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# Aspects of Low Anterior Resection Syndrome; prevalence, risk factors and treatment

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# Aspects of Low anterior resection syndrome; prevalence, risk factors and treatment
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By

**Emil Pieniowski**

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To Maria, Casper and Vanja

# POPULÄRVETENSKAPLIG SAMMANFATTNING

Vid operation för ändtarmscancer kan man, efter att ha opererat bort tumören, i många fall göra en tarmkoppling mellan tjocktarm och kvarvarande del av ändtarm eller analkanal. Många patienter får också en avlastande stomi (tarmen läggs ut på magen och man avleder avföringen) under läkningsfasen av tarmkopplingen. Efter en operation av denna typ drabbas en betydande andel av patienter av varierande grad av störd tarmfunktion som även riskerar att ha en påverkan på livskvaliteten. Störd tarmfunktion efter genomgången ändtarmsoperation benämns internationellt med begreppet ”Low Anterior Resection Syndrome” (LARS), eller låg främre resektions syndrom på svenska. Orsaken till LARS bedöms vara multifaktoriell där både kirurgin i sig, men även annan tilläggsbehandling som strålning (vilket ofta ges innan operation i de fall där det är aktuellt) kan påverka svårighetsgraden av tarmfunktionsstörningen. För att mäta graden av störd tarmfunktion finns ett validerat frågeformulär där olika svarsalternativ ger viktade poäng. Summan räknas ihop och beroende på hur man svarat bedöms man tillhöra en av tre grupper: no, minor eller major LARS. Till den sistnämnda gruppen tillhör de som bedöms ha mest uttalade symtom. De symtom som kan drabba patienten är inkontinens för gas och/eller avföring, frekventa tarmtömningar, trängningar och att man får tömma tarmen upprepade gånger under kort tid. För att värdera livskvalitet finns flera enkäter och en av dessa är EORTC QLQ-C30 (*European Organization for Reasearch and Treatment of Cancer*) där flera livskvalitets aspekter ingår och utvärderas.
Syftet med denna avhandling var att kartlägga hur vanligt LARS är och om besvären förändras över tid samt att utvärdera påverkan på patienters livskvalitet. Vidare studerades även om avlastande stomi har någon koppling till försämrad tarmfunktion i ett långtidsperspektiv. Slutligen att utvärdera om behandling med regelbunden tarmsköljning (Transanal irrigation, TAI) kan lindra besvären med LARS.

Den första studien hade som syfte att utvärdera om besvären med LARS förändras i ett långtidsperspektiv. En grupp patienter studerades vid två tillfällen (medel 5 års mellanrum) med avseende på graden av LARS i kombination med mätning av skattad livskvalitet. Resultaten visade att det var ingen statistisk skillnad i proportionen av patienter med major LARS då vi jämförde de två olika tidpunkterna. Gruppen med major LARS, i jämförelse med övriga grupper, skattade en sämre livskvalitet vid båda tillfällena. Slutsatsen blev att besvären med LARS förefaller kvarstå över tid och så även dess koppling till sämre livskvalitet.

Den andra studien syftade till att kartlägga hur vanligt LARS är in en väldefinierad grupp av patienter in Stockholm samt eventuell påverkan på livskvaliteten. Resultaten visade att i denna grupp besvärades 77.4% av patienterna av LARS och av dessa 53.1% av major LARS. Likaledes i denna studie var det en tydlig koppling mellan major LARS och sämre livskvalitet. Studien innehöll även en utvärdering av tarmfunktionens specifika påverkan på livskvalitet och denna visade tydligt att gruppen som upplevde stor påverkan på livskvalitet, relaterat till tarmfunktionen, också skattade en högre medelpoäng på LARS enkäten.

Slutsatsen i denna studie blev att LARS är väldigt vanligt och har en tydlig påverkan på livskvaliteten.

I den tredje studien var syftet att kartlägga om en avlastande stomi samt om tiden med stomi hade en koppling till försämrad tarmfunktion. Resultaten visade att oddsen för att drabbas av major LARS (om man jämförde med gruppen no LARS) var mer än dubbelt så höga om man hade fått en avlastande stomi jämfört men att om man inte hade fått en stomi. I denna analys vägde vi även in en eventuell inverkan av andra kända riskfaktorer för en försämrad tarmfunktion. Dock kunde vi inte finna någon tydlig koppling mellan major LARS och hur lång tid man hade haft stomin. Slutsatsen blev att en avlastande stomi var associerad till sämre tarmfunktion men att någon tydlig association mellan tarmfunktion och tiden med stomi, förelåg inte.

I den sista studien var syftet att utvärdera en tänkbar symtomatisk behandling för LARS. Patienter som inkluderades i studien lottades mellan två grupper: en grupp som undervisades i TAI (regelbunden tarmsköljning) i kombination med standardbehandling och en grupp som endast erhöll standardbehandling. Patienterna fick vid inkludering i studien besvara flera enkäter och följdes sedan upp under 1 år (6 och 12 månader) med telefonuppföljning samt att återigen besvara samma enkäter. Vid 12 månaders uppföljning skattade sig gruppen som fått lära sig TAI, tydligt bättre vad gäller tarmfunktion och livskvalitet jämfört med kontrollgruppen. Slutsatsen blev att behandling med TAI tydligt minskar symtomen av LARS och därför bör ingå i den behandling, sjukvården skall ha möjlighet att erbjuda, till patienter med svårare besvär med tarmfunktionen efter genomgången operation för ändtarmscancer.

# ABSTRACT

After sphincter sparing rectal cancer surgery an impaired bowel function, i.e. Low Anterior Resection Syndrome (LARS), is common. The symptoms included in LARS are incontinence for flatus and/or feces, urgency, fragmentation and frequent bowel movements. The cause is thought to be multifactorial and involves sphincter impairment, reduced compliance and capacity of the neorectum and altered motility, among others. With improved cancer survival the importance and focus on functional outcomes is increasing. The LARS-score is a validated questionnaire aimed to evaluate LARS and consists of five questions where each question has response alternatives with weighted scores. According to responses the total score is registered and depending on score a patient is classified into no, minor or major LARS group.

The overall aim of this thesis was to gain knowledge about Low Anterior Resection Syndrome, in order to better understand and manage patients post rectal cancer surgery.

Study I was a longitudinal cohort study evaluating long-term LARS and quality of life (QoL) at two different time-points (mean 5 years apart). In total, 282 patients were included in the final analysis and results showed no significant difference in proportion major LARS, comparing the different time-points (*p=0.455).* At second follow-up 49% of patients still experienced major LARS and the major LARS group reported inferior QoL, compared to the no/minor LARS group, at both time-points. This was one of the first studies with long-term longitudinal data on LARS and concluded that difficulties with LARS and the impact on patients QoL persists over time.

Study II was a population-based cross-sectional study with the aim to measure the prevalence of LARS and impact of QoL in a, clearly defined, Swedish cohort. The prevalence of LARS was 77.4% and the proportion with major LARS was 53.1%. Major LARS was associated to worse QoL reported with the EORTC QLQ-C30 questionnaire as well as worse bowel related QoL (BQoL). The study confirmed that major LARS is common after rectal cancer surgery and associated to significantly impaired QoL. This was one of the first studies providing population-based prevalence data in a Swedish cohort. The conclusion was that after anterior resection for rectal cancer a majority of patients suffer from major LARS which have a negative impact on QoL.

In Study III we evaluated the role of a defunctioning stoma and the association to major LARS. The adjusted OR for major LARS (vs. no LARS) was 2.43 (95% CI 1.14-5.20) comparing defunctioning stoma to no stoma. The results failed to show any evident association between time to stoma reversal and major LARS. This was one of the largest studies regarding this topic and one of a few with defunctioning stoma and association to major LARS, as primary endpoint. The study concluded that the results indicates that the presence of a defunctioning stoma is associated with major LARS in a long-term perspective, while failing to show any clear association to time to stoma reversal.

In the last Study (IV) the aim was to evaluate transanal irrigation (TAI) as a treatment strategy in patients with major LARS. In this RCT patients were randomized to either intervention group (TAI) or control group (conservative treatment). Patients were follow-up for 12 months and the primary endpoint was differences in bowel function at end of follow-up. In addition to the LARS-score three more outcome measures were used: CCFFIS questionnaire, four study specific questions and the EORTC QLQ-C30 quality of life instrument. An interim analysis was performed after 40 included patients with complete follow-up and the results from this analysis was clearly in favor of TAI which resulted in termination of further inclusion. The final results included follow-up data from 16 patients in the intervention group and 23 in the control group. At end of follow-up, statistical significant differences were reported in a majority of the outcome measures in favor of TAI. In LARS-score there were no differences at baseline but at 12 month of follow-up there were a 9.3 points mean difference in LARS-score ($p=0.002$) and 2.8 points mean difference in CCFFIS ($p=0.050$). Also, statistical significant results in 2 out of 4 study specific questions and 7 of 15 subscales on EORTC QLQ-C30.

This study was the first RCT evaluating TAI as treatment for major LARS and concluded that TAI reduces symptoms of LARS with improved QoL.

# LIST OF SCIENTIFIC PAPERS

I. Low Anterior Resection Syndrome and Quality of Life After Sphincter-Sparing Rectal Cancer Surgery: A Long-term Longitudinal Follow-up
**Pieniowski E**, Palmer G, Juul T, Lagergren P, Johar A, Emmertsen K, Nordenvall C, Abraham-Nordling M. *Dis Colon Rectum*. 2019; 62 (1):14-20

II. Prevalence of low anterior resection syndrome and impact on quality of life after rectal cancer surgery: population-based study
**Pieniowski E**, Nordenvall C, Palmer G, Johar A, Tumlin Ekelund S, Lagergren P, Abraham-Nordling M. *BJS Open*. 2020; (4):935-942

III. Defunctioning stoma and time to stoma reversal in rectal cancer surgery; risk factor for Low Anterior Resection Syndrome?
**Pieniowski E**, Nordenvall C, Johar A, Palmer G, Tumlin Ekelund S, Lagergren P, Abraham-Nordling M. *Submitted manuscript*

IV. A randomized controlled clinical trial of transanal irrigation versus conservative treatment in patients with Low Anterior Resection Syndrome after rectal cancer surgery
**Pieniowski E**, Bergström C, Nordenvall C, Westberg K, Johar A, Tumlin Ekelund S, Larsson K, Pekkari K, Palmer G, Lagergren P, Abraham-Nordling M. *Submitted manuscript*

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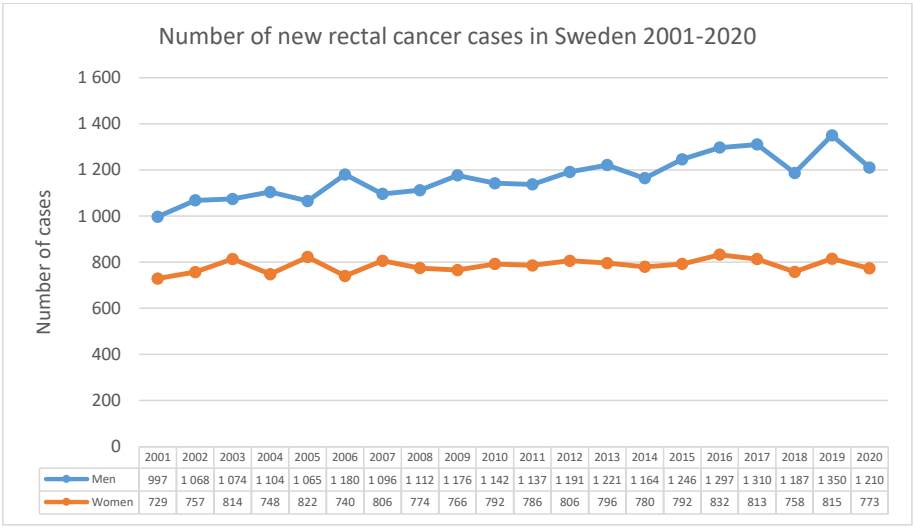
# LIST OF ABBREVIATIONS

| | |
|---|---|
| APR | Abdominal Perineal Resection |
| BQoL | Bowel related Quality of Life |
| CCFFIS | Cleveland Clinic Florida Fecal Incontinence Score |
| CEA | CarcinoEmbryonic Antigen |
| CI | Confidence Interval |
| CRC | Colorectal Cancer |
| CRT | Chemoradiotherapy |
| ESMO | European Society for Medical Oncology |
| Gy | Gray |
| IBD | Inflammatory Bowel Disease |
| LAR | Low Anterior Resection |
| LARS | Low Anterior Resection Syndrome |
| LRT | Long course Radiotherapy |
| MDT | Multidisciplinary Conference |
| MRI | Magnetic Resonance Imaging |
| pCR | Pathological Complete Response |
| PFR | Pelvic Floor Rehabilitation |
| PME | Partial Mesorectal Excision |
| QoL | Quality of Life |
| RCT | Randomized Controlled Trial |
| RR | Risk Ratio |
| RT | Radiotherapy |
| SD | Standard Deviation |
| Spp. | Species |
| SRT | Short course Radiotherapy |
| TAI | Transanal irrigation |
| TME | Total Mesorectal Excision |

# 1 INTRODUCTION AND BACKGROUND

## 1.1 EPIDEMIOLOGY RECTAL CANCER

Colorectal cancer (CRC) is the fourth most common form of cancer in the world and third deadliest with around 2 million new cases each year [1]. About one third of these cases are cancers in the rectum [2]. The incidence varies for different part of the world with the highest incidence in Australia and Nya Zeeland followed by Europe, Eastern Asia, North America and the lowest in Africa and South-Central Asia [1]. In Sweden around 2000 cases of rectal cancer are diagnosed annually, with an increasing incidence among young (<50 years) [3, 4].




| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | 997 | 1 068 | 1 074 | 1 104 | 1 065 | 1 180 | 1 096 | 1 112 | 1 176 | 1 142 | 1 137 | 1 191 | 1 221 | 1 164 | 1 246 | 1 297 | 1 310 | 1 187 | 1 350 | 1 210 |
| Women | 729 | 757 | 814 | 748 | 822 | 740 | 806 | 774 | 766 | 792 | 786 | 806 | 796 | 780 | 792 | 832 | 813 | 758 | 815 | 773 |

***Figure 1.*** *Line chart showing number of new rectal cancer cases in Sweden between 2001-2020. Presented according to gender. Source: Socialstyrelsen statistical database.*

The age standardized incidence for rectal cancer has been rather stable in Sweden for the past decades (in contrast to colon cancer with increasing incidence) with an incidence of 25/100 000 for men and 17/100 000 for women in during 2012-2015 [2]. The age specific incidence shows that rectal cancer is a rare condition among the young and only about 5% of the diagnosed cases are younger than 50 years but as mentioned with an increasing incidence in this age-group. About one fifth of the cases are older than 80 years at diagnosis.[2, 3] *(figure 2)*

In Sweden it is estimated that 9/100 000 men and 7/100 000 women dies every year due to rectal cancer which corresponds to around 800 cases [2].

In Swedish data from 2018 the relative 5-years survival among rectal cancer patients was 66% and has improved over the last decades resulting in a growing group of long-term rectal cancer survivors where a significant proportion have treatment related functional impairments [2].

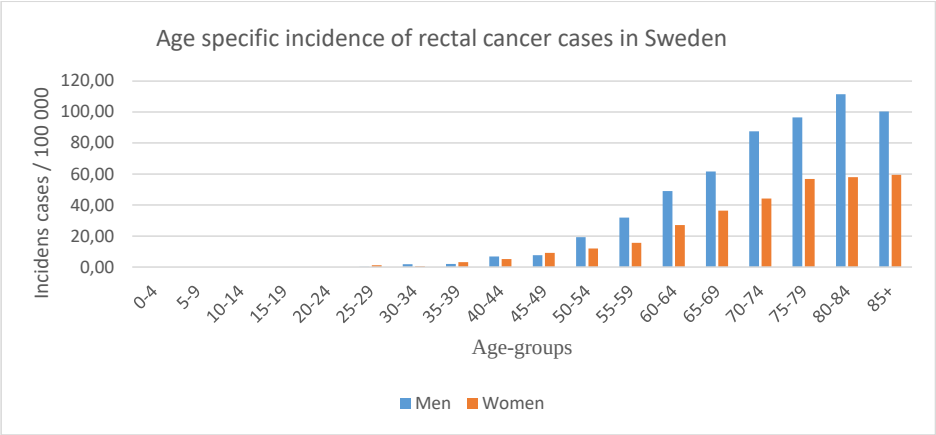



***Figure 2.*** *Column chart showing age-specific incidence of rectal cancer cases in Sweden, 2020. Source Socialstyrelsen statistical database.*

## 1.2 ETIOLOGY COLORECTAL CANCER

The current consensus is that most colorectal cancers arise from an adenoma, a neoplastic polyp. Most cancers are sporadic, nevertheless it is estimated that 20-25% has underlying hereditary factors. Known hereditary CRC syndromes are Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer, HNPCC), Familial Adenomatous Polyposis (FAP) and MYTYH-associated polyposis. Risk factors for CRC are Inflammatory Bowel Disease (IBD), diabetes, excessive alcohol consumption, smoking, high consumption of red and processed meat, obesity and infection with *Fusobacterium spp*.[2, 5, 6]

## 1.3 ANATOMY AND PHYSIOLOGY OF THE COLON AND RECTUM

### 1.3.1 Anatomy and physiology of the colon

The colon consists of five different segments cecum, ascending-, transverse- descending- and sigmoid colon and is about 1.1-1.3 meters long (varies between individuals and gender) [7, 8]. Embryologically, the cecum to the distal part of the transverse colon is developed from the midgut and distally from this point to the anal canal is developed from the hindgut [9]. The ascending and descending segments are located retroperitoneally. The colon can be distinguished from the small intestine by tenia coli (three bands of longitudinal muscle fibers), haustra (sacculations of the colon between the tenia), epiploic appendices and the caliber (internal diameter lager than the small intestine) [10].

The arterial blood is supplied from the superior mesenteric artery and inferior mesenteric artery which both are branches from the aorta. Superior mesenteric artery branches into

ileocolic artery, right colic artery (absent in 70% of individuals) and middle colic artery which supplies the cecum, ascending and two thirds of the transverse colon with arterial blood. The inferior mesenteric artery branches into left colic artery and superior rectal artery and supplies one third of the transverse-, descending and sigmoid colon. The marginal artery (Drummond´s artery) runs parallel to the colon connects the two main origins of blood supply. In some individuals a lager connecting branch is present (i.e the arch of Riolan). Venous drainage is provided by branches draining to superior- and inferior mesenteric vein.[11]

The sympathetic nerve supply originates differently for different parts of the colon. For the cecum, ascending- and two thirds of the transverse colon the nerves originate from the $5^{th}$ to the $12^{th}$ thoracic spinal segments. Via the celiac- and the superior mesenteric plexus the nerve fibers reach the colon through periarterial plexus following the superior mesenteric artery. For the left one third of transverse colon, descending- and sigmoid colon the sympathetic nerve supply originates form lumbar and upper sacral spinal segments. Lumbar splanchnic nerves reaching the inferior mesenteric plexus and sacral splanchnic nerves to the superior and inferior hypogastric plexus. The left and right hypogastric nerves connect superior hypogastric plexus with the inferior hypogastric plexus.[10, 11]

The parasympathetic nerve supply for cecum, ascending- and two thirds of transverse colon is provided by the vagus nerve via the celiac and superior mesenteric plexus. For the left third of the transverse colon and distally the parasympathetic nerves originate from the second to the fourth sacral segments and connect to the superior and inferior hypogastric plexus.[11]

The sympathetic nerves mediate relaxation of the colonic wall as well as contraction of the ileocecal valve and vascular smooth musculature. Sensation of visceral pain is enabled by afferent nerve fibers. The parasympathetic nerves stimulate contraction of the colonic musculature and has functions involving motility and secretion. Besides the sympathetic and parasympathetic nervous systems the bowel also has an intrinsic nervous system, the enteric nervous system, located within the bowel wall coordinating functions such as motility and secretion.[11]

The colon has four primary functions. The first function is absorption of fluid and electrolytes which is a requirement for transform the liquid content to more solid or semisolid stool. Second, colon absorbs short-chain fatty acids derived from catabolism or fermentation by colonic microflora. The third function is storage and the fourth is the ability to eliminate its content in a controlled way.[12]

The colon has several different types of described motor patterns but the terminology can be difficult to overview due to that different terms (depending on source) are used to described the same motor patterns. The non-propulsive segmentation produces circular muscle contractions which produce pressure and move the content in oral direction resulting in colonic content to be retained in the proximal part of the colon for rather long time promoting mix of luminal content and absorption. A few time every day mass peristalsis occurs moving the content to a more distal part of the colon. These mass peristalsis can be stimulated by

food intake. In the distal colon non-propulsive segmentation is dominating but occasional mass peristalsis propels the content into the rectum.[12] The gastrocolic reflex is a physiological response to food intake (stretch of the stomach) and involves the autonomic (sympathetic and parasympathetic) as well as the enteric nervous system resulting in increased motility in the colon, especially the sigmoid part, moving content distally towards the rectum [13]. High resolution manometry studies have revealed other motor patterns such as cyclic propagating motor pattern (CMP) which often occurs in short segments (but sometimes longer segments) with a frequency of 2-6/min and most often has its origin located to the recto-sigmoid junction [14]. CMP more often propagates in a retrograde direction and it has been proposed as a "rectosigmoid brake" with the purpose to prevent rectal filling [15]. Another is the retrograde slowly propagating motor pattern that occurs primary during fasting. These travels slowly along the colon originating in the sigmoid part [14].

### 1.3.2 Anatomy and physiology of the rectum

The definition of the rectum, in the context of rectal cancer, is ≤15 cm from the anal margin measured by rigid endoscope [16]. In an anatomical context the rectum is described as 15-19 cm long and characterized by tenia fusing into a continuous longitudinal smooth muscle layer, absence of epiploic appendices, intraluminal transverse folds (Kohlrausch- and Houston´s folds) and the extraperitoneal location of the lower and dorsal parts. The mesorectum, containing blood vessels, lymph vessel / nodes embedded in fatty tissue, surrounds the rectum and is covered by a visceral fascia, the mesorectal fascia. The rectum passes through the pelvic floor which comprises of multiple muscles, mainly striated muscles but also partly containing smooth muscle components. [9, 11] The rectum has close proximity to other organs in the pelvic cavity. Anteriorly limited by the prostate, seminal vesicles, vas deferens and urinary bladder in med and the dorsal wall of the vagina and uterus in women. Dorsally by the sacrum, coccyx, sacral nerves and laterally by the ureters, internal iliac vessels.

The anal canal is between 2.5-4 cm and forms an angle to the rectum (anorectal angle of 90-100° involving the puborectal muscle). It can be divided into the colorectal zone (covered with mucosa) and squamous zone (anoderm, covered with non-keratinized stratified squamous epithelium) divided by the dental line considered to be the junction between endoderm and ectoderm embryologically. The internal anal sphincter is a thickened portion of the smooth muscle layer of the rectal wall and is under involuntary control. In contrast the external anal sphincter consists of striated skeletal muscle and is controlled by both involuntary and voluntary mechanisms.[11, 12] To maintain continence the resting anal tone is important and the internal sphincter is responsible for about 55-75% but the anal vascular cushions also contributes. [17, 18]

The blood supply for rectum and anal canal is provided by rectal superior artery branching from inferior mesenteric artery and mid- and inferior rectal artery originating from internal iliac artery via branches.[11]

Nerve supply of the rectum is provided by sympathetic nerves, with origin in lumbar spinal segments, connecting to inferior mesenteric plexus, superior hypogastric plexus and via the left and right hypogastric nerves to the inferior hypogastric plexus (pelvic plexus). Sacral parasympathetic nerves connect to the inferior hypogastric plexus which also plays a role in innervation of other intrapelvic organs and involved in sexual and lower urinary tract functions (vesical plexus, prostatic plexus and the uterovaginal plexus). A part of the anal canal is innervated by somatic nerves branching from the pudendal nerves making the anoderm highly sensitive to touch, pressure, pain and temperature. Both the colonic and rectal motility is also influenced by higher cortical centers, hormonal- and immune system.[11]

The nerve supply to the internal sphincter originate from the pelvic plexus (inferior hypogastric plexus) and runs along the neurovascular bundles anterolaterally to the rectum and posterolaterally to the prostate / vagina. Directly above where the longitudinal muscle fibers of the rectum fuse with the levator ani muscle (pelvic floor) nerve branches penetrates the rectal wall to reach the internal sphincter. The innervation of the external sphincter is provided by the pudendal nerve. [11, 19]

The rectum and the anal canal have two main functions. The first is to sustain fecal continence and important structures and functions for this is the internal- and external anal sphincter muscles, the puborectal muscle, rectal compliance, anorectal sensitivity and coordinated anorectal motility. The second function is to allow for defecation when suitable.

