Quality of life and morbidity in patients with rectal cancer

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2016

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ISBN 978-91-628-9890-8 (PRINT); 978-91-628-9891-5 (PDF)
http://hdl.handle.net/2077/44857

Printed by Ineko, Gothenburg, Sweden 2016

To my wonderful
wife and our
gorgeous children

Realize deeply that the present moment is all you ever have.
Make the Now the primary focus of your life.

Eckhart Tolle

ABSTRACT

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Aim The aim of this thesis was to investigate patient-reported and clinical outcome in patients with rectal cancer with specific focus on treatment-associated morbidity and quality of life.

Method Three clinical studies were conducted: a prospective multicentre cohort study, a retrospective case series and a nationwide cross-sectional questionnaire survey. In addition, population normative data on quality of life were obtained. Two study-specific questionnaires were developed and validated. Clinical data were collected from medical records and national quality registries.

Results Cancer-related intrusive thoughts, a possibly treatable stress-related symptom, independently predicted pretreatment quality of life in patients with a newly diagnosed rectal cancer (paper I-II). Extralevator abdominoperineal excision was associated with an increased rate of perineal wound complications compared with the conventional technique but oncological outcome was no better (paper III). Three years after surgery 50 % of responding patients experienced perineal symptoms and impaired postoperative wound healing emerged as a risk factor (paper IV).

Conclusion Psychological factors should be considered as relevant confounders in relation to quality of life in clinical studies. Efforts to decrease perineal wound complications following abdominoperineal excision are important, as complications may increase the risk for chronic perineal symptoms. Such symptoms are common three years after abdominoperineal excision.

Keywords Rectal cancer; Quality of life; Morbidity; Abdominoperineal excision; Intrusive thoughts; Sense of coherence; Chronic perineal symptoms.

ISBN: 978-91-628-9890-8 (PRINT); 978-91-628-9891-5 (PDF)
http://hdl.handle.net/2077/44857

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Self-reported quality of life and functional outcome in patients with rectal cancer – QoLiRECT.**
Asplund D, Heath J, González E, Ekelund J, Rosenberg J, Haglind E, Angenete E.
Dan Med J 2014;61(5): A4841

II. **Pretreatment quality of life in patients with rectal cancer is associated with intrusive thoughts and sense of coherence.**
Asplund D, Bisgaard T, Bock D, Burcharth J, González E, Haglind E, Kolev Y, Matthiessen P, Rosander C, Rosenberg J, Smedh K, Åkerblom Sörensson M, Angenete E.
Submitted for publication

III. **Outcome of extralevator abdominoperineal excision compared with standard surgery: results from a single centre.**
Asplund D, Haglind E, Angenete E.
Colorectal Dis 2012;14(10): 1191-1196

IV. **Persistent perineal morbidity is common following abdominoperineal excision for rectal cancer.**
Asplund D, Prytz M, Bock D, Haglind E, Angenete E.
Int J Colorectal Dis 2015;30(11): 1563-1570

ABBREVIATIONS

APER	The AbdominoPErineal Resection study
ASA	American Society of Anesthesiologists physical status classification
COLOR II	The COlorectal cancer Laparoscopic or Open Resection trial
EORTC	European Organisation for Research and Treatment of Cancer
LARS	Low Anterior Resection Syndrome
TME	Total Mesorectal Excision
QoLiRECT	The Quality of Life in RECTal cancer study

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INTRODUCTION

Rectal cancer

Some 2000 people are diagnosed with rectal cancer each year in Sweden, making it one of the ten most common cancers[1]. While some carry an increased risk because of an inherited predisposition, most cases are sporadic. Dietary and lifestyle factors such as red and processed meat, alcohol and smoking may increase the risk for rectal cancer, whereas dietary fibre, calcium and physical activity seem to be protective[2-4].

Treatment has improved in recent decades resulting in a markedly increased five-year relative survival, which today exceeds 60 %[5]. In countries where surgery has been centralised, rectal cancer today has a better prognosis than colon cancer[6, 7].

Symptoms of rectal cancer include rectal bleeding and a change of bowel habits as well as anaemia, weight loss and sometimes abdominal or sacral pain. Symptoms are often vague, although some patients present with acute obstruction necessitating emergency surgery.

Pretreatment staging

Treatment algorithms are complex and dependent on both clinical and patient-related factors. Different treatments are associated with varying degrees of side effects and functional consequences, which emphasize the importance of correct pretreatment staging.

