systemic chemotherapy is often added to the surgery, depending on tumour-related risk factors, with the aim to minimising the risk of recurrence and enhance survival.[5]

Rectal cancer treatment often requires a multimodal approach. This often includes neoadjuvant radiotherapy or chemoradiotherapy prior to surgery, and possibly adjuvant chemotherapy afterwards.

A key surgical advancement since the 1980s has been the surgical shift to total mesorectal excision (TME), which includes the complete removal of the fatty tissue surrounding the rectum containing lymph nodes and blood vessels through dissection along natural anatomical planes.[6] Treatment advancements in surgical techniques, oncological treatments, and other improvements, such as centralisation of treatment, multidisciplinary team meetings, and intensified treatment of metastatic disease, have contributed to a reduced rate of local recurrence and improved oncological outcomes. Consequently, the age-standardised five-year relative survival after colorectal cancer is now close to 70% in all Nordic countries.[7, 8]

SURGICAL CONSIDERATIONS- ANASTOMOSIS OR STOMA

The ability to successfully perform an anastomosis largely depends on the availability of sufficient distal bowel length. While achieving an anastomosis is generally feasible for tumours located in the colon, it becomes more complex with rectal tumours, due to the limited space in the small pelvis and the necessity to preserve sphincter function for continence. For tumours located in the most proximal part of the rectum, preservation of the distal rectum may be possible and a partial mesorectal excision (PME) can be performed. In contrast, for lower tumours, complete removal of the rectum is necessary, achieved through total mesorectal excision (TME). Following TME, when the anastomosis inevitably is created close the anus, a temporary defunctioning stoma is usually established. This aims to protect the anastomosis by diverting bowel contents away, reducing the risk of complications from potential anastomotic leakage.[9]

In cases of very low rectal cancer, close to the anus, an abdominoperineal excision is performed, resulting in complete rectal removal and a permanent colostomy. An alternative surgical strategy is Hartmann's procedure characterised by the resection of the affected bowel segment, closure of the distal rectum, and the creation of a colostomy. A permanent stoma may also be necessary or preferred when a patient has known incontinence, significant comorbidity, or a high risk of not tolerating major post-operative complications.[10]

BOWEL FUNCTION FOLLOWING RECTAL RESECTION- LOW ANTERIOR RESECTION SYNDROME

The rectum primarily functions as a storage reservoir for bowel contents. As content moves through the bowel and mechanically distends the rectum, the rectum and the anal sphincter coordinate to enable bowel emptying, guided by nervous control. Treatment for rectal cancer can disrupt these structures as well as the involved mechanisms, directly or indirectly affecting defecation and continence. Altered bowel function following rectal cancer treatment can manifest in various forms, ranging from constipation-related symptoms (such as infrequent bowel movements or a sensation of incomplete emptying) to incontinence-related symptoms (including loss of control over gas or stools or a sense of urgency). The different symptoms are grouped under the term "low anterior resection syndrome" (LARS).[11]

It has been reported that up to 80-90% of patients experience some degree of bowel dysfunction after a low anterior resection.[11, 12] However, accurately evaluating functional outcomes has been complicated by the absence of definitive clear definition and the use of various, non-uniform tools for measurement. A recent systematic review highlighted this complexity, concluding that between 1986 and 2016, eighteen different bowel function instruments had been used to describe over 30 different symptoms after rectal cancer surgery, with a follow-up ranging from four weeks to almost 15 years.[13]

RISK FACTORS FOR LARS

The clinical presentation of LARS differs between individuals, the aetiology is multifactorial, and the exact underlying pathophysiological mechanisms remain unclear. The surgery itself can lead to bowel dysfunction, arising from a combination of factors such as:

- Reduced reservoir capacity in the newly formed rectum (from the sigmoid colon).
- Anal sphincter dysfunction due to surgical damage or nerve-related changes.
- Enhanced colon motility from denervation of the sympathetic nervous system.

The severity of these symptoms can be further exacerbated by adverse impact of tumour- and treatment related risk factors such as low tumour and anastomotic height, chemoradiotherapy, or a defunctioning stoma.[14, 15, 16-18] The influence of other potential risk factors, like age or sex, has shown conflicting results.[17]

Some factors involved in LARS might be modifiable. For example, various surgical techniques like the side-to-end anastomosis or the introduction of colonic pouches, have been developed to optimise the reservoir capacity of the neorectum. These alternative configurations have shown short-term functional superiority over the simpler straight anastomosis, though long-term functional outcomes are less clear due to lack of high-quality studies.[19, 20]

How a defunctioning stoma is associated with LARS has not been established. It has been is hypothesised that the diversion alters the bacterial flora, possibly leading to impaired intestinal renewal, atrophy and decreased motility.[21] The presence of a defunctioning stoma, as well as time to stoma closure, may negatively affect bowel function, and the optimal timing for stoma reversal is not clearly established. The results from a recent meta-analysis have shown a defunctioning stoma to be a risk factor for LARS, with stoma reversal within six months being beneficial, while reversal after one year was associated with a higher risk of LARS.[22]

TREATMENT OF LARS

As the mechanisms behind LARS are not completely understood, treatment primarily aims at reducing symptoms. Common interventions include dietary modifications, the use of bowel regulators such as antidiarrhoeal medications, and pelvic floor rehabilitation.

Transanal irrigation (TAI) is a treatment option for both faecal incontinence and constipation, which has shown positive functional results and improvement of QoL also among patients with LARS.[23, 24] The technique involves introducing water into the colon via the anus, either daily or every other day, to facilitate the thorough evacuation of bowel contents. For individuals with faecal incontinence, the goal of TAI is to reduce the risk of leakage between treatments. It also prevents constipation by promoting regular bowel movements. Despite its benefits, the treatment demands considerable time and effort from the patient.[25]

Neuromodulation, targeting the nerves of the pelvic organs, may be used as a secondary intervention for faecal incontinence.[26] The effect is achieved through direct stimulation of sacral spinal nerves, as in Sacral Nerve Stimulation (SNS), or indirectly via Percutaneous Tibial Nerve Stimulation (PTNS), when neuromodulation is achieved through stimulation of the posterior tibial nerve located near the ankle.[27] Since incontinence frequently occurs after rectal resection, it has been postulated that neuromodulation may also be effective in treating LARS.

To date, research has been limited, primarily involving single-centre studies with small participant groups. Three systematic reviews and meta-analyses on SNS in LARS patients have been published.[28-30] The most recent, published in 2023, included 18 studies but only 164 patients in total, with no individual study involving more than 25 participants. A clinically significant benefit from SNS implants was reported in over 90% of patients (although the criteria for what was regarded as beneficial varied between studies), along with significant improvement in incontinence and QoL. [28] Compared to SNS, PTNS is less invasive, simpler, and more cost-effective. However, the outcomes of PTNS have been generally less promising.[14] Two reviews analysing the same five studies on LARS patients have suggested a positive impact on symptoms and QoL.[31, 32] However, the reliability of these findings was constrained by the studies' small participant numbers and the short duration of follow-up, which did not exceed 12 months.

In 2023, the Swedish National Guidelines for Pelvic Cancer Rehabilitation were established. These guidelines include various treatments, such as dietary adjustments, bulking agents, antidiarrhoeals, and transanal irrigation. Neuromodulation with SNS and PTNS is recommended only within the context of studies due to the limited evidence available. [33]

For patients with therapy-resistant LARS, a final treatment option is surgical intervention to create a stoma, for most patients in the form of a permanent colostomy.

THE LARS SCORE

In 2012, a pragmatic definition of LARS was published, describing LARS as a "disordered bowel function after rectal resection, leading to a detriment in quality of life".[11] The same year, the development and validation of a 5-item tool, the low anterior resection syndrome (LARS) score was published.[34]

The LARS score is a simple score with five questions on frequency of bowel movements, urgency, clustering of stools, gas and faecal incontinence. It was developed by a Danish research group, based on the results from questionnaires sent to approximately 1000 patients who previously had undergone anterior resection, identified from the Danish quality registry. The questions in the questionnaire emerged from a literature review and were revised by an expert panel. After a development process including pilot testing, validation through test-retest reliability, and semi-structured interviews of a small number of patients, half of the study's participants were randomly chosen to answer the questionnaire. The selection of items included in the final score was based on the analysis of these responses.

