A Statistical Analysis of Bowel Function and Quality of Life after Anterior Resection for Rectal Cancer

Author: Amanda Andersson

June 30, 2019

UNIVERSITY OF GOTHENBURG

DEGREE PROJECT IN MEDICINE
Supervisors: Professor Eva Angenete, Department of Surgery Institute of Clinical
Sciences at Sahlgrenska Academy, Gothenburg
Associate Professor Marie-Louise Lydrup, Department of Surgery Institute of
Clinical Sciences at Lund University, Malmö

University of Gothenburg
Sahlgrenska Academy

Lund University

Abstract

A Statistical Analysis of Bowel Function and Quality of Life after Anterior Resection for Rectal Cancer

Amanda Andersson, Degree Project in Medicine, 2019
Department of Surgery, Sahlgrenska Academy at University of Gothenburg, Sweden

Background Colorectal cancer is the third most common cancer in Sweden and about a third is localized within the rectum. During the last decades, the 5-year survival rate has increased markedly due to improved oncological and surgical treatment. The postoperative morbidity is yet substantial, in terms of bowel dysfunction and impaired quality of life, motivating future research in this field.

Objective The aim of this study was to investigate if the surgical technique partial mesorectal excision is superior to total mesorectal excision regarding bowel function and quality of life in patients with rectal cancer.

Method The cohort was identified through the Swedish Colorectal Cancer Registry and consisted of 1495 patients treated with anterior resection for rectal cancer 2007-2013 at 15 Swedish hospitals. All patients alive received questionnaires about bowel function and quality of life. Bowel function was measured with a scoring system based on clusters of postoperative bowel symptoms, called low anterior resection syndrome (LARS), where "major LARS" represents the most severe form. Patients no longer alive or with permanent stoma were excluded (n=483) and registry data was completed with data from medical records. Univariate analyses for included patients were performed with Chi-square test for categorical data and ANOVA/Mann Whitney U test for continues data. The association between surgical procedure and bowel dysfunction was evaluated using binary logistic regression, with adjustments for potential confounders.

Results Of the 254 patients suffering from major LARS, 81,1% were operated with total mesorectal excision and 18.9% with partial mesorectal excision (p<0.001). Odds Ratio for major LARS comparing total- to partial mesorectal excision was 1.82 (95% CI 1.12 to 2.95, p=0.016). Partial mesorectal excision was also associated with better social function and less diarrhea (p<0.001).

Conclusion Patients operated with anterior resection for rectal cancer has a higher risk of developing severe bowel dysfunction, social dysfunction and higher frequency of diarrhea when treated with total mesorectal excision compared to partial mesorectal excision.

Key Words: Rectal neoplasm, Total mesorectal excision, Partial mesorectal excision, Bowel dysfunction

Populärvetenskaplig Sammanfattning

En Statistisk Analys av Tarmfunktion och Livskvalitet hos Patienter Opererade för Ändtarmscancer

Amanda Andersson, Degree Project in Medicine, 2019
Department of Surgery, Sahlgrenska Academy at University of Gothenburg, Sweden
Handledare: Professor Eva Angenete and Associate Professor Marie-Louise Lydrup

Cancer i tjock- och ändtarm är den tredje vanligaste cancerformen i Sverige och drabbar ca 6200 personer varje år. En tredjedel av denna cancer är belägen i ändtarmen, den sista delen av tarmen som övergår till anus några centimeter innanför analöppningen. De senaste decennierna har överlevnaden för patienter med ändtarmscancer ökat markant, tack vare ny kunskap inom både kirurgi, strålbehandling och cellgifter. Många patienter upplever dock svåra tarmrelaterade biverkingar efter operationen, något som även påverkar deras livskvalitet.

Förstahandsbehandlingen för ändtarmscancer är kirurgi vilken kan utföras med olika kirurgiska tekniker. För tumörer utan spridning är en kirurgisk teknik vid namn "främre resektion" lämplig. Främre resektion kan genomföras på två skilda sätt, med fullständig eller ofullständig borttagningen av ändtarmen. Den förstnämnda varianten tar bort större delen av ändtarmen nedom tumören, vilket lämpar sig bäst på lågt belägna tumörer med tillägg av strålbehandling. Den andra varianten sparar en del av ändtarmens nedre del och används i huvudsak för högt belägna tumörer. Den senare är något svårare att utföra för kirurgen varför ca en tredjedel av högt belägna tumörer ändå opereras med en fullständig borttagning av ändtarmen.

Syftet med denna studie var att undersöka skillnaden i tarmfunktion och livskvalitet hos patienter opererade med de två beskrivna operationsmetoderna. Frågeformulär som berör tarmfunktion och livskvalitet skickades ut till patienter med ändtarmscancer som mellan 2007 och 2013 opererats med främre resektion. Grupperna jämfördes med varandra och den grupp som hade opererat bort en mindre del av tarmen upplevde både bättre tarmfunktion som livskvalitet. Studiens slutsats var därför att man mer konsekvent borde operera bort en mindre del av tarmen, förutsatt att det alternativet är möjligt.

Contents

Acknowledgements

1   Abbreviations

APE	Abdominoperineal Excision
CT	Computed Tomography
EAS	External Anal Sphincter
EORTC	European Organization for Research and Treatment of Cancer
FAP	Familial Adenomatous Polyposis
FIT	Fecal Immunochemical Test
HNPCC	Hereditary Nonpolyposis Colorectal cancer
IAS	Internal Anal Sphincter
LARS	Low Anterior Resection Syndrome
MAP	MUTYH-Associated Polyposis
MDT	Multidisciplinary Team
PET	Positron Emission Tomography
PME	Partial Mesorectal Excision
QoL	Quality of Life
SCRCR	Swedish Colorectal Cancer Registry
SCREESCO	Screening of Swedish Colons
SVF	Standardiserat Vårdförlopp
TEM	Transanal Endoscopic Microsurgery
TME	Total Mesorectal Excision
UICC	Union for International Cancer Control

2   Background

2.1   Rectal Anatomy and Physiology

In modern literature, the rectum is defined as the final segment of the large intestines reaching 15 cm from the *anal verge*. This definition is derived from the anatomical features of the transition zone distinguishing sigmoid colon from rectum, the *rectosigmoid junction*, with a gradual loss of tenia colon and a lack of small peritoneal pouches called *appendices epiploicae*. The anal verge, from which clinical measurements with rigid sigmoidoscopy may be conducted, is defined as the transitional zone between anal epithelium and perianal skin. From this zone rectum can be further classified into low- (<5 cm), mid- (5-10 cm) and upper rectum (10-15 cm) (1-3).

Even though rectum is a Latin word for *rectus* it is in vivo curved following the concavity of *sacrum*. Viewed from a coronal section, the mid and upper part is smoothly shaped into three lateral curves which can be encountered during sigmoidoscopy as semilunar structures known as rectal shelfs or "Valves of Houston". The shelf in the middle is often the most prominent one, making it a clinically convenient structure for indicating the level of the *peritoneal reflexion*. This is where peritoneum abruptly leaves the anterior wall of rectum to reach the bladder (male) or the posterior vaginal fornix (female) in front, resembling a reflexion. Although the exact level

of the peritoneal reflexion is debated, the relationship between the rectum and the peritoneum is of importance during rectal surgery. Below these rectal shelves, the rectum is usually dilated forming a structure called *ampulla*, acting as a reservoir for fecal content (1,3).

In the most distal part of the rectum where rectum continues into anus, it is angled forward by the *puborectalis sling* of the *levator ani muscle*, viewed from a longitudinal section. Along with the *coccygeal muscle*, the levator ani muscle form the *pelvic diaphragm* leaving a gap for rectum called *levator hiatus*. At this level, in the anorectal junction, muscle fibers from the levator ani muscle blend with the deep striated muscles from the external anal sphincter (EAS) creating the *anorectal ring*. EAS is longer and wider than the internal anal sphincter (IAS), which instead is an extension of the inner layer of smooth circular muscles of the rectal wall. The edge of IAS, called the *intersphincteric groove*, is usually palpable during digital rectal examination. The striated muscles of EAS, with help from the puborectalis sling, have a ground state of tonic contraction acting under influence of the will. The smooth muscles of IAS are instead innervated by autonomic nerve fibers, acting entirely involuntarily. These smooth muscles also have a ground state of tonic contraction, predominantly maintained through sympathetic stimulation. As fecal content accumulates in the ampulla,the pressure in the rectum increases and stimulates stretch receptors in the rectal wall. In response to this increased pressure, IAS relaxes in a process called the rectoanal inhibitory reflex. A propulsive movement push faeces over the sphincter barrier. Under voluntary control, EAS is able to relax, eliminating the faeces through defecation. These vital functions implicates risk for postoperative side effects in rectal cancer patients (1, 3, 4).