Different patterns of rectal motility can be distinguished such as isolated contractions, short clusters of contraction and rectal motor complex (powerful phasic contractions) of which the physiological function is not fully understood. During rectal motor complex the content of the rectum can be moved orally or aborally. In contrast to the colon, where distension produces pain, stretching of the rectum produces a sensation of rectal filling and an urge to defecate. Another important feature of the rectum is the ability to determine if its content are solid or liquid stool or gas.[11]

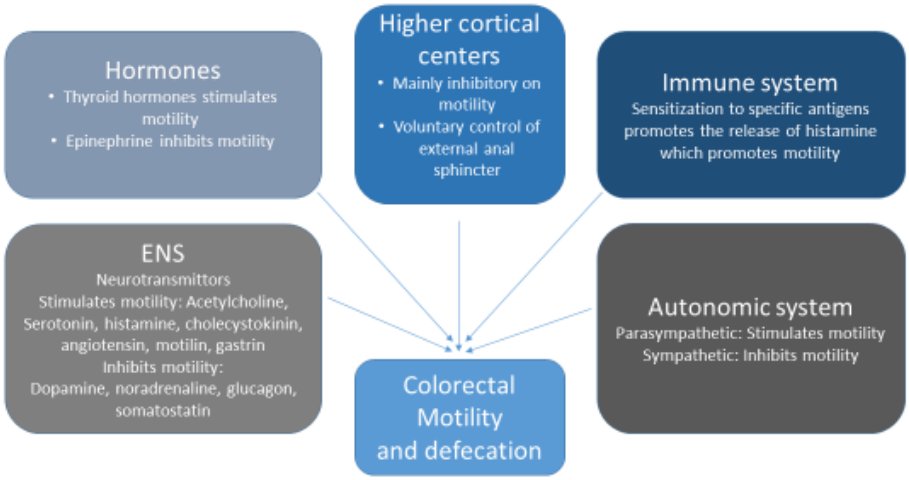



***Figure 3.*** *Systems involved in colorectal motility and defecation. ENS=Enteric Nervous System.*

## 1.4 COLONIC TRANSIT TIME, DEFECATION PROCESS AND EVALUATING ANORECTAL FUNCTION

### 1.4.1 Colonic transit time

Normal colonic transit time is between 20-56 h, thus varies between individuals [20]. Normally the transit is longer in the left colon compared to the right. Studies has shown that female have a slower colonic transit time than men [21, 22]. Colonic transit time can be measured by ingestion of plastic markers followed by x-rays at predetermined time-points or ingestion of radioisotope followed by multiple gamma camera images over a period of 5 days [20].

### 1.4.2 Defecation process

The defecation process is usually initiated by distension of the rectum due to colonic content propelled into the rectum by colonic mass movements. This initiates the defecation reflex (i.e rectosphincteric reflex) innervated by the enteric nervous systems and parasympathetic nerves from sacral spinal segments. Rectal contraction is followed by relaxation of the internal anal sphincter and puborectal muscle (reduces the anorectal angle). If defecation is desired relaxation the external sphincter occurs with concurrent contraction of the abdominal wall increasing the intraabdominal pressure. [11, 12] During the defecation process, in order to facilitate opening of the anal canal, the hiatal ligament functions as connective tissue. This is

mediated by contraction of the pubococcygeus muscle and the iliococcygeus muscle. The rectococcygeus muscle is contracted to shorten the rectum and assist defecation.[17]

The recto anal inhibitory reflex involves a transient relaxation of the rectum as a response to rectal distention and is physiologically hypothesized to play a role in discriminating between solid or flatus content [23]. If it is not a suitable time for defecation a voluntary contraction of the external sphincter and pelvic floor muscle inhibits defecation and in the normal rectum periodic motor activity propagates in retrograde direction and decrease the rectal pressure and reduces the urge to defecate [17].

### 1.4.3 Evaluating anorectal function

#### *1.4.3.1 Anorectal ultrasound*

Anorectal ultrasound, in the context of anorectal function and continence, is mainly used to assess the internal- and external anal sphincters. It is the most sensitive tool to diagnose sphincter defects and other structural abnormalities. [24, 25]

#### *1.4.3.2 Anorectal manometry*

Anorectal manometry can be used to evaluate different parts of the anorectal function. *Resting pressure* measures the resting tone of the internal- and external anal sphincters and *squeeze pressure* measure the voluntary contraction of the external anal sphincter [26]. Normal resting pressure values varies depending on the technique used and the population studied. In a study by Oblizajek et al, claiming to be the largest study measuring anorectal pressure with high resolution anorectal manometry in healthy individuals, mean resting pressure among women <50 years was 85 mmHg (SD ±22), women >50 years 66 mmHg (SD ±25) and for men 83 mmHg (SD ±25) [27].

During *simulated evacuation* of the rectum you will expect to see an adequate increase in rectal pressure which then can be recorded. The *cough reflex* (i.e contraction of the external sphincter as a response to increased intraabdominal pressure) can also be evaluated.

*The rectoanal (inhibitory) reflex* involves relaxation of the internal anal sphincter (IAS) as a response to rectal distension and triggered by inflating a balloon in the rectum while measuring sphincter pressure.

*Rectal sensation* is assessed by inflating a rectal balloon and record the threshold volume for the first sensation of; 1) desire to defecate 2) urge to defecate and 3) perception of discomfort and pain.[26, 28]

*Rectal compliance* is measured by inflating a balloon and record pressure changes that occurs and can be defined as the change in rectal volume per unit change in rectal pressure [29].

#### *1.4.3.3 Nerve studies*

Measurement of the conductivity of the pudendal nerve (pudendal nerve terminal motor latency, PTNML) quantifies the time it takes for the external anal sphincter to contract after stimulating the pudendal nerve [24].

#### *1.4.3.4 Defecography*

Both conventional- and MR defecography are available and evaluates the defecation process during attempted defecation, MR defecography with superior soft tissue resolution. The anorectal angle, anal diameter, degree of rectal emptying and pelvic floor descent can be evaluated. Also, morphological abnormalities such as rectocele, enterocele and intussusception can be detected and assessed. [30]

## 1.5 MANAGEMENT OF RECTAL CANCER

### 1.5.1 Investigation and staging

Clinical evaluation of a patient with confirmed or suspected rectal cancer tumor should comprise patient history, including comorbidities, physical examination and a general evaluation of the patient´s functional status. Routine bloodwork including Carcinoembryonic antigen (CEA) is a part of the investigation. More focused on the rectal tumor a digital examination should include assessment of sphincter status and, if reachable, an evaluation of the tumor (firm or soft, fixed or mobile). An examination with a rigid rectoscope should be performed to establish the tumor level, radial location and enable biopsies for morphological verification.[16, 31, 32] According to ESMO guidelines rectal cancer are categorized as low (up to 5 cm), middle (>5 cm to 10 cm) and high (from 10 cm to 15 cm) [16]. To exclude synchronous colon cancer tumors a complete colonoscopy is included in the investigation.

According to the TNM-classification system a radiological classification should be performed (cTNM, clinical or pretreatment TNM) [33]. Mandatory (if no contraindication) is to perform a computed tomography (CT) of the thorax and abdomen and an MRI of the pelvis. T-stage describes depth of local tumor invasion and N-stage involvement of regional lymph nodes and preferably evaluated with MRI (locoregional staging). CT is mainly focused on assessing the presence of distant metastasis, M-stage. In selected cases a PET-CT (Positron Emission Tomography) can add useful information. Anorectal ultrasound can be used for low, early tumors and supply useful information about T-stage. [16, 31, 32]

### 1.5.2 Multidisciplinary team conference (MDT)

Following clinical assessment and cTNM the next step is an individualized treatment plan. Multiple aspects should be considered in this planning such as patient factors including functional status, comorbidities, age and treatment aspects such as neoadjuvant treatment

(radiotherapy, chemoradiotherapy), possibility to treat distant metastasis (if present) and surgery for the primary tumor. The complexity emphasizing the need for involvement of a multidisciplinary team [34]. As a result, MDT has become the golden standard in cancer care. In rectal cancer care the MDT usually consists of a colorectal surgeon, oncologist, radiologist, pathologist and specialized nurse. Although randomized trials are lacking there is evidence supporting the concept of MDT. Studies have shown improved clinical staging, higher proportion neoadjuvant treatment and improved postoperative mortality [35-39]. Evaluation on a high quality rectal cancer specific multidisciplinary conference led to a change in treatment plan in 29% of the cases [40]. A study comparing three groups (1. preoperative staging + MDT; 2. preoperative staging + no MDT; 3. no preoperative staging + no MDT) showed statistically significant differences in proportion of R0 resections in favor of the MDT group ($p<0.001$) [36].

With increased experience and knowledge of organ-preserving watch and wait strategy, following neoadjuvant treatment with complete response (CR), the need for individualized MDT conferences has further increased [41].

### 1.5.3 Treatment of rectal cancer

#### *1.5.3.1 Neoadjuvant treatment*

Neoadjuvant treatment means that the treatment is given preoperatively and in rectal cancer care this treatment includes radiotherapy (RT) alone or in combination with chemotherapy. The addition of concurrent chemotherapy to radiotherapy (CRT) has the purpose to potentiate the effect of RT on the cancer cells. The primary purpose is to reduce the risk of local recurrence, but also to accomplish down-staging of the tumor and sterilize involved lymph nodes. In more advanced rectal cancer cases a more aggressive neoadjuvant treatment regime can be used with RT followed by chemotherapy (number of cycles depending on treatment protocol). Several studies have shown reduced rates of local recurrence attributed to neoadjuvant RT prior to rectal cancer surgery, a reduction that persists after more than 10 years of follow-up [42-48]. There is also data favoring to give RT preoperative (neoadjuvant) instead of postoperative and also that a higher dose of RT is needed postoperatively to reach the same efficiency as when given preoperatively [49-51]. A Swedish RCT comparing preoperative short course RT 5x5 Gray (Gy) to postoperative long course RT (30x2 Gy) showed statistically significantly lower rate of local recurrence in the preoperative RT group (13% vs. 22%) [49]. Another RCT, comparing preoperative RT 5x5 Gy and surgery to selective postoperative CRT 45 Gy (25 fractions) with concurrent 5-fluorouracil restricted to patients with an involved circumferential resection margin, showed an absolute difference in local recurrence of 6.2% (4.4% RT preoperative vs. 10.6% selective CRT postoperative). The same study also showed an improved disease free survival favoring preoperative RT [50]. Which RT regime used, neoadjuvant short course RT (SRT) or long course CRT, differs between countries in the world. Some studies have shown better local control for locally advanced

rectal cancers with the long course CRT regime compared to SRT [52, 53]. Two RCTs comparing SRT with long course CRT could not show any statistically significant differences in local recurrence, disease free survival or overall survival but a higher rate of acute toxicity in the group which received CRT [54, 55].

The timing of surgery after neoadjuvant treatment has been the focus in several studies. The Stockholm III study compared three groups SRT, SRT with delayed surgery and LRT with delayed surgery and found no differences in cumulative incidence of distant metastasis, overall survival and recurrence free survival but a higher proportion of pCR in the SRT delay group. When comparing SRT with SRT delay postoperative complications was lower in the SRT delay group. [56, 57]

As mentioned above, in cases with more locally advanced rectal cancer tumors SRT followed by chemotherapy can be the preferred treatment regime. In the RAPIDO study SRT followed by chemotherapy was compared to long course CRT with adjuvant chemotherapy in selected cases. The results showed no statistically significant differences in local recurrence and overall survival but lower proportion of distant metastasis and pCR in the SRT + chemotherapy group.[58]

Patient selection, regarding RT, is very important due to the potential side-effects, toxicity of the treatment. Patients treated with RT should have expected benefits from the treatment and not all patients should receive treatment. In Sweden between 60-65% of all rectal cancer patients receive RT [59]. Radiation leads to ionization which causes DNA-damage and cancer cells have an impaired capacity to repair RT-induced injury. The goal is to maximize effect while minimize damage to normal tissue by optimized RT technique. The effect on tumor tissue depends on total radiation dose, fraction dose and length of treatment. The impact on normal tissue depends on the same parameters with the addition of radiation volume [60]. The acute side effects of RT include erythema, nausea, cystitis and diarrhea while the late side effects include impaired sphincter function, sexual dysfunction, pelvic fractures and increased risk of small bowel obstruction [61].

#### *1.5.3.2 Surgical treatment*

Total mesorectal excision (TME) is the accepted gold standard method to surgically remove rectal cancer tumors. It involves removal of the rectum, including the tumor with at least 1 cm distal margin and the mesorectum with the mesorectal fascia intact. Dissection in the correct plane allows for complete TME while preserving the pelvic fascia and autonomic nerve plexuses. The method was first described by Heald and Ryall in 1982 [62]. In 1986 they reported a cumulative 5-years risk of local recurrence of 3.7% using the TME method and in 1993 a 5-years local recurrence rate of 5% compared to results from NCCTG, North Central Cancer Treatment Group, with local recurrence rates of 25% (conventional surgery and RT) and 13.5% (conventional surgery and CRT) [63, 64]. In the Dutch TME-trial TME alone had a

recurrence rate of 11% (vs. 5% in group with TME and SRT) [46]. A Swedish study evaluating local recurrence after the introduction of the TME concept and compared to historical controls presented significantly lower occurrence of local recurrences in the TME group [65]. For tumor in the upper rectum a Partial Mesorectal Excision (PME) can be performed if a distal margin of 5 cm can be achieved. Concerning the oncological safety of PME there are some diversities in the results of different studies. Kanso et al. showed comparable local recurrence- and survival rates to TME [66]. In contrast to this study Bondeven et al. presented a 3-years local recurrence rate of 13.5% for PME compared to 2.9% for TME [67].

For the surgical treatment different approaches / techniques can be used; open, laparascopic, robotic, TaTME (Transanal total mesorectal excision).

*Anterior resection*

Anterior resection includes central ligation of inferior mesenteric artery or superior rectal artery, TME or PME (low anterior resection or high anterior resection respectively) and construction of an anastomosis to restore bowel continuity. In many cases a defunctioning ileostomy is constructed to reduce the risk of a symptomatic anastomotic leakage [68-70]. The anastomosis can be constructed in different ways: end-to-end, side-to-end and colonic j-pouch.

*Hartmann´s procedure*

TME or PME with a residual rectal stump and a permanent colostomy is called Hartmann´s procedure (i.e low Hartmann). This procedure may be considered in high risk patients who may not tolerate an anastomotic leakage or in patients with prior anal incontinence. When compared to abdominal perineal resection (APR) there are some diversity in the results while some studies show higher rates of pelvic abscess, reoperation and readmission others did not [71-74]. A meta-analysis, comparing APR to Hartmann, concluded that extrasphincteric APR is associated with higher overall and pelvic-perineal complications but intersphincteric APR and Hartmann´s procedure have comparable morbidity [75].

*Abdominal Perineal Resection*

Abdominal Perineal Resection (APR) or APE (Abdominal Perineal Excision) can be used in patients in which the tumor location and oncological perspective do not exclude an anastomosis but the patient has significant comorbidities and may not tolerate a severe complication (i.e anastomotic leakage). In these cases, an intersphincteric APR is

preferable. In cases of low rectal tumors and tumors involving the pelvic floor and the sphincter complex an extrasphincteric APR or extralevator APR (i.e ELAPE) is necessary to accomplish adequate oncological outcomes.

*Local excision*

Early rectal tumors (T1) with no signs of lymph node involvement and low risk (no signs of lymph vascular or vascular involvement, R0, absence of tumor budding and well differentiated) local excision can be considered. If the pathology report reveals features indicating a high risk tumor a complementary TME surgery should be performed. Local excision can also be considered in more advanced tumors in high risk patients with extensive comorbidity. TEM (Transanal Endoscopic Microsurgery) or ESD (Endoscopic Submucosal Dissection) are the two preferable methods for local excision. [16, 76]

#### *1.5.3.3 Adjuvant treatment*

The evidence for adjuvant treatment (postoperative) with chemotherapy in rectal cancer care is lacking compared to colon cancer care in which adjuvant chemotherapy is used for stage II with risk factors and stage III disease [77, 78]. A Cochrane analysis from 2012 concluded that there is some support for 5-FU based adjuvant chemotherapy in patients treated with radical surgery and no metastasis but there is a need for RCTs evaluating the benefit of adjuvant chemotherapy in patients that have received neoadjuvant treatment [79]. Nevertheless, there are some data supporting adjuvant chemotherapy for patients with high tumors, treated with neoadjuvant (C)RT, in terms of disease free survival and distant recurrences [80]. In the Swedish national colorectal cancer guidelines, the recommendations states that stage II with risk factors and stage III should be assessed for adjuvant chemotherapy and patients with no neoadjuvant treatment should be assessed according to criteria for colon cancer. Patients which have received neoadjuvant RT may be relevant for discussion in contrast to CRT where adjuvant treatment is not recommended. Adjuvant treatment is not recommended for patients after neoadjuvant RT followed by chemotherapy or for patients pCR (unless cTNM indicates high risk tumor and adjuvant treatment may be considered). [2]

### 1.5.4 Swedish Colorectal Cancer Registry (SCRCR)

For rectal cancer the Swedish Colorectal Cancer Registry was initiated in 1995 and since 2007 is colon cancer also included in the registry. Multiple variables are recorded by surgeons, radiologists, oncologists and pathologists including age, gender, neoadjuvant treatment, surgical treatment, postoperative complications, pathological data, adjuvant treatment and follow-up data. The registry has a completeness (coverage) of >99% and has been validated with results showing an average agreement of 90% [81, 82]. The registry is

continuously revised and annual reports are available including comparisons between hospitals for several parameters. Given the excellent coverage and valid data the registry constitutes a valuable source of information for research [83].

# 2 LOW ANTERIOR RESECTION SYNDROME

## 2.1 DEFINITION AND OUTCOME MEASURES

Historically there has been a lack of precise definition of Low Anterior Resection Syndrome (LARS). A pragmatic definition proposed by Bryant et al. was “disordered bowel function after rectal resection, leading to a detriment in quality of life” [84]. In a systematic review by Keane et al. trying to define LARS the conclusion was that there is a substantial variation in reporting of functional outcomes after anterior resection [85]. In this review, studies between 1986-2016 were included and the used, instruments and outcome measures, were recorded. More than one third of the included studies did not use any specific instrument to evaluate bowel function (*figure 4*)

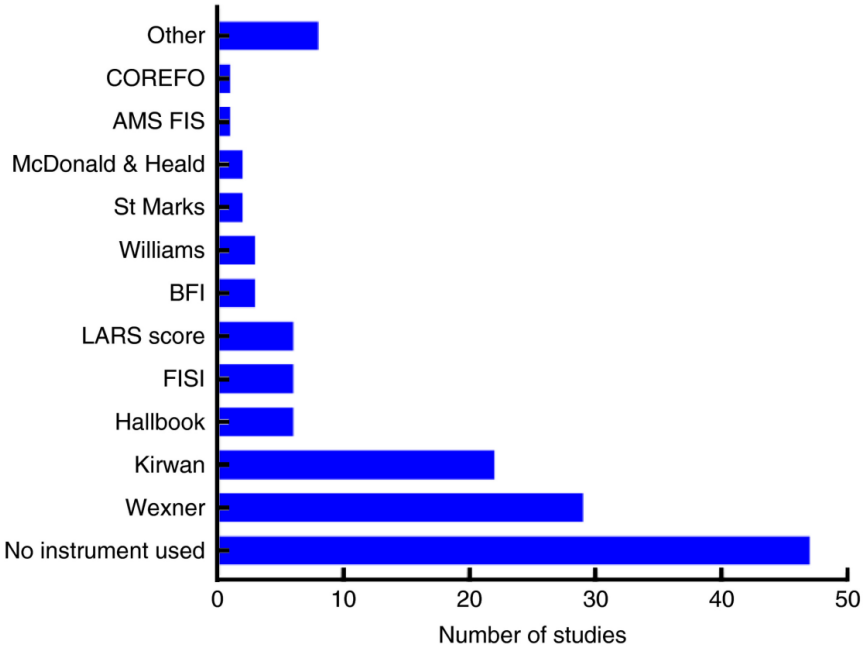



***Figure 4.*** *Instruments used to assess postoperative bowel function (COREFO, Colorectal Functional Outcome questionnaire; AMS FIS, American Medical System Fecal Incontinence Severity score; BFI, Memorial Sloan Kettering Cancer Center (MSKCC) Bowel Function Instrument; LARS score, Low Anterior Resection Syndrome score; FISI, Fecal Incontinence Severity Index; “Other” includes the MSKCC sphincter function criteria, Pecatori Anal Incontinence Score, Anal Sphincter Conserving Treatment questionnaire, Rotterdam symptom checklist, Komatsu score and Holschneider questionnaire).* [85] *Reprint with permission.*

Of the used instruments, the Wexner score (i.e CCFFIS, Cleveland Clinic Fecal Incontinence Score) was the most commonly used resulting in evaluation of symptoms related to incontinence [86]. Other commonly used outcome measures were Kirwan classification and Fecal Incontinence Severity Index [87, 88]. More than 30 different symptoms were reported and

the five most frequent were fecal incontinence, stool frequency, flatus incontinence, urgency and pad wearing.

In another cross-sectional review from Chapman et al. concerning reporting of postoperative bowel dysfunction after rectal cancer surgery, including 234 studies, the results were similar [89]. This study measured reporting of bowel dysfunction according to components of the LARS-score and of the 15 different instruments, used for measurement, only 9 were validated. Only 22% of the 234 reviewed articles reported all 5 components and 44.4% reported less than fifty percent of the components. Studies using bowel dysfunction as a primary outcome (61.5%) were associated with better completeness in reporting (OR 3.49; 95% CI 1.99-6.23).

| ***Instrument*** | ***Components included*** |
|---|---|
| *Wexner score / CCFFIS* [86] | Incontinence for stool |
| | Incontinence for flatus |
| *Kirwan grading system* [87] | Incontinence for stool |
| | Incontinence for flatus |
| *Hallböök questionnaire* [90] | Incontinence for stool |
| | Incontinence for flatus |
| | Stool frequency |
| | Fecal clustering / fragmentation |
| | Pain |
| | Fecal urgency |
| | Emptying difficulties |
| | Bowel function affects daily life |
| *FISI* [88] | Incontinence for stool |
| | Incontinence for flatus |
| *LARS-score* [91] | Incontinence for stool |
| | Incontinence for flatus |
| | Stool frequency |
| | Fecal urgency |
| | Fecal clustering / fragmentation |

***Table 1.*** *Components in the 5 most frequently used instrument in the review by Keane et al. [85]. CCFFIS = Cleveland Clinic Florida Fecal Incontinence Score. FISI = Fecal Incontinence Severity Index*

The variation in reporting bowel dysfunction and the difficulties to compare results from different surgical approaches and from different studies was the basis for the development of the Low Anterior Resection Syndrome score (LARS-score) which was published by Emmertsen and Laurberg in 2012 [91]. The 5 symptoms included in this questionnaire (described in detail below) are incontinence for flatus and / or feces, stool frequency, fragmentation / clustering and urgency. The LARS-score was only used in 6 studies according to the review from Keane el al. and in 7 studies according to Chapman et al. but in the period after these two reviews were conducted, the questionnaire has been used in several studies, as an outcome measure for bowel dysfunction (i.e LARS).

The lack of precise definition of LARS was the basis for the LARS collaboration group to present a consensus definition [92]. The collaboration group consisted of three expert groups: patients, surgeons and other health professionals from different parts of the world. The process, for the development of a consensus definition, included online Delphi survey [93, 94], patient consultation meetings and consensus meeting. The final definition provides 8 symptom complexes and 8 consequences and to meet the definition a patient must experience at least one symptom that results in at least one consequence (*figure 5*)

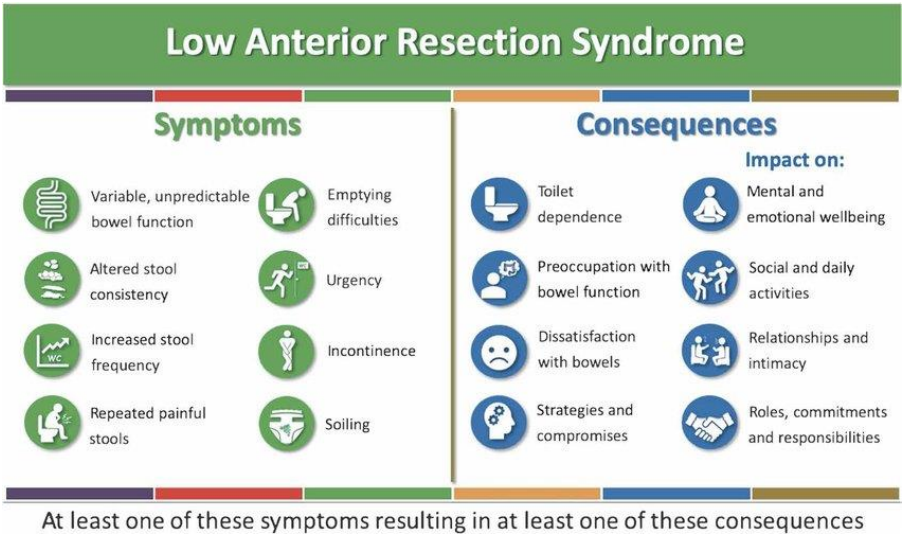



***Figure 5.*** *Consensus definition of Low Anterior Resection Syndrome provided by the LARS International Collaboration Group [92]. Reprint with permission.*

### 2.1.1 LARS-score questionnaire

As mentioned before was the LARS-score questionnaire published by Emmertsen and Laurberg in 2012 (*figure 6*) [91]. The basis for this, besides differences in prior reporting of bowel dysfunction, was also the lack of a scoring system that also took subjective bother and impact on QoL into consideration (i.e weighted scores). The questionnaire was developed

using a Danish cohort of rectal cancer patients which had undergone surgery (PME or TME) with an anastomosis. A total of 1143 patients eligible for participation were identified though the Danish Colorectal Cancer Groups database and cross-checking with the National Patient Registry. After exclusion of non-responders (n=82), patient re-operated with permanent stoma (n=42) and incomplete answering of questionnaire (n=58) 961 patient participated in the study. 483 patients were included in the process of developing the questionnaire and the other half (n=478) in the validation process. The basic questionnaire was developed by a process involving review of prior instruments / questionnaires, expert discussions, pilot testing, test-retest reliability testing and semi-structured interviews. To calculate the weighted scores, for each questions response alternatives, a separate question assessing the impact on QoL was used: "On overall, how much is your QoL influenced by your bowel function". The response alternatives for this question were "not at all", "a little", "some" and "a lot" and in analysis combined into the binary outcome variable "not at all" / "a little" and "some" / "a lot". Symptoms were grouped into four groups (incontinence, emptying difficulties, urgency and frequency). For each group the association to QoL, for each response alternative, was calculated using a binominal regression and presented as relative risk (RR). For each group an adjusted RR was calculated while adjusting for other independent variables. An adjusted RR >2.5 was mandatory for inclusion into the final multivariable analysis. The logarithmic values of corrected RRs from this analysis was multiplied with 10 to get the final scores for each response alternative. LARS scores were then plotted against impact on BQoL (now divided into: no impact, minor impact and some/major impact on QoL) and this plot along with mean LARS score was the basis for the three LARS groups, minor LARS (0-20 points), minor LARS 21-29 points) and major LARS (30-42 points). [91]

As mentioned, they used the other half of the participating patients, for validation of the questionnaire. The ability of the LARS-score to predict impact on QoL was presented as a ROC curve, sensitivity- and specificity values. Sensitivity meaning the questionnaires ability to predict impact on QoL if there is a "true" impact on QoL and specificity meaning the questionnaires ability to predict no impact on QoL if there is no "true" impact on QoL [95]. In analysis the sensitivity was 72.54% and specificity 82.52%. The prediction model showed a perfect fit in 62.21%, moderate fit in 31.94% and no fit in 5.85% [91].