First, the response options were categorised into three or four options depending on the distribution of answers. Then, the impact on QoL was evaluated using a single question regarding the extent of QoL impairment caused by bowel dysfunction, with response options ranging from "not at all" to "a lot". After dichotomisation of the response options into two groups (no/minor and some/major impact on QoL), the associations with the specific symptoms were calculated. Finally, each item's score was based on its impact on QoL. Out of initial 27 questions in the first draft, the five most important were selected for inclusion into the LARS score. Depending on the total score achieved, patients could be categorised into no, minor, or major LARS. The LARS score's validity was then assessed by using the second half of the study's cohort. The validity of the LARS score was assessed with the second half of the study's cohort.

The score was not developed as a definition of LARS, but as a validated scoring tool based on the symptoms and their impact on QoL to evaluate bowel dysfunction after anterior resection. Using the LARS score, estimated prevalence of major LARS after anterior resection has been reported to be somewhat over 40%.[16, 35]

CONSENSUS DEFINITION OF LARS

The LARS score has been validated in many languages over the last ten years.[36, 37] While the practical definition and the LARS score have facilitated prevalence estimations and led to numerous publications, some limitations have become evident. As the pragmatic definition of LARS does not enable precise prevalence estimates, and the LARS score may not fully capture the extent to which impaired bowel function affects a patient's QoL, a recent initiative has been undertaken to establish an international consensus definition.[38]

Through a process of three Delphi rounds, followed by patient consultation and consensus meeting, a definition of LARS has been proposed. In this definition, eight key symptoms and eight consequential effects have been identified as critical in capturing the essential aspects of LARS.

Table 1. The consensus definition of LARS[38]

Symptom	**Consequence**
Variable, unpredictable bowel function	Toilet dependence
Altered stool consistency	Preoccupation with bowel function
Increased stool frequency	Dissatisfaction with bowels
Repeated painful stools	Strategies and compromises
Emptying difficulties	Impact on mental and emotional wellbeing
Urgency	Impact on social and daily activities
Incontinence	Impact on relationships and intimacy
Soiling	Impact on roles, commitments, and responsibilities

According to this new definition, a patient must experience at least one of these identified symptoms, which in turn must lead to at least one of the outlined consequences, to be considered as having LARS. According to the authors, this definition sets the groundwork for a future development of a refined tool for estimating LARS.

FUNCTION FOLLOWING COLON RESECTION

Although colon cancer is more than twice as common as rectal cancer, a significant gap remains in research on functional outcomes following colon resection.

Theoretically, as the colon is not involved in storage and evacuation of bowel content in the same way as the rectum, but rather absorbing water and electrolytes while moving bowel content forward, symptoms of major bowel dysfunction have been considered less likely. Analogous to research on functional outcomes following rectal cancer, a variety of tools have been employed to assess bowel function. Most studies are cross-sectional and consist of small and heterogenous cohorts. Some studies have suggested that symptoms may vary depending on the type of resection: left-sided or sigmoid resections may lead to symptoms associated with constipation, while right-sided resections might result in symptoms related to incontinence, such as increased bowel movements, loose stools, faecal urgency, and incontinence.[39-43]

To date, only one systematic review and recent meta-analysis has been conducted.[44] The authors provided a descriptive analysis of postoperative symptoms over time but were unable to conclusively determine differences between right- and left-sided resections. This limitation was primarily due to the heterogeneity of the data and a lack of longitudinal studies.

BOWEL FUNCTION IN THE GENERAL POPULATION

In patients with symptomatic colorectal cancer, the cancer often manifests through signs including rectal bleeding, abdominal discomfort, and changes in bowel habits.[45] Consequently, impaired bowel function at diagnosis is expected, making it challenging to assess baseline bowel function. To overcome this, the bowel function of the general population can be used as a reference for "normal baseline function". However, what is considered as normal bowel habits vary widely and are influenced by numerous factors and conditions. For example, functional bowel disorders are prevalent, with women being affected approximately twice as often as

men.[46, 47] Irritable bowel syndrome (IBS), characterised by abnormal bowel habits and abdominal pain, is one of the most common functional bowel disorders. The reported prevalence globally varies greatly between countries. Using the former Rome III criteria, a global pooled prevalence has been estimated to approximately 9% (ranging from <1% to almost 30%) compared to less than 4% (ranging from <1% to 21%) with the new and stricter Rome IV criteria.[48, 49] In some countries, for example the United States, the prevalence has been estimated to exceed 20%.[44]

The transition from the Rome III to the Rome IV criteria for IBS has led to a significant reclassification of patients.[45] Using the new criteria, many individuals that previously would have been diagnosed with IBS are now categorised into other functional bowel disorders. A large-scale multi-national study has reported that the pooled prevalence of IBS declined to 4% with these criteria, whereas other disorders like functional constipation, unspecified functional bowel disorder and functional diarrhoea were more commonly diagnosed.[50] Overall, 33% of participants met the criteria for one of the Rome IV bowel disorders. Similar patterns have been observed in a multinational study involving populations from the United States, Canada, and the United Kingdom.[46]

A Swedish study has aimed to characterise the normal bowel habits in a healthy general population.[51] This was done by excluding individuals who had microscopic pathology identified through colonoscopy or known organic disease. The study found that urgency, straining, bloating, and incomplete evacuation were frequently reported symptoms. While women reported significantly more symptoms, this gender disparity vanished when subjects with IBS were excluded from the analysis.

Since the establishment of the LARS score, some studies investigating LARS-like symptoms in the general population have been conducted, predominantly in Europe.[52-57] These studies have reported a prevalence of major LARS ranging from 6-13% in men and 10-19% in women. Additionally, a study focusing on a North American population found that major LARS affected 7% of men and 11% of women.[58] A shared finding among the studies conducted on the general population is a higher prevalence of major LARS among women. This difference is suggested to be due to factors such as a shorter anal canal in women and the impact of childbirth on the pelvic floor, and the results align with the gender differences observed in functional bowel disorders.[52-55]

QUALITY OF LIFE AND BOWEL FUNCTION

The relationship between health-related QoL (HRQoL) and bowel function among colorectal cancer patients is complex, specific to each individual, depending on the timing of assessment and the measurement tool used.

Common instruments for measuring QoL include generic tools like the EuroQol Group's 5-Dimension Health Questionnaire (EQ-5D) and the Short Form Health Survey (SF-36), designed to assess overall health status across various diseases.[59, 60] Conversely, the European Organization for Research and Treatment of Cancer's Core Quality-of-Life Questionnaire (EORTC QLQ-C30) is an example of a disease-specific instrument tailored for cancer patients, providing detailed insights into the aspects of QoL particularly impacted by cancer.[61]

In addition to bowel dysfunction, patients with rectal cancer are also at risk of experiencing other impairments, like urinary and sexual dysfunction, which in turn is associated with impaired HRQoL.[62-64] Some studies have suggested an impairment in the short-term but recovery within 12 months.[65] Results based on the QoLiRECT study have reported that patients with rectal cancer rated their QoL worse than that of the general population at diagnosis but reported levels comparable to that of the general population after 12 and 24 months.[66] Compromised urinary, bowel, and stoma function were identified as risk factors for a decline in QoL.

Bowel dysfunction has repeatedly been found to negatively affect HRQoL.[67, 68] In 2022, a systematic review was published examining the impact of bowel dysfunction on HRQoL.[69] The most frequently used tool for measuring HRQoL in the included studies was the EORTC QLQ-C30. The review concluded that bowel dysfunction after rectal resection predominantly impacts the social and emotional domains of the EORTC QLQ-C30.