The rectum is also surrounded by a layer of fat called the *perirectal fat*. It contains vessels, lymph nodes and nerves draining and supplying the structures of rectum. The perirectal fat is in its turn limited and surrounded by a distinct circumferential fascial layer called the *fascia propria of the rectum*. This facia enclosing the perirectal fat with its lymph nodes is referred to as *mesorectum* and plays an important role in the performance of anterior resection, a surgical treatment for rectal cancer. For a successful outcome with low local recurrence and a high survival rate, a completely intact mesorectum should be resected (3, 5). Since the majority of pelvic nerves are located in a sensitive area close to the anterior of rectum, the knowledge of rectal innervation is also of great importance when operating patients with rectal cancer. The innervation is composed of both autonomic and somatic nerves, the latter originating from sacral roots (S3-S4), innervating the levator ani muscles and EAS. Anterior to the bifurcation of the *abdominal aorta* is a network of sympathetic and visceral nerves called the *superior hypogastric plexus*. Two trunks with sympathetic fibers from the plexus continue in caudal direction, forming the left and right hypogastric nerves. These converge with parasympathetic fibers from sacral roots (S2-S4), sometimes called *splanchnic nerves* or "nervi erigentes", to form the inferior hypogastric plexus. This plexus, consisting of both sympathetic and parasympathetic fibers, partially innervates rectum. These fibers are involved in the gastrocolic reflex, secondary to distention of the gastric wall, resulting in a defecatory reflex. Yet, the inferior hypogastric plexus mainly innervates other pelvic

structures such as the prostate, bladder, upper urethra and the root of penis and will if damaged affect the functions of these as well (6).

The arterial supply of rectum principally consists of five arteries. The main artery is the *superior rectal artery*, a prolongation of the *inferior mesenteric artery*, changing name when entering the pelvic cavity. It runs posterior to the rectum through the perirectal fat, branching into two smaller arteries supplying the rectal wall at each side. The four other supplemental arteries are the *left and right medial rectal artery* (from the *internal iliac artery*) and the *left and right internal rectal artery* (from the *internal pudendal artery*). Besides these arteries, the *median sacral artery* (branching posteriorly from aorta proximal to the aortic bifurcation) supplies lower rectum. The venous system is broadly similar to the arterial supply. As the lymphatic fluid can be a carrier of cancer cells, the lymphatic drainage is important in the clinical investigation when localizing the spread of cancer. Regional lymph nodes are localized both in the mucosa of rectum and in the mesorectal fat, draining the rectal tissue and passing it further onto the principal nodes. The main lymph nodes draining rectum are the *inferior mesenteric lymph nodes* and the *internal iliac lymph nodes*. However, very distal rectal cancers are drained to lymph nodes in the groins (3).

2.2 Epidemiology of Colorectal Cancer

Over 50 percent of the global incidence of colorectal cancer occurs in Asia and nearly a third in Europe. The same numbers also apply to mortality. However, when estimating the incidence of colorectal cancer per 100 000, Europe remains in a second place while Australia/New Zeeland ends up in first place.

In Sweden, colorectal cancer is the third most common cancer with up to 6200 cases per year. About a third of these tumors is localized within the rectum. While the incidence of colon cancer is increasing in the Swedish population the incidence of rectal cancer has been stabilized during the last years, now estimated to 14/100 000 amongst women and 25/100 000 amongst men. The mortality in rectal cancer ranges from 6/100 000 for women to 11/100 000 for men with a 5-year survival rate of 64% and 61% respectively. The prevalence of rectal cancer in Sweden, 2015 was estimated to be nearly 9000 women and over 10 000 men. The median age at time of diagnosis is 70 and only a few is diagnosed under the age of 50 (2, 5, 7-10).

2.3 Etiology of Colorectal Cancer

There is no single known factor triggering rectal neoplasms, instead the genesis of colorectal cancer relies upon two main factors, environmental and genetic. Environmental factors have been proven to affect the risk through studying generations moving from low- to high risk areas and several risk factors are included in the concept of a western lifestyle: red or processed meat, tobacco and moderate to heavy alcohol consumption. Other risk factors are high body mass index, abdominal fat, diabetes type II and longstanding inflammatory bowel disease (2, 5).

About 98% of all colorectal cancers are histologically classified as adenocarcinomas. They are often further classified by their chromosomal-, microsatellite- or epigenetic instability. Rectal cancer is mostly characterized by chromosomal instability, but about one third is associated to an abnormal DNA methylation. Its carcinogenesis involves several different pathways, e.g. the WNT-signaling pathway. Mutations are frequently seen in the tumor suppressor gene *Adenomatous Polyposis Coli* (APC), but inactivation of supplementary tumor suppressor genes in the *P53-* and *TGFβ-* pathways or activation of oncogenes such as *KRAS* and *PI3CKA* occur as well (11).

Hereditary factors account for about 20% of all colorectal cancers. The main inherited cancer syndromes are Lynch syndrome, *Familial Adenomatous Polyposis* (FAP) and *MUTYH-associated polyposis* (MAP). The Lynch syndrome, also known as *hereditary non-polyposis colorectal cancer* (HNPCC), is an autosomal dominant inherited cancer caused by mutations in genes for DNA-reparation. Additionally, it has a genetic predisposition for a variety of cancers, but with an increased risk for colorectal cancer. FAP also follows a pattern of autosomal dominant inheritance and is characterized by numerous adenomatous polyps in the epithelia of the duodenum, colon or rectum. The majority of cases are caused by mutations in the APC gene. In case of APC-negativity, MAP should be suspected since the clinical course is comparable to FAP. MAP is caused by a mutation in the MUTYH-gene and has an autosomal recessive inheritance pattern. Other inherited cancer syndromes are Juvenile Polyposis and Peutz-Jeghers syndrome (5).

2.4 Prevention

Prevention of colorectal cancer can be subdivided into three categories, primary, secondary and tertiary.

The main principal of primary prevention is to eliminate risk factors related to colorectal cancer and instead promote a healthy lifestyle with physical activity, weight control and smoking cessation (5).

The secondary prevention aims to discover the cancer in an early stage, for instance by screening high risk groups. The European Union suggested all members as early as 2003 to introduce screening for colorectal cancer. In 2008, a screening program was introduced in Sweden for the regions of Stockholm and Gotland. In the beginning of 2014, a five year long Swedish multicenter study called SCREESCO (Screening of Swedish Colons) was established with the purpose of determining which screening method is best for discovering colorectal cancer in early stages. This ongoing study compares Fecal Immunochemical Test (FIT) with colonoscopy and will include its final patients in 2019. By the time this is accomplished, the National Board of Health and Welfare in Sweden will suggest a national organized screening program to be introduced for men and women between 60 and 74 years of age. The suggested method of screening is primarily FIT, followed by colonoscopy if positive. Besides generating economical gains in a long term perspective, this is expected to save 300 lives per year (5).

The final tertiary prevention includes surgical and oncological treatment; how to increase the surveillance rate and decrease the morbidity with help from further research and new technical development. This is the main focus in this report, further described in the following paper (5).

2.5 Symptoms and Diagnosis

2.5.1 Clinical Presentation

Symptoms of rectal cancer are rather rare in early stages, complicating the diagnostic possibilities. A majority of rectal cancers present with blood in feces, but this is also a symptom of hemorrhoids, a very common but harmless condition. The positive predictive value for rectal bleeding is about 2% in the Swedish population. Other symptoms resulting in patients seeking medical care are pain during defecation or the impression of resistance in the lower rectum. Both patients' and doctors' delay is consequently an actuality (5, 12).

According to Swedish guidelines, colorectal cancer should always be suspected when presented with at least one of the following symptoms: blood in feces, anemia or a change in bowel habits for more than four weeks (with no other explanation) in conjunction with an age over 40. A medical history in accordance with the latter justifies a legitimate suspicion and should always be followed by immediate remittance for further investigation, in Sweden pursuant to a standardized procedure termed "Standardiserat Vårdförlopp" (SVF). In practice, this would also be the case for younger patients with the same symptomatology, even though the guidelines are limited to patients over 40 years of age (5).

However, from the suspicion of colorectal cancer, SVF implies a clinical assessment within ten days to minimize time to diagnosis. In the Swedish Colorectal Cancer Registry (SCRCR), the date of diagnosis is equal to the date of the clinical diagnosis, often validated through rectal endoscopy. According to Swedish guidelines from the National Board of Health and Welfare, the time from diagnosis to the start of treatment should not exceed 42 days (5, 7).

2.5.2 Clinical Assessment

Clinical assessment is based on medical history, physical examination and endoscopy with biopsy, supplemented with a full blood count, carcinoembryonic antigen and liver- and renal function tests. If the histopathological investigation verifies neoplasia, a computer tomography (CT) scan of thorax and abdomen should be completed to investigate the presence of metastases. This is necessary for staging of the tumor, explained in the next section. For rectal cancers, the primary imaging technique to assess the preoperative pelvic extent of disease is pelvic MRI, determining whether or not preoperative oncological treatment is appropriate. Endoscopic ultrasound can be employed as a complement to the MRI, improving the accuracy of early T-

staging. Patients with extrapelvic spread or locally advanced tumors can also be offered positron emission tomography (PET) providing additional information for assessing the condition being either palliative or curative. Current knowledge is not strong enough to motivate the use of PET for all patients. In case of increasing age or comorbidity, associated with a higher postoperative mortality and morbidity, a geriatric examination or screening for frailty should be considered (5, 13).