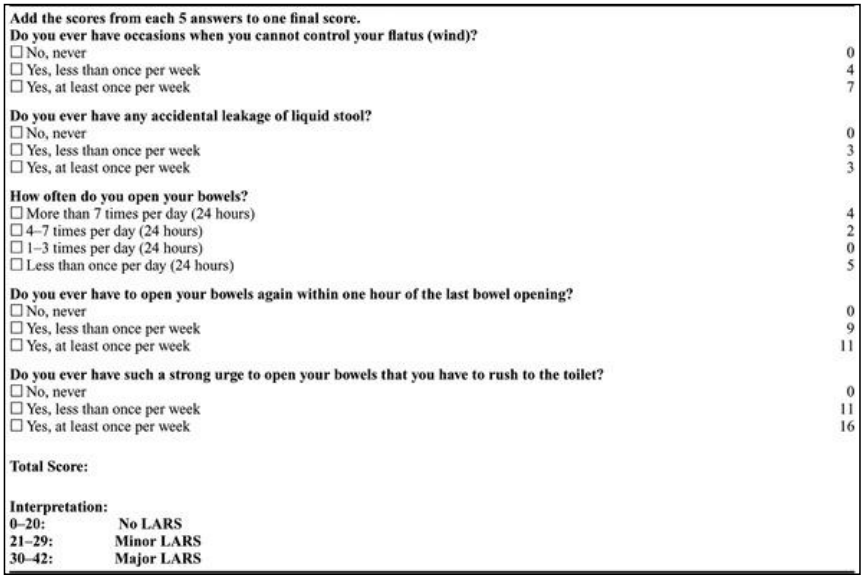
An international validation using a Swedish, Spanish, German and Danish version has also been conducted and concluded the LARS-score to be a valid and reliable tool for measuring LARS in European rectal cancer patients [96]. Since then, several validations for different nationalities, have been conducted with results showing the questionnaire to be valid and reliable [97-103]. Following the publication of the questionnaire in 2012 the LARS-score is now a widespread instrument frequently used in measurement of bowel function after rectal cancer surgery and the simple design makes it useful in the daily clinical care.

There is also a strong correlation between results on LARS-score and the CCFFIS (Wexner score) but assessment with CCFFIS may often underestimate LARS [104]. A study

comparing LARS-score with the Memorial Sloan Kettering Bowel Function Instrument (MSK-BFI) also showed good correlation [105].

But there are also limitations in the questionnaire. In one study assessing the clinical application of the LARS-score the results showed that the questionnaire overestimates impact on QoL in some cases and underestimates the impact of severe evacuatory dysfunction [106]. The authors from this study stated in a correspondence article that they recommend including a detailed clinical assessment, use of multiple instruments and a bowel diary when evaluating bowel dysfunction or compare function after different treatment regimes[107]. The LARS-score may also be insensitive for measuring improvement or deterioration when used in a longitudinal context.

Which outcome measure to use for assessment of bowel dysfunction may depend on situation and aim but by using different instruments the difficulties in comparison persists. In an article by Chen el al. focusing on which questionnaire are the best to capture anorectal function after rectal cancer surgery they suggest CCFFIS if the aim is focused assessment of incontinence, MSK BFI for a more in-depth evaluation of LARS and LARS-score for a rapid screening or assessment of LARS [108].



**Add the scores from each 5 answers to one final score.**

| | |
|---|---|
| **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 |
| **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 |
| **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 |
| **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 |
| **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 |
| **Total Score:** | |

**Interpretation:**

| | |
|---|---|
| **0–20:** | **No LARS** |
| **21–29:** | **Minor LARS** |
| **30–42:** | **Major LARS** |

***Figure 6.*** *LARS-score questionnaire. Reprint with permission*

Although the LARS-score has limitations it can, in contrast to more extensive questionnaires, easily be used in clinical practice and if also used in research one can easy establish a link between results in research and the clinical daily care.

*POLARS score*

In order to be able to predict postoperative bowel function prior to surgery Battersby el al. developed a nomogram and online tool named POLARS score (Pre-Operative LARS-score) [109]. The tool includes age (at surgery), gender, TME or PME, tumor height, stoma (yes or no) and preoperative radiotherapy (yes or no) as variables. The tool predicts postoperative LARS group for an individual patient and was developed from a cohort of UK patients and was validated on a cohort of Danish patients.

## 2.2 PATOPHYSIOLOGI

The cause of LARS is thought to be multifactorial including sphincter dysfunction, impaired capacity and compliance of the neorectum, colonic dysmotility and neorectal evacuatory dysfunction [84].

After LAR surgery anal manometry has shown a reduction in mean anal pressure which does not recover over time and reflects dysfunction of the internal sphincter [110-112]. Damage to the internal anal sphincter may be caused by direct structural damage (dissection or insertion of anastomotic device) or nerve damage. It has also been proposed that damage to the rectococcygeus (involved in defecation) muscle during dissection can contribute to anorectal dysfunction.[113] It has been reported that up to 18% who underwent surgery with LAR and a stapled anastomosis had long-term evidence of sphincter injury [114]. In a study comparing 125 patients, which had undergone sphincter sparing LAR, with 25 healthy controls using manometry they found statistically significantly lower- anal resting pressure, maximal squeeze pressure, threshold for first sensation and urge to defecate, maximal tolerance for defecation and a reduced maximal compliance in the LARS group [115]. Similar results have been reported by Inhát et al. from a single center study including 65 patients in which they also found an association between reduced function, measured with manometry, and LARS [116]. In a study by Williamson et al. they compared 11 patients after LAR with 9 controls (after left colonic resection with a colorectal anastomosis) and results showed a lower anal resting pressure and (neo)rectal pressure in the LAR group resulting in a lower anorectal pressure gradient (difference between (neo)rectal and anal resting pressure) [117]. There is also data supporting postoperative impairment of the rectoanal inhibitory reflex [118]. Nevertheless, there are also studies showing no effect on anal sphincter resting- and squeeze pressures [119-121]. Although there are some diversity concerning sphincter impairment after LAR surgery there is data supporting a lower mean anal resting pressure in LAR patients with major incontinence when compared to LAR patients with minor incontinence or normal continence [122]. In a recently published article by Vollebregt using high-resolution anorectal manometry they showed altered anal slow-wave pressure activity in 52.4% of examined LARS patients but only in 5.4% of the healthy controls [123]. To evaluate the clinical significance of this

findings and correlation to different treatment regimes, as well as severity of symptoms, further studies are needed.

The capacity and compliance of neorectum is reduced compared to the normal rectum after rectal cancer surgery. Nesbakken et al. presented, in a prospective study, preoperative and postoperative (12-months follow-up) manometry results for 35 patients after rectal cancer surgery. The results showed reduced postoperative maximum tolerable volume and volume provoking the urge to defecate. There was also a difference in maximum tolerable volume between TME and PME showing a reduced volumes for the TME group.[119] In another study comparing 19 LAR patients (9-12 months postoperatively) to aged and sex matched controls the results showed reduced maximal tolerable volume and compliance in the LAR group [118]. The importance of the rectum acting as a reservoir for stool and the impaired capacity of the neorectum is also supported by the increased risk of bowel dysfunction after TME compared to PME [124].

The neorectum is constructed using the distally available colonic segment. During the mobilization of the colon there is inevitable denervation of the colon and several studies has proposed altered colonic motility, due to denervation, to be one component in the multifactorial etiology of LARS. In a study by Lee et al. using rats, they compared autonomic denervation of the left colon (n=6) to simple manipulation of the left colon (n=6), and showed that denervation resulted in increased motility which probably can be attributed to destruction of inhibitory pathways [125]. The hypothesis of denervation is supported by a study by Koda et al. comparing patients assigned to either short-denervation group or long denervation group depending on whether the superior rectal artery (short) or the inferior mesenteric artery (long) was divided during surgery[126]. When comparing groups, propagated contractions down the neorectum was less common in the long-denervation group (i.e more extensive denervation) whereas spastic minor contractions were more common. Transit time in the neorectum segment was significantly longer for the long-denervation group compared to the short. Keane et al. compared 23 patients which had undergone anterior resection (11 no LARS; 12 LARS) with 9 controls using high-resolution colonic manometry before and after a standardized meal [15]. In the study they showed fewer postprandial antegrade (*p=0.028*) and retrograde (*p=0.004*) propagating contractions in LARS patients compared to control. Comparing no LARS to control only fewer retrograde propagating contraction was recorded (*p=0.047*). The LARS group also had a lower percentage of post-prandial cyclic motor pattern (CMP) compared to control (*p=0.009*). As mentioned earlier it is hypothesized that CMP are involved in the "rectosigmoid brake" preventing rectal filling and this study indicates that LARS patients may have an impairment of this physiological function. The loss of propagating contractions and existence of spastic waves, in anterior resection patients, has also been correlated to urgency and multiple evacuations [127].

A study on meal-induced colonic motility in patients treated with LAR showed that, in patients with high stool frequency postoperatively, the neorectum contracted earlier than in those with normal stool frequency [128].

Using single-photon emission CT/CT scintigraphy Ng et al. compared colonic transit for patients, which had undergone anterior resection, with no LARS vs. major LARS presenting accelerated colonic transit in the major LARS group [129].

The pathophysiology of evacuatory disorder (i.e emptying difficulties), in the context of LARS, has not been studied in detail. One hypothesis, that has been proposed, is the loss of rectoanal coordination [84]. In patients with constipation and evacuatory difficulties impaired rectal contraction, paradoxical anal contraction or inadequate anal relaxation are present indicating impaired rectoanal coordination[130]. Neorectal sensory dysfunction may also play a role in evacuatory impairment among LARS patients [131]. Also structural damage to structures important in defecation process has been suggested. During TME surgery and dissection near the pelvic floor there is a risk of damaging (intentionally for oncological reasons or unintentionally) the hiatal ligament of the levator ani muscle and the rectococcygeus muscle which both play a role in the defecation and damaging these may therefor contribute to emptying difficulties [17].

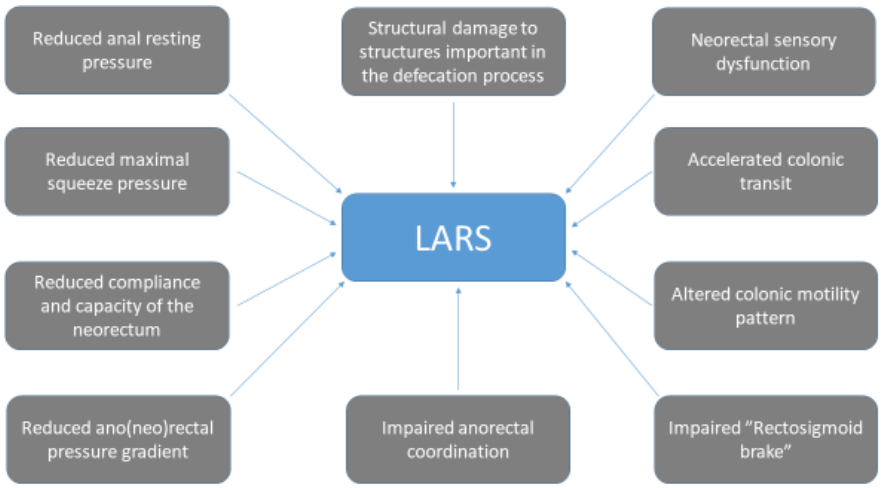



***Figure 6.*** *Proposed factors involved in the pathophysiology of LARS*

## 2.3 PREVALENCE

To be able to compare prevalence numbers an essential condition is the use of the same outcome measure. To measure prevalence of LARS it is essential to state how you define LARS. For the purpose of this review LARS is defined according to the LARS-score questionnaire [91]. There is some data, although scarce, supporting that functional bowel symptoms improves during the first 12 months after surgery, before stabilizing [111, 124]. Studies focused on longitudinal long-term evaluation is lacking. This does not mean that

LARS symptoms disappear over time. Chen et al. reported 46% major LARS after a median follow-up of 14.6 years [132].

In 2018 the first normative data for LARS (using the LARS-score questionnaire) was published [133]. In this study a random sample of 3440 age and sex stratified individuals from the Danish general population were approached and 1875 responded (response rate 54.5%). In the age group 50 to 79 years, which the authors considered the most relevant in rectal cancer research, the response rate was 70.5%. Besides the LARS-score questionnaire the participants were also asked if they had a physical disease (yes or no). In some age groups the response rate was low and the risk for selection bias is evident with the risk of overestimating the true level of bowel dysfunction in the general population. The prevalence of major LARS, in the total cohort of responders, was 15.0% for females and 9.9% for men. In the age group 50-79 years 18.8% of females and 9.6% of men experienced major LARS. Multivariable statistical analysis showed that female sex (OR 1.6, 95% CI 1.2-2.2) and presence of a physical disease (OR 2.2, 95% CI 1.6-2.9) was associated with major LARS. Incontinence for flatus, fragmentation and urgency were statistically significantly more frequent among females, compared to men.

Since then, two additional studies have presented normative data for LARS, both from the Netherlands. The first study approached 600 patients who visit the outpatient clinic because of general or surgical indications [134]. The response rate was 83.5% and major LARS was observed in 15%, minor LARS 14% and no LARS in 71%. In females major LARS was observed in 18.9% and in men 11.4%. Female sex was associated with major LARS (OR 1.82, 95% CI 1.10-3.01). Incontinence for flatus and urgency were significantly more frequent among females. Since the presence of a physical disease was associated with major LARS in the previous study there is a risk of selection bias and overestimation of the prevalence due to the recruitment strategy in the study design of the present study. The second study used a random sample from cohort (n=1259) representative to the general population of the Netherlands according to sex, age and religion [135]. Data on comorbidities was also collected to be able to perform analysis on association to LARS. The total number of eligible participants or response rate was not presented making the results more difficult to assess. In the cohort, major LARS was observed in 12.2% (13.2% females; 10.9% men). In the subgroup with comorbidity the prevalence of major LARS was 19.7% (8.9% in group without comorbidity). In univariable analysis the presence of irritable bowel syndrome and diabetes mellitus were associated with major LARS (OR 5.38, 95 CI 2.89-9.99; OR 3.68, 95% CI 2.2-6.16 respectively). Previous vaginal birth in females showed no association major LARS in either of the studies from the Netherlands.

The only Swedish normative data on LARS was published in 2020 as part of the QoLiRECT study [136]. In this study a reference population was used which answered questions regarding bowel function but without using the LARS-score questionnaire. This study reported a prevalence of major LARS-like symptoms in 8% (10% women; 6% men).

| Study | Sex / Gender | Major LARS % |
|---|---|---|
| **Juul et al.[133]** | Male | 9.9 |
| | Female | 15.5 |
| **van Heinsbergen et al.[134]** | Male | 11.4 |
| | Female | 18.9 |
| **Al-Saidi et al. [135]** | Men | 10.9 |
| | Female | 13.2 |

***Table 2.*** *Normative data, using LARS-score, on the prevalence of major LARS*

As previously discussed, there has been a historical diversity in the reporting of bowel dysfunction after rectal cancer surgery and many studies did not use a validated instrument and instead only reporting prevalence of different symptoms [85]. Many studies were also small in numbers regarding participating patients. The proportion with fecal incontinence has a reported rage between none to 71% [84, 121, 137]. In a systematic review from 2011 Scheer et al. they reported prevalence for different symptoms with incontinence in for solid feces in 0-40%, incontinence for flatus in 9-76%, emptying difficulties in 2-85%, fragmentation in 6-88% and urgency in 0-69% of patients after rectal cancer surgery [138]. Pooled analysis of the proportions in the same study showed incontinence in for solid feces in 14%, incontinence for flatus in 37%, emptying difficulties in 55%, fragmentation in 59% and urgency in 35%.

The largest study reporting prevalence numbers, using LARS-score, included 1087 patients and was conducted in Denmark. All patients which had undergone curative surgery with TME and PME were included. The response rate was 90% and mean follow-up time 54 months [139]. In this cohort only 20% had received neoadjuvant RT or CRT. Major LARS was reported in 41% of the patients and minor LARS in 24%. Another study, also from Denmark, including 193 patients in the results (at 1-year follow-up) reported 58.0% major LARS at 3 months follow-up, declining to 45.9% at one year follow-up [124]. An Italian study including 93 patients in analysis and 13.7 years follow-up presented only 20.5% with major LARS [140]. The study was small and only 110 out of 413 patients that underwent surgery during the chosen time period (1998-2005) were eligible for inclusion and results should be interpret with caution. Another previously mentioned study, with long term follow-up data from the Netherlands, reported data from 242 patients (49% neoadjuvant RT) with major LARS in 46% of patients [132].

There are only a few studies reporting prevalence of LARS from countries outside of Europe. A Chinese study including 220 patients in the results with a mean follow-up time of 40.2 months [141]. In total 54.1% experienced major LARS in the cohort but the patients included was part of a RCT comparing different neoadjuvant treatment strategies which prevents from generalizability to a more heterogeneous cohort treated for rectal cancer. A regional Australian study including only 76 patients showed 37.5% major LARS and a study from Thailand only 17.8 major LARS [142, 143].

The range on prevalence of LARS in the literature range between 36-63% with major LARS [144-148]. A meta-analysis of the prevalence of LARS was published in 2018 and only studies using the LARS-score questionnaire was eligible for inclusion [149]. The estimated prevalence for major LARS in this meta-analysis was 41% and five of the eleven included studies were from Denmark or the United Kingdom and the largest patient numbers were also from these studies. The study concluded that further studies, concerning the prevalence of LARS, from various parts of the world is required, as well as clarifying the pattern of LARS over time.

From the recent QoLiRECT study Swedish prevalence numbers has been reported including 309 patients at 1-year follow-up and 334 patients at 2-year follow-up. The prevalence of major LARS was 63% at 1-year and 46% at 2-years follow-up [136]. In an international cross-sectional study, including four countries, Swedish prevalence numbers were presented with 60% experience major LARS at a mean follow-up time of 5.3 years [150]. The Swedish participants in this study came from two hospitals and one of these acts as a referral center for more locally advanced rectal cancer cases which could increase the risk for selection bias if the aim is to the report the prevalence in a more general cohort of patients treated with anterior resection. In order to get as close as possible to the "true" prevalence one should include patients from at least one region of a country to ensure inclusion of patients both from referral centers and the more general centers, managing rectal cancer patients.

## 2.4 RISK FACTORS FOR LARS

Several risk factors for LARS has been identified but there are also some diverting results. The quality and size of the studies also differs significantly. There is also differences in how the outcome is defined; LARS vs. no LARS or major LARS vs. no/minor LARS or major LARS vs. no LARS which for sure has an impact on the results. Some studies only presented unadjusted OR, making the results more uncertain.

### 2.4.1 Age and gender / sex

In most studies gender (i.e sex) has no statistically significant association to major LARS [124, 132, 142, 143, 145, 151]. Although a number of studies failed to show any association a large Danish study by Bregendahl et al. showed an adjusted higher risk for major LARS in females compared to men (OR 1.35, 95% CI 1.02-1.79) [139]. This study was the largest and there could be an issue with inadequate power in the other studies and thereby failing to show an association. One study reports male gender as a risk factor in adjusted analysis (OR 2.16, 95% CI 1.00-4.64) [152]. Studies focused on specific symptoms within LARS showed no association between gender and incontinence except one study reporting more incontinence among men [153-155]. This is in line with community prevalence number for fecal incontinence showing similar prevalence among females and men [156]. Several studies have not been able to establish an association between age and LARS (i.e bowel dysfunction) [143, 151, 157, 158]. The variable age is also categorized different and sometimes presented as a continuous variable in

some and in other studies stratified into age groups making different studies more difficult to compare. In studies reporting an association, older age seems to be protective. Chen et al. showed, in multivariable analysis, an association between major LARS and age ≤75 years at follow-up (OR 2.4, 95% CI 1.1-5.5) [132]. In another study using age at a continuous variable presented an OR of 0.97 (95% CI 0.94-1.0, *p=0.035*) [145]. There is also evidence for age ≤64 years at surgery and an increased risk for major LARS [139]. Kupsch et al. showed similar results with an association to younger age and LARS in general and not to major LARS separately [146]. Only isolated studies presented reversed results, i.e older age and increased risk [140]. A possible explanation for younger age as risk factor could be the fact that the risk for constipation increases with age and the colonic dysmotility in the elderly could be protective [159]. Conversely, there may be a higher risk for incontinence among the elderly due to a worse baseline continence compared to younger, a statement supported by some data [155, 156].

### 2.4.2 Tumor level and TME vs. PME

In many cases, of rectal cancer, the tumor level and oncological considerations makes TME the only option for surgical treatment but in higher tumor levels PME may be considered. Due to this fact TME vs. PME highly confounded by tumor level.

There is some evidence for an association between low tumor level and major impairment of bowel function. Two studies showed data that tumor level ≤5 cm and ≤6 cm was associated with major LARS and impaired bowel related QoL, respectively [157, 160]. Another study (n=93 in analysis) showed a significantly higher proportion of LARS in tumors levels <5 cm, 5-10 cm compared to >10 cm and conversely a higher proportion of no LARS in tumor level >10 cm [140]. Other studies failed to present an association [149].

Accordingly, there is evidence that TME is associated with worse bowel function compared to PME [139, 145, 146]. In a study, using MRI to measure the length of the remnant rectum in patients treated with surgery alone, a clear association between shorter length and the risk for major LARS was reported. In the same study the same association was not present in patient treated with neoadjuvant CRT and the authors concluded that the functional benefits from a larger remnant rectum is lost in the irradiated rectum [147]. Nevertheless, in a study by Sun et al. the anastomotic height (cm) had an adjusted OR of 0.74 (95% CI 0.63-0.88) indicating that a higher anastomotic level seems to be protective [141].

### 2.4.3 Defunctioning stoma and time to stoma reversal

There are some studies reporting defunctioning stoma as a risk factor for LARS and other studies failing to present a statistical significant association. Gadan et al. reported

functional outcomes from a RCT in which patients were randomized to defunctioning stoma or no stoma [161]. The primary endpoint in this RCT was symptomatic anastomotic leakage. The original study included 234 patients and functional results was only presented in 87 patients. Statistical significant differences, in favor of no stoma, were seen in incontinence for flatus and liquid stool but no differences in frequency, clustering, urgency or proportion with major LARS (although mean LARS score was higher in the defunctioning stoma group). In non RCT studies many failed to show an association in adjusted analysis (if performed). In a prospective multicenter study by Sandberg et al. the adjusted RR (adjusted for tumor level) for major LARS (vs. no/minor LARS) comparing defunctioning stoma vs. no defunctioning stoma was 1.77 (95 % CI 1.27-2.46) [136]. Sun et al reported an OR 2.59 (95% CI 1.27-5.30) in adjusted model (adjusted for neoadjuvant therapy, tumor level, height of anastomosis and anastomotic leakage) [141]. A study by Wells et al. used a broad definition of LARS stating that if one or more out of six symptoms were present it was defined as LARS [162]. Using this questionable definition an adjusted association between defunctioning stoma was reported.

In four studies including between 129 to 184 patients defunctioning stoma was associated to major LARS in unadjusted analysis but failing to show any statistical association in adjusted analysis [143, 145, 147, 152]. Another four studies including between 64 to 142 patients failed to show even an unadjusted association [140, 142, 144, 157].

Two meta-analysis were published in 2020, one including two studies and the other including seven studies. In pooled analysis of the crude ORs from the individual studies both showed a statistical significant association between defunctioning stoma and major LARS (OR 2.84, 95% CI 1.70-4.71; OR 1.96, 95% CI 1.10-3.48) [163, 164]. The quality of a meta-analysis is depending on the quality of the included studies and adjustment (or lack of) for potential confounders may have influenced the results.