When a rectal tumour is suspected, investigations aim to verify the diagnosis microscopically (Figure 1) and to stage the tumour, i.e. to establish how far it has grown and spread. Investigations include rigid rectoscopy (to determine the distance from the distal tumour border to the anal verge, and to acquire biopsies), magnetic resonance imaging of the abdomen and pelvis (to determine loco-regional tumour growth and exclude intra-abdominal metastases) (Figure 2), computed tomography of the chest (to exclude lung metastases) and colonoscopy (to exclude synchronous tumours in the colon). Endoscopic ultrasound may be helpful to identify those few tumours that may be removed by a local excision[8, 9].

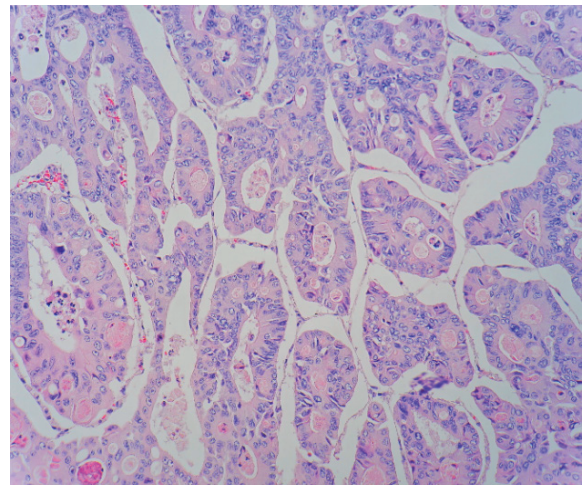


Figure 1. Microscopy image of a rectal adenocarcinoma. Courtesy of Dr Mats Wolving, Department of Clinical Pathology and Cytology, Sahlgrenska University Hospital.

When investigations are completed, the treatment for the individual patient is discussed in a multidisciplinary team conference where the imaging is reviewed[10, 11]. The distance from the distal tumour border to the anal verge has implications for the choice of surgical procedure, i.e. if a sphincter-saving operation can be performed or if a permanent colostomy is necessary. The relationship of the tumour to the mesorectal fascia is important (Figure 2). If the tumour extends to the mesorectal fascia, there is a risk of an involved circumferential resection margin if a standard total mesorectal excision is performed, as will be discussed in the next section[12]. Presence or absence of lymph node metastases, malignant cells within blood vessels beyond the muscularis propria, referred to as extramural vascular invasion, and the relation of the tumour to the surrounding anatomy are other factors that affect treatment decisions. The detection of distant metastases (most commonly in the liver or the lungs) makes curative treatment impossible in some cases, as will be further discussed[13]. Patient characteristics such as age, comorbidity, performance status and sphincter function as well as patient preferences are also important to consider in relation to available treatment options. Accurate staging by magnetic resonance imaging, multidisciplinary management and, more importantly, better use of preoperative radiotherapy and improvements in surgical technique have all contributed to improved results of treatment in the last decades[13-23]. Treatment options and considerations are discussed below.

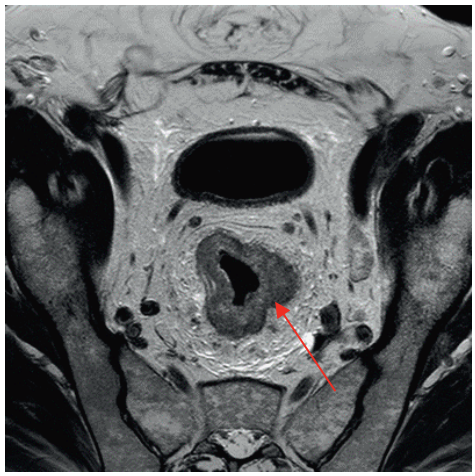


Figure 2. Magnetic resonance image in the transverse plane depicting a rectal tumour located 10 cm from the anal verge. The tumour is visible as a thickening of the rectal wall and surrounded by the mesorectum. Courtesy of Dr Göran Andersson Ekebrån, Department of Radiology, Sahlgrenska University Hospital/Östra.

Surgery

Surgery is the cornerstone of curative treatment for rectal cancer. There are two main abdominal procedures: anterior resection[24] and abdominoperineal excision[25, 26]. An anterior resection involves the partial or complete removal of the rectum followed by the creation of an anastomosis with or without a temporary diverting loop ileostomy, while an abdominoperineal excision results in the complete removal of the rectum including the anus and a permanent colostomy.