2.5.3 Clinical- and Pathological Staging

The internationally accepted standard for cancer staging is the classification according to the Union for International Cancer Control (UICC), named UICC TNM Classification. UICC have published classifications of malignant tumors for over 50 years, summarized for rectal cancer in **Fig. 1.** T refers to the primary tumor and its depth of growth into the bowel lining, N describes the spread to regional lymph nodes and M the presence of extrapelvic metastatic spread, including extraregional lymph nodes. The c prescript (cTNM) indicates the clinical staging, especially important when discussing neoadjuvant treatment, whereas the p prescript (pTNM) defines the postoperative pathological stage. By the time cTNM is determined, a multidisciplinary team (MDT) along with radiologists, surgeons, oncologists and pathologists should attend a multidisciplinary team conference discussing and customizing the treatment for each individual patient (5, 13, 14).

2.6 Treatment of Rectal Cancer

2.6.1 Oncological Treatment

The treatment of rectal cancer consists of surgical treatment and in applicable cases additional oncological treatment, in times a combination of both. Oncological treatment preceding surgery is called *neoadjuvant therapy*, a concept including both radio- and chemotherapy, where radiotherapy is used for a large part of patients with rectal cancer. Postoperative treatment is termed *adjuvant therapy* and includes both treatments as well. Adjuvant chemotherapy is commonly used in the treatment of colon- and rectal cancer, even though the evidence for its efficiency in treating rectal cancer is weak. Adjuvant radiotherapy is seldom an option (5).

When customizing the oncological treatment for patients with rectal cancer, rectal tumors may be discussed in terms of three general appellations: *good* (early), *bad* (intermediate) or *ugly* (locally advanced). "Good" rectal tumors (cT1-T2) are found to have a low potential for local recurrence, hence there is considered to be no need for neoadjuvant treatment, while the risk for local recurrence in "bad" rectal tumors is considered high enough to motivate the expected side- and long-term effects of radiotherapy. The probability of radical resection in "ugly" rectal tumors is considered so low that adjuvant chemoradiotherapy is needed for the tumoricidal effect. Another factor to take into account is the height of the tumor. Very low

"good" rectal tumors are generally recommended radiotherapy due to limitations of the surgical margin, while its not necessarily recommended for "bad" rectal tumors in the upper rectum (19).

As mentioned, radiotherapy is considered necessary for a large number of rectal tumors, partly for the tumoricidal effect but also to shrink the tumor before surgery. Tumors are treated according to different schedules, with different quantities of radiation, depending on their characterizations. The short course (5x5 Gy) with a total of 25 Gy is an alternative for "bad" tumors, ideally followed by surgery within 2-4 days. For "ugly" tumors the long course (1,8- 2,0 Gy every day for 5 weeks) together with chemotherapy is an alternative followed by surgery after 6-8 weeks (5).

2.6.2   Surgical Treatment

The primary treatment for rectal cancer is surgery. Besides anterior resection, Hartmann's operation, abdominoperineal resection of the rectum (APR) and local excision are all valid methods of choice. The latter is only justifiable in exceptional cases. The decision of treatment should be thoroughly discussed at a multidisciplinary conference regarding tumor level, TNM-stage and the status of the patient.

Hartmann's operation is a valid alternative for patients with poor function of the sphincter, high comorbidity or patients not fit enough to handle complications due to anastomotic dehiscence. This procedure implicates resection of the rectum and surrounding mesorectum along with a permanent sigmoid colostomy and closure of the anorectal remnant (5). This is thought to reduce the risk of anastomotic leakage, a life-threatening condition for frail patients, but also prevent the risk for fecal incontinence which would be the risk with a sphincter-sparing operation. Still, there has been some disagreements over the last years, questioning the benefits of Hartmann's operation and pointing to the high risk of a pelvic abscess. Instead, as an alternative for this category of patients, the surgical procedure APR has been put forward. APR is generally indicated as a treatment for locally advanced tumors in the lower rectum, also implicating removal of the rectum and the surrounding mesorectum along with a permanent sigmoid colostomy, but it also includes resection of anus and dissection of pelvic structures. However, a randomized multicenter study comparing functional outcomes between Hartmann's operation and APR (HAPIrect) is in progress in Sweden since 2014. The APR in this study is performed with an intersphincteric approach, resulting in less damage to the perineum (5). At last, local excision is mainly performed for benign tumors or early stage rectal cancer, often performed as transanal endoscopic microsurgery (TEM). As the operation is performed with a transanal approach, hence less invasive, it is also valuable for patients with more advanced tumors, medically unfit for radical surgery.

2.7 Anterior Resection

Anterior resection with mesorectal excision is a valid alternative in the majority of patients with rectal cancer, performed with two different surgical procedures: total mesorectal excision (TME) or partial mesorectal excision (PME). TME is typically performed for mid and low rectal tumors and includes excision of all surrounding mesorectum enclosed by the visceral pelvic fascia at the level of the pelvic floor. PME is typically performed for upper rectal tumors and is defined as resection of the rectum and the surrounding mesorectum to an intraoperatively determined level of at least 5 cm from the distal tumor margin. Provided that the rectum is dissected perpendicularly to the bowel lining with sharp edges and no coning of the mesorectum, the radicality of PME is comparable to TME (5, 15, 16).

In resectioning of the mesorectum, important nerves and arteries must be identified to minimize postoperative side effects. E.g. the hypogastric- and pelvic nerves supplying important pelvic structures and the inferior mesenteric artery supplying the upper rectum, left- and sigmoid colon. The inferior mesenteric artery may be dissected either proximally to the branch of the left colic artery ("high tie") or below ("low tie"). No present studies have indicated any difference in survival, but a "high tie" has been suggested to increase the risk of damaging the nerves supplying left colon, affecting the rectal function (5, 17, 18).

Anterior resection is preferably completed with a construction of an anastomosis, often together with a proximal defunctioning stoma protecting the distal anastomosis. In patients operated with TME the rectal remnant will naturally end up very short, entailing technical limitations in the choice of anastomosis. Alternatives for low anastomosis is a colonic reservoir (J-pouch) or side-to-end anastomosis, both with similar functional outcomes. Patients treated with PME will most frequently receive an end-to-end anastomosis, rarely being in need of a defunctioning stoma (19).

Both laparotomy and laparoscopy are sensable surgical approaches for both TME and PME. Laparoscopy is in general associated with a shorter hospital stay, lesser need for analgesics and a faster recovery, however there is no evidence for a lower mortality or long-term morbidity compared to laparotomy (5).

2.7.1 Oncological Outcome After Anterior Resection

In the original series by Heald et al 1982, TME was recommended for rectal cancer at all levels, resulting in a low local recurrence, low mortality and at the time acceptable morbidity. However, anterior resection with total excision of the mesorectum results in the loss of an organ with distinct qualities, which adversely affects bowel function, e.g. the reservoir function of ampulla and the neural coordination of defecation (20, 21). Lopez-Kostner et al demonstrated 1998 that oncological outcomes, in terms of local recurrence and survival rate for upper rectal tumors treated with PME, were similar to those of sigmoid tumors. In their conclusion, TME was not considered

necessary for upper rectal tumors (22). Law et al reached the same conclusion in their study from 2004, implicating that a selective approach regarding use of total mesorectal excision for mid and distal rectal cancer is more appropriate and reasonable concerning postoperative morbidity. Independent factors for poor survival in this study were instead an advanced tumor stage or presence of lymphovascular or perineural invasion (4). In a recent study from 2016, Kanso et al also indicated that the prognosis with PME in terms of local recurrence and survival rate, is not different compared to TME and should therefore be recommended in the treatment of upper as well as some mid rectal tumors (23).

2.8 Functional Outcome

2.8.1 LARS-Score

The majority of patients that undergo an anterior resection develop bowel dysfunctions such as urgency, incontinence and increased stool frequency, often referred to as low anterior resection syndrome (LARS). Based on these postoperative clusters of symptoms, Emmertsen et al developed a validated and reliable scoring system called LARS-score (**appendix 1**) correlating with quality of life (QoL). The questionnaire consists of five simple questions related to bowel habits, each with three different alternative answers and different scores, and is easy to use in the assessment of bowel function. The sum of the patients LARS-score is divided into three categories: no LARS (0-20 points), minor LARS (21-29 points) and major LARS (30-42 points). Up to 40 % of patients treated with anterior resection suffer from major LARS, the most severe form of bowel dysfunction (24), confirmed to have a high sensitivity and specificity for impairment of QoL (25). Although LARS-score in its original form was developed using a Danish population, the scoring system has been demonstrated to be easily applicable for other populations across Europe and one could infer global relevance as well (26).