In some studies, time to stoma reversal seems to have an association with major LARS (i.e longer time to reversal the greater the risk). Sturiale et al. presented significantly longer median time to stoma reversal in the major LARS group compared to no and minor (*p=0.0002*) but performed no adjustments [140]. In other studies, using time as a continuous variable, showed no statistically significant differences [141, 145, 152]. Hughes et al. reported an adjusted OR for no stoma at 6 months of 0.1 (95% CI 0.1-0.3) and OR for ileostomy closed after 1 year 2.8 (95% CI 0.7-10:5). The only RCT on the subject was published by Keane et al in 2019 [165]. In this study they compared early closure (8-13 days) to late closure (after 12 weeks) and the primary endpoint was rate of complications. The functional results presented from this study had a median follow-up of 49 months and showed no significant differences in proportions of LARS or major LARS between the groups according to the LARS score. In the MSKCC Bowel Function Instrument the late closure group scored worse on the urgency and soiling subscales. Since the early closure group had their stoma reversal within 8-13 days, regarding functional outcome, this group could be considered equal to no defunctioning stoma. In one of the above mentioned meta-analysis, concerning defunctioning stoma or not, time to stoma reversal was also evaluated. In the pooled unadjusted analysis, the mean time to

stoma reversal was 2.39 months longer in the major LARS group compared to the no LARS group [164].

### 2.4.4 Neoadjuvant radiotherapy

In the literature there is strong evidence for an association between neoadjuvant RT and major LARS / significantly impaired bowel function [124, 139-147]. Before the introduction of the LARS score questionnaire a systematic review and meta-analysis by Loos et al. revealed in pooled analysis a significantly higher rate of stool incontinence after neoadjuvant (C)RT and TME compared to TME alone (RR 1.67, 95% CI 1.36-2.05) [166]. This was in line with the results from manometric studies, included in analysis, showing reduced mean anal resting pressures and maximum squeeze pressures. Pollack et al. analyzed a subgroup from two RCTs (Stockholm I and II trials) with focus on anorectal function in relation to RT [167]. The study included 21 patients treated with RT and surgery and 43 with surgery alone. The results showed significantly more scarring of the anal (examined with endoanal ultrasound) sphincters among the irradiated as well as lower anal resting- and squeeze pressures. The irradiated patients also experienced significantly more fecal incontinence, soiling and more bowel movements. A strong association to major LARS was reported by Chen et al. (OR 3.0, 99% CI 1.3-6.9) [132].

In a study by Qin et al. they evaluated the thickness of the rectal wall, obturator internus muscle and levator ani with MRI before and after RT [157]. The results showed that thickening of the rectal wall post-RT had an OR for major LARS of 9.14 (95% CI 2.79-29.95). In the same study they compared neoadjuvant treatment with chemotherapy to CRT showing an association between CRT and major LARS, illustrating that RT is probably responsible for the main negative effect on bowel function. Concerning different RT regimes, no significant difference between short-course RT and long-course (C)RT was reported in a large study from Bregendahl et al. [139].

Battersby et al. reported that neoadjuvant RT is associated with impaired bowel related QoL (adjusted OR 1.67, 95% 1.16-2.42) [160].

In a study describing functional outcome in patients treated with CRT and then followed with the watch and wait program reported major LARS in 33% of patients, a proportion which is much higher than normative data [133, 168].

### 2.4.5 Chemotherapy

In the neoadjuvant setting chemotherapy is rarely given as the sole treatment, instead combined with RT, concomitant or administered prior or after RT depending on disease stage and treatment protocol. A study, excluding patients which had received neoadjuvant RT and compared neoadjuvant chemotherapy and surgery to surgery alone, showed no

differences in mean LARS score between the groups at 6 months of follow-up. Other studies confirm these results [136, 160]. Ekkarat et al. present an unadjusted OR of 3.37 (95% CI 1.07-10.60) for major LARS if treated with chemotherapy (not specified if pre- or postoperative) [143]. In the adjuvant setting there are occasional studies indicating an association between adjuvant chemotherapy and major LARS [145] and in a recently published meta-analysis adjuvant chemotherapy had an OR of 1.53 (95% CI 1.53-2.27) for LARS [169].

### 2.4.6 Type of anastomosis

To improve the capacity of the neorectum several different techniques can be used. A meta-analysis compared colonic J pouch, side-to-end, tranverse coloplasty and straight anastomotic techniques concluded that colonic J pouch, side-to-end and transverse coloplasty lead to better functional outcome for the first year after surgery [170]. The same results were seen in a prior Cochrane systematic review from 2008 [171]. A more recent meta-analysis comparing colonic J pouch to side-to-end showed comparable results between the techniques [172].

### 2.4.7 Anastomotic leakage

Anastomotic leakage is probably a strong risk factor for major functional bowel impairment. Due to relative low incidence of anastomotic leakage and the fact that a significant proportion of patients with leakage are left with a permanent stoma many studies probably lacking power to show an association [124, 132, 140, 144, 157]. The large study from Bregendahl et al. presented a crude OR for major LARS of 2.44 (95% CI 1.14-5.22) but failed to show significant association in adjusted analysis (OR 2.06, 95% CI 0.93-4.55) [139]. Sun et al reported a crude OR for major LARS of 3.23 (95% CI 1.29-8.11) and a adjusted OR of 2.63 (95% CI 0.99-6.95) [141]. In a study by Kim et al they used propensity score matching analysis and showed an adjusted OR for major LARS of 6.39 (95% CI 2.11-19.39) comparing anastomotic leakage grade B/C (therapeutic intervention needed) to no leakage/grade A (no intervention needed) [173]. A meta-analysis including six studies showed a pooled OR for LARS of 2.19 (95% CI 1.45-3.31) comparing anastomotic leakage to no leakage [169].

### 2.4.8 Surgical approach

It can be hypothesized that functional outcomes may differ between TaTME, open-, laparascopic- and robotic-TME due to superior possibilities for nerve-preserving surgery in robotic through optimized visualization and exact dissection. However, high quality evidence is scarce. In a recently published systematic review and meta-analysis they compared the different surgical approaches in relation to functional outcome [174]. In this study they

compared proportions in the three LARS groups between the different techniques but only one relevant study including functional results following robotic surgery was identified resulting in a significantly skewed number of representing participants for each group (TaTME n=163, open n=5039, laparascopic n=165 and robotic n=71). In the results robotic surgery had a significantly lower proportion of major LARS indicating overall better anorectal function compared to laparascopic, open and TaTME. Moreover, TaTME was reported having significantly less LARS than open surgery.

Due to the lack of evidence for robotic surgery further high quality studies is needed to confirm these results. Until then, the results should be interpreted with caution.

### 2.4.9 Summary

In a review article by Garfinkle and Boutros, concerning predisposing factor and treatment of LARS, they propose a structural grading of risk factors based on the strengths of the underlying evidence [175]. High association was considered for neoadjuvant RT, low tumor level (or anastomotic height) and TME (vs. PME). A moderate association for history of fecal diversion (i.e defunctioning stoma), history of anastomotic leakage and extremes of age. A weak association for female sex and higher comorbidity burden.

Identifying the potential risk factors for impaired bowel function is of greatest important to be able to improve functional outcomes and incorporate, the perspective of function, when choosing the appropriate treatment regime and evaluation of new treatments.

## 2.5 LARS AND QUALITY OF LIFE

Previous studies have shown an association between the QoL and the severity of LARS. One of the first studies concerning the association between LARS and QoL was published by Juul et al. in 2014 [150]. In this international cross-sectional study four countries contributed with a total number of 796 patients in analysis and the mean follow-up time since surgery was 5.6 (SD 2.1). They concluded that “the quality of life in patients who have had rectal cancer is closely associated with the severity of the low anterior resection syndrome”. In the study they used the EORTC QLQ-C30 instrument for measurement of QoL (described in detail below). In the study the major LARS group had a mean score ($p<0.001$) worse than the mean score in the no LARS group for the global health status / QoL subscale which may be considered the most important QoL aspect. The same difference was seen in all selected subscales except constipation. Similar results has been reported from other studies also [124, 132].

The problem with most studies analyzing an association between LARS and QoL is that the study designs prevents from evaluation of causality. There are no prospective cohort studies evaluation QoL preoperatively with a follow-up measurement postoperatively.

Battersby et al used an anchor question assessing to which extent patients experienced their bowel related QoL (BQoL) [109]. In this study the mean LARS score of 34 points corresponded to major BQoL indicating that patients experienced that bowel function had a substantial direct effect on QoL.

### 2.5.1 EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 questionnaire

This instrument contains 30 items that generates 9 multi-item scales: 1 global health status / QoL scale, 5 functional scales (physical-, role-, emotional-, cognitive- and social functioning), 3 symptom scales (fatigue, nausea and vomiting, pain) and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). The generated score for each scales and single items ranges from 0-100. A high score on the global health status / QoL and functional scales represents a high level of QoL and functioning. Conversely, a high score on the symptom scales and single items is equivalent to a high grade of symptoms [176]. The score is generated using s specific formula described in the EORTC QLQ-C30 scoring manual [177]. First you calculate a *RawScore*, including the individual score for each item which is then divided by the number of included items generating a mean score of the component items. A linear transformation formula (different depending if functional scale or not) is used to standardize the *RawScore* into scores ranging between 0-100.

The first version of EORTC QLQ-C30 was described by Aaronson et al. in 1993 [176]. The questionnaire was a development from the first generation core questionnaire which was developed in 1987. To the core questionnaire there are several additional available modules for specific types of cancer. The study for development of the questionnaire included 346 patients from 13 different countries (including Sweden). Only lung cancer patients were selected for inclusion motivated by: "(a) The high incidence of the disease would facilitate efficient patient accrual, and (b) the rapid progression of the disease would permit an examination of the responsiveness of the questionnaire to (i.e, its ability to reflect) changes in health status within a relatively compressed time frame" [176]. The results showed good acceptability for the questionnaire. Further, the development process included multitrait scaling (examine whether individual item could be aggregated into a more limited number of subscales), validity checking (inter scale correlation, known-groups comparison and responsiveness to change) and reliability (assessing internal consistency).

When interpreting cross-sectional differences in scores statistically significant differences are not by definition clinically relevant. Cocks et al. has provided guidelines for interpretation of clinically relevant differences. For cross-sectional differences in mean scores the differences are divided into trivial, small, medium and large, according to clinical relevance. Trivial differences were used to describe differences unlikely to have any clinical relevance [178, 179].

The EORTC QLQ-C30 is available in several different languages including Swedish. All translations involve two native speaking for the language in question and also fluent in the original language [177].

Reference values for EORTC QLQ-C30 has been published for a random sample of the Swedish population [180]. The sample was frequency-matched according to age and gender to match the distribution of upper gastrointestinal cancer. The overall participation rate was 70.5% which was considered acceptable but there is always a concern with normative data that the patients with impaired QoL could be more likely to answer the questionnaire.

## 2.6 TREATMENT OF LARS

Treatment of LARS aims to reduce symptoms and there is no definitive treatment. The regional treatment program for Stockholm / Gotland for LARS mainly consists of dietary regimes, treatment with bulky agents and loperamide [181].

There is some evidence for the benefit of pelvic floor rehabilitation (PRF) in patients with LARS showing better functional outcome (mainly continence measured) after PRF [182]. However, several randomized trials have recently been registered with the aim of evaluating the role of pelvic floor rehabilitation in the treatment of LARS, hopefully increasing the level of evidence [183-185].

Kim et al. reported, in a retrospective review, some benefits of biofeedback therapy in patients with LARS [186].

Sacral nerve stimulation (SNS) can be used for patients with incontinence and has been studied also for patients with LARS after anterior resection. A systematic review, including 7 studies (a total of 43 patients included), showed that 94.1% of patients that after peripheral nerve evaluation had a definitive implantation (34 patients) experienced improvement of symptoms [187]. In a more recent systematic review and meta-analysis these results were confirmed. In the meta-analysis using CCFFIS as outcome measure 7 studies were included and for LARS-score 3 studies (no RCTs) [188]. The pooled analysis revealed statistically significant improvements in both outcome measures with a reduction of 11.2 (mean difference) in CCFFIS and 17.8 for LARS-score. It should be noted that SNS implantation is usually a two-stage procedure including a first stage of evaluation before a selection is made and only those which experienced a significant improvement are chosen for permanent implantation. Therefor there is a significant risk of selection bias in the results.

Percutaneous tibial nerve stimulation (PTNS) has also been evaluated in LARS patients with encouraging results [189]. In a multicenter, double blinded RCT by Marinello et al. PTNS was evaluated. 46 patients were randomized (1:1) to either PTNS or sham therapy [190]. Primary outcome measure was LARS-score and the results showed that in both groups

a reduction in LARS-score was reported at 1 month of follow-up but only the intervention group showed a reduction (compared to baseline LARS-score) at 12 months of follow-up. However, no statistically significant differences between the groups were reported at any of the time points of follow-up.

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter affecting both central- and enteric nervous system. In a RCT a 5-$HT_3$ receptor antagonist (Ramosetron ®) was evaluated as a treatment for LARS [191]. Only male patients were included (the drug only approved for males in Korea) and were randomized to either Ramosetron (n=48) or conservative treatment (n=50). The primary outcome was differences in proportion of major LARS at 4 weeks of follow-up. The result showed no differences in proportion of major LARS but a statistically significant difference at follow-up (*p=0.004*). Benefits of 5-$HT_3$ receptor antagonist has also been reported by Inagaki et al. in a prospective study in males with LARS [192].

The use of probiotics has been evaluated in one RCT showing no improvement in bowel function [193]. In this study patients were randomized to either probiotic therapy or placebo after they had undergone stoma reversal and evaluated after 4 weeks of treatment.

Transanal irrigation (TAI) is a treatment used to assist the evacuation of feces from the bowel introducing water to bowel through the anus. Regular irrigation aims to ensure emptying of the left colon and rectum/neorectum [194]. It is unclear if the result of washout is achieved by simple mechanical washout or by colonic mass movements induced by the enema. The estimated risk of enema-induced perforation is less than 0.002 percent [195]. There is no available estimated perforation risk for LARS patients. In 1989 Iwama et al. published data including 10 patients treated with TAI after low anterior resection and in all cases the frequent urge to defecate disappeared [196]. A qualitative study suggested that TAI, for patients with LARS, is an acceptable method of treatment [197]. Koch et al. reported that 57% of patients became completely (pseudo-) continent after using TAI [198]. A prospective study, including 14 patients with LARS, showed a significant decrease in number of defecations (both day and night), improved incontinence score and QoL [199]. Martellucci et al. reported, in a prospective study including 27 patients (at end of follow-up) that the median LARS-score was reduced from baseline 35.1 to 12.2 at 6 months of follow-up [200].

Despite encouraging results for TAI there has been a lack of RCTs evaluating the benefits of TAI. Only one RTC has been published by Rosen et al. evaluating TAI as a prophylactic treatment [201, 202]. The study reports 12 months of follow-up data comparing TAI to control (best supportive treatment). In the intervention group the TAI treatment was initiated shortly after stoma reversal. No intention to treat analysis was performed, instead there were the nine patients in the TAI group, which decided to stop the treatment, analyzed in the control group. At 12 months of follow up 10 patients were analyzed in the TAI group and 21 in the control group. Results showed lower median maximum number of bowel movements day and night in favor of the TAI group (*p=0.018* and *0.004* respectively). No statistically significant differences were seen in Wexner score, LARS-score or SF-36 questionnaire (mental and physical component).

No RCT evaluating TAI as a treatment (not prophylactic) for LARS has been published.

There also sporadic studies evaluating antegrade enema via a percutaneous cecostomy showing improvement in both LARS score and Wexner score [203].

## 2.7 OTHER FUNCTIONAL OUTCOMES

Both urinary dysfunction and sexual dysfunction are relatively common as a consequence of rectal cancer treatment. Both the surgery and other treatment (i.e RT) can cause damage to the autonomic nervous system involved in urinary and sexual function. In a review by Lange and van de Velde potential associations between autonomic nerve damage and impaired urinary and sexual function are discussed [204]. During surgery the sympathetic nerves are at risk during central arterial ligation, presacral dissection and venterolateral dissection of the mesorectum. Parasympathetic nerves are at risk during deep dissection laterally of the mesorectum. RT can also cause nerve damage. Sympathetic nerve damage may lead to urge incontinence as a result of detrusor instability and reduced capacity while parasympathetic nerve damage may lead urinary emptying difficulties. In men sympathetic nerve damage may lead to absent, retrograde or painful ejaculation while parasympathetic damage may lead to impotence. The mechanism for the association between autonomic nerve damage and female sexual dysfunction is still unclear. In theory sympathetic nerve damage may lead to lubrication problems, impaired sensation of the internal genitalia and orgasm problems while parasympathetic may lead to reduced labial swelling response.

Long-term urinary incontinence has been reported in 38.1% of patients after rectal cancer surgery (72% normal continence preoperatively) and difficulties with bladder emptying in 30.6% (65% with normal function preoperatively). Independent risk factors for incontinence were preoperative incontinence, female gender and for emptying difficulties peroperative blood loss and autonomic nerve damage [205]. A Swedish study recorded baseline prevalence (before treatment) and 1 year of follow-up prevalence of urinary dysfunction [206]. At baseline prevalence of urinary incontinence was 14% for women and 8 % for men increasing to 29% and 14% respectively, at 1 year of follow-up. Bladder emptying difficulties had a baseline prevalence of 28% in women and 43% in men and at 1 year of follow-up the prevalence was 41% and 49% respectively. However, it seems to be an improvement in symptoms over time [207]. In a large Danish cross-section study including only males (5710 patients, response rate 52.8%) they compared urinary dysfunction between patients after colon cancer surgery to patients after rectal cancer surgery [208]. In the results they found that both scores on voiding (emptying) and incontinence were significantly higher after rectal cancer surgery indicating a higher level of impairment. Similar results were reported for women by the same research group [209]. Both studies showed an association between urinary dysfunction and impaired QoL.

Sexual dysfunction has been reported in up 70% postoperatively in rectal cancer patients [210]. But, as in studies regarding urinary dysfunction, baseline data (pre-treatment) is lacking in many studies. Sexual dysfunction is probably multifactorial and sexual dysfunction is not necessarily equal to a sexual physiological dysfunction [211]. One study which included baseline measurements was published by Stamopoulos et al. in 2009 [212]. Participants were evaluated with International Index of Erectile Function (IIEF) at baseline (n=56), 6 months (n=34) and 12 months (n=12) of follow-up. The results showed significant difference in total IIEF-score at both 6 and 12 months of follow up when compared to baseline, indicating treatment-related sexual dysfunction. Hendren et al. reported a reduction in the proportion sexually active postoperatively compared to preoperatively (median follow up time 52 months women; 58 months men) [213]. Specific sexual problems that were reported by sexually active women were libido (28%), arousal (20%), lubrication problems (56%), orgasm problems (24%), dyspareunia (36%) and sexual problem due to worry/embarrassment (8.7%). Sexually active men reported libido (35.4%), impotence (13%), partial impotence (40.4%), orgasm problems (28.3%), ejaculation problems (36.2%) and sexual problems due to worry/embarrassment (15.2).

# 3 RESEARCH AIMS

The **overall aim** was to gain knowledge about Low Anterior Resection Syndrome to better understand and manage patients post rectal cancer surgery.

**Specific aims**:

I. To evaluate whether post surgery bowel dysfunction, measured with the LARS-score, changed over time and if an association to impaired QoL persisted.

II. To investigate the prevalence of LARS in a large population-based Swedish cohort and the association to QoL.

III. To assess if a defunctioning stoma and time to stoma reversal were associated with major LARS in a population-based cohort of Swedish rectal cancer patients.

IV. To evaluate transanal irrigation (TAI) as a treament strategy for LARS.

# 4 PATIENTS AND METHODS

| | | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|---|
| **Study period** | **Exposure** | Exposure 2001-2009 | Exposure 2007-2013 | Exposure 2007-2013 | 2017-2020 |
| | **Outcome** | Outcome 2011-2012 and 2016-2017 | Outcome 2017 | Outcome 2017 | 6 and 12 months FU |
| **Design** | | Longitudinal cohort study | Population-based cross-sectional study | Population-based cohort study | Randomized Controlled Trial |
| **Population** | | Study specific Swedish and Danish cohort | Inhabitants of Stockholm / Gotland county | Inhabitants of Stockholm / Gotland county | Stockholm county** |
| **Participants** | | Patients which had undergone anterior resection with anastomosis | Patients which had undergone anterior resection with anastomosis | Patients which had undergone anterior resection with anastomosis | Patients which had undergone low anterior resection with anastomosis |
| **N*** | | 282 | 478 | 430 | 39 |
| **Data sources** | | SCRCR + medical journals + outcome questionnaires | SCRCR + medical journals + outcome questionnaires | SCRCR + medical journals + outcome questionnaires | Medical journals + outcome questionnaires + follow-up phone calls |
| **Outcome measures** | | LARS-score + anchor question BQoL + EORTC QLQ-C30 | LARS-score + CCFFIS + anchor question BQoL + EORTC QLQ-C30 | LARS-score + anchor question BQoL | LARS-score + CCFFIS + 4 study specific questions + EORTC QLQ-C30 |

***Table 3.*** *Overview of patients and methods for study I-IV. Abbreviations: RCT Randomized Controlled Trial, SCRCR Swedish Colorectal Cancer Registry, LARS-score Low Anterior Resection Syndrome score, CCFFIS Cleveland Clinic Florida Fecal Incontinence Score, BQoL Bowel related quality of life, EORTC European Organization for research and treatment of Cancer. N*=Total number of patients included in final analysis. **Patients included from South General Hospital (SöS), Danderyd Hospital and Karolinska University Hospital.*

## 4.1 STUDY I

In 2014 an international cross-sectional study was published by Juul et al. including patients from Sweden, Denmark, Spain and Germany [150]. The aim for this study was to investigate the association between QoL and LARS. Due to the lack of longitudinal long-term data on LARS this cohort posed an opportunity for a second follow-up. Study I included all patients from the Swedish and Danish cohorts which had been included in the study by Juul et al. Patients from Spain and Germany were not included for logistical reasons. Patients aged ≥18 which had undergone curative rectal cancer surgery with either TME or PME during 2001-2009 were eligible for inclusion. In Sweden patients from two hospitals were invited (Karolinska University Hospital and Ersta Hospital) and in Denmark all alive patients were considered eligible for inclusion. Exclusion criteria were the presence of a stoma and/or known disseminated or recurrent disease at any of the time points. Data regarding patient characteristics and exclusion criteria was retrieved form national databases (SCRCR for Swedish patients) and medical records. The study consisted of two different time points for follow-up, FU 1 and FU 2. Outcome data for FU 1 was collected between March 1, 2011 and April 1, 2012 and for FU 2 during January 2016 for Danish patients and between February 1 and March 31, 2017 for Swedish patients.

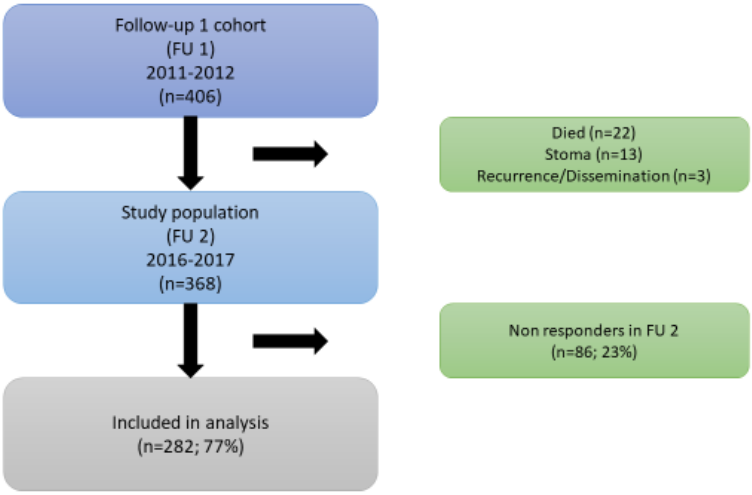



***Figure 7.*** *Flow chart for Study I*

The outcome measures consisted of LARS-score, EORTC QLQ-C30 questionnaire and an anchor question regarding bowel related QoL. The study design provided a basis for one

of the first studies with the potential of providing longitudinal long-term data on LARS and QoL.

### 4.1.1 Statistical analysis Study I

To test differences in patient characteristics between the different LARS-groups, responders vs. non-responders and included vs. excluded *Chi Square* test was used for categorical variables and *Student t test* for continuous variables. Descriptive statistics was presented as frequencies and percentage for categorical variables and with mean and SDs for continuous variables. *Chi Square test* is used for nominal or ordinal data (categorical) and test for differences in proportions between groups. Categories are mutually exclusive meaning that one sample can only add data into one category / level of the variable. The test assumes that the study groups are independent. It is a non-parametric test meaning that it does not assume anything about the underlying distribution from which the sample was taken. [214] *Student t test* (independent t test) is used to compare means between two independent groups. The test is parametric in which it assumes that the dependent variable is approximately normally distributed within each group. The test also assumes equal variances but in many statistical software this assumption is tested and in the output you will get an alternative p-value for unequal variances. [215]

In order to test the main outcome (i.e proportion with major LARS changed over time) the no LARS and minor LARS groups were merged into one group. After dichotomization of the LARS group variable *McNemar´s test* was used to test differences in proportions between FU 1 and FU 2. *McNemar´s test* is a non-parametric test useful in the context of repeated measures and assesses the difference between paired proportions. The test requires a dichotomous outcome variable. In a 2x2 table the test null hypothesis is that the number in the discordant cells are equal. [216]

To test association between LARS-groups and QoL, as well as BQoL at the two different time-points a *linear mixed effect model* was used, including a time interaction term, adjusting for age at test, years since operation, tumor level, T-stage, sex, surgical approach (PME/TME), radiotherapy and chemotherapy. For this study a mean difference ≥10 points in EORTC QLQ-C30 score was considered clinically relevant [217]. Responses on BQoL were divided into three groups in analysis; “Not at all”, “A little” and “Some” / ”A lot”. A *linear mixed effect model* can be used for comparison of means when you have repeated measures. The model allows for observations within a subject to be correlated and both between- and within-subject variability may be estimated [218].