An anterior resection is performed when the tumour is located in the upper or middle part of the rectum (see Table 1 for definitions). It may also be considered for lower tumours as long as the tumour does not infiltrate the pelvic floor. This may, however, have functional consequences, as will be discussed below (p. 15). In Europe, the percentage of patients operated by anterior resection has increased from 25 up to 50-75 % over the past 30 years[7]. In Sweden, an abdominoperineal excision is generally preferred when the tumour is located within 6 cm from the anal verge[13]. Approximately 30 % of all primary rectal cancers are operated by abdominoperineal excision in Sweden[5, 13].

Following the introduction of total mesorectal excision (TME) surgery by Bill Heald in the 1980s, results of treatment improved[14, 15, 17]. As opposed to blunt dissection, total mesorectal excision surgery implies that dissection is performed in the embryological plane just outside the mesorectal fascia[14, 20]. Local recurrence rates, however, remained higher after abdominoperineal excision compared with anterior resection[5, 27-33]. One reason may be that achieving a radical resection is more difficult in lower tumours due the challenging anatomy. Some have proposed that another reason might be that the

principles of total mesorectal excision surgery wrongfully have been applied to abdominoperineal excision[34]. If the TME dissection is carried downwards all the way to the pelvic floor, where the mesorectum is thin, the result may be a non-radical resection if the tumour is located in this region[28, 35]. To address this problem, extralevator abdominoperineal excision was introduced in 2007[36]. The extralevator technique closely resembles the original abdominoperineal excision as described by Ernest Miles 100 years earlier[25]. Dissection in the abdominal phase is stopped before entering the levator plane and the perineal phase of the operation is performed with the patient in the prone position (chest down, back up). Compared with the conventional technique, more tissue is removed with the specimen, including most of the levator muscles, i.e. the pelvic floor[37] (Figure 3). The extralevator technique rapidly gained acceptance in Sweden and abroad, without compelling evidence of its safety or superiority[37-45].

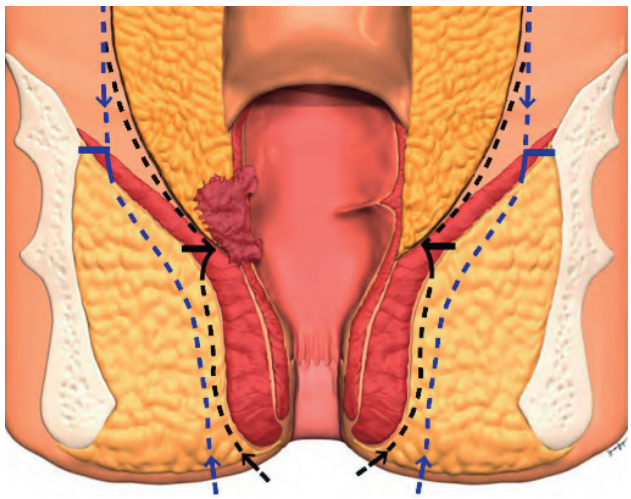


Figure 3. Schematic illustration of dissection in conventional and extralevator abdominoperineal excision, as depicted by the black and blue interrupted lines, respectively.

Prytz et al. Int J Colorectal Dis 2014[39]. Reprinted with permission from the author.

Other surgical procedures

The Hartmann procedure, i.e. resection of the tumour-bearing segment of the bowel with blind closure of the distal stump and formation of a colostomy, may be a good option if an anastomosis is not feasible and the patient is not fit to undergo an abdominoperineal excision. In such cases, the rectal stump may be left in place following the TME dissection or removed during an intersphincteric abdominoperineal excision. The possible benefits of the intersphincteric resection are currently being studied[46]. In early cancers, transanal endoscopic microsurgery may be an option in selected patients[47], although the oncological results are uncertain.

Open and laparoscopic resection

Laparoscopic surgery is associated with less blood loss, less pain, earlier return of bowel function and shorter hospitalization compared to open surgery and oncological outcomes are similar[48]. Compared to open surgery, laparoscopy may also decrease the risk of subsequent short bowel obstruction due to postoperative adhesions[49-52]. Locally advanced tumours are generally not cases for laparoscopic resection. Increasingly, robot assisted laparoscopic surgery is becoming part of clinical routine[53]. There is, however, no evidence that robotic surgery adds any advantage compared to conventional laparoscopy in rectal cancer and in principle, it should only be used within clinical trials.