According to a follow-up study from Emmertsen et al, LARS often arises immediately after surgery, sometimes decreasing a few months post operation, reaching a steady state usually within the first two years. Some patients recover almost normal bowel function while others suffer from lifelong morbidity (9). The suggested long-term effects are confirmed in a new study from 2019, by Pieniowski et al, where LARS-score and its impact on QoL were concluded to persist over time (27). In 2018, Battersby et al were the first ones to create a nomogram called "Pre-Operative LARS score" (POLARS) to predict the bowel dysfunction prior to anterior resection. The POLARS model is suggested to provide an individualized and quantifiable measure of the patients' predicted LARS-score and may be useful when customizing individual treatment (28).

2.8.2 Quality of Life

To illustrate the QoL for rectal cancer patients more precisely, another relevant questionnaire is the European Organization for Research and Treatment of Cancer (EORTC) generic questionnaire QLQ-C30 (**appendix 2**). This is a self-administered questionnaire developed especially for cancer patients, with 30 simple questions summarized to a 15 variables. These variables are then separated into three different segments: global health status, functional outcomes (e.g. physical- and social function) and specific symptoms (e.g. fatigue and pain). The summation for every variable ranges from zero to one hundred points; a high functional score represents a high level of function whereas a high symptom score represents a high level of symptoms (29).

2.8.3 Factors Associated with Bowel Dysfunction

A plethora of variables have been presented in previous research to affect bowel function in rectal cancer patients after anterior resection. In 2004, Law et al demonstrated an association between surgical procedure (TME compared with PME) and postoperative morbidity (4). In a study from Bregendahl et al (2013), TME was declared to be an independent risk factor for major LARS (24), the same result as Kupsch et al (2018) demonstrated several years later (30). In the study from Kupsch et al, radiotherapy and young age were also confirmed to be associated to the severity of LARS, while no association was found with sex, anastomotic leakage, time since surgery or tumor characteristics. In the study where Emmertsen et al first presented their developed LARS-score (2012), a significant increase in LARS-score correlating to radiotherapy, low tumor height and TME compared with PME was found (25). The key variables identified in the POLARS model (2018) was age, sex, tumor height, defunctioning stoma, preoperative radiotherapy and TME compared with PME. Anastomotic leakage has also been determined to correlate with bowel dysfunction but could naturally not be integrated in this preoperative nomogram (28).

3 Research Question

Several international studies have demonstrated comparable oncological outcomes in terms of mortality and local recurrence between PME and TME (4, 22, 23). A difference in functional outcomes, such as bowel dysfunction and impaired QoL has also been demonstrated to be higher in patients treated with TME (4, 9, 24, 25, 28). Yet, the Swedish general guidelines for PME are still rather vague, resulting in local differences for these patients at Swedish hospitals. The aim of this study was to investigate if PME is superior to TME concerning bowel function and QoL, a valuable knowledge when developing new guidelines of treatment with anterior resection for patients with rectal cancer.

Null hypotheses within this study:

- There is no significant difference in bowel dysfunction in patients treated with anterior resection for rectal cancer when comparing TME to PME.

- There is no significant difference in quality of life in patients treated with anterior resection for rectal cancer when comparing TME to PME.

4 Method

4.1 Data Collection Procedures

The cohort in this quantitative retrospective study consists of 1495 patients, operated with anterior resection for rectal cancer between 2007 and 2013 in 15 different hospitals in Northern, Southern and Western healthcare regions in Sweden, identified through the Swedish Colorectal Cancer Registry (SCRCR). All patients alive received questionnaires about bowel function (LARS-Score, **Appendix 1**) and QoL (EORTC QLQ-30 version 3.0, **Appendix 2**), sent and collected during the spring of 2018. Inclusion criteria for participating in this study was bowel continuity; patients with permanent stoma were consequently excluded from the statistical analyses. Registry data was completed with data from medical records concerning defunctioning stoma, type of anastomosis and anastomotic leakage. Patient demographics such as age, sex, ASA classification, tumor stage, surgical approach, surgical procedure and neoadjuvant therapy were already acquired from SCRCR, used in a previous study analyzing NSAIDs effect on anastomotic leakage in the same cohort (31).

4.2 Variable Analyses

LARS-score was calculated and categorized into no LARS, minor LARS or major LARS. These categories were later dichotomized into no major LARS (no LARS +

minor LARS) and major LARS. Age at surgery and months since surgery were dichotomized according to their median value. Tumor height was divided in accordance to the thirds of rectum: low- ($<$5 cm), mid- (5-10 cm) and upper rectum (5-10 cm). ASA classification was dichotomized into grade I-II and grade III-IV while tumor stage, due to its distribution, was divided into three categories: stadium I, stadium II and stadium III-IV. Since the sample size was considered large enough, continuous data was presumed to have a normal distribution. This was visually and descriptively confirmed in SPSS for tumor height and age at surgery, whereas LARS-score and months since surgery were confirmed to have a skewed distribution. However, since all continuous data was categorized into groups of two or three, all variables were treated as categorical data in further analyses.

Scoring of the QoL data was performed according to the EORTC QLQ-C30 scoring manual. Missing answers were dealt with in accordance with the prescribed methods for multi-item scales: "If at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which are present for that respondent" (29). Mean values were recalculated into scales of 0-100 and treated as continuous values. A skewed distribution was visually encountered for all items in SPSS, motivating further analysis with non-parametric tests.

4.3 Statistical Analysis

Univariate analysis was performed comparing both surgical procedures (TME and PME) and LARS-score (no major LARS and major LARS) and a significance level of $p<0.050$ was considered statistically significant. Chi-square tests were performed for categorical data, i.e. all relevant variables. The association between surgical procedure and major LARS was evaluated using binary logistic regression with adjustment for potential confounders.

Statistical significance for the QoL data was performed using Mann Whitney U-test, also with a significance level of $p<0.050$. Levene's median based homogeneity of variance test was performed to verify if the skewed distribution was equally distributed between groups, validating the result of the Mann Whitney U-test.

4.4 Ethical Approval

The study was approved by the regional ethical review boards at Umeå University and the University of Gothenburg. All patient data was treated confidentially and is preserved under the Healthcare's obligations to observe silence.

5   Results

From the original cohort consisting of 1495 Swedish patients with rectal cancer, 398 patients were no longer alive when sending out questionnaires and were consequently excluded from the study according to the study flowchart, **Fig. 2**. A number of 85 patients received the questionnaires but reported having a permanent stoma and were also excluded from the study. A cohort of 1012 patients was eligible for the inclusion-questionnaires, from which 193 patients declined participation, 247 did not answer the questionnaires and 52 patients responded with an incomplete LARS-score. These groups, consisting of 492 patients in total, were referred to as "non-participants" and the remainder of 520 patients were included for further analysis. The response rate including those declining participation was 77%.

When comparing patient and treatment characteristics for included patients with non-participants, **table 1**, this group had fewer females (39.6% versus 52.8 %), a lower median age (65 versus 68), less anastomotic leakage (7.9% versus 12.8%), fewer months since surgery (84 versus 89) and were more frequently treated with chemotherapy (15.9 % versus 9.8%). Other variables were similar between groups.

Out of the included patients, 48.8 % suffered from major LARS, described in **table 2**. The characteristics of this group compared to No major LARS were more females (47.2% versus 32.3%, p=0.001), more anastomotic leakage (10.6% versus 5.3%, p=0.023), more TME (81.1% versus 58.5 %, p<0.001), more side-to-end/J- pouch (80.9% versus 71.6%, p=0.015), more defunctioning stoma (90.9% versus 76.5%, p<0.001) and more neoadjuvant radiotherapy (72.3% versus 46.2%, p<0.001). A statistically significant difference was also found comparing major LARS to tumor height (p<0.001) and months since surgery (p=0.038). A schematic illustration between these associations is presented in **Fig 3**.

When analyzing variables comparing surgical procedure, 29.1% of upper rectal tumors were treated with TME and 15.1% of mid rectal tumors were treated with PME, presented in **Table 3**. Of those treated with TME, 57.1% had major LARS compared to 30.3 % treated with PME (p<0.001). Statistical significance was also achieved for tumor height, defunctioning stoma, type of anastomosis and neoadjuvant therapy, all with p-values <0.001. There was no statistically significant difference between groups considering age, ASA classification, open surgery or anastomotic leakage.

The results from the binary logistic regression for major LARS in **Table 4** demonstrates a strong association with several variables: treatment with TME (OR 1.82; 1.12 to 2.95; p=0.016), female gender (OR 1.975; 1.32 to 2.95; p=0.001), anastomotic leakage (OR 2.54; 1.20 to 5.38; p=0.015) and neoadjuvant therapy (OR 2.7; 1.79 to 4.08; p<0.001). Defunctioning stoma did not reach statistical significance (p=0.067) in this model.

Table 5 describes the median value and its range for 15 different variables related to QoL, comparing PME to TME. The result demonstrates a statistically significant

difference for social function (p<0.001) and diarrhea (p<0.001). When performing Levene's median based homogeneity of variance test, the skewed distribution was equally distributed for the variables in question.