This suggests, that while impaired bowel function has a clinically relevant effect on certain aspects of HRQoL, it may not influence all components equally.

The relationship between bowel function and HRQoL in patients with colon cancer, though less extensively researched than rectal cancer, seems to follow a similar pattern. It has been reported that about 20% of patients experience a decline in QoL following colon resection.[40, 70, 71] One study has reported the observed QoL after colon resection was comparable to that of a large reference population.[72]

Impaired function, such as the occurrence of loose stools or major LARS-like symptoms, seems to be associated with an impairment in HRQoL.[39, 40, 73]

QUALITY OF LIFE AND STOMA FUNCTION

The presence of a stoma among colorectal cancer patients may cause negative changes in body image and social life and have a negative impact on QoL. Complications, such as stoma stenosis or herniation, alongside stoma-related problems, like leakage, odour, pain, or parastomal herniation, are common and may further contribute to this negative impact.[74-76]

It has been assumed that patients with a permanent stoma experience a poorer QoL compared to patients with an anastomosis.[77] Some studies have challenged this assumption showing overall little or no impact on QoL, or high levels of satisfaction and acceptance, among patients with a permanent stoma.[78-80]

Recent reviews have suggested that the QoL may be equivalent between these groups.[81, 82] In 2012, a Cochrane review found no conclusive evidence that QoL is better after anterior resection compared to QoL following abdominoperineal excision or Hartmann's procedure, a conclusion further corroborated by a subsequent systematic review in 2021.[81, 83]

DISTRESS

How a symptom is perceived varies among individuals, depending on factors like the type of symptom involved, its frequency, its intensity, its duration, and the patient's coping mechanisms (how effectively the person manages or adapts to the symptom).[84]

The concept of "symptom-induced distress" or "symptom-induced bother" has been used to describe how a symptom affects an individual's emotional well-being and social engagement.[85, 86] In *papers I*, *II*, and *IV*, each question regarding various symptoms was accompanied by a follow-up question asking whether and to what extent the specific symptom caused distress to the patient. This strategy enabled us to specifically measure the patient's level of distress associated with the symptom.

This methodology of assessing distress through specific, symptom-related questions has been employed in previous research, particularly in studies exploring the effects of treatment-related symptoms in cancers of the urinary bladder, prostate, and cervix.[84,87, 88]

AIM

The primary aim of this thesis was to explore bowel and stoma function following colorectal cancer surgery, to investigate associated distress and identify possible risk factors.

SPECIFIC AIMS

PAPER I

To investigate the longitudinal prevalence of bowel dysfunction and associated distress one and two years following anterior rectal resection, and to identify potential risk factors contributing to impaired bowel function. Bowel function in a Swedish reference population served as a comparison.

PAPER II

To characterise stoma function, related distress and acceptance one and two years following rectal resection with the formation of a permanent stoma. The study also aimed to identify preoperative individual factors as predictors for stoma-related distress one and two years following surgery.

PAPER III

To explore the influence of anastomotic type on bowel function three after rectal resection, using the LARS score, as well as its impact on postoperative complications.

PAPER IV

To examine bowel dysfunction and the associated distress one and three years following right- or left-sided resection, using the LARS score and specific validated items.

PATIENTS AND METHODS

Table 2. Overview of papers included in the thesis and their respective study design.

Paper	Design	Study	Population	Inclusion years
I	Prospective observational cohort	QoLiRECT	433	2012-2015
II	Prospective observational cohort	QoLiRECT	379	2012-2015
III	National cross-sectional study		494	2015-2017
IV	Prospective observational cohort	QoLiCOL	1221	2015-2019

STUDY DESIGN

PROSPECTIVE OBSERVATIONAL COHORT STUDY- THE QOLIRECT AND THE QOLICOL STUDY (*PAPER I, II AND IV*)

Three of the papers included in this thesis (*paper I, II,* and *IV*) are based on two large, prospective observational cohort studies- the QoLiRECT (Quality of Life in RECTal cancer) study and the QoLiCOL (Quality of Life in COLon cancer) study. In short, the primary objectives of the studies were to longitudinally follow patients' experiences following a cancer diagnosis, using comprehensive questionnaires to assess various aspects of functionality and QoL at different time-points.

The inclusion of patients with newly diagnosed rectal cancer into the QoLiRECT study (*paper I* and *II*) commenced in February 2012 and was completed in September 2015. It was conducted through a collaborative effort involving sixteen Swedish and Danish surgical clinics, resulting in

the enrolment of 1248 participants, with 977 from Sweden and 271 from Denmark. The QoLiCOL study (*paper IV*) included patients with newly diagnosed colon cancer and engaged 21 surgical clinics in Sweden and Denmark. From 2015 to 2019, the study recruited 1,891 patients.

The questionnaires used in both studies consisted of established instruments integrated with questions specifically developed for the target population (patients with rectal or colon cancer) as well as questions previously validated and used in other studies on gynaecological and urological cancer.[88-91] The specific questions of functional impairments were accompanied by questions on the duration, intensity and severity of each specific symptom.[84, 92]

The questionnaire development method is well-established and has been extensively described previously.[93] In summary, the process involved initial interviews with a small number of patients to generate relevant questions. The questions were subsequently refined and validated for content by professionals. This step was followed by face-to-face testing with patients with cancer, to ensure the questions were relevant, accurate, and understandable. Revisions were made based on the results of this process. For the Danish translation, forward and backward translation techniques were employed by native-speaking translators.[94]

The final questionnaires consisted of approximately 250 questions, varying slightly between the initial and follow-up versions. The questionnaire distributed at diagnosis primarily explored the patients' functional status before treatment, as well as their expectations and concerns. In contrast, the follow-up questionnaires were designed to evaluate the impact of treatment, concentrating on the prevalence, severity, and distress caused by various symptoms. Not all questions are assessed in the papers of this thesis.

The recruitment for the study was structured as follows: Participants were approached for inclusion after being informed about their cancer treatment but prior to its initiation. Upon agreeing to participate, the patients provided informed consent and filled out a baseline questionnaire. They were then asked to complete additional questionnaires at several intervals throughout the study. In the QoLiRECT study, follow-up assessments were one, two, and five years after treatment. In the QoLiCOL study, the

follow-up questionnaires were sent to participants one and three years after treatment.

PATIENT SELECTION

Overall, there were no exclusion criteria applied in the QoLiRECT and QoLiCOL studies other than age below 18 years, language difficulties (Swedish/Danish) or cognitive impairments.

The patient cohort in *paper I* consisted of patients from the QoLiRECT study who had undergone rectal resection with the construction of an anastomosis. Patients who had a temporary defunctioning stoma entered the study after stoma closure. Patients that, on the other hand, had been operated with a Hartmann´s procedure or with an abdominoperineal excision, both procedures resulting in the creation of a permanent colostomy, were considered eligible for *paper II.* At the time these papers were written, the five-year follow-up data were not yet available, hence the analyses were based on data from the time of inclusion and follow-up after one and two years.

In *paper IV*, which consisted of patients from the QoLiCOL study, all patients who had been operated with either a right- or a left-sided colon resection followed by the creation of an anastomosis were considered possible to include in analyses.

DATA COLLECTION

Following a patient's consent to participate, the recruiting hospital notified the study's secretariat, situated within the office of the Scandinavian Surgical Outcome Research Group (SSORG) at Sahlgrenska University Hospital/Östra in Gothenburg, Sweden. Thereafter, all further communication with the included patients (telephone calls, sending and receiving questionnaires and reminders) were administered by the research nurses at the study secretariat.

THE REFERENCE POPULATION

In *Paper I*, data from a sample from the Swedish population was used as a reference.[57] According to the same methodology as described above, a similar questionnaire was developed. The study was carried out from June 2014 to November 2015, involving a sample of Swedish residents born who had randomly been selected from the Swedish Tax Agency.

The overall results of the general population have been published previously and the results from the specific functional domains as well as the quality of life have been used in several publications by our research group.[66, 95, 96] In this thesis, results on bowel function and associated distress were included.