For those patients that changed groups (no/minor LARS and major LARS) between the time-points a separate analysis was performed to assess factors associated with deterioration and improvement. Long term deterioration defined as no/minor LARS at FU 1 and major LARS at FU 2, improvement as major LARS at FU 1 and no/minor LARS at FU 2, stable as being

in the same LARS group at both FU 1 and FU 2 (stable "good" as no/minor LARS at both FU1 and FU 2 and stable "bad" as major LARS at both FU 1 and FU 2). A *multivariable logistic regression model*, including patient characteristics, was used to assess associations to the defined outcomes.

## 4.2 STUDY II

The basis for this population-based cross-sectional study was to use all patients who had underwent curative surgery for rectal cancer between January 2007 and December 2013 in Stockholm Gotland county in order to be able determine the prevalence of LARS in a, clearly defined, Swedish cohort. Patients eligible for inclusion were identified through the SCRCR.

Patients which responded, were >18 years, did not have a stoma or diagnosis of dementia or recurrent disease, were included in analysis (*figure 8*). The LARS-score, CCFFIS, EORTC QLQ-C30 were used as outcome measures. A specific questionnaire concerning presence of a stoma or not was also sent to all eligible patients. Medical records were reviewed for both responders and non-responders according to exclusion criteria. The CCFFIS (i.e CCFIS or Wexner score) was used to acquire a more detailed evaluation of the incontinence part of LARS and to enable comparison to studies evaluating bowel dysfunction prior to the development of the LARS-score. As previously mentioned CCFFIS is one of the most commonly used outcome measure for bowel dysfunction after rectal cancer surgery [85].

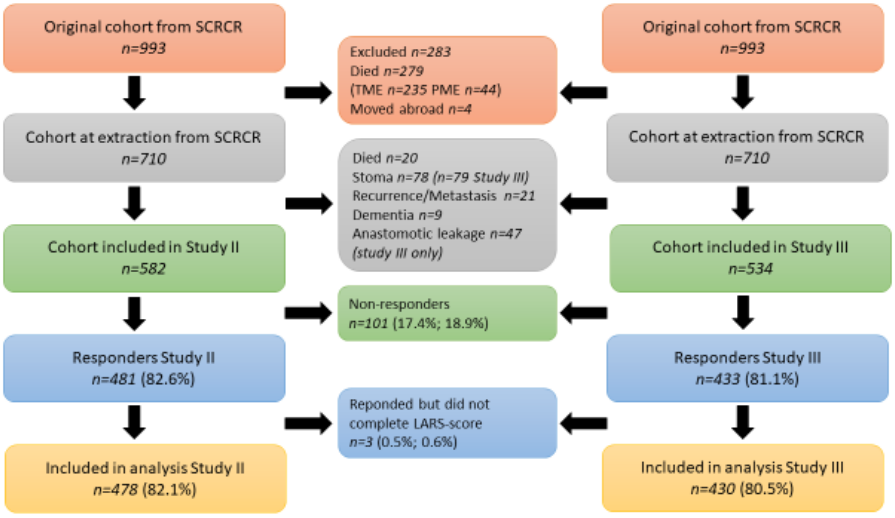



***Figure 8.*** *Flow chart Study II and III*

### 4.2.1 Statistical analysis Study II

*Chi square test* (categorical variables) and *ANOVA* (continuous variables) was used to test for differences in patient characteristics between the LARS groups. *ANOVA* (analysis of variance) can be used to test means between three groups or more and is a parametric test. A significant p-value in *ANOVA* indicates a statistically significant difference between at least two of the groups. To determine which groups multiple pair-wise comparisons are needed. [215] Variance ($\sigma^2$; $\sigma$=standard deviation) is a measurement of the spread between numbers in a data set. Simplified, *ANOVA* can be described as the ratio between variability of the group mean to the overall mean and variability within each group. A high ratio indicates a significant difference. [219] *Chi square test* and *Student´s t test* were used to test differences between responders vs. non-responders and included vs. excluded. ANCOVA is an extension of ANOVA enabling adjusted for covariates (potential confounders) [215]. To explore associations between the different LARS groups and adjusted EORTC QLQ-C30, CCFFIS mean score and BQoL an ANCOVA regression model was used. The covariates included in the model were age (per year), tumor level (per cm), preoperative T-stage, sex, surgical approach (TME/PME), radiotherapy and chemotherapy. Clinically relevant differences in EORTC QLQ-C30 mean score were interpreted according to guidelines provided by Cocks et al. and fractionated into trivial (not clinically relevant), small, medium and large [178]. A EORTC QLQ-C30 summary score was also calculated for this study according to available guidelines [177].

## 4.3 STUDY III

For study III the same cohort was used as in study II *(figure 8)*. The primary endpoint was to evaluate if a formation of a defunctioning stoma and time to stoma reversal were associated with impaired bowel function in the long term perspective. The secondary endpoint was, using the same exposures, the association to bowel related QoL. The inclusion / exclusion criteria were the same as in study II with the exception that patients with an anastomotic leakage were also excluded (n=47). The rationale for this was to only include patients in where a defunctioning stoma or not, was optional. For this study a meticulous review of medical records was done to ensure high quality data on the exposure and covariates. Among the excluded patients an additional patient with stoma at follow-up was identified in study III. Outcome measures used in the study were LARS-score and an anchor question regarding BQoL. A study specific questionnaire concerning the presence of a stoma was also used. If a stoma was present participants were also asked to state, the reason for this, among three different response alternatives.

### 4.3.1 Statistical analysis Study III

*Chi-square test* and *Student´s t test* were used to test variables in patient characteristics between responders vs. non-responders and included vs. excluded. Both univariable and multivariable *binary logistic regression models* were used to test association between exposures (defunctioning stoma vs. no stoma and time to stoma reversal) and outcomes (major LARS and impaired BQoL). Using DAGs (Directed Acyclic Graph) and clinical knowledge about potential confounders a selection was made, for each of the *logistic regression models*, regarding which covariates to include. Results were presented as crude and adjusted ORs with 95% CI. *Binary logistic regression models* require that the dependent variable (outcome) is binary and that observations are independent of each other. The covariates included in the model can be both categorical or continuous. Highly correlated variables should be avoided (multicollinearity) and the model assumes a uniform (particular direction) relationship between predictor variables and outcome variable. [220] In Study III age at operation, gender, neoadjuvant RT, tumor level and surgical method were included in the models for the outcomes major LARS and impaired BQoL. The variable time to stoma reversal was divided into 60-days interval groups using 121-180 days as a reference. The reference group was selected based on clinical experience regarding "normal" time for stoma reversal. Selection of time intervals were made on the basis of not being too short, assuming that small differences in time probably would not have an effect on the outcome and that the number of patients in each group would be too small. Using longer time intervals would increase the variations within groups and potentially dilute the results. Nevertheless, only 4 patients were included in 0-60 days' group reflecting that stoma reversal this early was very rare during the study period. In the model using time to stoma reversal as the exposure variable the covariates age at surgery and adjuvant chemotherapy were included as potential confounders. *ANOVA* was used for comparison of mean time to stoma reversal between the three LARS groups.

## 4.4 STUDY IV

The fourth study was different in design being a multicenter non-blinded RCT. Participating hospitals were South General Hospital (Södersjukhuset), Danderyd Hospital and Karolinska University Hospital. As mentioned the aim was to evaluate transanal irrigation (TAI) as a treatment for LARS. Primary endpoint was differences in bowel function at 12 moths of follow-up and secondary endpoint was differences in QoL. Eligible for inclusion were patients who had undergone TME with a defunctioning stoma between May 2016 and November 2019, aged >18 years, with major LARS, normal endoscopic examination of the anastomosis (defined as no signs of local recurrence, leakage and clinically relevant stenosis) at 1-year follow-up visit and understanding of the Swedish language. Patients with recurrence / metastasis or previous or concurrent other colorectal surgery or no stoma reversal or inflammatory bowel disease were excluded.

Block randomization was used with blocks randomly varying between 4 and 6. For every block 6 sealed paper envelopes were sealed in a larger envelope, representing one block. Blocks including 4 had two blank envelopes in order to reduce the ability to predict the next randomization group. One member of the research team was responsible for the randomization process and was contacted after inclusion of a new participant and performed the randomization. Patients were randomized to either the TAI group or control group (1:1). The TAI group was trained to perform TAI by a urotherapist or a stoma nurse, both familiar with the procedure. The Peristeen™ System (Coloplast Group, Humlebaek, Denmark) was used according to manufacturer´s instructions. Both groups received conservative treatment with medication and support regarding medication. LARS-score, CCFFIS, four study specific questions were used as primary outcome measures and EORTC QLQ-C30 was used as secondary outcome measure. Patients were followed up at 3 (only telephone), 6, 12 months, in which follow-up at 6 and 12 months included both telephone follow up according to a study specific questionnaire and the outcome questionnaires. In the four study specific questions (Q1-Q4) the scale was 1-10 in Q1 and Q2 whereas in Q3 and Q4 (questions related to specific symptoms) the scale was 0-10 where 0 corresponded to *"Do not experience any urgency / fragmentation"*.

### 4.4.1 Statistical analysis Study IV

Due to multiple outcome measures the power calculation became more complicated. At the time of initiating the study the available data, regarding using TAI as a treatment for LARS, was lacking. Based on this two power calculation were performed and an interim analysis, was planned, after 40 patients with completed follow-up. In order to demonstrate a 5 points difference in the LARS-score (with 80% certainty) 34 patients (17 in each group) was needed. In CCFFIS 72 patients (36 in each group) were needed in order to show a 2.9 points difference (with 80% certainty). The interim analysis showed results, strong in favor of TAI, and resulted in a termination of inclusion. Means at baseline was tested with Student´s t test. To compare means, between the groups at the two follow-up time points, a linear mixed effect model was used, including a time interaction term with exposure and adjusted for baseline LARS-score. The time interaction term included in order to be able estimate exposure effect at different time points. Clinically relevant differences in EORTC QLQ-C30 scores were interpreted as described in Study II.

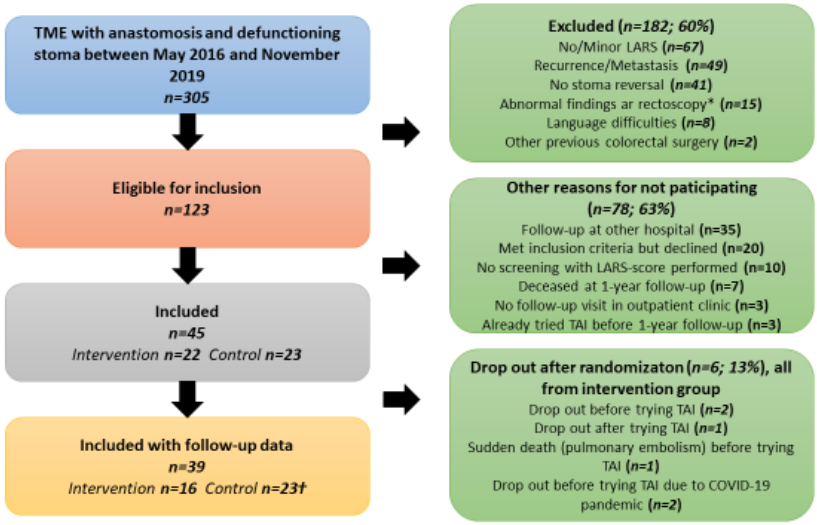



***Figure 9.*** *Flow chart study IV. *Stenosis or defect in anastomosis. †One drop out after 6-months of follow-up and one patient did not respond to the 6-months questionnaires. TME=Total Mesorectal Excision. TAI=Transanal irrigation. LARS=Low Anterior Resection Syndrome.*

The four study specific question regarding bowel dysfunction were validated with a test-retest reliability test including 33 patients which completed the questions at two different time points (1-2 weeks apart) before any intervention was initiated. An intraclass correlation coefficient was calculated for each question showing all through excellent correlation (0.90, 0.92, 0.94 and 0.92 respectively).

An intention to treat approach was used in statistical analysis.

For all studies 5% was set as level of significance and the basis for analysis was separate pre-written study protocols.

## 4.5 ETHICAL CONSIDERATIONS

All studies were approved by the regional Ethical Review Board at Karolinska Institute. All participants included in analysis had given their informed consent. Study I-III were observational studies and had no effect on the patient´s treatment. In Study IV we conducted a structured follow-up according to a protocol including questions concerning adverse effect of the TAI treatment. Patients were also instructed to contact the TAI-instructor if any problems occurred. After completed follow-up, the patients randomized to the control group, were offered an opportunity to try the TAI treatment.

All databases were anonymized and kept separate from the original data, both at secure locations.

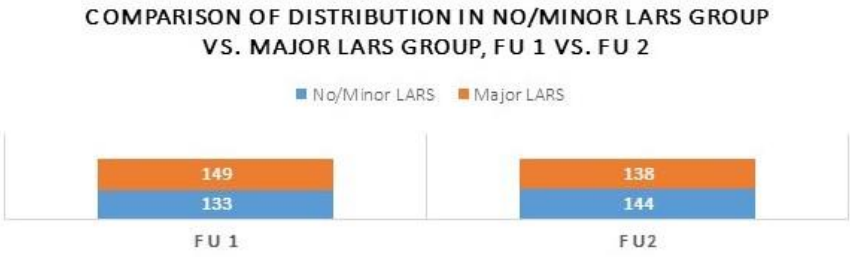
# 5 RESULTS

## 5.1 STUDY I

A total of 282 patients were included in the analysis (49% men, mean age 72.5 at FU 2). The mean follow-up time from primary surgery to FU 2 was 11.1 years (range 7.1-16.1) and between FU 1 and FU 2 5 years (range 4.3-5.9). Divided into LARS groups there were some differences in patient characteristics. In the major LARS group, the patients were younger, had a slightly lower mean tumor level, higher proportion with TME (vs. PME) and a higher proportion with neoadjuvant RT compared to the no and minor LARS groups.

The response rate was 77% and comparison of patient characteristics between responders and non-responders (n=86) revealed that the non-responders were older (at surgery) and had a lower proportion of TME.

The McNemar´s test showed no statistically significant difference in distribution proportions between no/minor LARS and major LARS groups when comparing FU 1 to FU 2 (*p=0.185*).




| | No/minor LARS FU 2 | Major LARS FU 2 | Total (%) |
|---|---|---|---|
| No/minor LARS FU 1 | 104 | 29 | 133 (47) |
| Major LARS FU 1 | 40 | 109 | 149 (53) |
| Total (%) | 144 (51) | 138 (49) | 282 |

***Figure 10.*** *Distribution (number of patients) in LARS groups no/minor LARS and major LARS at both FU 1 and FU 2, including number of patients which changed group. McNemar´s test of marginal homogeneity showed that time effect was not statistically significant on the change between no/minor LARS-group and major LARS-group (p=0.185). FU 1 = Follow-up 1; FU 2 = Follow-up 2. LARS = Low Anterior Resection Syndrome*

Comparing EORTC QLQ-C30 mean scores between no/minor LARS to major LARS groups revealed worse (statistically significant and clinically relevant) QoL in 6 out 15 subscales at FU 1 and in 7 out of 15 at FU 2 (*table 4*). The reversed relationship could not be seen in any of the subscales. A higher LARS score were associated with impaired BQoL. Comparing the response groups regarding BQoL showed a statistically significant difference in mean LARS between all of the groups at both FU 1 and FU 2. (*Table 5*)

| Pairwise comparisons of EORTC QLQ-C30 subscale means by LARS groups at follow up 1 (FU 1) and 2 (FU 2) | | | | |
|---|---|---|---|---|
| | FU 1 No/minor LARS – Major LARS | | FU2 No/minor LARS – Major LARS | |
| QoL scales / items | Mean score differences | p-value | Mean score differences | p-value |
| Global health status/QoL (ql2) | **14** | **<0.001** | **10** | **<0.001** |
| Physical functioning (pf2) | 8 | <0.001 | 8 | <0.001 |
| Role functioning (rf2) | **13** | **<0.001** | **14** | **<0.001** |
| Emotional functioning (ef) | 6 | 0.012 | 4 | 0.11 |
| Cognitive functioning (cf) | 5 | 0.020 | 5 | 0.056 |
| Social functioning (sf) | **10** | **<0.001** | **10** | **<0.001** |
| Fatigue (fa*) | **-12** | **<0.001** | **-14** | **<0.001** |
| Nausea and vomiting (nv*) | -3 | 0.028 | -3 | 0.011 |
| Pain (pa*) | **-11** | **<0.001** | **-10** | **<0.001** |
| Dyspnea (dy*) | -6 | 0.057 | **-12** | **<0.001** |
| Insomnia (sl*) | -9 | 0.009 | -9 | 0.012 |
| Appetite loss (ap*) | -3 | 0.17 | -6 | <0.001 |
| Constipation (co*) | -6 | 0.064 | -9 | 0.006 |
| Diarrhea (di*) | **-20** | **<0.001** | **-21** | **<0.001** |
| Financial difficulties (fi*) | -5 | 0.026 | -2 | 0.50 |

***Table 4.*** *Differences in scales / item means (no/minor LARS group EORTC QLQ C-30 score mean minus major LARS group EORTC QLQ C-30 score mean). Differences that were both statistically significant (p<0,05) and clinically relevant (≥10 p) are presented in bold. ***Symptom scales and items**, a high score equivalent to a high grade of symptoms. In **ql2, pf2, rf2, ef, cf** and **sf** a high score represents a high level of QoL and functioning.*

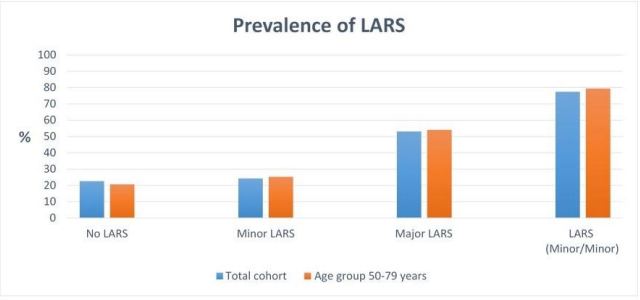
| Mean LARS-score and pairwise comparison of response groups on question on impact of LARS on QoL, FU 1 *versus* FU 2 | | | | |
|---|---|---|---|---|
| Impact on QoL response groups | Mean LARS-score (FU 1) | Mean LARS-score (FU 2) | Mean score difference; FU 1 *vs.* FU 2 (p-value) | |
| "Not at all" (1) | 15.2 | 17.3 | -2.1 (0.231) | |
| "A little" (2) | 26.4 | 26.8 | -0.4 (0.731) | |
| "Some" / "A lot" (3) | 33.5 | 32.2 | 1.3 (0.244) | |
| | | | | |
| Response group vs. response group | Differences in mean LARS-score between groups FU 1 | p-value | Differences in mean LARS-score between groups FU 2 | p-value |
| 1 vs 3 | 18.3 | <0.001 | 14.9 | <0.001 |
| 2 vs 3 | 7.1 | <0.001 | 5.4 | <0.001 |
| 1 vs 2 | 11.2 | <0.001 | 9.5 | <0.001 |

***Table 5.*** *Comparison of mean LARS-score for each different response alternatives on question "Overall, how much does your bowel function affect your quality of life?".*

Results for predicting factors for stable dysfunction, long-term deterioration or improvement of LARS symptoms are not presented here but are available in the full article.

## 5.2 STUDY II

Out of a total of 993 patients which underwent anterior resection during the selected time period (2007-2013) 478 patients were included in the final analysis (*figure 8*). In order to evaluate potential selection bias due to exclusion and non-responders, a comparison to included patients, was made regarding patient characteristics. There were no statistically significant differences between included and excluded. The only difference between responders and non-responders was that the non-responders had a slightly lower mean tumor level (10.0 vs. 10.6; *p=0.048*). The prevalence of LARS is presented in *figure 11*, including prevalence numbers for the age-group 50-79 years enabling better comparison to normative data [133]. The overall prevalence of LARS was 77.4% and for major LARS 53.1%.




| LARS group | Total cohort, n = 478 ( %) * | Age group 50-79 years n = 412 (%) |
|---|---|---|
| No LARS | 108 (22.6) | 85 (20.6) |
| Minor LARS | 116 (24.3) | 104 (25.3) |
| Major LARS | 254 (53.1) | 223 (54.1) |
| Minor + Major LARS | 370 (77.4) | 327 (79.4) |

***Figure 11.*** *Prevalence of LARS in the selected cohort*

The mean LARS score for the three different LARS groups was associated to a difference in CCFFIS. The major LARS group had a mean LARS score of 35.6 and the corresponding CCFFIS was 10.5. For the minor and no LARS group the mean scores were 26.1 vs. 5.2 and 9.9 vs. 3.2, respectively. When comparing score differences in CCFFIS, between LARS groups, there were statistically significant differences between all groups. A higher mean score was also clearly associated to impaired BQoL (*table 6*)

| **Mean LARS-score and pairwise comparison of response groups on question concerning impact of bowel function on QoL** | | | | | |
|---|---|---|---|---|---|
| **Response to question (number)** | **No. of patients *** | **LARS-score†** | **Group vs. Group** | **Score difference†** | **p-value††** |
| **"Not at all" (1)** | 52 (10.9) | 11.4 (8.6, 14.1) | **2** vs.**3** | 8.8 (7.2, 10.4) | **<0.001** |
| **"A little" (2)** | 204 (42.7) | 24.3 (22.4, 26.2) | **1** vs.**2** | 12.9 (10.3, 15.5) | **<0.001** |
| **"Some"/"A lot"(3)** | 222 (46.4) | 33.1 (31.2, 34.9) | **1** vs **3** | 21.7 (19.1, 24.3) | **<0.001** |

***Table 6.*** **Values in parentheses are percentages.† Values are mean (95% CI).†† ANCOVA regression model adjusted for age, sex, tumor level, preoperative T-stage, type of operation, neoadjuvant RT and neoadjuvant chemotherapy. QoL= Quality of Life. Statistically significant p-values in bold.*

Comparing mean EORTC QLQ-C30 score for the different LARS groups the results showed only two subscales in where no LARS scored statistically significant and clinically relevant worse than minor LARS. Minor LARS scored worse in 11 out of 15 subscales than major LARS, whereas no LARS scored worse than major LARS in all subscales (summary score included) except financial difficulties. (*table 7*)

| Pairwise comparisons of EORTC QLQ-C30 subscale means by LARS groups | | | | | | |
|---|---|---|---|---|---|---|
| **Subscale** | **No LARS – Minor LARS** | | **Minor LARS – Major LARS** | | **No LARS – Major LARS** | |
| | **Mean score differences (95% CI)** | **p-value** | **Mean score differences (95% CI)** | **p-value** | **Mean score differences (95% CI)** | **p-value** |
| **Summary score** | 2.3 (-1.6, 6.3) | 0.246 | 9.5 (6.1, 12.9) | <0.001 | **11.8** (8.2, 15.4) | **<0.001** |
| **Global health status/QoL (ql2)** | 4.5 $^{S}$ (4.5, 10.6) | 0.140 | **12.4** $^{M}$ (7.3, 17.6) | **<0.001** | **17.0** $^{L}$ (11.5, 22.4) | **<0.001** |
| **Physical functioning (pf2)** | 3.9 $^{T}$ (-1.2, 9.1) | 0.136 | **5.2** $^{S}$ (0.8, 9.6) | **0.021** | **9.1** $^{S}$ (4.4, 13.8) | **0.001** |
| **Role functioning (rf2)** | 4.8 $^{T}$ (-2.3, 12.0) | 0.182 | **9.6** $^{S}$ (3.5, 15.7) | **0.002** | **14.4** $^{S}$ (8.0, 20.9) | **<0.001** |
| **Emotional functioning (ef)** | 3.0 (-3.8, 9.8) | 0.383 | 9.7 (3.9, 15.5) | 0.001 | **12.8** (6.6, 18.9) | **<0.001** |
| **Cognitive functioning (cf)** | -0.5 $^{T}$ (-6.1, 5.1) | 0.860 | **7.5** $^{S}$ (2.7, 12.3) | **0.002** | **7.0** $^{S}$ (1.8, 12.1) | **0.008** |
| **Social functioning (sf)** | 1.9 $^{T}$ (-5.1, 8.9) | 0.589 | **17.3** $^{L}$ (11.3, 23.3) | **<0.001** | **19.2** $^{L}$ (12.8, 25.6) | **<0.001** |
| **Fatigue (fa)** | **-6.8** $^{S}$ (-13.1, -0.5) | **0.034** | **-10.2** $^{S}$ (-15.6, -4.9) | **<0.001** | **-17.0** $^{M}$ (-11.3, -22.7) | **<0.001** |
| **Nausea and vomiting (nv)** | 0.10 $^{T}$ (-2.6, 2.9) | 0.944 | **-4.3** $^{S}$ (-6.6, -1.9) | **<0.001** | **-4.2** $^{S}$ (-6.6, -1.7) | **0.001** |
| **Pain (pa)** | -5.2 $^{T}$ (-11.3, 0.9) | 0.092 | -3.6 $^{T}$ (-8.8, 1.5) | 0.168 | **-8.8** $^{S}$ (3.3, 14.4) | **0.002** |
| **Dyspnea (dy)** | -3.4 $^{T}$ (-10.8, 3.9) | 0.355 | -5.9 $^{S}$ (-12.1, 0.3) | 0.063 | **-9.4** $^{M}$ (-15.9, -2.8) | **0.006** |
| **Insomnia (sl)** | -4.1 $^{S}$ (-11.9, 3.7) | 0.304 | **-11.2** $^{S}$ (-17.9, -4.6) | **0.001** | **-15.3** $^{M}$ (-22.4, -8.3) | **<0.001** |
| **Appetite loss (ap)** | 0.8 $^{T}$ (-4.6, 6.3) | 0.771 | **-6.2** $^{S}$ (-1.6, -10.9) | **0.009** | **-5.4** $^{S}$ (-10.4, -0.5) | **0.031** |
| **Constipation (co)** | 2.5 $^{T}$ (-5.0, 10.0) | 0.510 | **-11.1** $^{S}$ (-4.8, -17.5) | **<0.001** | **-8.6** $^{S}$ (-15.3, -1.9) | **0.012** |
| **Diarrhoea (di)** | **-10.5** $^{M}$ (-17.6, -3.3) | **0.004** | **-20.1** $^{M}$ (-26.2,-14.0) | **<0.001** | **-30.6** $^{M}$ (-37.1,-24.1) | **<0.001** |
| **Financial difficulties (fi)** | -2.3 $^{T}$ (-8.0, 3.4) | 0.424 | -2.4 $^{T}$ (-7.3, 2.5) | 0.330 | -4.7 $^{S}$ (-9.9, 0.4) | 0.073 |