Treatment in patients with metastatic disease

If the tumour has already spread to other organs at diagnosis, curative treatment may be possible if the metastases are resectable. Resection of limited colorectal metastases to the liver or lung is associated with five-year survival rates ranging from 30 to 50 %[4, 54]. In cases of peritoneal metastases, without or with very limited distant metastases, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) may lead to improved survival in selected patients[55]. The result of this combined treatment is heavily dependent on careful patient selection, which is primarily based on performance status and the extent of intraperitoneal tumour dissemination.

About 20 % of patients present with incurable disease, most frequently due to non-resectable distant metastases. In these cases, treatment is palliative. Radiotherapy may decrease pain and bleeding from the rectal tumour. In the event of bowel obstruction, a deviating colostomy is necessary. In many cases, patients are offered palliative chemotherapy, which may delay disease progression but can be associated with adverse effects[56]. Palliative surgery, i.e. resection of tumours without curative intent, is becoming less common[13], although it is sometimes indicated to reduce clinical symptoms.

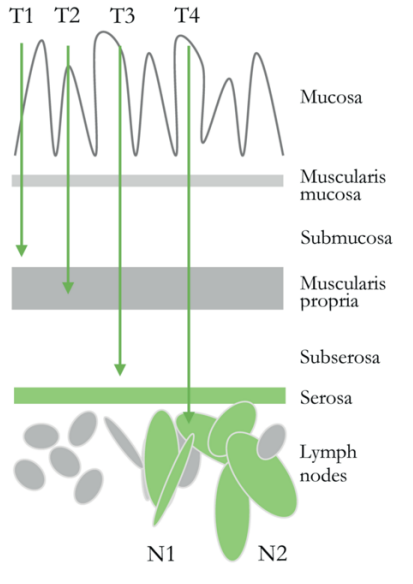
Neoadjuvant treatment

Surgery may be combined with preoperative neoadjuvant therapy. The purpose is to increase the chances of complete tumour clearance at surgery and thus decrease the risk of tumour recurrence in the pelvis, as will be discussed below[15, 17, 56]. Depending on the clinical stage of the tumour, short-course radiotherapy or chemoradiotherapy is recommended (Table 1 and Figure 4).

	T1-T2	T3a-b < 5 mm invasion	T3c-d > 5 mm invasion	T4a	T4b[1]	N1	N2	MRF+[2]	Lat. Nodes[3]	EMVI[4]
High rectal tumours (10-15 cm)	0	0	5x5	5x5	5x5/ CRT	0	5x5	CRT	CRT	5x5
Mid rectal tumours (5-10 cm)	0	5x5	5x5	5x5	5x5/ CRT	5x5	5x5	CRT	CRT	5x5
Low rectal tumours (0-5 cm)	5x5	5x5	5x5	----	5x5/ CRT	5x5	5x5	CRT	CRT	5x5

Source: The national treatment guidelines, available at www.cancercentrum.se

Table 1. *Algorithm for preoperative treatment. The highest level of treatment is chosen. Example: A low T3 tumour with potential mesorectal fascia involvement should receive chemoradiotherapy (CRT).*
[1]Short-course radiotherapy (5x5) if the tumour invades an "easily" resectable organ; chemoradiotherapy (CRT) if tumour invasion necessitates more extensive resections.
[2]Mesorectal fascia involvement (free margin <1 mm).
[3]Lymph node metastases outside the mesorectal fascia.
[4]Extramural vascular invasion.



Primary tumour (T)
T1: Tumour invades submucosa
Sm 1: upper-third
Sm 2: middle-third
Sm 3: lower-third
T2: Tumour invades muscularis propria
T3: Tumour invades through the muscularis propria
T3a: <1 mm
T3b: 1-5 mm
T3c: 5-15 mm
T3d: > 15 mm
T4a: Tumour penetrates through the visceral peritoneum
T4b: Tumour invades or is adherent to other organs or structures

Regional lymph nodes (N)
N0: No regional lymph node metastases
N1: 1-3 regional lymph nodes metastases
N2: >4 regional lymph nodes metastases