NATIONAL CROSS-SECTIONAL STUDY (*PAPER III*)

In Sweden, all patients with a diagnosis of colorectal adenocarcinoma are reported to the Swedish Colorectal Cancer Registry (SCRCR).[97] *Paper III* was a registry-based cross-sectional study of rectal cancer patients three years after surgery. Based on information obtained from the SCRCR, patients who had undergone anterior resection between 2015 and 2017 were mailed questionnaires three years after the surgery. To explore bowel function the LARS score was used, as well as inquiries about current or previous stoma and assessment of HRQoL via the EORTC QLQ-C30 and QLQ-CR29 scales.[61, 98]

PATIENT SELECTION

To identify individuals who had been operated with a low anterior resection with total mesorectal excision, the variable "tumour height" from the registry was used. Eligibility was restricted to those with tumours located no more than ten centimetres from the anal verge. To reflect the methodology of the most rigorously designed randomised clinical trial available at the time of designing *paper III*, but with extended follow-up, we adhered closely to the inclusion and exclusion criteria used in the randomised trial.[99]

DATA COLLECTION

After patients had been identified from the registry, letters including the questionnaire and an invitation to participate were sent from the study secretariat located at Skåne University Hospital, Malmö, Sweden to eligible patients during the winter of 2019. A reminding letter was sent four to six weeks later if no response had been received. Clinical variables were assessed from the SCRCR.

OUTCOME MEASURES

LONG-TERM BOWEL FUNCTION

When the QoLiRECT study was initially designed, as well as the questionnaire used in the study of the general population, the LARS score had yet not been published. Consequently, the questions on bowel function used in *paper I* were slightly different from the original LARS score items. They included a few additional response options and incorporated a time aspect, specifying "one month" in the questions (unlike the LARS score items, which do not specify a time frame). The time aspect was added to harmonise with other questions in the questionnaires. The included questions covered the same symptoms addressed by the LARS score items and were fully transferrable to the LARS score.

The LARS score was used in *paper III*, as well as in *paper IV*. As the LARS score has not been validated for colon cancer patients, additional questions on bowel function were included in *paper IV*.

STOMA FUNCTION

In *paper II*, the evaluation of stoma functionality covered issues including leakage from the stoma, anxiety regarding potential leakage, occurrence of foul-smelling or loud gas (flatulence), irritation of the skin surrounding the stoma, and challenges in stoma management.

Additionally, we evaluated the acceptance of stoma in daily life by five targeted questions. These questions were specifically designed to assess the effect of the stoma on patients' everyday activities and lifestyle. However, the reported acceptance may not directly correlate with functionality. Given this potential discrepancy, we have reported the findings from these questions, but we chose not to include them in our further analyses.

DISTRESS

In *paper I, II* and *IV* an anchoring question regarding distress associated with function was employed, aiming to determine whether patients were troubled by their functional outcome. The question posed was, "*If you, for the rest of your life, would live with your bowel/stoma function as it has*

been during the last month, how would you feel about it?". It featured five response options on an ordinal scale ranging from 'not applicable' to 'much' (not applicable-none-little-some-much). In our analysis, we dichotomised the responses, treating "some/much distress" as indicative of "distress" and the other responses as "no distress". This cut-off was considered the most clinically appropriate and has been utilised in previous studies.[86]

The level of distress experienced by patients can be influenced by a mix of personal and clinical factors. In *paper I*, we analysed the longitudinal course of distress. *Paper II* aimed to identify factors present at the time of diagnosis that could affect the level of stoma-related distress years after surgery resulting in a permanent stoma. In *paper IV*, we examined both the prevalence of distress and conducted a risk factor analysis to identify specific symptoms associated with distress, alongside examining how the relationship between symptoms and distress evolved over time.

CLINICAL DATA

Clinical data were collected from national quality registries to complement the information obtained from the questionnaires in all papers (*I-IV*). The Swedish Colorectal Cancer Registry (SCRCR) was initiated in 1995 for rectal cancer and expanded to encompass colon cancer in 2007. The registry is a high quality registry with a very high completeness.[100]

To *paper I, II* and *IV*, clinical data from the Danish quality registry was used (Danish Colorectal Cancer Group). Like the Swedish quality registry, this registry has a high coverage and quality of data.[101]

MAIN STATISTICAL ANALYSES

General statistical considerations are discussed further on page 23.

PAPER I

In the analysis of the longitudinal course of major LARS and distress, a Generalised Linear Mixed Effects Model (GLMM) was utilised. This method effectively handles repeated measurements from the same patients. A risk factor analysis with major LARS as the outcome was conducted using log-binomial regression. The average LARS score was

used if data from both follow-ups were available, or a single score was used if data were available from only one follow-up. Risk ratios (RR), 95% confidence intervals (CI) and p-values were reported.

PAPER II

In *paper II*, we used a multiple logistic regression model with the intention to identify variables known already at the cancer diagnosis, either clinical or individual, that would be predictive of the level of stoma-related distress several years after the surgery.

To optimise our data for prediction we used the “least absolute shrinkage and selection operator” (LASSO) strategy.[102] The predictive performance was evaluated through the "area under the receiver operating characteristic" (AUROC) and the Brier score. The AUROC quantifies a model's predictive accuracy and a value of 1 implies a perfect model, whereas a value of 0.5 suggests no better predictive capability than random guessing. The Brier score represents the mean squared difference between predicted probabilities and the actual outcomes, spanning from 0 for perfect prediction accuracy to 1 for the lowest accuracy. Additionally, a calibration plot was produced for illustrative purposes.

PAPER III

In *paper III*, inverse probability weighting using propensity score was employed. A propensity score is a statistical tool used to harmonise the distribution of observed factors among treatment options and thereby aiming to create a situation similar to a randomised controlled trial. This approach aimed to assess the likelihood of worse outcomes (major LARS) in patients with a reservoir (J-pouch or side-to-end anastomosis) compared to those with end-to-end anastomosis.

The Concordance Index (C-index) was computed to transform the estimated treatment effect into a clinically more interpretable measure. The influence of the anastomotic type on complications after surgery was analysed using a weighted logistic regression model. Outcomes were expressed as odds ratios (OR) accompanied by 95% confidence intervals (CI).

PAPER IV

To model the prevalence of major LARS and distress related to bowel function, we used a GLMM to account for the repeated measurements over time. This method was similarly applied in analysing each symptom's association with distress. By incorporating interaction terms between symptoms and time into the model, we were able to investigate whether and how the impact of each symptom on distress changed over time. Factors such as sex and age were identified as potential confounders and were controlled for in our analysis. Results were reported as odds ratios (OR), 95% confidence intervals (CI) and p-values.

METHODOLOGICAL CONSIDERATIONS

STUDY DESIGN

This thesis comprises three different observational studies. The QoLiRECT (*paper I* and *II*) and QoLiCOL studies (*paper IV*) are prospective cohort studies, while *paper III* is a cross-sectional study. Observational studies differ from randomised controlled trials (RCTs) as they do not involve any interventions. Prospective observational studies are suited for exploring natural disease progressions and long-term effects. They allow for extensive data collection on a large number of variables that might be impractical or unethical to manipulate in experimental designs.

In the hierarchy of evidence, interventional studies rank higher than observational studies due to their design. The randomisation serves to minimise influence of confounders (variables that influence both the exposure and outcome and possibly disturbs the interpretation if not controlled for). This random assignment is key to establishing causation rather than association, offering control over biases and confounders not possible in observational studies. Although statistical methods can adjust for known confounders, the challenge of unmeasured confounders persists.

A cross-sectional study, conducted at a single point in time, offers a cost-effective and efficient means to collect prevalence data. However, it cannot determine cause-and-effect relationships, as it collects information on exposures and outcomes simultaneously.

The study's findings can be affected by who is included in the study sample, potentially leading to biased results if the sample is not representative. In *paper III*, patients who underwent surgery during 2017-2019 were analysed, with assessments conducted three years post-surgery. A different selection time frame or follow-up time point might have led to different results.