***Table 7****. P-values (adjusted for age, sex, tumor level, type of operation, T-stage, radiotherapy and chemotherapy).* $^{L}$ *= Large-,* $^{M}$ *= Medium-,* $^{S}$ *= Small clinical difference.* $^{T}$ *= Trivial mean difference were not considered clinical relevant. Differences that were both statistically significant (p>0,05) and clinically relevant (small-, medium and large difference) are presented in bold.*

## 5.3 STUDY III

In final analysis 430 patients were included (*figure 8*). The mean follow-up time since surgery was 6.7 years (range 3.4-10.7), As in previous studies an analysis of patient characteristics between included vs. excluded and responders vs. non-responders, was performed, without revealing any major differences. Mean and median LARS score was higher in the defunctioning stoma group compared to the no stoma group (29, 32 vs. 21, 20, *p<0.001*). (*figure 12*)

| Patient characteristics of 430 patients surgically treated for rectal cancer stratified by the presence of a defunctioning stoma | | |
|---|---|---|
| | **Groups** | |
| **Variable** | **No stoma** (n=80) | **Defunctioning stoma** (n=350) |
| **Age at primary surgery, mean years (SD) *** | 67 (12) | 64 (9) |
| **Gender male, n (%) / female, n (%)*** | 37 (46) **/** 43 (54) | 206 (59) **/** 144 (41) |
| **Follow up time since primary operation, mean years (SD)*** | 7.1 (2.3) | 6.6 (2.0) |
| **Tumor level, n (% within group) *** | | |
| **0-5 cm** | 0 (0) | 9 (3) |
| **6-10 cm** | 15 (19) | 182 (52) |
| **11-15 cm** | 65 (81) | 159 (45) |
| **BMI, n (% within group) †** | | |
| **<18.5** | 0 (0) | 5 (1.6) |
| **18.5-24.9** | 40 (51) | 166 (48) |
| **25-30** | 32 (40) | 138 (40) |
| **>30** | 7 (9) | 38 (11) |
| **Preoperative T-stage --** | | |
| **T-stage ≤ 2, n (% within group)** | 24 (30) | 99 (28) |
| **T-stage ≥ 3, n (% within group)** | 48 (60) | 243 (70) |
| **Unknown** | 8 (10) | 7 (2) |
| **Preoperative n-stage *** | | |
| **n-stage ≥1, n (% within group)** | 22 (28) | 180 (52) |
| **Unknown** | 8 (10) | 11 (3) |
| **Metabolic comorbidity, n (% within group) --** | 27 (34) | 116 (33) |
| **Prior radiotherapy to the pelvic area, n (% within group) --** | 5 (6) | 10 (3) |
| **Neoadjuvant radiotherapy, n (% within group) *** | 37 (46) | 247 (71) |
| **Neoadjuvant radiochemotherapy, n (% within group) *** | 4 (5) | 67 (19) |
| **Surgical approach, n (% within group) --** | | |
| **Open** | 62 (77) | 323 (93) |
| **Minimally invasive (laparascopic or robotic)** | 18 (23) | 25 (7) |
| **Operation time, mean in minutes (SD) *** | 193 (63) | 295 (109) |
| **Level for central ligature, n (% within group) *** | | |
| **Inferior mesenteric artery** | 43 (54) | 239 (68) |
| **Superior rectal artery** | 37 (46) | 111 (32) |
| **Proportion TME (vs PME), n (% within group) *** | 23 (29) | 312 (89) |
| **Adjuvant chemotherapy, n (% within group) --** | 16 (20) | 92 (26) |
| **LARS groups, n (% within group) *** | | |
| **No LARS** | 36 (45) | 66 (19) |
| **Minor LARS** | 21 (26) | 86 (24) |
| **Major LARS** | 23 (29) | 198 (57) |
| **Mean time to stoma reversal, Days (SD) --** | | |
| **All** | - | 211 (143) |
| **No LARS** | - | 208 (127) |
| **Minor LARS** | - | 219 (147) |
| **Major LARS group** | | 210 (146) |

***Table 9.*** *Patients characteristics Study III*

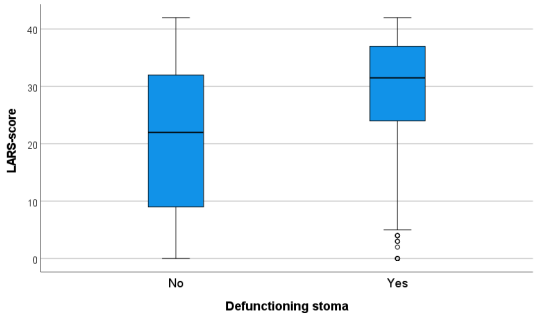



***Figure 12.*** *Box plot of LARS scores divided into defunctioning stoma and no stoma.*

Defunctioning stoma had a statistical significant association to Major LARS (vs. no LARS) in multivariable logistic regression (OR 2.43, 95% CI 1.14-5.20) but the association did not remain when changing the outcome reference to minor LARS (OR 1.42, 95% CI 0.67-3.00). (*Table 9*)

**Defunctioning stoma and association to major LARS adjusted for age, gender, neoadjuvant treatment, tumor level and surgical method.**

| **Variable** | | Crude OR (95% CI) Major LARS (vs. No LARS†) | Adjusted OR (95% CI) Major LARS (vs. No LARS†) | Crude OR (95% CI) Major LARS (vs. Minor LARS†) | Adjusted OR (95% CI) Major LARS (vs. Minor LARS†) |
|---|---|---|---|---|---|
| **Defunctioning stoma** | Yes (n=350)<br>No (n=80) | **4.70** (2.60-8.49)<br>Ref. | **2.43** (1.14-5.20)<br>Ref. | **2.10** (1.11-4.00)<br>Ref. | 1.42 (0.67-3.00)<br>Ref. |
| Age at primary operation | Years (mean 64) | **0.95** (0.93-0.98) | 0.98 (0.95-1.01) | 0.98 (0.95-1.01) | 0.99 (0.96-1.01) |
| Gender | Female (n=187)<br>Male (n=243) | 0.77 (0.48-1.23)<br>Ref. | 0.99 (0.58-1.68)<br>Ref. | 1.29 (0.80-2.07)<br>Ref. | 1.32 (0.81-2.16)<br>Ref. |
| Neoadjuvant treatment (RT) | Yes (n=284)<br>No (n=146) | **5.22** (3.14-8.69)<br>Ref. | **3.50** (1.98-6.23)<br>Ref. | **2.36** (1.42-3.93)<br>Ref. | **1.91** (1.12-3.26)<br>Ref. |
| Tumor level | 0-5 cm (n=9)<br>6-10 cm (n=197)<br>11-15 cm (n=224) | 4.19 (0.50-34.85)<br>**1.68** (1.04-2.71)<br>Ref. | 1.11 (0.13-9.73)<br>0.76 (0.41-1.39)<br>Ref. | 4.18 (0.50-34.84)<br>1.49 (0.93-2.38)<br>Ref. | 2.54 (0.30-21.66)<br>1.15 (0.69-1.91)<br>Ref. |
| Surgical method | TME (n=335)<br>PME (n=95) | **5.71** (3.22-10.13)<br>Ref. | **2.60** (1.20-5.66)<br>Ref. | **2.64** (1.45-4.84)<br>Ref. | 1.75 (0.84-3.64)<br>Ref. |

***Table 9.*** *Multivariable logistic regression model with defunctioning stoma as exposure and major LARS as outcome. Statistically significant OR presented in bold. No missing data. Ref.= Reference. † Outcome reference*

In the model, using BQoL as the outcome, defunctioning stoma had an unadjusted statistically significant association to impaired BQoL (OR 2.64, 95% CI 1.54-4.53) but failed to reach statistically significance in the adjusted model (OR 1.56, 95% CI 0.82-2.97). The only variable in the adjusted model reached statistically significance was TME (vs. PME) with an OR of 2.02 (95% CI 1.06-3.87). Table available in full article.

The exposure *time to stoma reversal* stratified into time groups revealed no statistically significant associations to major LARS (vs. no LARS), neither in unadjusted or adjusted model (*figure 13*). Using minor LARS as outcome reference, the group 61-120 days (compared to reference group 121-180 days) had an unadjusted OR for major LARS of 2.41 (95% CI 1.13-5.14) and adjusted OR of 2.34 (1.09-5.05). We found no other statistical significant associations for major LARS when using minor LARS as outcome reference.

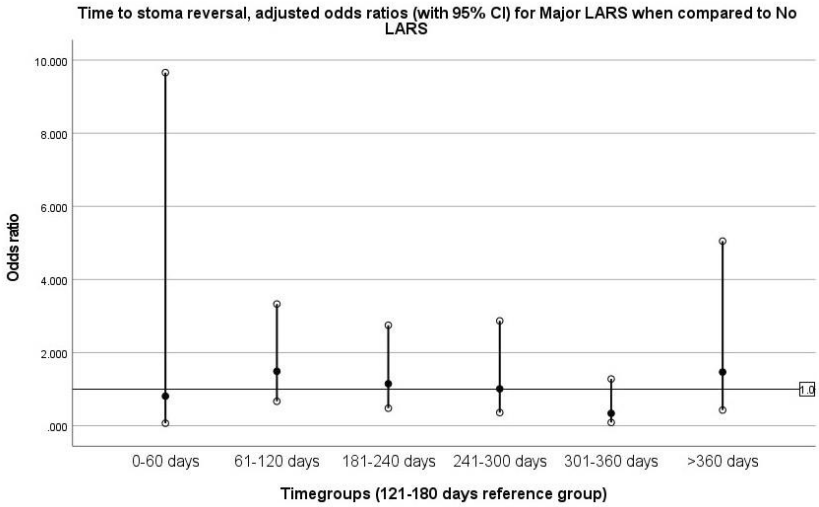



***Figure 13.*** *Forest plot. Exposure: Time to stoma reversal stratified into time groups. Outcome Major LARS (vs. no LARS).*

## 5.4 STUDY IV

As in many RCTs the strict inclusion criteria exclude a large number of patients from participating in the study. Starting with 305 patients which underwent TME with anastomosis and defunctioning stoma during the study period, exclusion left only 123 patients eligible for inclusion. Due to different factors an additional 78 patients did not participate which resulted in the final 45 patients that were included and randomized (*figure 9*). After randomization and before the first follow-up a drop out of 6 patients was registered. All within the intervention group (TAI) but only one participant dropped out after trying TAI. In final analysis the intervention group consisted of 16 patients and the control group of 23 patients. Analyzing differences in patient characteristics between patients included in analysis and drop out showed no statistical significant differences.

### 5.4.1 Primary outcome LARS-score

At baseline there was no difference in mean LARS score between the groups. The linear mixed effect model revealed statistically significant differences in mean LARS-score at both 6 and 12 months, in favor of the intervention group (*table 10*). The distribution of LARS-score in the two groups are displayed in *figure 14*.

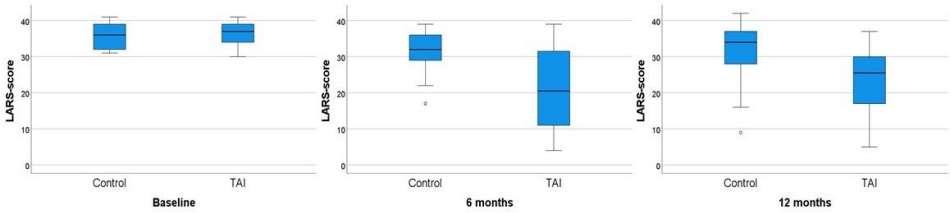



***Figure 14.*** *Box plot showing the distribution of LARS-scores at the different time-points.*

### 5.4.2 Primary outcome CCFFIS and the four study specific questions

In CCFIS there were no statistically significant differences between the groups at baseline and 6 months of follow-up but at 12 months of follow-up the differences reached statistical significance (border significant; p=0.050). Although not significant at 6 months there were a clear trend favoring TAI with a difference in points of 2.0 (no difference at baseline). (*table 10*, *figure 15*)

| **Comparison of mean scores at different time points between intervention group (TAI) and control group in LARS score, CCFIS and scores on the four study specific questions** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **0 months** | | **6 months** | | **12 months** | |
| **Outcome measure** | **Group** | **Mean score** | **Difference in mean score *(95% CI)*** | **Mean score** | **Difference in mean score (*95% CI**)** | **Mean score** | **Difference in mean score (*95% CI**)** |
| **LARS score** | TAI | 36.4 | 0.7 (-1.4, 2.8) | 20.4 | **-11.3 (-17.1,-5.6)** | 22.9 | **-9.5 (-15.2, -3.7)** |
| | Control | 35.6 | | 31.7 | | 32.4 | |
| **CCFFIS** | TAI | 9.6 | 0.0 (-2.7, 2.8) | 6.1 | -2.0 (-4.8, 0.8) | 6.4 | **-2.8 (-5.6, 0.0)** |
| | Control | 9.6 | | 8.1 | | 9.2 | |
| **Question 1. "How would you in general describe your bowel function?"** | | | | | | | |
| | TAI | 6.1 | -0.4 (-1.6, 0.8) | 4.1 | **-1.7 (-3.0, -0.3)** | 4.6 | -1.0 (-2.3, 0.3) |
| | Control | 6.5 | | 5.8 | | 5.6 | |
| **Question 2. "How much does your bowel function affect your daily life?"** | | | | | | | |
| | TAI | 5.5 | -0.4 (-1.8, 0.9) | 3.6 | -1.4 (-2.9, 0.1) | 3.7 | **-1.6 (-3.2, -0.2)** |
| | Control | 5.9 | | 5.0 | | 5.3 | |
| **Question 3. "If you have trouble with urgency, how does it affect your daily life?"** | | | | | | | |
| | TAI | 5.9 | -0.3 (-1.8, 1.2) | 2.0 | **-2.7 (-4.6,-0.9)** | 3.2 | -1.4 (-3.2, 0.4) |
| | Control | 6.2 | | 4.7 | | 4.6 | |
| **Question 4. "If you have trouble with fragmentation, how does this affect your daily life?"** | | | | | | | |
| | TAI | 6.3 | -0.5 (-1.9, 0.9) | 2.4 | **-3.0 (-4.7, -1.2)** | 2.8 | **-2.7 (-4.5, -0.9)** |
| | Control | 6.8 | | 5.4 | | 5.5 | |

***Table 10.*** *Results primary outcome measures Study IV. *Adjusted for baseline LARS-scores*

At baseline no significant differences were present for any of the four study specific question (Q1-Q4). At 6 months of follow-up the TAI group scored significantly better in 3 out of 4 questions (Q1, Q3 and Q4). At 12 month of follow-up the results were slightly different revealing significant differences in 2 out of 4 questions (Q2 and Q4). Although not significant results in all questions the overall main trend was clearly in favor of TAI. (*table 10*)

### 5.4.3 Secondary outcome EORTC QLQ-C30

At baseline there were no statistically significant differences in any of the subscales on the EORTC QLQ-C30 questionnaire. At 6 months the TAI group scored clinically relevant and significantly superior than the control group in the subscales physical functioning, diarrhea. The secondary endpoint was QoL at 12 months of follow-up and at this time point the TAI group scored clinically relevant and significantly superior in summary score, global health/QoL, physical functioning, role functioning, social functioning, fatigue, pain and diarrhea. The reversed relationship did not occur in any of the subscales.

| **Comparison of EORTC QLQ-C30 subscale mean scores at different time points** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **0 months** | | **6 months** | | **12 months** | |
| **Subscale / Item** | **Group** | **Mean score** | **Difference in mean score *(95% CI)*** | **Mean score** | **Difference in mean score *(95% CI *)*** | **Mean score** | **Difference in mean score *(95% CI *)*** |
| **Summary score** | TAI | 82.8 | 1.2 (-5.7, 8.0) | 90.4 | 6.7 (-0.6-14.0) | 91.7 | **10.7$^{L}$ (3.5-18.1)** |
| | Control | 81.6 | | 83.7 | | 81.0 | |
| **Global Health status/QoL** | TAI | 70.1 | 2.3 (-9.4, 14.0) | 72.1 | 5.3 (-8.8-19.4) | 80.5 | **17.8$^{L}$ (3.7-31.8)** |
| | Control | 67.8 | | 66.8 | | 62.7 | |
| **Functional scales** | | | | | | | |
| Physical functioning | TAI | 87.9 | 0.4 (-8.6, 9.2) | 96.9 | **11.0$^{S}$ (2.8, 19.2)** | 96.5 | **11.5$^{S}$ (3.2, 19.6)** |
| | Control | 87.5 | | 85.9 | | 85.0 | |
| Role functioning | TAI | 77.3 | -2.4 (-14.6, 9.7) | 94.6 | 11.2 (-2.6, 25.0) | 93.6 | **16.2$^{S}$ (2.4, 30.0)** |
| | Control | 79.7 | | 83.4 | | 77.4 | |
| Emotional functioning | TAI | 82.6 | -1.8 (-12.6, 8.9) | 84.7 | 0.7 (-12.3, 10.9) | 86.8 | 7.8 (-3.8, 19.4) |
| | Control | 84.4 | | 85.4 | | 79.0 | |
| Cognitive functioning | TAI | 84.8 | -1.4 (-12.5, 9.8) | 85.7 | 0.5 (-11.5, 10.5) | 89.8 | 4.4 (-6.6, 15.4) |
| | Control | 86.2 | | 86.2 | | 85.4 | |
| Social functioning | TAI | 78.0 | 2.6 (-10.2, 15.5) | 90.6 | 10.3 (-4.1, 24.7) | 89.6 | **15.3$^{L}$ (0.9, 29.7)** |
| | Control | 75.4 | | 80.3 | | 74.3 | |
| **Symptom scales** | | | | | | | |
| Fatigue † | TAI | 22.2 | -3.9 (-16.7, 9.0) | 13.7 | -13.8 (-28.3, 0.7) | 9.5 | **-21.4$^{L}$ (-35.9, -6.9)** |
| | Control | 26.1 | | 27.5 | | 30.9 | |
| Nausea and vomiting † | TAI | 3.0 | -0.6 (-5.2, 4.0) | 1.8 | 0.8 (-2.9, 4.6) | 2.8 | 0.3 (-3.3, 4.1) |
| | Control | 3.6 | | 1.0 | | 2.5 | |
| Pain † | TAI | 12.1 | -0.2 (-13.1, 12.7) | 5.9 | -8.1 (-21.1, 4.9) | 3.8 | **-14.6$^{M}$ (-27.6, -1.7)** |
| | Control | 12.3 | | 14.0 | | 18.4 | |
| **Single items** | | | | | | | |
| Dyspnea † | TAI | 18.2 | 6.6 (-8.0, 21.1) | 21.1 | 0.0 (-16.5, 16.6) | 6.5 | -10.0 (-26.5, 6.6) |
| | Control | 11.6 | | 21.1 | | 16.5 | |
| Insomnia † | TAI | 19.7 | 0.9 (-13.1, 14.9) | 14.8 | -7.8 (-24.1, 8.6) | 19.0 | -0.5 (-16.8, 15.8) |
| | Control | 18.8 | | 22.6 | | 19.5 | |
| Appetite loss † | TAI | 4.6 | -5.6 (-16.8, 5.6) | 3.7 | 1.8 (-6.2, 9.8) | 1.6 | -4.8 (-12.8, 3.1) |
| | Control | 10.1 | | 1.9 | | 6.4 | |
| Constipation † | TAI | 30.3 | -0.1 (-23.3, 23.1) | 16.2 | -8.4 (-28.7, 11.8) | 12.0 | -18.6 (-38.8, 1.6) |
| | Control | 30.4 | | 24.6 | | 30.6 | |
| Diarrhea † | TAI | 24.2 | -14.9 (-33.1, 3.3) | 0.4 | **-20.5$^{M}$ (-34.0, -6.9)** | 8.8 | **-15.1$^{M}$ (-28.7, -1.6)** |
| | Control | 39.1 | | 20.9 | | 23.9 | |
| Financial † difficulties | TAI | 1.5 | -1.4 (-6.5, 3.7) | 0.2 | -4.2 (-13.1, 4.6) | 2.2 | -3.7 (-12.5, 5.1) |
| | Control | 2.9 | | 4.4 | | 5.9 | |

***Table 11.*** *Clinically and statistical significant differences are presented in bold. $^{S}$=small, $^{M}$=medium, $^{L}$=Large clinically relevant difference. *Adjusted for baseline LARS-score.*

| Patient characteristics of 45 included patients divided into intervention group (TAI) and control group | | |
|---|---|---|
| | **Intervention (TAI) (n=22)** | **Control (n=23)** |
| **Age at primary operation, mean years (SD)** | 65 (10) | 64 (13) |
| **Gender, male n (%) / female n (%)** | 11 (50) / 11 (50) | 14 (61) / 9 (39) |
| **BMI (SD)** | 26.1 (4) | 27.2 (5) |
| **Tumor level, mean cm (SD)** | 10 (2) | 10 (3) |
| **Preoperative T-stage ≥3, n (%)** | 16 (63) | 19 (83) |
| **Preoperative N-stage ≥1, n (%)** | 16 (73) | 17 (74) |
| **Neoadjuvant radiotherapy, n (%)** | 16 (73) | 17 (74) |
| **Neoadjuvant chemoradiotherapy, n (%)** | 7 (32) | 6 (26) |
| **Surgical approach** | | |
| **Open, n (%)** | 5 (23) | 7 (30) |
| **Minimally invasive approach, n (%)** | 17 (77) | 16 (70) |
| **Laparascopic, n (%)** | 2 (12) | 3 (19) |
| **Robotic, n (%)** | 15 (88) | 13 (81) |
| **Conversion, n (%)** | 0 (0) | 2 (13) |
| **Type of anastomosis** | | |
| **End to end, n (%)** | 1 (5) | 1 (4) |
| **Side to end, n (%)** | 21 (95) | 22 (96) |
| **Pathology T-stage ≥3, n (%)** | 9 (41) | 10 (43) |
| **Pathology N-stage ≥1, n (%)** | 8 (36) | 10 (43) |
| **Adjuvant chemotherapy, n (%)** | 4 (18) | 5 (22) |
| **Anastomotic leakage, n (%)** | 0 (0) | 2 (9) |
| **Time to stoma reversal, mean days (SD)** | 192 (85) | 192 (81) |
| **Time from primary surgery to inclusion, mean days (SD)** | 439 (83) | 441 (95) |

***Table 12.*** *Patient characteristics Study IV*

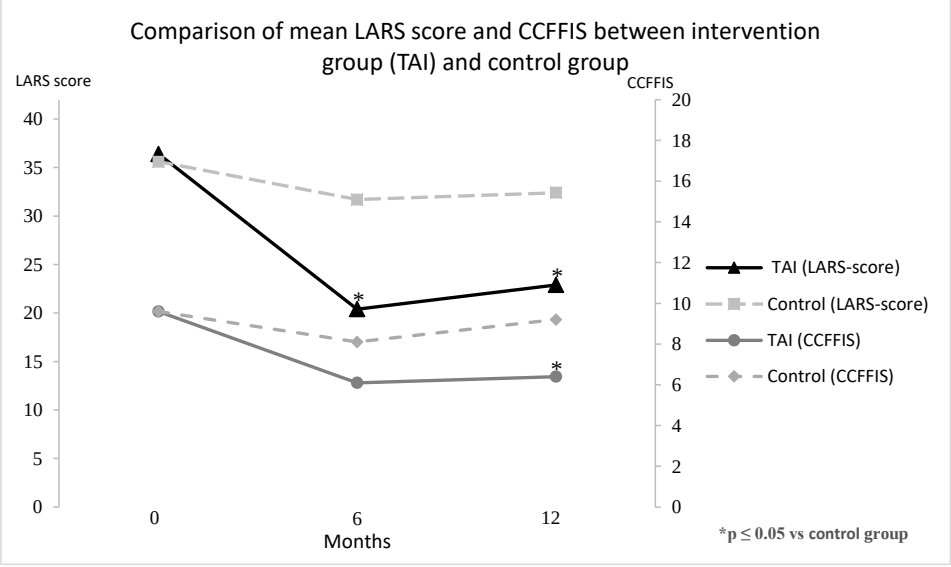



***Figure 15.*** *Line chart included LARS-score and CCFFIS as outcome measures (Study IV).*

# 6 DISCUSSION

With improved long term cancer survival, the need for continued focus on functional outcomes is evident. When evaluating different treatment regime functional outcome should be a part of the study design along with the more traditional oncological outcomes. In Study I and II we showed that the prevalence of LARS was approximately fifty percent and that the distribution within LARS groups did not change significantly over time, despite five years between points of measure. Moreover, the fact that severe bowel dysfunction is clearly associated with impaired QoL. Longitudinal data on LARS has been lacking but in a recently published meta-analysis (including data from study I) they concluded: "LARS improves by 18 months postoperatively then remains stable up to 3 years" [221]. This is in line with the conclusion in Study I, in the sense that difficulties with LARS is stable in the long-term perspective.