6   Discussion

The principal finding of this study is the strong association between major LARS and TME for patients treated with anterior resection for rectal cancer. A secondary finding is the association between TME and impaired social function and higher frequency of diarrhea. Since major LARS is confirmed to have a high sensitivity and specificity for impairment of QoL (25), these findings are all of great importance in the clinical practice of rectal cancer surgery.

The associations of TME with major LARS is in line with previous research (9, 24, 28, 30). In 2013, shortly after the introduction of LARS-score, Bregendahl et al presented an increased risk of major LARS when comparing TME with PME. The risk increased with neoadjuvant therapy. In 2018 Battersby et al published a nomogram to predict bowel dysfunction in patients treated with anterior resection, TME being one of the six predictors to major LARS. As early as 2004, Law et al also declared TME to be associated with a higher postoperative morbidity compared to PME (4).

The difference in major LARS between TME and PME can partly be explained by the difference in surgical procedure. As a consequence of TME, a larger part of the rectum is dissected with a greater loss of its reservoir function, partially explaining the increased frequency of diarrhea for this group. Mesorectum is also resected to a larger extent in the performance of TME, resulting in a greater loss of important nerves and arteries supplying the rectal tissue, consequently affecting the rectal function.

However, the clinical practice of TME is also associated with other factors affecting major LARS, e.g. tumor height, defunctioning stoma, type of anastomosis and neoadjuvant therapy, underlined in **Table 3** with p-values <0.001. Since neoadjuvant therapy and low tumor height is expected to independently affect the bowel function (24, 28, 30), these variables can be considered confounders for major LARS, while other variables can be treated as mediators. In a trial to explain the association of these variables to both TME and major LARS, a schematic illustration is presented in **Fig.3**. In actuality the clinical practice is a lot more complex than this illustration suggests.

Disregarding the choice of surgical procedure, a majority of patients treated with anterior resection will naturally experience some side effects affecting bowel function. In a Danish cohort of 938 patients treated with anterior resection, Bregendahl et al stated that 64% experienced some degree of LARS and 41% suffered from major LARS (24). Of those with major LARS, 74% were treated with TME. These numbers are somewhat lower than in this study, whereas our findings are at a rate of 49%

suffering from major LARS and TME performed in 81% of the cases.

The present study also finds that TME is performed in almost a third of all cases of upper rectal tumors, even though several studies have confirmed PME to be as oncologically safe as TME for these tumors (4, 22). The reason for this is not investigated in the present study, but the results are in line with a Danish study from 2013, authored by Emmertsen et al, where 30% of patients with tumors >10 cm were treated with TME instead of PME, consequently with an increased risk of developing major LARS (24). The underlying logic for performing TME on patients presenting upper rectal tumors may be due to specific surgical limitations (such as overweight patients) or local differences in practice between hospitals.

Since over a fourth of the original cohort in this study was excluded because of death, a reasonable conclusion would be that our data consists of a younger population than the original sample. Several studies have demonstrated younger age to correlate to major LARS (24, 28) and may partly explain the high prevalence of major LARS in this study. The difference in symptoms comparing age-groups have been hypothesized before and may be explained by the fact that younger patients have higher expectations on daily activities and therefore perceive symptoms as worse. Battersby et al reflect - in a study from 2013 - over the fact that old patients with sphincter dysfunction may be considered candidates for other surgical treatments, such as APE, and that the reduction of colonic motility in the elderly population reduces the degree of urgency and frequency. Nevertheless, a young population may explain the high prevalence of major LARS in this study, but there was no difference between age-groups in our analysis.

People with permanent stoma were also excluded from this study. In contrast, since a permanent stoma is highly associated with anastomotic leakage (32), the frequency of anastomotic leakage should be higher in the original cohort, presumptively with a worse bowel function. In addition, a Swedish study from 2017 demonstrated that anastomotic leakage is underreported in the SCRCR from where our data was retrieved (33), implying even higher numbers of anastomotic leakage in the population. Anastomotic leakage was also higher in the group of non-participants, which may reflect a more severe condition averting patients from responding to the questionnaires. For those included, the rate of anastomotic leakage was similar between patients treated with TME and PME.

The non-participants in this study represent almost a third of the original cohort, and is compared with descriptive statistics to the included patients in **Table 1** revealing a difference in sex, age, anastomotic leakage, chemotherapy and months since surgery. The rate of non-responders could both represent the patients with the worst morbidity, not having the energy to answer the questionnaires, but also the patients with the lowest morbidity, not having the incitement to respond or participate in the study. For example, female gender being more common for non-responders, has previously been described to affect the severity of LARS-scores (24, 28), and may also explain the difference between these groups. The cause of this difference in sex is as far as I know not fully understood and can only be hypothesized within this discussion. One explanation could be a higher prevalence of preoperative pelvic

disorders (24). Furthermore, considering the difference in months since surgery, one explanation could be that patients over time adjust to their bowel dysfunction, being less motivated to respond or participate in the study. Unfortunately, this study does not present the characteristics of the subgroups to non-participants, why these reflections are somewhat limited.

6.1 Strengths and Weaknesses

The strengths of this study are both the large cohort consisting of patients from 15 different hospitals in Sweden, all registered in the Swedish Colorectal Cancer Registry, as well as the study design with clear, measurable and validated outcomes, easy to interpret when comparing results to previous research. The long-term perspective ranging from four to eleven years after surgery, is also beneficial, confirming LARS-score persisting over time in accordance with a recently published study from Pieniowski et al (27).

Limitations of this study is partially the major loss of patients because of death; about a fourth from the original cohort. On the other hand since the long-term follow-up of the primary outcome is beneficial in terms of other perspectives this is an inevitable situation. Additionally the non-participants represented almost a third of the original cohort, a fraction that could have been smaller if investing a lot more time into receiving responses from all living patients. The fact that these patients did not respond to the questionnaires is still valuable information in the trial to explain the characteristics of patients treated with anterior resection. Finally, a more powerful study would preferably be a prospective study, observing patients with TME and PME at several follow-ups, with major LARS as the primary outcome.

6.2 Conclusions and Implications

This study implies that PME is superior to TME regarding bowel function and quality of life in patients treated with anterior resection for rectal cancer. Provided that both TME and PME are feasible options when planning anterior resection, these results should have an impact on the clinical practice of rectal cancer surgery and on the discussion with these patients.

In terms of future research, it would be interesting to see a more proper comparison of the functional outcomes between TME and PME for mid rectal tumors in conjunction with the oncological outcome. Since LARS-score is a non-linear scoring system describing bowel function, it would be of interest to investigate the association of TME with the different aspects of LARS. Future research is also motivated considering anastomotic level and its effect on bowel function and quality of life, as well as other aspects of postoperative morbidity, e.g. sexual- and urinary dysfunction comparing TME to PME.

7 References

1. Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. Defining the rectum: surgically, radiologically and anatomically. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2006;8 Suppl 3:5-9.

2. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv22-iv40.

3. Mahadevan V. Anatomy of the rectum and anal canal. Surgery (United Kingdom). 2017;35(3):121-5.

4. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: A prospective evaluation of 622 patients. Annals of Surgery. 2004;240(2):260-8.

5. Regionala Cancercentrum i Samverkan. Gällande vårdprogram tjock- och ändtarmscancer 2016 [updated 2016-03-15. Available from: https://www.cancercentrum.se/samverkan/cancerdiagnoser/tjocktarm-andtarm-och-anal/tjock--och-andtarm/vardprogram/gallande-vardprogram/.

6. Church JM, Raudkivi PJ, Hill GL. The surgical anatomy of the rectum - a review with particular relevance to the hazards of rectal mobilisation. International journal of colorectal disease. 1987;2(3):158-66.

7. Socialstyrelsen C. Cancer i siffror 2018 - Populärvetenskapliga fakta om cancer 2018 [updated 2018-6-10. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20976/2018-6-10.pdf.

8. World Health Organization. International Agency for Research on Cancer (IARC) - Colorectal cancer 2018 [updated September, 2018. Available from: http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf.

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

10. NORDCAN AotNCRARR. Faktablad Cancerstatistik Sverige - Ändtarm och anus 2018 [updated 180301. Available from: http://www-dep.iarc.fr/NORDCAN/SW/StatsFact.asp?cancer=120&country=752.

11. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(SUPPL.6):vi81-vi8.

12. Hamilton W, Sharp D. Diagnosis of colorectal cancer in primary care: The evidence base for guidelines. Fam Pract. 2004;21(1):99-106.

13. Edge SBea. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. New York: Springer New York Dordrecht Heidelberg London; 2010.

14. (UICC) UfICC. What is TNM? 2019 [updated 2017-06-30. Available from: https://www.uicc.org/resources/tnm.

15. Rutegard M, Bostrom P, Haapamaki M, Matthiessen P, Rutegard J. Current use of diverting stoma in anterior resection for cancer: population-based cohort study of total and partial mesorectal excision. International journal of colorectal disease. 2016;31(3):579-85.

16. Bondeven P, Laurberg S, Hagemann-Madsen RH, Ginnerup Pedersen B. 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.