INTERNAL AND EXTERNAL VALIDITY

Internal validity refers to how well a study measures the relationship between the variables it intends to study, without interference from other factors. A high response rate can contribute to the internal validity of an observational study. A high response rate is important to minimise the risk of selection bias- the possibility that respondents may not represent a truly representative cohort, which could limit the validity of the study's conclusions. In studies using questionnaires, the implementation of a close follow-up regime with written reminders and follow-up made by telephone calls as used by our research group are methods that have been reported to improve response rate to postal questionnaires.[103]

External validity refers to the generalisability of study findings to the broader population or other settings. The registries employed in this thesis provide nearly complete coverage, thereby offering assurance of external validity. The external validity of results may also be increased using few exclusion criteria in the QoLiRECT and the QoLiCOL studies, as well as the multicentre setting, with different hospital sizes from University Hospitals to regional hospitals.

DICHOTOMISATION

In this thesis, some variables were dichotomised before analysis. For example, in *paper II*, which focuses on stoma function, and in *paper IV*, which addresses bowel function, the response options for certain symptoms were dichotomised with a weekly frequency as the threshold. Similarly, the concept of "distress" was dichotomised, categorising responses “not applicable/none/little distress” as “no distress”, and “some/much distress” as “distress”. Moreover, the validated LARS score was categorised multiple times during its development. The final score was then further categorised into three distinct categories, of which only the highest level, major LARS, is typically used as an outcome measure.

The aim of dichotomising or categorising variables is to simplify data analysis and interpretation.[104] However, this method has its disadvantages, including the potential for information loss. The choice of cut-off points can sometimes seem arbitrary and might lead to misleading conclusions or complicate comparisons with other studies. Although most of the categorisations in this thesis involve categorical variables, which often is less problematic as it is easier to identify appropriate cut-off points, the implications of dichotomisation must be carefully considered.

STATISTICAL CONSIDERATIONS

CONFOUNDING

A *confounder* is a variable that is associated with both the exposure (the cause) and the outcome (the effect) in a study. This association can create the illusion of a causal relationship where none exists, or it can hide a true causal connection. Such confounding introduces bias into study results, potentially leading to conclusions that either overstate or understate the actual influence of the independent variable on the dependent variable. Therefore, identifying and adjusting for confounders is essential to maintaining the validity.

A *mediator*, on the other hand, is a variable that explains part, or all, of the relationship between the exposure and the outcome. Whether to adjust for a mediator depends on the research question. To understand the total effect of an independent variable on an outcome, it is advisable not to adjust for mediators. However, to explore the direct effect of the exposure, independent of the mediator, adjusting for the mediator becomes appropriate. A *collider* is a variable that is influenced by two or more variables in a causal pathway. Adjusting for a collider can introduce bias, creating an association between the influencing variables that was not present before.

In observational studies, where randomisation is not feasible, it is essential to account for confounding factors in the analyses. To facilitate the understanding of the relationships between variables, 'directed acyclic graphs' (DAGs) can be used. DAGs serve as visual tools to create a map of different variables and how they interact with each other. In the different analyses of this thesis, possible influencing variables were identified based on clinical experience and previous research.

DAGs were drawn to identify possible confounders and their significance were assessed by statistical analyses.

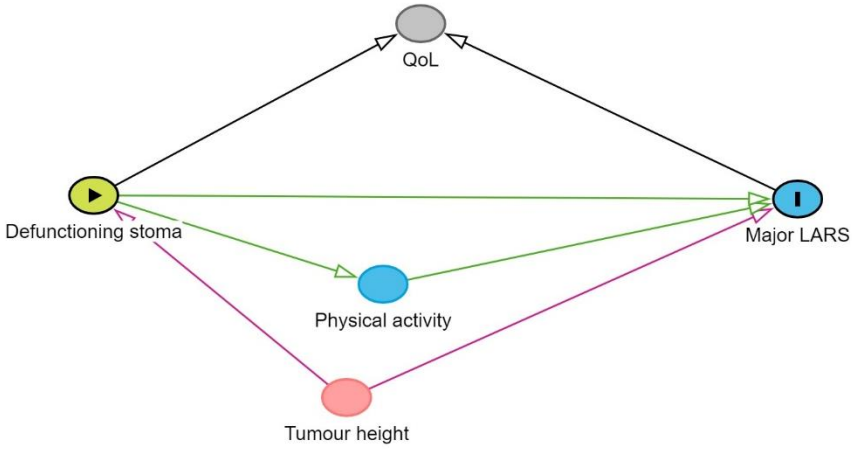

Figure 1. Directed Acyclic Graph (DAG) illustrating the hypothesised relationships between defunctioning stoma (exposure) and major LARS (outcome). Physical activity, for example, may be regarded as a possible mediator. Tumour height is considered a confounder affecting both the exposure and the outcome. QoL is represented as a collider influenced by both the exposure and outcome. Arrows indicate the direction of the hypothesised causal relationships.

There are several methods to statistically address confounders. One common approach is multivariable regression analysis, where the outcome is analysed in relation to multiple independent variables. This method adjusts for the influence of all included variables, controlling for confounders. Another strategy is stratification, which involves dividing the dataset into subgroups based on similar characteristics.

This allows for comparisons within subgroups, thereby controlling for confounding factors. In *paper III*, inverse probability weighting was used, with the aim to balance confounder effects between groups, mimicking a randomised controlled trial.

STATISTICAL MODELS FOR BINARY OUTCOMES

Different regression models were used in this thesis, such as logistic regression analysis and log-binomial regression analysis.

Both models are designed to assess the probability of dichotomous outcomes. However, they differ in how they link exposure to the outcome's probability. Logistic regression uses the logit function to estimate odds ratios (OR), which indicate the effect of exposure on the odds of the outcome occurring. In contrast, log-binomial regression uses the natural logarithm function to calculate risk ratios (RR), showing how exposure modifies the actual risk of the outcome.

In *paper II*, a logistic regression analysis optimised for predictions was used. This was done by Least Absolute Shrinkage and Selection Operator (LASSO). A prediction model with too few variables might lack predictive strength, whereas one with excessive variables can become "over-fitted" to the training data, reducing its efficacy on new, unseen data. One of the key features of LASSO is its ability to perform variable selection. This is done by identifying variables that are important by reducing the impact of less important variables or eliminating the least important variables. This makes the model suited for prediction, as it is less adjusted to the existing data.

These statistical models are examples of Generalised Linear Models, GLMs, which extend traditional linear regression models by allowing the outcome variable to have error distributions other than the normal distribution. Another variant of a GLM is the Generalised Linear Mixed Model (GLMM), which incorporates both fixed and random effects, making it suitable for longitudinal data with repeated measurements.

REPEATED MESUREMENTS

As the QoLiRECT study as well as the QoLiCOL study are longitudinal studies, the statistical approach must be able to handle the complexities of repeated measurements of the same patients. Multiple observations from the same patients are likely to show greater similarity than measurements from independent groups. The GLMM is a statistical model that meets this need. A GLMM was used in the statistical analyses in *paper I and IV*.

In GLMM, the term “mixed” refers to its ability to incorporate both “fixed” and “random” effects. Fixed effects, like sex, are assumed to be consistent across all participants in the study. Conversely, random effects account for individual variances.

This includes aspects such as a random intercept for each patient and treating time as a random factor, which allows for different starting points for each individual and individual variations over time.

This method is designed to manage the uniqueness of each participant, acknowledging individual differences at baseline as well as change throughout the study period, while also integrating other consistent effects that apply to all individuals in the study.

ETHICAL APPROVALS

Papers I and *II*: The QoLiRECT study was officially registered with ClinicalTrials.gov (NCT01477229) and received ethical approval from the Central Ethical Review Board in Sweden (595-11), the Danish Data Protection Agency (HEH.750.89-21; HGH-2016-016), and the Regional Ethical Review Board in Denmark (H-3-2012-FSP26).