Distant metastases (M)
M0: No distant metastases
M1: Distant metastases

Figure 4*. Definitions of tumour (T), lymph node (N) and metastasis (M) status in rectal cancer.*

Short-course radiotherapy is delivered as five grays for five consecutive days (referred to as 5x5 Gy) followed by surgery within 2-3 days. Chemoradiotherapy involves the administration of a total radiation dose of 46-50.4 grays over a period of three months in combination with chemotherapy and is followed by renewed radiological evaluation. Surgery is planned 6-8 weeks after treatment, although there is a current trend towards a longer delay period. Chemoradiotherapy has the potential to downsize and downstage the tumour which increases the chance of a radical resection in advanced cases. If the patient is not fit for chemoradiotherapy, short course radiotherapy with delayed surgery may be an alternative[57] but this approach needs further evaluation. The administration of concomitant chemotherapy during chemoradiotherapy makes cells more sensitive to radiation[58] but offers little protection against the development or progression of distant metastases. In cases of a locally advanced tumour with synchronous resectable metastases, this can be a clinical dilemma.

Although short-course radiotherapy and chemoradiotherapy both reduce the risk of local recurrences, neither has been shown to improve overall survival[17] – except in the Swedish rectal cancer trial[59] where a survival benefit of short-course radiotherapy was demonstrated. Patients with low tumours are likely to benefit most from radiation and all patients scheduled for abdominoperineal excision are routinely treated with radiotherapy in Sweden.

Adjuvant treatment

Postoperative adjuvant chemotherapy aims to decrease the risk of systemic recurrences[56, 60]. Evidence for the use of adjuvant chemotherapy is weaker for rectal cancer than for colon cancer and clinical practice varies across Europe. In Sweden it is generally given to patients with a high risk for recurrent disease, i.e. if the pathological examination of the resected specimen reveals lymph node metastases or a combination of two other risk factors for recurrence such as tumour deposits, perineural growth or extramural vascular invasion. Emergency as opposed to elective surgery and peroperative tumour perforation is also generally considered to be indications for adjuvant treatment.

Radiotherapy is associated with acute adverse effects such as diarrhoea, increased bowel frequency and dysuria. The addition of chemotherapy during chemoradiotherapy may exacerbate symptoms[7, 61]. Long term complications associated with preoperative radiotherapy include bowel enteritis, adhesions, small bowel obstruction and anorectal, sexual and urinary dysfunction, as will be discussed below. Adjuvant chemotherapy is associated with reversible adverse effects as well as irreversible neuropathy[56].

Follow-up

The aim of follow-up after curative treatment is to detect recurrences or new colorectal tumours in time to allow for a second curative procedure. There is little evidence to support one follow-up regime over another or even the benefit of follow-up at all[62]. The as yet unpublished results of the COLOFOL trial will possibly help decide the optimal follow-up regimen[63]. In Sweden patients are generally monitored by annual abdominal and chest computed tomography and clinical exam for three years, with the addition of magnetic resonance imaging in selected patients. Colonoscopy is performed after three years and then every five years until the age of about 75. Patients operated with local excision need closer surveillance[4].

Postoperative complications

Overall, about 35 % of patients experience complications within 30 days after surgery[5]. Complications directly related to the surgical procedure such as bleeding, wound infection, wound dehiscence and anastomotic leaks account for about 24 %[13]. To lessen the consequences of an anastomotic leak, a temporary defunctioning loop-ileostomy is generally recommended following low anterior resection[64]. However, the loop-ileostomy may also cause morbidity, with dehydration, obstruction and parastomal hernia being the most common complications[65-67].

An abdominoperineal excision may be complicated by infection or dehiscence of the perineal wound which may necessitate local revision under general anaesthesia. Such complications may result in a delayed wound healing, generally defined as a healing time in excess of one month[68]. Neoadjuvant radiotherapy is considered to be the major risk factor for perineal wound complications[68, 69, 70]. In addition, studies have indicated an increased risk of complications after extralevator compared with conventional abdominoperineal excision[43, 71].

Outcome measures in clinical research

Clinical outcome measures

Clinical studies are concerned with the measurement and interpretation of different kinds of outcomes. Clinical outcome measures generally refer to variables that are readily measurable by health care professionals, often called “objective” variables. They may be collected prospectively or derived retrospectively from medical records, pathology reports or, increasingly from national quality registries[72].