17. Campbell A, Macdonald A, Oliphant R, Russell D, Fogg QA. Neurovasculature of high and low tie ligation of the inferior mesenteric artery. Surg Radiol Anat. 2018;40(12):1343-8.

18. Sato K, Inomata M, Kakisako K, Shiraishi N, Adachi Y, Kitano S. Surgical technique influences bowel function after low anterior resection and sigmoid colectomy. Hepato-Gastroenterology. 2003;50(53):1381-4.

19. Hallböök O, Hass U, Wänström A, Sjödahl R. Quality of life measurement after rectal excision for cancer: Comparison between straight and colonic J-pouch anastomosis. SCAND J GASTROENTEROL. 1997;32(5):490-3.

20. Heald RJ, Ryall RDH. RECURRENCE AND SURVIVAL AFTER TOTAL MESORECTAL EXCISION FOR RECTAL CANCER. The Lancet. 1986;327(8496):1479-82.

21. Heald RJ, Ryall RDH. RECURRENCE AND SURVIVAL AFTER TOTAL MESORECTAL EXCISION FOR RECTAL CANCER. The Lancet. 1986;327(8496):1479-82. 21. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery— the clue to pelvic recurrence? British Journal of Surgery. 1982;69(10):613-6.

22. Lopez-Kostner F, Lavery IC, Hool GR, Rybicki LA, Fazio VW. Total mesorectal excision is not necessary for cancers of the upper rectum. Surgery. 1998;124(4):612-8.

23. Kanso F, Lefevre JH, Svrcek M, Chafai N, Parc Y, Tiret E. Partial Mesorectal Excision for Rectal Adenocarcinoma: Morbidity and Oncological Outcome. Clinical colorectal cancer. 2016;15(1):82-90.e1.

24. Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. 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.

25. 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.

26. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. Annals of Surgery. 2014;259(4):728-34.

27. Pieniowski EHA, Palmer GJ, Juul T, Lagergren P, Johar A, Emmertsen KJ, et al. Low Anterior Resection Syndrome and Quality of Life After Sphincter-Sparing Rectal Cancer Surgery: A Long-term Longitudinal Follow-up. Dis Colon Rectum. 2019;62(1):14-20.

28. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, Branagan G, 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 - BMJ 2018;67(4):688-96.

29. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, 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. Journal of the National Cancer Institute. 1993;85(5):365-76.

30. Kupsch J, Jackisch T, Matzel KE, Zimmer J, Schreiber A, Sims A, et al. Outcome of bowel function following anterior resection for rectal cancer-an analysis using the low anterior resection syndrome (LARS) score. International journal of colorectal disease. 2018;33(6):787-98.

31. Kverneng Hultberg D, Angenete E, Lydrup ML, Rutegard J, Matthiessen P, Rutegard M. Nonsteroidal anti-inflammatory drugs and the risk of anastomotic leakage after anterior resection for rectal cancer. Eur J Surg Oncol. 2017;43(10):1908-14.

32. Jutesten H, Draus J, Frey J, Neovius G, Lindmark G, Buchwald P, et al. High risk of permanent stoma after anastomotic leakage in anterior resection for rectal cancer. Colorectal Dis. 2018.

33. Rutegård M, Kverneng Hultberg D, Angenete E, Lydrup ML. Substantial underreporting of anastomotic leakage after anterior resection for rectal cancer in the Swedish Colorectal Cancer Registry. Acta Oncologica. 2017;56(12):1741-5.

8 Appendix

8.1 Patient and Treatment Characteristics

Table 1: Patient and treatment characteristics of the 1012 patients in this study who underwent anterior resection for rectal cancer in Sweden between 2007 and 2013 and were eligible for inclusion questionnaires.

	Included (n=520) n (%)	Non-Participants (n=492) n (%)	Total n=1012 n (%)	Missing Values
Sex				
Male	314 (60.4)	232 (47.2)	546 (54)	
Female	206 (39.6)	260 (52.8)	466 (46)	
Age at Surgery†	65 (58-71)	68 (60-75)	66 (59-72)	3
≤ 66	291 (56.3)	214 (43.5)	505 (50)	
> 66	226 (43.7)	278 (56.5)	504 (50)	
ASA Classification				27
I	159 (31.4)	128 (26.7)	287 (29.1)	
II	295 (58.3)	305 (63.7)	600 (60.9)	
III	51 (10.1)	46 (9.6)	97 (9.8)	
IV	1 (0.2)	0 (0)	1 (0.1)	
Tumor Stage				32
I	154 (30.7)	146 (30.5)	300 (30.6)	
II	158 (31.5)	148 (31)	306 (31.2)	
III	176 (35.1)	184 (38.5)	360 (36.7)	
IV	14 (2.8)	0 (0)	14 (1.4)	
Tumor Height†	10 (9-12)	10 (8-12)	10 (9-12)	12
< 5 cm	7 (1.4)	11 (2.3)	18 (1.8)	
6-10 cm	269 (52.3)	256 (52.7)	525 (52.5)	
> 11 cm	238 (46.3)	219 (45.1)	457 (45.7)	
Surgical Procedure				23
Total Mesorectal Excision	354 (69.5)	349 (72.7)	703 (71.1)	
Partial Mesorectal Excision	155 (30.5)	131 (27.3)	286 (28.9)	
Surgical Approach				12
Laparotomy⋆	469 (91.4)	439 (90.1)	908 (90.8)	
Laparoscopy	44 (8.6)	48 (9.9)	92 (9.2)	
Defunctioning Stoma				2
No	84 (16.4)	94 (19.1)	179 (17.7)	
Yes	433 (83.6)	398 (80.9)	831 (82.3)	
Type of Anastomosis				62
Side-to-End/J-Pouch	374 (76.2)	364 (79.3)	738 (77.7)	
End-to-End	117 (23.8)	95 (20.7)	212 (22.3)	
Anastomotic Leakage				
No	479 (92.1)	429 (87.2)	908 (89.7)	
Yes	41 (7.9)	63 (12.8)	104 (10.3)	
Neoadjuvant Therapy				3
No	201 (38.9)	207 (42.1)	408 (40.4)	
Yes	316 (61.1)	285 (57.9)	601 (59.6)	
Radiotherapy-	212 (41)	210 (42.7)	422 (41.8)	
Radiotherapy+	305 (59)	282 (57.3)	587 (58.2)	
Short Course	204 (81.9)	215 (86.3)	419 (84.1)	
Long Course	45 (18.1)	34 (13.7)	79 (15.9)	
Chemotherapy-	435 (84.1)	444 (90.2)	879 (87.1)	
Chemotherapy+	82 (15.9)	48 (9.8)	130 (12.9)	
Months Since Surgery†	84 (66-111)	89 (70-112)	87 (68-111)	1
51-87	281 (54.1)	239 (48.6)	520 (51.4)	
88-135	238 (45.9)	253 (51.4)	491 (48.6)	

ASA: American Society of Anesthesiologists
† Median (Inter Quartile Range)
⋆ Laparotomy including converted laparoscopy

Table 2: Univariate analyses comparing LARS-score of the 520 patients in this study who underwent anterior resection for rectal cancer in Sweden between 2007 and 2013 and were included for further analyses.

	No Major LARS: 0-29 (n=266) n (%)	Major LARS: 30-42 (n=254) n (%)	P-Value χ^2	Missing Values
Sex				
Male	180 (67.7)	134 (52.8)	0.001	
Female	86 (32.3)	120 (47.2)		
Age at Surgery†	66 (66-71)	65 (58-71)		3
$\leq$ 65	131 (49.6)	131 (51.8)	0.624	
> 65	133 (50.4)	122 (48.2)		
ASA Classification				14
I-II	227 (88.7)	227 (90.8)	0.431	
III-IV	29 (11.3)	23 (9.2)		
Tumor Stage				18
I	78 (30.2)	76 (31.1)	0.761	
II	85 (32.9)	73 (29.9)		
III-IV	95 (36.8)	95 (38.9)		
Tumor Height†	11 (11-13)	10 (8-11)		6
< 5 cm	3 (1.1)	4 (1.6)	<0.001	
5-10 cm	105 (39.9)	164 (65.3)		
> 10 cm	155 (58.9)	83 (33.1)		
Surgical Procedure				11
Total Mesorectal Excision	152 (58.5)	202 (81.1)	<0.001	
Partial Mesorectal Excision	108 (41.5)	47 (18.9)		
Type of Anastomosis				29
Side-to-End/J-pouch	179 (71.6)	195 (80.9)	0.015	
End-to-End	71 (28.4)	46 (19.1)		
Anastomotic Leakage				
No	252 (94.7)	227 (89.4)	0.023	
Yes	14 (5.3)	27 (10.6)		
Defunctioning Stoma				2
No	62 (23.5)	23 (9.1)	<0.001	
Yes	202 (76.5)	231 (90.9)		
Surgical Approach				7
Laparotomy⋆	243 (92.7)	226 (90)	0.274	
Laparoscopy	25 (7.3)	19 (10)		
Neoadjuvant Therapy			<0.001	3
Radiotherapy-	142 (53.8)	70 (27.7)	<0.001	
Radiotherapy+	122 (46.2)	183 (72.3)		
Chemotherapy-	224 (84.8)	211 (83.4)	0.652	
Chemotherapy+	40 (15.2)	42 (16.6)		
Months Since Surgery†	87 (87-112)	81 (64-109)		1
51-84	123 (46.4)	141 (55.5)	0.038	
85-135	142 (53.6)	113 (44.5)		

χ^2: Chi-Square Test
LARS: Low Anterior Resection Syndrome
ASA: American Society of Anesthesiologists
† Median (Inter Quartile Range)
⋆ Laparotomy including converted laparoscopy

Table 3: Univariate analyses comparing surgical procedure of the 509 included patients in this study who underwent anterior resection for rectal cancer in Sweden between 2007 and 2013.