Paper III: Obtained ethical consent from the Central Ethical Review Board in Sweden (2016/992, 2017/946).

Paper IV: The QoLiCOL study was listed on ClinicalTrials.gov (NCT02530593) with ethical approvals from the Regional Ethical Review Boards in Gothenburg, Sweden (957-14), and Denmark (H-16027323).

RESULTS

STUDY COHORTS

PAPER I & II

In *paper I*, we analysed 433 patients who had undergone rectal resection with primary anastomosis (87% response rate). Non-responders tended to be older (median age 70 vs. 66) and predominantly men (68% vs. 57%). The non-responders had more advanced tumours (UICC III/IV 54% vs. 41%) but similar ASA classifications (13% vs 12%). In *paper II*, 379 patients with permanent stoma were analysed (80% response rate). Non-responders were older (median age 74 vs. 70), had higher ASA classifications (34% vs. 18%), and more advanced tumours (UICC III/IV 46% vs. 40%).

To assess external validity, we compared QoLiRECT participants to patients from non-participating hospitals using national registry data. Non-responders with anastomosis (n = 787) showed higher severe systemic disease rates (ASA III/IV 17% vs. 13%) and more advanced tumours (UICC III/IV 53% vs. 48%) compared to responders. Non-responders with a permanent stoma (n = 809) had more advanced tumour stages (UICC III/IV 61% vs. 43%) but were otherwise comparable.

THE REFERENCE POPULATION

A sample of 3,000 Swedish residents aged 30 to 89 was selected through the Swedish Tax Agency. Questionnaires was distributed to 2,094 individuals consisting of individuals who had previously given their informed consent over the telephone or those who could not be contacted.

The questionnaire was returned by 1,078 individuals, rendering a response rate of 51%. The responders had a median age of 63 years, with an equal distribution between men and women (48% men).

PAPER III

The final analyses comprised 494 patients (response rate 64%). Demographically, the study cohort had a median age of 66 years and men represented 59%.

In terms of health status, 14% were classified as ASA III/IV, and 62% of the patients had an advanced tumour stage (UICC III/IV). Basic characteristics among responders and non-responders were similar, except for a slightly higher comorbidity among non-responders (ASA III/IV 21%).

PAPER IV

A total of 1,221 patients were available for analyses (83% response rate). Non-responders showed similar baseline characteristics but were slightly older (median age 76 vs.72) and had more comorbidity (ASA III/IV 41% vs. 25%).

Data was available on 7,207 non-included patients from the Swedish quality registry. Overall, non-included patients were comparable with included patients (48% men, median age 74, UICC III/IV 52%). The ASA classification was not available.

LONG-TERM BOWEL FUNCTION

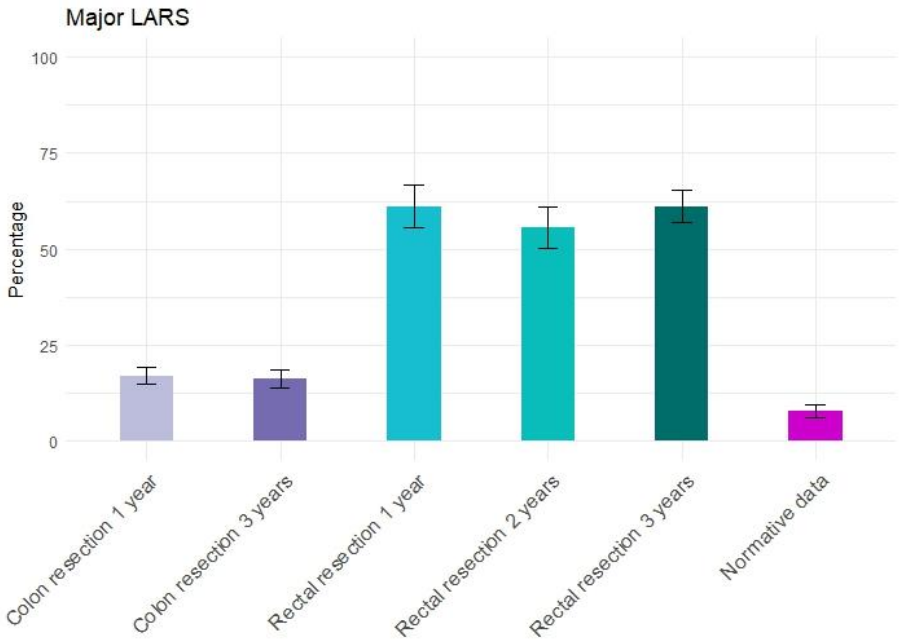

Figure 2. Major LARS/major LARS like symptoms after colon resection, rectal resection and on normative data. Extracted observed results from paper I, III and IV on the different study populations included in the thesis.

We found bowel dysfunction to be common after rectal resection. Results from *paper I* and *III* showed that more than half of patients experienced major LARS (63% and 61% respectively). The prevalence of major LARS remained consistent between follow-ups (*paper I*). The highest prevalence was noted among younger women, but the difference between men and women was not statistically significant (*paper I*) and we found no significant differences across different anastomotic configurations (*paper III*).

In contrast, after colon resection (*paper IV*) most patients (>80%) did not experience impaired bowel function using major LARS as outcome measure, regardless of right-or left-sided resection. Irrespective of the type of resection, major LARS was more common among women (23% vs. 11%, $p<0.001$). After three years, the only significant difference between right- and left-sided resections was a higher rate of loose stools after right-sided resections (31% vs. 20%, $p < 0.001$), with no gender

difference. Other symptoms, like incontinence for flatus, clustering, and urgency, were reported more often by women, irrespective of type of resection.

In the general population (*paper I*) we found an overall prevalence of major LARS-like symptoms of 8%, with a significantly higher prevalence among women (10% vs. 6%, p-value 0.03).

LONG-TERM STOMA FUNCTION

In *paper II*, we observed discrepancies in stoma dysfunction symptoms between patients experiencing distress and those without. Specific symptoms, such as leakage and fear of leakage, were up to three times more common among distressed patients. Interestingly, loud flatulence was common across all patients, irrespective of their level of distress.

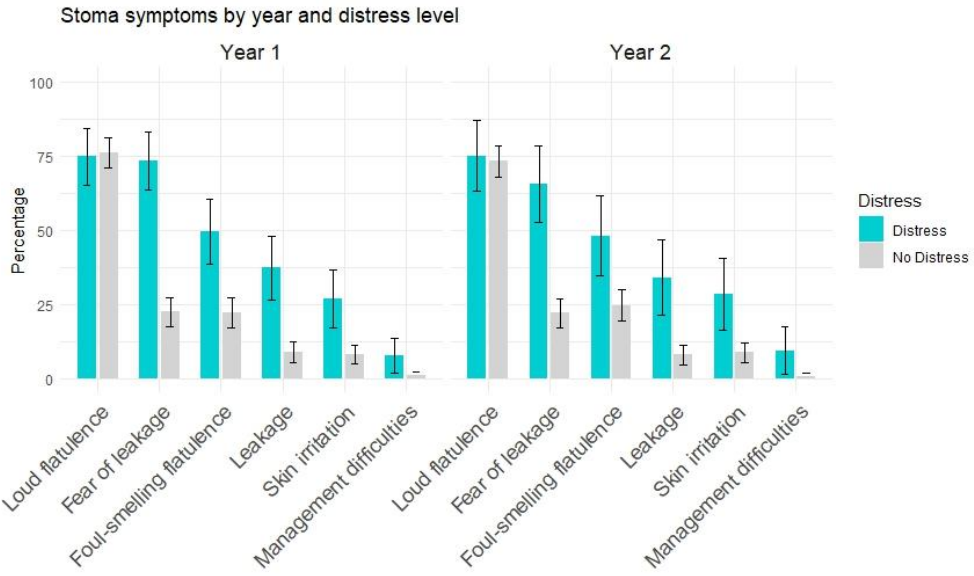

Figure 3. Observed prevalence of stoma symptoms occurring at least once per week, one and three years after rectal resection with a permanent stoma.