The prevalence of major LARS in Study II was in the higher range compared to other previously published studies. In the large study by Bregendahl et al. (n=938) the prevalence of major LARS was 41% compared to 53% in Study II [139]. A main contributor to this difference may be the large difference in proportion of patients which received neoadjuvant RT and underwent surgery with TME, which are both strong risk factors for LARS [169, 175]. Bregendahl et al. reported only 20% neoadjuvant therapy and 59% TME whereas in Study II 66.5% received neoadjuvant RT and 85% underwent TME surgery. Our results are more in line with recently reported Swedish data with a prevalence of major LARS of 56% at 2 years of follow-up [136]. In the only meta-analysis regarding prevalence of LARS the prevalence was estimated to 41% (95% CI 34-48) but among the included studies the prevalence ranged from 17.8%-56% [149]. Obviously prevalence is not a fixed proportion over time or between study-populations but it is nevertheless of great importance to study the prevalence in order to gain understanding and knowledge regarding the burden of certain outcome in the population. Results should also be related to published normative data before making any conclusions from the data. In our results the prevalence of major LARS clearly exceeded the normative prevalence numbers, which supports a significant impact on bowel function from the cancer treatment [133-135].

However, there are some limitations in the cross-sectional study design [222]. In study I-III we aimed to measure LARS in a defined population. The exposure in these study was the primary surgery for rectal cancer (Study I and II) and defunctioning stoma (Study III). Since the time point of exposure, a number of patients had died (i.e could not respond). Exclusion criteria and non-responders excluded a number of patients from analysis which lead to that less than half of the original population provided outcome measure in Study II and III. This is of course of concern if your aim is to measure the overall prevalence in a selected population. In this perspective, the long follow-up time was both a strength and a weakness. A strength, is the addition of knowledge about long-term bowel related consequences after rectal cancer surgery, and a weakness is the fact that a fair number of patients within the population, had already died at follow-up. A non-controlled selection of patients had been made but this is

inevitable in the context of clinical research involving oncological patients. The exclusion criteria were set to exclude patients with a potential risk of highly bias the results and the selection on which exclusion criteria to use or not use, may be subject for debate. Should we have included patients with recurrence or metastasis despite that the disease itself and its treatment may potentially have biased the results? There is no correct answer to this question, instead you as a researcher have to make a choice and clearly state your position.

Of greater importance is the risk of non-responder bias, i.e patients who get the opportunity to provide outcome measures but are not willing to participate for unknown reasons. In a systematic review on response rates in patient and health care professional surveys in surgery by Meyer et al. the average response rate was 70% over 811 studies [223]. In Study I-III the response rates were 77%, 82.6% and 80.5% respectively which in this context should be considered more than acceptable. Nevertheless, there is a risk for non-responder bias, i.e *selection bias*. Patients with less bowel dysfunction may be more reluctant to respond. In order to attempt an assessment of the potential effect of exclusion and non-respondents on the results an analysis of patient characteristics was conducted (in Study I-III). Differences in patient characteristics between excluded and included, as well as non-responders and responders was analyzed and showed no major differences. This was at least some indication of limited effect. In Study IV the analysis was made between patients which provided follow-up data and drop outs with similar results. In Study II and III a study specific questionnaire concerning stoma was used in order to investigate reasons for the stoma. Of responders with a stoma 32% had received a new stoma due to severe bowel dysfunction and it would be fair to assume that these patients also suffered from major LARS prior to the stoma operation.

Another issue, in studies using questionnaires, is the concern regarding the accuracy in measuring the selected outcomes. In all studies we used validated questionnaires (LARS-score, EORTC QLQ-C30, CCFFIS) in order to minimize this concern. If the outcome measures failing to accurately measure the outcome there is a risk for *misclassification bias of the outcome*. If failing to perfectly measuring the exposure there is a risk of *misclassification bias of the exposure. Misclassification bias (type of information bias)* can be *differential* and *non-differential*; *differential misclassification* meaning that the error rate differs between groups while *non-differential* meaning that error rates are evenly distributed between groups (generally bias results towards the null). In study I and II the exposure should be defined as a selection-criteria for inclusion in the selected cohort, with a minimal risk for misclassification. Risk for misclassification of exposure in Study III (i.e. defunctioning stoma) was minimized through cross-checking register data with medical records. If misclassification bias was present in the presented studies it is most likely of non-differential type. The LARS-score may not be optimal in the longitudinal setting due intrinsic limitations in detecting improvement or deterioration but these limitations should be evenly distributed among the LARS groups. Using a more sensitive instrument may have altered the results, but unlikely in any major way.

In Study I an additional analysis was performed with the purpose to identify predictors for deterioration, improvement and stable function over time (data not shown in results but available in full article). Retrospectively, since the study design was not optimal, these analyses should probably have been omitted.

Another concept worth mentioning is *statisficing* which involves to which degree participants chose the most accurate response alternative [224]. Participants may, due to several factors, compromise their standards and give imprecise responses. In relation to this aspect it should be an advantage using short questionnaires that are clear and easy to understand (e.g. LARS-score). This phenomenon is impossible to test for but is an important concept to keep in mind when interpreting results based on questionnaire data.

In cross sectional studies making causal inference is difficult. In all present studies an anchor questions, concerning BQoL was added in order to assess LARS causal association to QoL. In Study I and II a higher LARS score was associated with a greater impact on BQoL which is in line with a prior study by Battersby et al. [160]. Adding the results, showing an association between major LARS and impaired QoL (Study I and II), measured with the EORTC QLQ-C30 questionnaire strengthens the basis for assuming that a causal association does exists between impaired bowel function and impaired QoL. The consistent results throughout the literature also supports this [124, 132, 150]. Otherwise the association could be the result of an unknown confounder, associated with both the exposure and the outcome. Hypothetical patients with major LARS are probably at a higher risk of developing urinary and sexual dysfunction after rectal cancer treatment, i.e. an association between major LARS and sexual- and urinary dysfunction. Sexual- and urinary dysfunction are associated with impaired QoL. In this scenario the association between major LARS and QoL may not be causal but instead explained by impact on QoL by the unknown confounder (sexual- and urinary dysfunction).

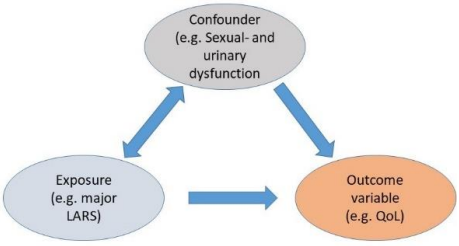



***Figure 16.*** *Example of relationship between exposure, confounder and outcome.*

In study II and IV multiple outcome measures for bowel dysfunction was used which could be considered a strength given that the results were clearly correlated. In study II the mean score in the major LARS group was associated with statistically significant higher score in CCFFIS. Reporting CCFFIS also enables comparisons to studies on postoperative anorectal function in which CCFFIS (i.e. Wexner score) was used as the outcome measure. Having multiple outcome measures with correlated results probably also reduces the risk for a type I error (i.e. reject the null hypothesis when it is actually true).

Study I and II were more descriptive in nature while still reporting inference on association between bowel related outcome measures and LARS-groups to QoL. Study III however had a more clearly defined exposure, i.e. defunctioning stoma. Using a logistic regression an adjusted association between defunctioning stoma and major LARS (vs. no LARS) was identified. Known potential confounders were included in the model. However, the association could not be reproduced when changing the outcome reference to minor LARS. This could be result of lack of power in the study design. Minor and major LARS are more closely related than no and major LARS which increases the number of participants needed to have a sufficient power in the study. Changing the outcome to BQoL resulted in a non-significant adjusted OR for more severe impaired BQoL. This could be explained by how the outcome variable was dichotomized. Also in this case there could be a lack of power due to merging of response alternatives. If we instead had compared the response alternatives "some" / "a lot" to only "not at all" the adjusted OR was 2.57 (95% CI 1.08-6.05) and would probably increase even more if we restricted the analysis to only comparing "a lot" vs. "not at all". During, the time of planning, the study there were a diversity in the results in the literature concerning defunctioning stoma and association to impaired bowel function. Since then, two meta-analyzes have been published, both reporting results in line with the results from Study III [163, 164].

In Study III 29 patients had a defunctioning stoma preoperatively to the rectal cancer operation. Out of these, 27 patients remained in the defunctioning stoma group and only 2 patients were stoma free postoperatively. Due to the low number of patients, which ended up in the no stoma group, this was not included in the analysis.

The second part of the primary endpoint in study III was time to stoma reversal and association to more severe bowel function (i.e. major LARS). In the 0-60 days' group there were only 4 patients making the results to uncertain to interpret. Using 121-180 days as the reference category the only statistical significant results (crude and adjusted) was reported in comparison to the 61-120 days' group. The 61-120 days' group had an adjusted OR of 2.34 (95% CI 1.09-5.05) for major LARS (vs. minor LARS) but strangely non-significant OR when changing the outcome reference category to no LARS. Several factors are involved in the timing of a stoma reversal, e.g. hospital resources and prioritization between different surgical procedures and diseases. In cases with early stoma closure there is more often related to a medical reason and in many cases stoma complications (e.g. high output stoma). There may have been patient-related factor (i.e. unknown confounders) associated with the outcome for which we were unable to control for. Comparing the results, to other previous studies, is difficult due to differences in study design. However, no clear conclusion can be drawn from the results and they should be interpreted with caution. The ideal study would be an RCT randomizing patients to stoma reversal at different time points while evaluating bowel function.

The rational for using multiple outcome measures in Study IV was an uncertainty whether is LARS-score was sensitive enough to detect improvements. Since the aim was to evaluate LARS, using only the CCFFIS questionnaire was not sufficient because it does not cover all aspects within the syndrome. The four study specific questions were also added and validated through a test-retest. A strength of the RCT design is the often excellent internal validity (i.e. confidence in causal relationship) which mainly arises from the randomization process. But the study design has some limitations in regard to external validity (i.e. to what extent the results can be generalized beyond the study population), mainly because of strict inclusion- and exclusion criteria. Internal validity can be negatively affected by loss to follow up / drop out. In Study IV six patients from the intervention group were lost at follow-up. Only one of these patients dropped out after trying TAI. However, since the total number of patients in the TAI group was limited it cannot be excluded that full participation of these patients may have altered the results in either direction.

Study IV was the first published RCT evaluating TAI as a treatment (prior RCT used TAI prophylactic) for LARS showed results strongly favoring TAI which confirms results from prior observational studies [196-198, 200].

# 7 CONCLUSIONS

**Study I:** This longitudinal study shows that long-term difficulties with LARS appears to be stable over time and the impact of LARS on BQoL and overall QoL persists.

**Study II:** This population-based study shows that after anterior resection surgery a majority of patients suffers from severe bowel dysfunction which is also associated to impaired BQoL and overall QoL.

**Study III:** The results from this population-based study indicates that the presence of a defunctioning stoma is associated with a higher risk for major LARS in the long-term perspective. However, the results failed to show any clear association between time to stoma reversal and major LARS.

**Study IV:** This RTC shows clear benefits of TAI in the treatment of major LARS after rectal cancer surgery with TME. With results confirming reduced symptoms of LARS and improved QoL the TAI treatment should be a natural part of the treatment arsenal in treating postoperative bowel dysfunction.

# 8 POINTS OF PERSPECTIVE

Since bowel dysfunction is so common after rectal cancer surgery every colorectal unit should have a clear and structured plan for supporting these patients, in regard to treatment-related functional impairment. Although oncological outcomes are our primary concern when choosing a treatment strategy, functional outcomes should be incorporated in this decision process. Evaluating new treatments, studies would benefit from adding functional outcomes along with oncological outcomes. Take for instance robotic surgery. The majority of patients in Study I-III underwent surgery in the pre-robotic era. Hopefully, optimized vision and increased possibilities for precise dissection (nerve preserving) in robotic surgery can improve functional outcomes but still there is a lack of evidence supporting this assumption. Regarding RT there may still be room for improved patient selection, (i.e. which patients benefits from treatment) to avoid overtreatment.

There is also a need for more prospective studies evaluating bowel function pre- and post-treatment. Certainly there will be some difficulties in interpreting bowel function in the pre-treatment setting due to bias from the presence of a tumor, but nevertheless, for many studies it would be beneficial providing baseline measurements.

If the LARS-score is the optimal instrument measuring LARS is debatable. In the clinical setting it is an easy and fast screening tool for measuring bowel dysfunction but for a more detailed evaluating it has some limitations. Since the LARS-groups are quite established, the use of other instruments limits comparison between studies. The optimal situation, for measurement, would be to have a more comprehensive instrument that is somehow link to the LARS-score making comparison possible. In this scenario the current LARS score could be used for screening and then the more comprehensive instrument could be used for evaluation of treatment interventions among those with more severe bowel dysfunction (i.e. major LARS). The LARS international collaboration group presented a consensus definition of LARS in 2020 and in this article stating an intention to develop a new more robust scoring system based on this definition [92]. Such an instrument would further improve the ability to assess LARS and evaluate different treatment options. Development, on the basis of an international collaboration, would also improve the likelihood of future coherence in the use outcome measure regarding LARS.

Regardless of which instrument used, as outcome measure, there is still a need for studies concerning different treatments for LARS. As mentioned earlier several RCTs has been registered regarding pelvic floor rehabilitation which is promising [183-185]. Also additional studies that involves tools for improved patient selection for specific treatment would be desirable.

Hopefully, in the future we will have an improved and more robust instrument for measuring LARS and a treatment algorithm based on high quality scientific evidence. This would constitute a well-grounded foundation to improve management and QoL among rectal cancer patients.

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# 10 REFERENCES


1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 2019; 14(2):89-103.
2. Swedish National Guidelines for Colorectal Cancer, 2021. Available at: . Available at: https://cancercentrum.se/samverkan/cancerdiagnoser/tjocktarm-andtarm-och-anal/tjock--och-andtarm/vardprogram/. Accessed 01-02, 2022.
3. Petersson J, Bock D, Martling A, et al. Increasing incidence of colorectal cancer among the younger population in Sweden. *BJS Open* 2020; 4(4):645-658.
4. Socialstyrelsen statistikdatabas. Available at: https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikdatabasen/. Accessed 23-01, 2022.
5. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; 383(9927):1490-1502.
6. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. *Gastroenterology* 2010; 138(6):2044-58.
7. Irving MH, Catchpole B. ABC of colorectal diseases. Anatomy and physiology of the colon, rectum, and anus. *BMJ* 1992; 304(6834):1106-8.
8. Sadahiro S, Ohmura T, Yamada Y, et al. Analysis of length and surface area of each segment of the large intestine according to age, sex and physique. *Surg Radiol Anat* 1992; 14(3):251-7.
9. Heald RJ, Moran BJ. Embryology and anatomy of the rectum. *Semin Surg Oncol* 1998; 15(2):66-71.
10. Moore KL, Agur AMR, Moore KL, et al. Essential clinical anatomy. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2002.
11. Herold A LP-A, Matzel K E, O´Connell P R. Coloproctology. Second Edition ed: Springer, 2017.
12. Boron WF, Boulpaep EL. Medical physiology : a cellular and molecular approach. 1st ed. Philadelphia, PA: W.B. Saunders, 2003.
13. Malone JC, Thavamani A. Physiology, Gastrocolic Reflex. StatPearls. Treasure Island (FL); 2022.
14. Dinning PG. A new understanding of the physiology and pathophysiology of colonic motility? *Neurogastroenterol Motil* 2018; 30(11):e13395.
15. Keane C, Paskaranandavadivel N, Vather R, et al. Altered colonic motility is associated with low anterior resection syndrome. *Colorectal Dis* 2021; 23(2):415-423.
16. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28(suppl_4):iv22-iv40.
17. Koda K, Yamazaki M, Shuto K, et al. Etiology and management of low anterior resection syndrome based on the normal defecation mechanism. *Surg Today* 2019; 49(10):803-808.

18. Lestar B, Penninckx F, Rigauts H, et al. The internal anal sphincter can not close the anal canal completely. *Int J Colorectal Dis* 1992; 7(3):159-61.

19. Stelzner S, Bottner M, Kupsch J, et al. Internal anal sphincter nerves - a macroanatomical and microscopic description of the extrinsic autonomic nerve supply of the internal anal sphincter. *Colorectal Dis* 2018; 20(1):O7-O16.

20. Southwell BR, Clarke MC, Sutcliffe J, et al. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. *Pediatr Surg Int* 2009; 25(7):559-72.

21. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. *Scand J Gastroenterol* 2003; 38(1):36-42.

22. Meier R, Beglinger C, Dederding JP, et al. Influence of age, gender, hormonal status and smoking habits on colonic transit time. *Neurogastroenterol Motil* 1995; 7(4):235-8.

23. Cheeney G, Nguyen M, Valestin J, et al. Topographic and manometric characterization of the recto-anal inhibitory reflex. *Neurogastroenterol Motil* 2012; 24(3):e147-54.

24. Saldana Ruiz N, Kaiser AM. Fecal incontinence - Challenges and solutions. *World J Gastroenterol* 2017; 23(1):11-24.

25. Saranovic D, Barisic G, Krivokapic Z, et al. Endoanal ultrasound evaluation of anorectal diseases and disorders: technique, indications, results and limitations. *Eur J Radiol* 2007; 61(3):480-9.

26. Basilisco G, Bharucha AE. High-resolution anorectal manometry: An expensive hobby or worth every penny? *Neurogastroenterol Motil* 2017; 29(8).

27. Oblizajek NR, Gandhi S, Sharma M, et al. Anorectal pressures measured with high-resolution manometry in healthy people-Normal values and asymptomatic pelvic floor dysfunction. *Neurogastroenterol Motil* 2019; 31(7):e13597.

28. Rasijeff AMP, Garcia-Zermeno K, Di Tanna GL, et al. Systematic review and meta-analysis of anal motor and rectal sensory dysfunction in male and female patients undergoing anorectal manometry for symptoms of faecal incontinence. *Colorectal Dis* 2022.

29. Madoff RD, Orrom WJ, Rothenberger DA, et al. Rectal compliance: a critical reappraisal. *Int J Colorectal Dis* 1990; 5(1):37-40.

30. Lalwani N, El Sayed RF, Kamath A, et al. Imaging and clinical assessment of functional defecatory disorders with emphasis on defecography. *Abdom Radiol (NY)* 2021; 46(4):1323-1333.

31. Wilkinson N. Management of Rectal Cancer. *Surg Clin North Am* 2020; 100(3):615-628.

32. You YN, Hardiman KM, Bafford A, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer. *Dis Colon Rectum* 2020; 63(9):1191-1222.

33. Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. Eighth edition. ed. Chichester, West Sussex, UK ; Hoboken, NJ: John Wiley & Sons, Inc., 2017.

34. Berho M, Narang R, Van Koughnett JA, et al. Modern multidisciplinary perioperative management of rectal cancer. *JAMA Surg* 2015; 150(3):260-6.

35. Brannstrom F, Bjerregaard JK, Winbladh A, et al. Multidisciplinary team conferences promote treatment according to guidelines in rectal cancer. *Acta Oncol* 2015; 54(4):447-53.

36. Palmer G, Martling A, Cedermark B, et al. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. *Colorectal Dis* 2011; 13(12):1361-9.

37. Wille-Jorgensen P, Sparre P, Glenthoj A, et al. Result of the implementation of multidisciplinary teams in rectal cancer. *Colorectal Dis* 2013; 15(4):410-3.

38. Levine RA, Chawla B, Bergeron S, et al. Multidisciplinary management of colorectal cancer enhances access to multimodal therapy and compliance with National Comprehensive Cancer Network (NCCN) guidelines. *Int J Colorectal Dis* 2012; 27(11):1531-8.

39. Richardson B, Preskitt J, Lichliter W, et al. The effect of multidisciplinary teams for rectal cancer on delivery of care and patient outcome: has the use of multidisciplinary teams for rectal cancer affected the utilization of available resources, proportion of patients meeting the standard of care, and does this translate into changes in patient outcome? *Am J Surg* 2016; 211(1):46-52.

40. Snelgrove RC, Subendran J, Jhaveri K, et al. Effect of Multidisciplinary Cancer Conference on Treatment Plan for Patients With Primary Rectal Cancer. *Dis Colon Rectum* 2015; 58(7):653-8.

41. Lopez-Campos F, Martin-Martin M, Fornell-Perez R, et al. Watch and wait approach in rectal cancer: Current controversies and future directions. *World J Gastroenterol* 2020; 26(29):4218-4239.

42. Cedermark B, Johansson H, Rutqvist LE, et al. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. *Cancer* 1995; 75(9):2269-75.

43. Swedish Rectal Cancer T, Cedermark B, Dahlberg M, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; 336(14):980-7.

44. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345(9):638-46.

45. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; 23(24):5644-50.

46. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; 12(6):575-82.

47. Colorectal Cancer Collaborative G. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; 358(9290):1291-304.

48. Abraha I, Aristei C, Palumbo I, et al. Preoperative radiotherapy and curative surgery for the management of localised rectal carcinoma. *Cochrane Database Syst Rev* 2018; 10:CD002102.

49. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; 36(6):564-72.

50. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; 373(9666):811-20.

51. Glimelius B, Isacsson U, Jung B, et al. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. *Int J Radiat Oncol Biol Phys* 1997; 37(2):281-7.

52. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; 24(28):4620-5.

53. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355(11):1114-23.

54. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; 93(10):1215-23.

55. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012; 30(31):3827-33.

56. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol* 2017; 18(3):336-346.

57. Erlandsson J, Lorinc E, Ahlberg M, et al. Tumour regression after radiotherapy for rectal cancer - Results from the randomised Stockholm III trial. *Radiother Oncol* 2019; 135:178-186.

58. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22(1):29-42.

59. Nationella kvalitetsregisterrapporter Tjock- och Ändtarmscancer. Regionala cancercentrum i Samverkan. Available at: https://cancercentrum.se/samverkan/cancerdiagnoser/tjocktarm-andtarm-och-anal/tjock--och-andtarm/kvalitetsregister/rapporter/. Accessed 8/2, 2022.

60. Hafström L NP, Glimelius B (editors). Mag- Tarmkanalens Cancersjukdomar: Studentlitteratur, 2013.

61. Joye I, Haustermans K. Early and late toxicity of radiotherapy for rectal cancer. *Recent Results Cancer Res* 2014; 203:189-201.

62. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* 1982; 69(10):613-6.

63. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; 1(8496):1479-82.

64. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 341(8843):457-60.

65. Martling AL, Holm T, Rutqvist LE, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; 356(9224):93-6.

66. Kanso F, Lefevre JH, Svrcek M, et al. Partial Mesorectal Excision for Rectal Adenocarcinoma: Morbidity and Oncological Outcome. *Clin Colorectal Cancer* 2016; 15(1):82-90 e1.

67. Bondeven P, Laurberg S, Hagemann-Madsen RH, et al. Suboptimal surgery and omission of neoadjuvant therapy for upper rectal cancer is associated with a high risk of local recurrence. *Colorectal Dis* 2015; 17(3):216-24.

68. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg* 2007; 246(2):207-14.

69. Lee BC, Lim SB, Lee JL, et al. Defunctioning Protective Stoma Can Reduce the Rate of Anastomotic Leakage after Low Anterior Resection in Rectal Cancer Patients. *Ann Coloproctol* 2020.

70. Huser N, Michalski CW, Erkan M, et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. *Ann Surg* 2008; 248(1):52-60.

71. Molina Rodriguez JL, Flor-Lorente B, Frasson M, et al. Low rectal cancer: abdominoperineal resection or low Hartmann resection? A postoperative outcome analysis. *Dis Colon Rectum* 2011; 54(8):958-62.

72. Frye JN, Carne PW, Robertson GM, et al. Abdominoperineal resection or low Hartmann's procedure. *ANZ J Surg* 2004; 74(7):537-40.

73. Sverrisson I, Nikberg M, Chabok A, et al. Low risk of intra-abdominal infections in rectal cancer patients treated with Hartmann's procedure: a report from a national registry. *Int J Colorectal Dis* 2018; 33(3):327-332.

74. Westerduin E, Musters GD, van Geloven AAW, et al. Low Hartmann's procedure or intersphincteric proctectomy for distal rectal cancer: a retrospective comparative cohort study. *Int J Colorectal Dis* 2017; 32(11):1583-1589.

75. Ahmad NZ, Azam M, Coffey JC. A meta-analysis of low Hartmann's procedure versus abdominoperineal resection for non-restorative treatment of rectal cancer. *Int J Colorectal Dis* 2021; 36(12):2585-2598.

76. Young DO, Kumar AS. Local Excision of Rectal Cancer. *Surg Clin North Am* 2017; 97(3):573-585.

77. Meyers BM, Cosby R, Quereshy F, et al. Adjuvant Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: A Cancer Care Ontario Systematic Review. *Clin Oncol (R Coll Radiol)* 2017; 29(7):459-465.

78. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. *Cochrane Database Syst Rev* 2008(3):CD005390.

79. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012(3):CD004078.

80. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; 16(2):200-7.

81. Jorgren F, Johansson R, Damber L, et al. Validity of the Swedish Rectal Cancer Registry for patients treated with major abdominal surgery between 1995 and 1997. *Acta Oncol* 2013; 52(8):1707-14.

82. Moberger P, Skoldberg F, Birgisson H. Evaluation of the Swedish Colorectal Cancer Registry: an overview of completeness, timeliness, comparability and validity. *Acta Oncol* 2018:1-10.

83. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. *Br J Surg* 2007; 94(10):1285-92.