	PME (n=155) n (%)	TME (n=354) n (%)	P-Value χ^2	Missing Values
Sex				
Male	93 (60)	216 (61)	0.829	
Female	62 (40)	137 (39)		
Age at Surgery†	66 (60-71)	65 (58-71)		3
≤ 65	73 (47.4)	183 (52)	0.342	
> 65	81 (52.6)	169 (48)		
LARS-Score†	21 (12-32)	31 (24-37)		
No Major LARS	108 (69.7)	152 (42.9)	<0.001	
Major LARS	47 (30.3)	202 (57.1)		
ASA Classification				14
I-II	133 (87.5)	313 (91.3)	0.197	
III-IV	19 (12.5)	30 (8.7)		
Tumor Stage				17
I	45 (29.8)	107 (31.4)		
II	47 (31.1)	107 (31.4)	0.914	
III-IV	59 (39.1)	127 (37.2)		
Tumor Height†	13 (12-14)	10 (8-11)		6
< 5 cm	0 (0)	7 (2)	<0.001	
5-10 cm	23 (15.1)	242 (68.9)		
> 10 cm	129 (84.9)	102 (29.1)		
Surgical Approach				7
Laparotomy⋆	138 (90.8)	320 (91.4)	0.816	
Laparoscopy	14 (9.2)	30 (8.6)		
Defunctioning Stoma				1
No	69 (44.8)	16 (4.5)	<0.001	
Yes	85 (55.2)	338 (95.5)		
Type of Anastomosis				29
Side-to-End/J-Pouch	70 (48.6)	294 (87.2)	<0.001	
End-to-End	74 (51.4)	43 (12.8)		
Anastomotic Leakage				
No	148 (95.5)	320 (90.4)	0.052	
Yes	7 (4.5)	34 (9.6)		
Neoadjuvant Therapy				3
No	96 (62.3)	102 (29)	<0.001	
Yes	58 (37.7)	250 (71)		
Months Since Surgery†	87 (68-111)	83 (65-111)		1
51-84	73 (47.1)	185 (52.4)	0.270	
85-135	82 (52.9)	168 (47.6)		

PME: Partial Mesorectal Excision
TME: Total Mesorectal Excision
χ^2: Chi Square Test
LARS: Low Anterior Resection Syndrome
ASA: American Society of Anesthesiologists
† Median (Inter Quartile Range)
⋆ Laparotomy including converted laparoscopy

8.4 Binary Logistic Regression

Table 4: Binary logistic regression describing the risk of major LARS for patients treated with anterior resection for rectal cancer in Sweden between 2007 and 2013.

	OR for Major LARS	95 % CI	P-Value
Sex			
Male	1	(reference)	0.001
Female	1.98	1.32-2.95	
Neoadjuvant Therapy			
No	1	(reference)	<0.001
Yes	2.7	1.79-4.08	
Surgical Procedure			
Total Mesorectal Excision	1.82	1.12-2.95	0.016
Partial Mesorectal Excision	1	(reference)	
Anastomotic leakage			
No	1	(reference)	0.015
Yes	2.54	1.20-5.38	
ASA Classification			
I-II	1	(reference)	0.933
III-IV	1.03	0.54-1.96	
Defunctioning Stoma			
No	1	(reference)	0.067
Yes	1.79	0.96-3.3	
Age at Surgery			
≤ 65	1.00	0.98-1.02	0.82
> 65	1	(reference)	

LARS: Low Anterior Resection Syndrome
ASA: American Society of Anesthesiologists
95% CI=95 Percent Confidence Intervals

8.5 Quality of Life Comparing Surgical Procedure

Table 5: Quality of life comparing surgical procedure of the 520 included patients in this study who underwent anterior resection for rectal cancer in Sweden between 2007 and 2013, using the EORTC QLQ-C30 questionnaire.

	PME n	Mean (SD)	Median (range)	TME n	Mean (SD)	Median (range)	P-Value	Missing Values
Global Health Status								
Global Health Status	156	76.3 (18.8)	83 (100)	351	72.7 (19.6)	75 (100)		13
Functioning Scales								
Physical Function	154	87.1 (18.2)	93 (80)	351	87.2 (17.3)	93 (80)		15
Role Function	154	88.1 (21.0)	100 (100)	351	84.8 (24.7)	100 (100)		15
Emotional Function	155	85.7 (16.2)	92 (67)	351	83.1 (20.3)	92 (100)		14
Cognitive Function	155	86.8 (16.6)	83 (67)	349	86.2 (17.3)	83 (83)		16
Social Function	155	87.8 (20.1)	100 (100)	349	80.1 (24.5)	83 (100)	<0.001	16
Symptom Scales								
Fatigue	155	19.9 (20.9)	11 (100)	350	23.5 (22.8)	22 (100)		15
Nasuea/Vomiting	154	1.4 (5.0)	0 (33)	349	3.4 (11.2)	0 (100)		17
Pain	155	10.5 (19.9)	0 (100)	350	12.0 (21.6)	0 (100)		15
Dyspnoea	154	17.7 (26.5)	0 (100)	349	20.0 (26.0)	0 (100)		17
Insomnia	154	22.9 (27.4)	17 (100)	348	20.8 (27.2)	0 (100)		18
Appetite Loss	153	4.4 (13.6)	0 (67)	349	5.8 (17.2)	0 (100)		18
Constipation	154	13.6 (22.1)	0 (100)	349	13.3 (24.2)	0 (100)		17
Diarrhoea	155	15.5 (27.5)	0 (100)	350	24.3 (27.7)	33 (100)	<0.001	15
Financial Problems	155	4.3 (15.1)	0 (100)	347	7.4 (19.9)	0 (100)		18

EORTC: European Organisation for Research and Treatment of Cancer
PME: Partial Mesorectal Exicison
TME: Total Mesorectal Excision
P-Value calculated via Whitney-U test

Primary Tumor (T)	
TX	Primary tumor cannot be assesed
T0	No evidence for primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissue
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherrent to other organs or structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assesed
N0	No regional lymph node metastasis
N1	Metastatis in 1-3 regional lymph nodes
N1a	Metastatis in one regional lymph node
N1b	Metastatis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastatis in four or more regional lymph nodes
N2a	Metastatis in 4-6 regional lymph nodes
N2b	Metastatis in seven or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1B	Metastases in more than one organ/site or the peritoneum

Stage	T	N	M
0	Tis	N0	M0
1	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Figure 1: TNM staging following the UICC Classification. UICC= Union for International Cancer Control.
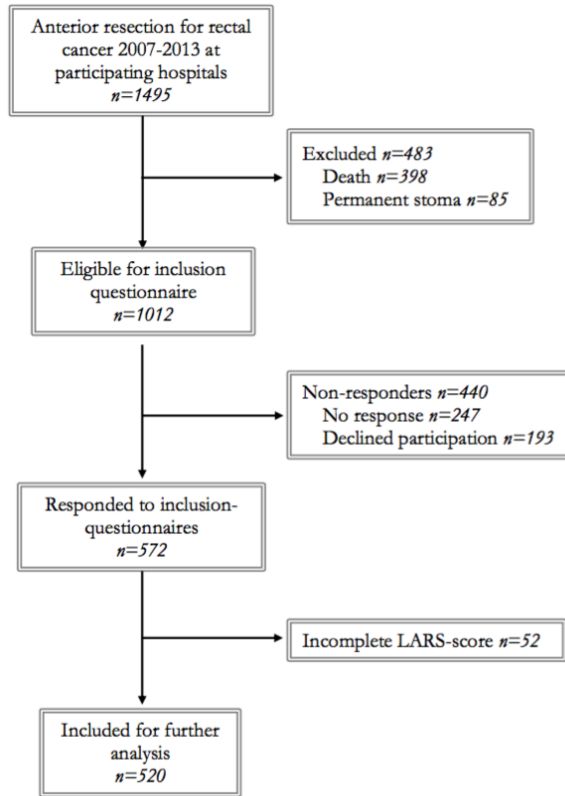
8.7 Selection Flowchart

Figure 2: Flowchart presenting the selection process of the 1495 patients in this study who underwent anterior resection for rectal cancer in Sweden between 2007 and 2013 . LARS=Low Anterior Resection Syndrom.
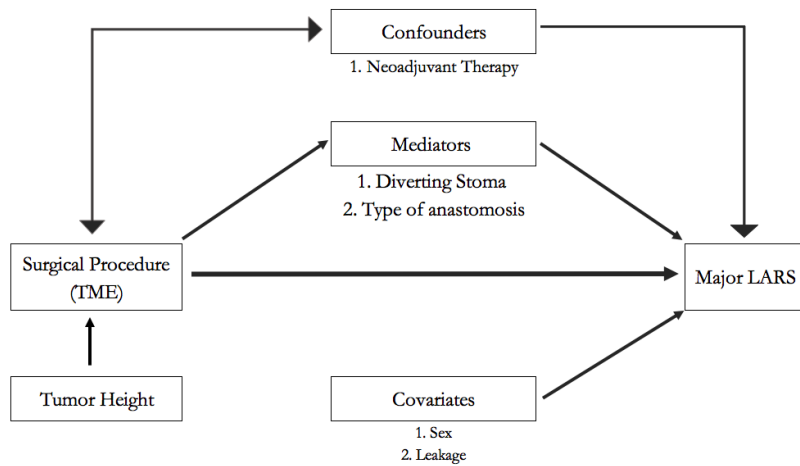
8.8 Schematic Illustration

Figure 3: Schematic illustration explaining associated factors to major LARS.