As a complement to the analysis on stoma function, we explored the stoma acceptance as visualised in Figure 4. In general, most patients had a high acceptance of their stoma, but consistent with the analysis of the different symptoms, there were differences between patients depending on distress-level. Patients experiencing stoma-related distress demonstrated significantly lower levels of stoma acceptance.

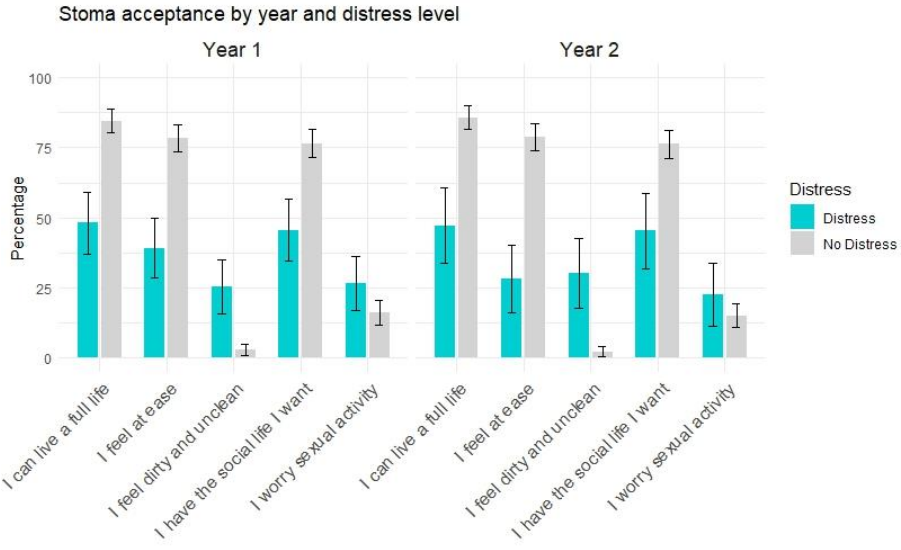

Figure 4. Stoma acceptance one and two years after rectal resection with a permanent stoma.

PATIENT-REPORTED DISTRESS

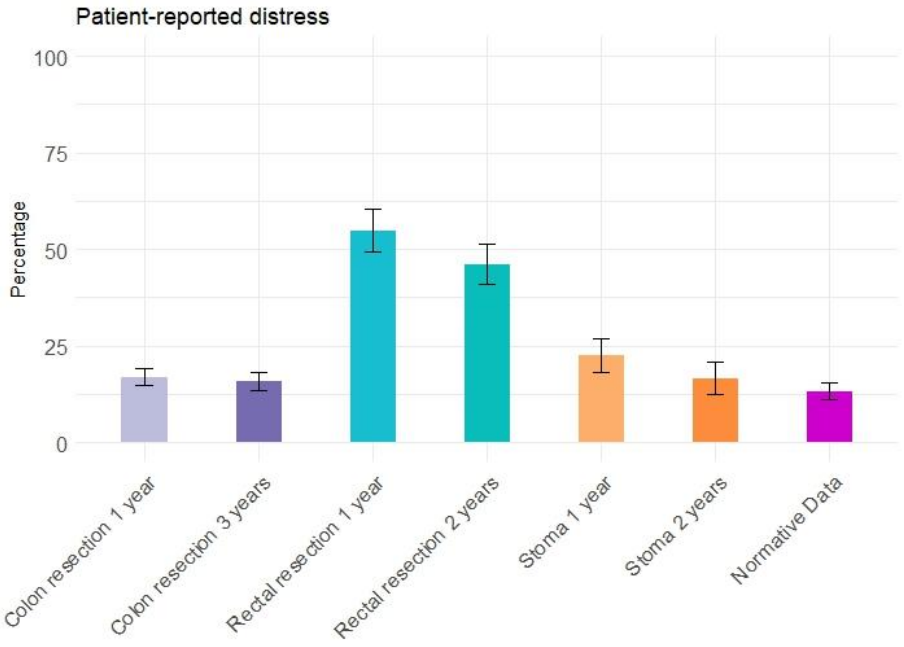

Figure 5. Distress related to bowel- or stoma function at the different follow-up points, regardless of function. Observed results extracted from paper I, II and IV.

The assessment of distress showed different prevalence estimations across the different cohorts. After rectal resection (*paper I*), distress related to bowel function was common (55% one year after surgery). Of patients with major LARS, approximately half of patients experienced distress, regardless of sex. Distress significantly decreased between the first and second years, especially among older men (OR 0.53, 95% CI 0.31-0.90, p-value 0.02).

Conversely, after colon resection (*paper IV*), distress was reported by less than 20% of patients. Of patients with major LARS, approximately half of the patients experienced distress. Regardless of resection type, distress was significantly more common among women. Following rectal resection with a permanent stoma (*paper II*), 23% of patients reported distress after one year, with no gender differences observed. The distress level remained unchanged over time.

In analyses of the reference population, 13% of individuals overall experienced distress, women more often than men (18% versus 8%, p <0.001). Of those with major LARS-like symptoms, 46% experienced distress.

RISK FACTOR ANALYSES

RISK FACTORS FOR MAJOR LARS

In *paper I*, the variables tumour height, neoadjuvant radiotherapy and defunctioning stoma were found to increase the risk for major LARS. After adjusting for tumour height in our analyses, the significance of defunctioning stoma as a risk factor remained. Between the different anastomotic types, explored in *paper III*, we found no difference between a straight anastomosis or a reservoir configuration, regardless of considering the LARS score as a numerical score, categorised into categories or in analyses of the specific items.

RISK FACTORS FOR DISTRESS

In *paper II*, we investigated potential predictors of stoma-related distress following rectal cancer surgery. Particularly, a high QoL and a high level of physical health at baseline lowered the risk for distress. However, the predictive model was ineffective at distinguishing between distressed and non-distressed individuals.

Paper IV analysed distress-associated symptoms in colon cancer patients, identifying incontinence (for both flatus and stools), clustering, and loose stools as significant distress factors. While most associations remained constant over time, the association between clustering and distress decreased.

DISCUSSION

Given the increasing incidence of colorectal cancer and the improvements in overall survival rates, optimising the functionality and QoL after treatment is becoming increasingly important. This thesis aimed to investigate various aspects of long-term post-operative bowel and stoma function, as well as the distress perceived by patients.

LONG-TERM BOWEL FUNCTION

Our findings indicate that long-term bowel dysfunction is common following rectal resection, well beyond the initial postoperative phase. These results support the findings of a growing number of studies indicating that bowel dysfunction persists over time.[17]

Our analyses revealed a marginally higher occurrence of major LARS than reported in other studies.[16] This variation could be attributed to several factors, including differences in the timing of follow-up assessments, the proportion of patients receiving neoadjuvant radiotherapy, the use of a defunctioning stoma, and variations in tumour height or the extent of total mesorectal excision, all considered as risk factors for LARS. The significance of these risk factors was supported by the findings in *paper I*.

The analyses of another possible risk factor, the anastomotic configuration, did not reveal any differences in terms of LARS score or post-operative complications (*paper III)*. Earlier research, often limited by small participant numbers, short follow-up periods, and the use of different assessment tools, has suggested a potential short-term advantage of forming some kind of reservoir over the standard end-to-end anastomosis. Yet, more recent studies with larger sample sizes have not confirmed a difference in post-operative functionality, thereby corroborating our results.[99, 105, 106]

After colon resection, the impairment of bowel function seems to be limited. An approximate prevalence of 20% for major LARS after colon resection has previously been reported.[39, 44] We found an overall corresponding prevalence, regardless of the type of resection and with no

change over time, but noted a significant difference between men and women.

However, to evaluate the specific association between bowel dysfunction and resection, it is necessary to compare the findings to normative values.