84. Bryant CL, Lunniss PJ, Knowles CH, et al. Anterior resection syndrome. *Lancet Oncol* 2012; 13(9):e403-8.

85. Keane C, Wells C, O'Grady G, et al. Defining low anterior resection syndrome: a systematic review of the literature. *Colorectal Dis* 2017; 19(8):713-722.

86. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; 36(1):77-97.

87. Kirwan WO, Turnbull RB, Jr., Fazio VW, et al. Pullthrough operation with delayed anastomosis for rectal cancer. *Br J Surg* 1978; 65(10):695-8.

88. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. *Dis Colon Rectum* 1999; 42(12):1525-32.

89. Chapman SJ, Bolton WS, Corrigan N, et al. A Cross-Sectional Review of Reporting Variation in Postoperative Bowel Dysfunction After Rectal Cancer Surgery. *Dis Colon Rectum* 2017; 60(2):240-247.

90. Hallbook O, Sjodahl R. Surgical approaches to obtaining optimal bowel function. *Semin Surg Oncol* 2000; 18(3):249-58.

91. 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.

92. Keane C, Fearnhead NS, Bordeianou LG, et al. International Consensus Definition of Low Anterior Resection Syndrome. *Dis Colon Rectum* 2020; 63(3):274-284.

93. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. *Med Teach* 2005; 27(7):639-43.

94. Boulkedid R, Abdoul H, Loustau M, et al. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. *PLoS One* 2011; 6(6):e20476.

95. Saah AJ, Hoover DR. "Sensitivity" and "specificity" reconsidered: the meaning of these terms in analytical and diagnostic settings. *Ann Intern Med* 1997; 126(1):91-4.

96. Juul T, Ahlberg M, Biondo S, et al. International validation of the low anterior resection syndrome score. *Ann Surg* 2014; 259(4):728-34.

97. Resendiz A, Martini G, Sensi B, et al. The Italian version of the LARS score: cross-cultural adaptation and validation. An Italian Society of Surgical Oncology-Colorectal Cancer Network (SICO-CCN) collaborative study. *Int J Colorectal Dis* 2021; 36(8):1805-1810.

98. Kim CW, Jeong WK, Son GM, et al. Validation of Korean Version of Low Anterior Resection Syndrome Score Questionnaire. *Ann Coloproctol* 2020; 36(2):83-87.

99. Akizuki E, Matsuno H, Satoyoshi T, et al. Validation of the Japanese Version of the Low Anterior Resection Syndrome Score. *World J Surg* 2018; 42(8):2660-2667.

100. Hupkens BJP, Breukink SO, Olde Reuver Of Briel C, et al. Dutch validation of the low anterior resection syndrome score. *Colorectal Dis* 2018; 20(10):881-887.

101. Keramati MR, Abbaszadeh-Kasbi A, Keshvari A, et al. Translation, validation and psychometric evaluation of the Persian (Farsi) version of the Low Anterior Resection Syndrome Score (LARS-P). *PLoS One* 2021; 16(2):e0247054.

102. Carpelan A, Elamo E, Karvonen J, et al. Validation of the low anterior resection syndrome score in finnish patients: preliminary results on quality of life in different lars severity groups. *Scand J Surg* 2021; 110(3):414-419.

103. Grosek J, Kosir JA, Novak J, et al. Validation of The Slovenian Version of the Low Anterior Resection Syndrome Score for Rectal Cancer Patients after Surgery. *Zdr Varst* 2019; 58(4):148-154.

104. Akizuki E, Okita K, Noda A, et al. Clinical Utility and Characteristics of the LARS Score Compared to the CCIS. *World J Surg* 2022.

105. Quezada-Diaz FF, Elfeki H, Emmertsen KJ, et al. Comparative analysis of the Memorial Sloan Kettering Bowel Function Instrument and the Low Anterior Resection Syndrome Questionnaire for assessment of bowel dysfunction in rectal cancer patients after low anterior resection. *Colorectal Dis* 2021; 23(2):451-460.

106. Ribas Y, Aguilar F, Jovell-Fernandez E, et al. Clinical application of the LARS score: results from a pilot study. *Int J Colorectal Dis* 2017; 32(3):409-418.

107. Ribas Y, Munoz-Duyos A. How useful is the LARS score in the evaluation and treatment of LARS? *Tech Coloproctol* 2019; 23(2):195-196.

108. Chen TY, Emmertsen KJ, Laurberg S. What Are the Best Questionnaires To Capture Anorectal Function After Surgery in Rectal Cancer? *Curr Colorectal Cancer Rep* 2015; 11:37-43.

109. Battersby NJ, Bouliotis G, Emmertsen KJ, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. *Gut* 2017.

110. Williamson ME, Lewis WG, Finan PJ, et al. Recovery of physiologic and clinical function after low anterior resection of the rectum for carcinoma: myth or reality? *Dis Colon Rectum* 1995; 38(4):411-8.

111. van Duijvendijk P, Slors F, Taat CW, et al. A prospective evaluation of anorectal function after total mesorectal excision in patients with a rectal carcinoma. *Surgery* 2003; 133(1):56-65.

112. Horgan PG, O'Connell PR, Shinkwin CA, et al. Effect of anterior resection on anal sphincter function. *Br J Surg* 1989; 76(8):783-6.

113. Nguyen TH, Chokshi RV. Low Anterior Resection Syndrome. *Curr Gastroenterol Rep* 2020; 22(10):48.

114. Farouk R, Duthie GS, Lee PW, et al. Endosonographic evidence of injury to the internal anal sphincter after low anterior resection: long-term follow-up. *Dis Colon Rectum* 1998; 41(7):888-91.

115. Luo BJ, Zheng MC, Xia Y, et al. Assessment of defecation function after sphincter-saving resection for mid to low rectal cancer: A cross-sectional study. *Eur J Oncol Nurs* 2021; 55:102059.

116. Ihnat P, Vavra P, Prokop J, et al. Functional outcome of low rectal resection evaluated by anorectal manometry. *ANZ J Surg* 2018; 88(6):E512-E516.

117. Williamson ME, Lewis WG, Holdsworth PJ, et al. Decrease in the anorectal pressure gradient after low anterior resection of the rectum. A study using continuous ambulatory manometry. *Dis Colon Rectum* 1994; 37(12):1228-31.

118. Vassilakis JS, Pechlivanides G, Zoras OJ, et al. Anorectal function after low anterior resection of the rectum. *Int J Colorectal Dis* 1995; 10(2):101-6.

119. Nesbakken A, Nygaard K, Lunde OC. Mesorectal excision for rectal cancer: functional outcome after low anterior resection and colorectal anastomosis without a reservoir. *Colorectal Dis* 2002; 4(3):172-176.

120. Pedersen IK, Christiansen J, Hint K, et al. Anorectal function after low anterior resection for carcinoma. *Ann Surg* 1986; 204(2):133-5.

121. Tsunoda A, Shibusawa M, Kusano M. Anorectal function after anterior resection with side-to-side anastomosis for carcinoma of the rectum. *Dis Colon Rectum* 1999; 42(1):77-81.

122. Rao GN, Drew PJ, Lee PW, et al. Anterior resection syndrome is secondary to sympathetic denervation. *Int J Colorectal Dis* 1996; 11(5):250-8.

123. Vollebregt PF, Wiklendt L, Ang D, et al. Altered anal slow-wave pressure activity in low anterior resection syndrome: short case series in two independent specialist centres provide new mechanistic insights. *Colorectal Dis* 2021; 23(2):444-450.

124. Emmertsen KJ, Laurberg S, Rectal Cancer Function Study G. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *Br J Surg* 2013; 100(10):1377-87.

125. Lee WY, Takahashi T, Pappas T, et al. Surgical autonomic denervation results in altered colonic motility: an explanation for low anterior resection syndrome? *Surgery* 2008; 143(6):778-83.

126. Koda K, Saito N, Seike K, et al. Denervation of the neorectum as a potential cause of defecatory disorder following low anterior resection for rectal cancer. *Dis Colon Rectum* 2005; 48(2):210-7.

127. Iizuka I, Koda K, Seike K, et al. Defecatory malfunction caused by motility disorder of the neorectum after anterior resection for rectal cancer. *Am J Surg* 2004; 188(2):176-80.

128. Mochiki E, Nakabayashi T, Suzuki H, et al. Barostat examination of proximal site of the anastomosis in patients with rectal cancer after low anterior resection. *World J Surg* 2001; 25(11):1377-82.

129. Ng KS, Russo R, Gladman MA. Colonic transit in patients after anterior resection: prospective, comparative study using single-photon emission CT/CT scintigraphy. *Br J Surg* 2020; 107(5):567-579.

130. Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. *Am J Gastroenterol* 1998; 93(7):1042-50.

131. Lunniss PJ, Gladman MA, Benninga MA, et al. Pathophysiology of evacuation disorders. *Neurogastroenterol Motil* 2009; 21 Suppl 2:31-40.

132. Chen TY, Wiltink LM, Nout RA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clin Colorectal Cancer* 2015; 14(2):106-14.

133. Juul T, Elfeki H, Christensen P, et al. Normative Data for the Low Anterior Resection Syndrome Score (LARS Score). *Ann Surg* 2018.

134. van Heinsbergen M, Van der Heijden JAG, Stassen LP, et al. The low anterior resection syndrome in a reference population: prevalence and predictive factors in the Netherlands. *Colorectal Dis* 2020; 22(1):46-52.

135. Al-Saidi AMA, Verkuijl SJ, Hofker S, et al. How Should the Low Anterior Resection Syndrome Score Be Interpreted? *Dis Colon Rectum* 2020; 63(4):520-526.

136. Sandberg S, Asplund D, Bisgaard T, et al. 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):1367-1378.

137. Lazorthes F, Chiotasso P, Gamagami RA, et al. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. *Br J Surg* 1997; 84(10):1449-51.

138. Scheer AS, Boushey RP, Liang S, et al. The long-term gastrointestinal functional outcomes following curative anterior resection in adults with rectal cancer: a systematic review and meta-analysis. *Dis Colon Rectum* 2011; 54(12):1589-97.

139. Bregendahl S, Emmertsen KJ, Lous J, et al. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Dis* 2013; 15(9):1130-9.

140. Sturiale A, Martellucci J, Zurli L, et al. Long-term functional follow-up after anterior rectal resection for cancer. *Int J Colorectal Dis* 2017; 32(1):83-88.

141. Sun W, Dou R, Chen J, et al. Impact of Long-Course Neoadjuvant Radiation on Postoperative Low Anterior Resection Syndrome and Quality of Life in Rectal Cancer: Post Hoc Analysis of a Randomized Controlled Trial. *Ann Surg Oncol* 2018.

142. Croese AD, Zubair ON, Lonie J, et al. Prevalence of low anterior resection syndrome at a regional Australian centre. *ANZ J Surg* 2018.

143. Ekkarat P, Boonpipattanapong T, Tantiphlachiva K, et al. Factors determining low anterior resection syndrome after rectal cancer resection: A study in Thai patients. *Asian J Surg* 2016; 39(4):225-31.

144. Hughes DL, Cornish J, Morris C, et al. Functional outcome following rectal surgery-predisposing factors for low anterior resection syndrome. *Int J Colorectal Dis* 2017; 32(5):691-697.

145. Jimenez-Gomez LM, Espin-Basany E, Trenti L, et al. Factors associated with low anterior resection syndrome after surgical treatment of rectal cancer. *Colorectal Dis* 2017(Sep 29. doi: 10.1111/codi.13901. Epub ahead of print).

146. Kupsch J, Jackisch T, Matzel KE, et al. Outcome of bowel function following anterior resection for rectal cancer-an analysis using the low anterior resection syndrome (LARS) score. *Int J Colorectal Dis* 2018; 33(6):787-798.

147. Bondeven P, Emmertsen KJ, Laurberg S, et al. Neoadjuvant therapy abolishes the functional benefits of a larger rectal remnant, as measured by magnetic resonance imaging after restorative rectal cancer surgery. *Eur J Surg Oncol* 2015; 41(11):1493-9.

148. Bolton WS, Chapman SJ, Corrigan N, et al. The Incidence of Low Anterior Resection Syndrome as Assessed in an International Randomized Controlled Trial (MRC/NIHR ROLARR). *Ann Surg* 2021; 274(6):e1223-e1229.

149. Croese AD, Lonie JM, Trollope AF, et al. A meta-analysis of the prevalence of Low Anterior Resection Syndrome and systematic review of risk factors. *Int J Surg* 2018; 56:234-241.

150. Juul T, Ahlberg M, Biondo S, et al. Low anterior resection syndrome and quality of life: an international multicenter study. *Dis Colon Rectum* 2014; 57(5):585-91.

151. Nuytens F, Develtere D, Sergeant G, et al. Perioperative radiotherapy is an independent risk factor for major LARS: a cross-sectional observational study. *Int J Colorectal Dis* 2018.

152. Jimenez-Rodriguez RM, Segura-Sampedro JJ, Rivero-Belenchon I, et al. Is the interval from surgery to ileostomy closure a risk factor for low anterior resection syndrome? *Colorectal Dis* 2017; 19(5):485-490.

153. Denost Q, Laurent C, Capdepont M, et al. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. *Dis Colon Rectum* 2011; 54(8):963-8.

154. Zutshi M, Hull T, Shedda S, et al. Gender differences in mortality, quality of life and function after restorative procedures for rectal cancer. *Colorectal Dis* 2013; 15(1):66-73.

155. Afshari K, Smedh K, Wagner P, et al. Risk factors for developing anorectal dysfunction after anterior resection. *Int J Colorectal Dis* 2021; 36(12):2697-2705.

156. Ng KS, Sivakumaran Y, Nassar N, et al. Fecal Incontinence: Community Prevalence and Associated Factors--A Systematic Review. *Dis Colon Rectum* 2015; 58(12):1194-209.

157. Qin Q, Huang B, Cao W, et al. Bowel Dysfunction After Low Anterior Resection With Neoadjuvant Chemoradiotherapy or Chemotherapy Alone for Rectal Cancer: A Cross-Sectional Study from China. *Dis Colon Rectum* 2017; 60(7):697-705.

158. Nicotera A, Falletto E, Arezzo A, et al. Risk factors for Low Anterior Resection Syndrome (LARS) in patients undergoing laparoscopic surgery for rectal cancer. *Surg Endosc* 2022.

159. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol* 2011; 106(9):1582-91; quiz 1581, 1592.

160. Battersby NJ, Juul T, Christensen P, et al. Predicting the Risk of Bowel-Related Quality-of-Life Impairment After Restorative Resection for Rectal Cancer: A Multicenter Cross-Sectional Study. *Dis Colon Rectum* 2016; 59(4):270-80.

161. Gadan S, Floodeen H, Lindgren R, et al. Does a Defunctioning Stoma Impair Anorectal Function After Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial. *Dis Colon Rectum* 2017; 60(8):800-806.

162. Wells CI, Vather R, Chu MJ, et al. Anterior resection syndrome--a risk factor analysis. *J Gastrointest Surg* 2015; 19(2):350-9.

163. Keane C, Sharma P, Yuan L, et al. Impact of temporary ileostomy on long-term quality of life and bowel function: a systematic review and meta-analysis. *ANZ J Surg* 2020; 90(5):687-692.

164. Vogel I, Reeves N, Tanis PJ, et al. Impact of a defunctioning ileostomy and time to stoma closure on bowel function after low anterior resection for rectal cancer: a systematic review and meta-analysis. *Tech Coloproctol* 2021; 25(7):751-760.

165. Keane C, Park J, Oberg S, et al. Functional outcomes from a randomized trial of early closure of temporary ileostomy after rectal excision for cancer. *Br J Surg* 2019.

166. Loos M, Quentmeier P, Schuster T, et al. Effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013; 20(6):1816-28.

167. Pollack J, Holm T, Cedermark B, et al. Long-term effect of preoperative radiation therapy on anorectal function. *Dis Colon Rectum* 2006; 49(3):345-52.

168. van der Sande ME, Hupkens BJP, Berbee M, et al. Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme. *Radiother Oncol* 2019; 132:79-84.

169. Ye L, Huang M, Huang Y, et al. Risk factors of postoperative low anterior resection syndrome for colorectal cancer: A meta-analysis. *Asian J Surg* 2022; 45(1):39-50.

170. Huttner FJ, Tenckhoff S, Jensen K, et al. Meta-analysis of reconstruction techniques after low anterior resection for rectal cancer. *Br J Surg* 2015; 102(7):735-45.

171. Brown CJ, Fenech DS, McLeod RS. Reconstructive techniques after rectal resection for rectal cancer. *Cochrane Database Syst Rev* 2008(2):CD006040.

172. Wang Z. Colonic J-pouch versus side-to-end anastomosis for rectal cancer: a systematic review and meta-analysis of randomized controlled trials. *BMC Surg* 2021; 21(1):331.

173. Kim S, Kang SI, Kim SH, et al. The Effect of Anastomotic Leakage on the Incidence and Severity of Low Anterior Resection Syndrome in Patients Undergoing Proctectomy: A Propensity Score Matching Analysis. *Ann Coloproctol* 2021; 37(5):281-290.

174. Grass JK, Chen CC, Melling N, et al. Robotic rectal resection preserves anorectal function: Systematic review and meta-analysis. *Int J Med Robot* 2021; 17(6):e2329.

175. Garfinkle R, Boutros M. Low Anterior Resection Syndrome: Predisposing Factors and Treatment. *Surg Oncol* 2021:101691.

176. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85(5):365-76.

177. Fayers P AN, Bjordal, Groenvold M, Curran D, Bottomley A On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Ed). 2001.

178. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; 29(1):89-96.

179. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer* 2012; 48(11):1713-21.

180. Derogar M, van der Schaaf M, Lagergren P. Reference values for the EORTC QLQ-C30 quality of life questionnaire in a random sample of the Swedish population. *Acta Oncol* 2012; 51(1):10-6.

181. Buchli C S, A. Regionalt vårdprogram. Low anterior resection syndrome (LARS). *In* Gotland RCS, ed., 2017.

182. Visser WS, Te Riele WW, Boerma D, et al. Pelvic floor rehabilitation to improve functional outcome after a low anterior resection: a systematic review. *Ann Coloproctol* 2014; 30(3):109-14.

183. Kalkdijk-Dijkstra AJ, van der Heijden JAG, van Westreenen HL, et al. Pelvic floor rehabilitation to improve functional outcome and quality of life after surgery for rectal cancer: study protocol for a randomized controlled trial (FORCE trial). *Trials* 2020; 21(1):112.

184. Asnong A, D'Hoore A, Van Kampen M, et al. Randomised controlled trial to assess efficacy of pelvic floor muscle training on bowel symptoms after low anterior resection for rectal cancer: study protocol. *BMJ Open* 2021; 11(1):e041797.

185. Sacomori C, Lorca LA, Martinez-Mardones M, et al. A randomized clinical trial to assess the effectiveness of pre- and post-surgical pelvic floor physiotherapy for

bowel symptoms, pelvic floor function, and quality of life of patients with rectal cancer: CARRET protocol. *Trials* 2021; 22(1):448.

186. Kim KH, Yu CS, Yoon YS, et al. Effectiveness of biofeedback therapy in the treatment of anterior resection syndrome after rectal cancer surgery. *Dis Colon Rectum* 2011; 54(9):1107-13.

187. Ramage L, Qiu S, Kontovounisios C, et al. A systematic review of sacral nerve stimulation for low anterior resection syndrome. *Colorectal Dis* 2015; 17(9):762-71.

188. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior resection: a systematic review and meta-analysis. *Colorectal Dis* 2019; 21(11):1240-1248.

189. Dulskas A, Smolskas E, Kildusiene I, et al. Treatment possibilities for low anterior resection syndrome: a review of the literature. *Int J Colorectal Dis* 2018; 33(3):251-260.

190. Marinello FG, Jimenez LM, Talavera E, et al. Percutaneous tibial nerve stimulation in patients with severe low anterior resection syndrome: randomized clinical trial. *Br J Surg* 2021; 108(4):380-387.

191. Ryoo SB, Park JW, Lee DW, et al. Anterior resection syndrome: a randomized clinical trial of a 5-HT3 receptor antagonist (ramosetron) in male patients with rectal cancer. *Br J Surg* 2021; 108(6):644-651.

192. Itagaki R, Koda K, Yamazaki M, et al. Serotonin (5-HT3) receptor antagonists for the reduction of symptoms of low anterior resection syndrome. *Clin Exp Gastroenterol* 2014; 7:47-52.

193. Stephens JH, Hewett PJ. Clinical trial assessing VSL#3 for the treatment of anterior resection syndrome. *ANZ J Surg* 2012; 82(6):420-7.

194. Christensen P, Krogh K. Transanal irrigation for disordered defecation: a systematic review. *Scand J Gastroenterol* 2010; 45(5):517-27.

195. Christensen P, Krogh K, Buntzen S, et al. Long-term outcome and safety of transanal irrigation for constipation and fecal incontinence. *Dis Colon Rectum* 2009; 52(2):286-92.

196. Iwama T, Imajo M, Yaegashi K, et al. Self washout method for defecational complaints following low anterior rectal resection. *Jpn J Surg* 1989; 19(2):251-3.

197. McCutchan GM, Hughes D, Davies Z, et al. Acceptability and benefit of rectal irrigation in patients with Low Anterior Resection Syndrome: a qualitative study. *Colorectal Dis* 2017.

198. Koch SM, Rietveld MP, Govaert B, et al. Retrograde colonic irrigation for faecal incontinence after low anterior resection. *Int J Colorectal Dis* 2009; 24(9):1019-22.

199. Rosen H, Robert-Yap J, Tentschert G, et al. Transanal irrigation improves quality of life in patients with low anterior resection syndrome. *Colorectal Dis* 2011; 13(10):e335-8.

200. Martellucci J, Sturiale A, Bergamini C, et al. Role of transanal irrigation in the treatment of anterior resection syndrome. *Tech Coloproctol* 2018; 22(7):519-527.

201. Rosen HR, Kneist W, Furst A, et al. Randomized clinical trial of prophylactic transanal irrigation versus supportive therapy to prevent symptoms of low anterior resection syndrome after rectal resection. *BJS Open* 2019; 3(4):461-465.

202. Rosen HR, Boedecker C, Furst A, et al. "Prophylactic" transanal irrigation (TAI) to prevent symptoms of low anterior resection syndrome (LARS) after rectal resection: results at 12-month follow-up of a controlled randomized multicenter trial. *Tech Coloproctol* 2020; 24(12):1247-1253.

203. Didailler R, Denost Q, Loughlin P, et al. Antegrade Enema After Total Mesorectal Excision for Rectal Cancer: The Last Chance to Avoid Definitive Colostomy for Refractory Low Anterior Resection Syndrome and Fecal Incontinence. *Dis Colon Rectum* 2018; 61(6):667-672.

204. Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. *Nat Rev Urol* 2011; 8(1):51-7.

205. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. *Br J Surg* 2008; 95(8):1020-8.

206. Karlsson L, Bock D, Asplund D, et al. Urinary dysfunction in patients with rectal cancer: a prospective cohort study. *Colorectal Dis* 2020; 22(1):18-28.

207. Del Rio C, Sanchez-Santos R, Oreja V, et al. Long-term urinary dysfunction after rectal cancer surgery. *Colorectal Dis* 2004; 6(3):198-202.

208. Kristensen MH, Elfeki H, Sinimaki S, et al. Urinary dysfunction after colorectal cancer treatment and impact on quality of life-a national cross-sectional study in males. *Colorectal Dis* 2021; 23(2):394-404.

209. Sinimaki S, Elfeki H, Kristensen MH, et al. Urinary dysfunction after colorectal cancer treatment and its impact on quality of life - a national cross-sectional study in women. *Colorectal Dis* 2021; 23(2):384-393.

210. Perry WRG, Abd El Aziz MA, Duchalais E, et al. Sexual dysfunction following surgery for rectal cancer: a single-institution experience. *Updates Surg* 2021; 73(6):2155-2159.

211. Ho VP, Lee Y, Stein SL, et al. Sexual function after treatment for rectal cancer: a review. *Dis Colon Rectum* 2011; 54(1):113-25.

212. Stamopoulos P, Theodoropoulos GE, Papailiou J, et al. Prospective evaluation of sexual function after open and laparoscopic surgery for rectal cancer. *Surg Endosc* 2009; 23(12):2665-74.

213. Hendren SK, O'Connor BI, Liu M, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg* 2005; 242(2):212-23.

214. McHugh ML. The chi-square test of independence. *Biochem Med (Zagreb)* 2013; 23(2):143-9.

215. Mishra P, Singh U, Pandey CM, et al. Application of student's t-test, analysis of variance, and covariance. *Ann Card Anaesth* 2019; 22(4):407-411.

216. Hazra A, Gogtay N. Biostatistics Series Module 4: Comparing Groups - Categorical Variables. *Indian J Dermatol* 2016; 61(4):385-92.

217. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; 16(1):139-44.

218. Schober P, Vetter TR. Repeated Measures Designs and Analysis of Longitudinal Data: If at First You Do Not Succeed-Try, Try Again. *Anesth Analg* 2018; 127(2):569-575.

219. Larson MG. Analysis of variance. *Circulation* 2008; 117(1):115-21.

220. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Logistic regression. *Perspect Clin Res* 2017; 8(3):148-151.

221. Varghese C, Wells CI, O'Grady G, et al. The Longitudinal Course of Low-Anterior Resection Syndrome: An Individual Patient Meta-Analysis. *Ann Surg* 2022.

222. Wang X, Cheng Z. Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. *Chest* 2020; 158(1S):S65-S71.

223. Meyer VM, Benjamens S, Moumni ME, et al. Global Overview of Response Rates in Patient and Health Care Professional Surveys in Surgery: A Systematic Review. *Ann Surg* 2022; 275(1):e75-e81.

224. Krosnick JA. Survey research. *Annu Rev Psychol* 1999; 50:537-67.