För dig som i nuläget <u>inte har stomi</u> och väljer att delta i studien:

Vänligen signera och datera *"Samtycke till deltagande i enkätstudien, LARS-SCORE, SCRCR, avseende tarmfunktion och livskvalitet efter behandling av ändtarmstumör"*, blanketten finns på nästkommande sida. Denna returneras tillsammans med de besvarade enkäterna "Frågeformulär: Förekomst stomi", "Frågeformulär: Tarmfunktion" samt livskvalitetsenkäterna "EORTC QLQ-CR-29" och "EORTC QLQ-C30" i medföljande svarskuvert.

För dig som i nuläget <u>har stomi</u> och väljer att delta i studien:

Vänligen signera och datera *"Samtycke till deltagande i enkätstudien, LARS-SCORE, SCRCR, avseende tarmfunktion och livskvalitet efter behandling av ändtarmstumör"*, blanketten finns på nästkommande sida. Denna returneras tillsammans med de besvarade enkäterna "Frågeformulär: Förekomst stomi" samt livskvalitetsenkäterna "EORTC QLQ-CR29" och "EORTC QLQ-C30".

För dig som vill avstå från deltagande i studien:

Väljer du *att* <u>inte</u> delta, är vi ändå tacksamma för returnerat *" Samtycke till deltagande i enkätstudien, LARS-SCORE, SCRCR, avseende tarmfunktion och livskvalitet efter behandling av ändtarmstumör"* med markering i "Nej tack" i rutan, så att vi inte besvärar dig med påminnelsebrev.

Om du har några frågor om studien kan du kontakta:

Ingrid Palmquist, telefon: 040-33 18 46

Frågeformulär: Förekomst av stomi

1. **Har du i nuläget en stomi (en påse på magen)?**

☐ Ja – Gå nu vidare till fråga 2-7!
☐ Nej

Om du svarade "nej" på fråga 1, gå nu vidare till fråga 8!

För dig som har en stomi i nuläget (fråga 2-6):

2. **Fick du din stomi, exempelvis inför strålning eller cytostatikabehandling, vid ett tillfälle *före* din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

3. **Fick du din stomi *samtidigt* som du genomgick din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

4. **Fick du din stomi vid ett nytt tillfälle *efter* din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

5. **Planeras din stomi att opereras bort?**

☐ Ja
☐ Nej
☐ Vet ej

6. **Om "ja" på fråga 5, ange om möjligt ungefärligt planerat datum för bortoperation av din stomi (År/månad/datum)**

20____/_____/_____

Det går bra att kontakta mig efter att min stomi är bortopererad

☐ Ja
☐ Nej tack!

För dig som har en stomi, vänligen besvara nu enkäterna QLQ-CR29 och QLQ-C30!

För dig som <u>inte har</u> en stomi (fråga 7):

7. **Har du tidigare haft en stomi?**

☐ Ja
☐ Nej

Om du svarade "ja" på fråga 7, vänligen gå nu till fråga 8!

Om du svarade "nej" på fråga 7, vänligen besvara nu enkäterna "Frågeformulär:

Tarmfunktion", QLQ-CR29 och QLQ-C30!

För dig som <u>tidigare har haft</u> en stomi (fråga 8-11):

8. **Fick du din stomi, exempelvis inför strålning eller cytostatikabehandling, vid ett tillfälle *före* din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

9. **Fick du din stomi *samtidigt* som du genomgick din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

10. **Fick du din stomi vid ett nytt tillfälle *efter* din ändtarmsoperation?**

☐ Ja
☐ Nej
☐ Vet ej

11. **När blev din stomi bortopererad? Ange ungefärligt datum!**

(År/månad/datum) 20____/_____/_____

Vänligen besvara nu enkäterna "Frågeformulär: Tarmfunktion", QLQ-CR29 och QLQ-C30!

Frågeformulär: Tarmfunktion

Syftet med denna enkät är att bedöma din tarmfunktion.

Kryssa bara i en ruta för varje fråga. Det kan vara svårt att välja endast ett svar eftersom vi vet att symtomen varierar från dag till dag hos vissa patienter. Vi ber dig välja det svar som bäst beskriver ditt dagliga liv. Om du nyligen haft någon infektion som påverkat tarmfunktionen, ska du inte räkna med den utan fokusera på att besvara frågorna för att återspegla din vanliga tarmfunktion varje dag.

12.   **Finns det tillfällen då du inte kan kontrollera gaser?**

☐ Nej, aldrig   0
☐ Ja, mer sällan än en gång i veckan   4
☐ Ja, minst en gång i veckan   7

13.   **Har du någon gång oavsiktligt läckage av lös avföring?**

☐ Nej, aldrig   0
☐ Ja, mer sällan än en gång i veckan   3
☐ Ja, minst en gång i veckan   3

14.   **Hur ofta tömmer du tarmen?**

☐ Mer än 7 gånger per dygn   4
☐ 4-7 gånger per dygn   2
☐ 1-3 gånger per dygn   0
☐ Mer sällan än en gång per dygn   5

15.   **Finns det tillfällen då du behöver tömma tarmen igen inom en timme efter senaste tarmtömningen?**

☐ Nej, aldrig   0
☐ Ja, mer sällan än en gång i veckan   9
☐ Ja, minst en gång i veckan   11

16.   **Finns det tillfällen då du är i stort behov av att tömma tarmen att du måste rusa till toaletten?**

☐ Nej, aldrig   0
☐ Ja, mer sällan än en gång i veckan   11
☐ Ja, minst en gång i veckan   16

EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med dig och din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på dig.

		Inte alls	Lite	En hel del	Mycket
1.	Har du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har du svårt att ta en <u>lång</u> promenad?	1	2	3	4
3.	Har du svårt att ta en <u>kort</u> promenad utomhus?	1	2	3	4
4.	Måste du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver du hjälp med att äta, klä dig, tvätta dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har du varit begränsad i dina möjligheter att utföra antingen ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har du varit begränsad i dina möjligheter att utöva dina hobbyer eller andra fritidssysselsättningar?	1	2	3	4
8.	Har du blivit andfådd?	1	2	3	4
9.	Har du haft ont?	1	2	3	4
10.	Har du behövt vila?	1	2	3	4
11.	Har du haft svårt att sova?	1	2	3	4
12.	Har du känt dig svag?	1	2	3	4
13.	Har du haft dålig aptit?	1	2	3	4
14.	Har du känt dig illamående?	1	2	3	4
15.	Har du kräkts?	1	2	3	4
16.	Har du varit förstoppad?	1	2	3	4

Under veckan som gått:

	Inte alls	Lite	En hel del	Mycket
17. Har du haft diarré?	1	2	3	4
18. Har du varit trött?	1	2	3	4
19. Har dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20. Har du haft svårt att koncentrera dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21. Har du känt dig spänd?	1	2	3	4
22. Har du oroat dig?	1	2	3	4
23. Har du känt dig irriterad?	1	2	3	4
24. Har du känt dig nedstämd?	1	2	3	4
25. Har du haft svårt att komma ihåg saker?	1	2	3	4
26. Har ditt fysiska tillstånd eller den medicinska behandlingen stört ditt familjeliv?	1	2	3	4
27. Har ditt fysiska tillstånd eller den medicinska behandlingen stört dina sociala aktiviteter?	1	2	3	4
28. Har ditt fysiska tillstånd eller den medicinska behandlingen gjort att du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på dig för följande frågor:

29. Hur skulle du vilja beskriva din hälsa totalt sett under den vecka som gått?

     1   2   3   4   5   6   7

Mycket dålig   Utmärkt

30. Hur skulle du vilja beskriva din totala livskvalitet under den vecka som gått?

     1   2   3   4   5   6   7

Mycket dålig   Utmärkt