Existing data of major LARS-like symptoms in the general population have shown a gender difference, some studies have reported a prevalence of major LARS-like symptoms among women close to 20%.[53, 54] Our results of the general population showed the same gender difference but with a slightly lower prevalence of major LARS-like symptom. Thus, when relating our results to existing data on bowel dysfunction in the general population, it seems that the effect of colon resection on bowel function is relatively modest, or possibly negligible, at least when measured using the LARS score. The LARS score, however, was not primarily developed for colon cancer and has not been validated for this indication. Loose stools, which are not included in the LARS score, were prevalent after right-sided resection in both men and women. The occurrence of loose stools have been previously reported after right-sided resection and found to negatively affect QoL.[40] Given this, the LARS score may not be sufficient to evaluate bowel dysfunction after colon resection comprehensively.

LONG-TERM STOMA FUNCTION

The deterioration of bowel function and the associated decline in QoL following rectal cancer surgery can be avoided by the creation of a permanent stoma. While establishing a permanent stoma may be required in certain cases, there are situations where it could be considered an optional or even preferable choice for some patients. In the literature, it has been difficult to conclude which option yields the best outcome in terms of QoL.[78, 81, 82] This context formed the background of *paper II*, which explored stoma function in a large prospective cohort with the aim to potentially develop a model for predicting which patients might experience distress from a future stoma. This would enhance preoperative patient counselling by enabling tailored advice on the prospective benefits of a stoma for individual patients.

It was encouraging to find that the majority of patients reported their stoma as well-functioning and expressed high acceptance. However, due

to the complex nature of distress, the limited size of our cohort, and the challenges in long-term predictions, constructing a reliable predictive model proved unfeasible.

DISTRESS

To estimate the relevance of specific physical symptoms, we have chosen to analyse the subjective concept of symptom-induced distress throughout this thesis. Summarising the results from the various papers, we found that distress was common after rectal resection with anastomosis, whereas relatively few patients experienced distress after colon resection, after surgery with a permanent stoma, and in the sample from the general population. Distress decreased over time only among patients who had undergone rectal resection with anastomosis, although this decrease was not accompanied by a reduction of major LARS. Given that this group clearly experienced impaired bowel function, these findings likely indicate a gradual adaptation to the impaired bowel function.

When limiting analyses to patients with major LARS, about half of the patients in each cohort experienced distress. This discrepancy between distress and symptom prevalence has been reported previously.[66, 86, 107] It has also been observed that an increased number of symptoms per patient is strongly associated with greater psychological distress and a reduced QoL.[86] While our question regarding distress focused specifically on distress related to bowel function, patients who have undergone treatment for rectal cancer may encounter additional challenges, including sexual and urinary dysfunction, pain, and fatigue, which could potentially affect the levels of distress reported.

CLINICAL IMPLICATIONS

The bowel dysfunction captured by the LARS score, as well as the reported distress, most likely reflect preoperative bowel dysfunction to some extent. This could partly explain the gender differences observed in our results, given that conditions such as functional bowel disorders and pelvic floor dysfunction are more prevalent among women. Regardless of preoperative bowel function, it is evident that not all patients experience poor bowel or stoma function following colorectal cancer surgery, nor are all individuals troubled by their function.

These findings underscore the importance of identifying patients with suboptimal bowel function before surgery and, more importantly, early identifying those distressed by their function after surgery.

Given that our results do not show any major long-term changes in function or associated distress, focusing on patients who report distress can yield considerable benefits for the individual. Potential interventions may include preoperative and postoperative counselling, support from stoma therapists or physiotherapists, and symptom-based medical treatment. Extensive follow-up for those who are content with their bowel or stoma function after surgery may not be necessary.

GENERAL DISCUSSION

In general, a high response rate and comparability between responders and non-responders contribute to external and internal validity. We received high response rates for the extensive questionnaires in *paper I* and *II* based on the QoLiRECT study, 87% and 80%, respectively, as well as in *paper IV* based on the QoLiCOL study, 83%. In *paper III*, only 64% of patients responded to the questionnaire. However, the response rate seems acceptable since patients were contacted only by mail and three years had passed since treatment. We have reported basic patient characteristics of responders, non-responders, and non-included patients. Generally, minor differences were observed between responders and non-responders, as well as between included and non-included patients, such as a slightly higher ASA score and more advanced tumour stages in the latter groups. Although it is uncertain if these differences affect the generalisability of the results, it is important to reflect on this aspect.

The implementation of the LARS score has greatly enabled prevalence estimations of LARS. The score has rapidly gained popularity and has been validated in many different languages. It has also been used to evaluate bowel function in patients with other cancer forms or conditions without being developed or validated for other indications than rectal cancer.

The development of the LARS score was based on patients with non-disseminated rectal cancer with a mean follow-up of 4.5 years. It is possible that the weighting of the impact on QoL would have differed if the patients had been evaluated in the earlier post-operative phase.

Similarly, the weighting might have been different if the score had been based on a different patient group. For example, in our analysis of bowel dysfunction after colon resection, in *paper IV,* we found that incontinence-related symptoms and the occurrence of loose stools, had a persistent association with distress. Incontinence for flatus and incontinence for loose are included in the LARS score, but given relatively low points, compared to clustering and urgency.

Some concerns have emerged regarding the LARS score, particularly its specificity, due to the presence of similar symptoms within the general population.[108] Concerns have also been raised about its ability to precisely estimate the impact on quality of life or accurately reflect the severity of specific symptoms.[109] Moreover, it has been pointed out that the score may lack sensitivity in tracking changes over time. To add value, a clinical evaluation in combination with the LARS score has been suggested.[17, 109]

We have used the LARS score, as well as the specific items included in the score, and other questions, to capture the variability of bowel dysfunction more thoroughly. By the nature of the studies, our results were limited to the responses provided by the patients. Even so, the included papers in this thesis fill a knowledge gap of the long-term functional aspects after surgery for colorectal cancer and the associated distress. There has been a need for large and prospective studies to expand existing literature on functional impairments beyond 12 months after treatment.

CONCLUSIONS

- We found major LARS to be common after rectal resection. The bowel function did not improve over time, but the related distress decreased somewhat gradually. A defunctioning stoma was found to constitute a risk factor for major LARS. The anastomotic configuration did not have any impact on major LARS or post-operative complications.

- Overall, most patients did not experience major LARS or distress after right- or left sided colon resection. Loose stools were common after right-sided resection which, as well as other incontinence related symptoms, were associated with distress. As in the general population, women experienced worse bowel function.

- Most patients with a permanent stoma after rectal resection were found to have a well-functioning stoma with high stoma acceptance. Distress was accompanied by a high occurrence of symptoms and worries as well as a low stoma acceptance. We were not able to construct a prediction model of post-operative distress.

- Providing information and addressing the patient's expectations before surgery is important. After surgery, early detection of dysfunction and treatment of symptoms are essential for patients who experience distress. However, for those with minimal or no impairment during the early phase, extensive functional follow-up is likely unnecessary.

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APPENDIX

The LARS score

Paper I-IV

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 patient's 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.

Q.1 : Do you ever have occasions when you cannot control your flatus (wind)?		
□	No, never	0
□	Yes, less than once per week	4
□	Yes, at least once per week	7
Q.2 : Do you ever have any accidental leakage of liquid stool?		
□	No, never	0
□	Yes, less than once per week	3
□	Yes, at least once per week	3
Q.3 : How often do you open your bowels?		
□	More than 7 times per day (24 hours)	4
□	4-7 times per day (24 hours)	2
□	1-3 times per day (24 hours)	0
□	Less than once per day (24 hours)	5
Q.4 : Do you ever have to open your bowels again within one hour of the last bowel opening?		
□	No, never	0
□	Yes, less than once per week	9
□	Yes, at least once per week	11
Q.5 : Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?		
□	No, never	0
□	Yes, less than once per week	11
□	Yes, at least once per week	16

Add the scores from each of the five answers to one final score.
Interpretation: 0-20 = No LARS 21-29 = Minor LARS 30-42 = Major LARS

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