Local recurrence is an important outcome in rectal cancer[73-75]. Local recurrence means a recurrence of the rectal cancer in the pelvis as a result of insufficient clearance of cancer cells by neoadjuvant treatment and/or surgery. A local recurrence is a dreaded condition that is difficult to treat and may lead to severe suffering for the patient[74]. The

frequency of local recurrences has decreased and is now reported to be as low as 5 % in Sweden[13].

Since local recurrences are uncommon today, studies need to be large if this outcome measure is to be used. A commonly used surrogate variable for local recurrence in rectal cancer research is *circumferential resection margin involvement*. The circumferential resection margin refers to the surgical margin around the mesorectum when total mesorectal excision surgery is performed. An involved circumferential resection margin is usually defined as the presence of tumour cells within 1 mm from the circumferential resection margin. This outcome is strongly associated with local recurrences as well as with the development of distant metastases and decreased survival[4, 12].

Patient-reported outcome measures

There has been increasing understanding that clinical measures alone are not sufficient in the follow-up and evaluation of patients with cancer[76, 77]. For example, a treatment that appears effective in terms of survival or local recurrence may be associated with unacceptable side effects and symptoms. The inclusion of *patient-reported* outcomes in clinical studies may reveal consequences of treatment that would otherwise be invisible. One patient-reported outcome that is considered especially valuable is quality of life[77-79].

Quality of life

Quality of life is a broad concept that is not only concerned with matters of health. The term was coined by American national economists in the 1950s, reflecting the realization that quantitative measures of societal development say nothing about how satisfied people are with their lives[80, 81]. In the context of health care, the term health-related quality of life is often used to stress that it is the impact of health on quality of life that is of interest. Health-related quality of life may be defined as the patient's experience of general health and well-being, symptoms and physical, emotional and social function as a consequence of illness or treatment[82].

Health-related quality of life is generally measured by way of self-administered questionnaires. Questionnaires may be generic (general), such as SF-36[83, 84] and EQ-5D[85], or disease-specific, such as QLQ-C30[86, 87] which was developed for patients with cancer by the European Organization for Research and Treatment of Cancer (EORTC). The EORTC has also developed cancer-specific questionnaires for use in many different types of cancer, such as QLQ-C38[88] and the updated version QLQ-C29[89-91] for colorectal cancer patients, which can be used in combination with QLQ-C30 in clinical studies. Unlike disease-specific questionnaires, which focus on issues that are relevant to patients with a specific disease, generic questionnaires may be used to

compare quality of life between patient groups and healthy people[79]. Interestingly, such comparisons often reveal small differences or even paradoxical results[82]. This is perhaps explained by insufficient sensitivity of the generic questionnaire in some cases, but may also be related to issues like response shift, as discussed below.

Questionnaires are often divided into several subscales or domains, reflecting the multidimensional properties of quality of life. The individual questions of each subscale are often summated into a score. Many questionnaires combine such subscales with global single questions on overall quality of life or general health[82]. Global questions are considered by some to be especially useful as they represent a summation of many factors that are often difficult to quantify[92-94]. Within the works of this thesis quality of life has been measured by global single questions on overall as well as health-related quality of life, as discussed in more detail below (p. 31).

Interpretation

As mentioned above, quality of life results are sometimes difficult to interpret. For instance, patients with disabling disease may perceive better quality of life than "healthy" people. This may in part be explained by the fact that for patients, the meaning of quality of life may change over time as internal standards are shifted and concepts like health, happiness or love are redefined in response to their disease. This phenomenon is referred to as response shift[78, 95, 96]. In addition, quality of life results may be influenced by the way a questionnaire is administered[97, 98], the order of questions in the questionnaire, the circumstances surrounding the patient and his or her state of mind at the moment. Questions about symptoms and physical function may be less sensitive to psychosocial, cultural and situational circumstances compared to general questions on quality of life[82]. On the other hand there is often no immediate correlation between symptoms and physical dysfunctions and patient-reported quality of life[99]. For example, as will be discussed below, sexual function is often deteriorated after treatment for rectal cancer, but this is not reflected in a lower quality of life in many studies[100-102]. It may of course be that some symptoms and dysfunctions are not very important to patients' quality of life in relation to other aspects of life. Alternatively such findings may be explained by lack of detail or insufficient sensitivity or even validity of the questionnaires used, which will be described in more detail below (p. 12).

Statistical significance and clinical relevance

An important issue in relation to the interpretation of results is the distinction between statistically significant and clinically relevant findings[77]. An observed difference in quality of life between two groups of patients or an observed change in quality of life over time may be statistically significant, but is it clinically relevant? This may be particularly important to consider in relation to large clinical studies where the large sample size may contribute to a statistical significance – also for clinically irrelevant

differences. Notably this is a general phenomenon that applies to all kinds of outcomes, clinical as well as patient-reported; with growing sample size, statistical significance will eventually always be declared. This emphasizes the importance of reporting not only p-values but estimated group differences as well.

Efforts have been made to establish the minimal important difference in relation to many quality of life outcomes. The minimal important difference is defined as the smallest change in quality of life that the patient would identify as important[103, 104]. The minimal important difference can be established by different methods[103, 105, 106]. *Anchor-based* methods aim to determine if a change in quality of life is important to the patient by relating it to an anchor question on changes in symptoms or physical function. For example, when completing a follow-up questionnaire of a prospective study on quality of life, patients could be asked to rate themselves as "much better", "better", "unchanged" or "worse" with regard to symptoms or physical function. The minimal important difference could then be determined as the mean change in a quality of life score among patients rating themselves as "better"[103]. As opposed to anchor-based methods, *distribution-based* methods build on statistical analyses of data variation. For instance, half a standard deviation has been found to correspond to the minimal important difference across a variety of studies[107]. Distribution-based methods allow for the calculation of effect size, which is a standardized measure of change from baseline to post-treatment obtained by dividing the difference in scores between measurements by the standard deviation of the baseline scores. The effect size can be used to determine clinical relevance and to compare results between studies.

On the way to work: early morning mist over Svarttjärn.

Validation of quality of life questionnaires

In this context, validation is the process of evaluating the quality of a questionnaire and investigating whether it is useful and reliable. Table 2 summarizes some of the elements in this process.

Validity	Does the questionnaire measure what it is intended to measure?
Internal validity	Are results reliable on the basis of the methodology used in the development of the questionnaire?
External validity	Are results generalizable beyond the particular study population?
Content validity	Is the questionnaire and the included questions relevant for the purpose?
Construct validity	Refers to aspects such as *floor and ceiling effects*, missing data and the relations between items, subscales and the "hidden construct" (i.e. the aspect of quality of life that the subscale aims to measure, see text below).
Floor and ceiling effects	If a large proportion of respondents have minimum or maximum score on individual items or subscales, this may lead to poor *responsiveness* and *sensitivity.*
Responsiveness	Ability to measure change over time, e.g. disease progression.
Sensitivity	Ability to detect changes over time or differences between groups.
Reliability	Are results reproducible on repeated measurement, given that there has been no change between measurements (regarding disease progression, for instance)?
Discriminative validity (or known-groups validity)	Ability to distinguish between clinical groups of patients.
Face validity	A rather ill-defined term that refers to the overall impression of the questionnaire.
Face-to-face validity (or respondent validation)	An important step in the development process, where patients sit face-to-face with the researcher and review the questionnaire and the individual questions for acceptability, comprehensibility, relevance, clarity and ambiguity.

Table 2. Terms related to the validation of quality of life questionnaires.

Many of the terms in Table 2 refer to important aspects of *psychometric* validation. The questionnaires we have used within this thesis were not validated by psychometric methods. Psychometric methods were originally developed in the context of personality, intelligence and educational attainment tests, where the majority of items were so called *indicator* variables, designed to reflect either a level of ability or a state of mind (the "hidden construct"). However, like most health-related quality of life questionnaires, our questionnaire mainly contains questions on symptoms and impairments. These questions are examples of so called *causal* variables: the experience of a specific symptom is believed to *cause* a reduction in quality of life. Whereas indicator variables *reflect* the level of quality of life, quality of life is *affected* by causal variables. Although psychometric methods are frequently used in the validation of quality of life questionnaires, some authors argue that these methods are a less appropriate means to validate a questionnaire with predominantly causal variables. Instead they stress the importance of a rigorous development process[82].

Treatment-related morbidity

Following treatment for rectal cancer, patients may experience chronic symptoms or functional impairments. This includes sexual, urinary or bowel dysfunction as well as problems related to a permanent colostomy. Chronic perineal symptoms have been

reported following extralevator abdominoperineal excision[108, 109]. Below is a summary of treatment-related morbidity and consequences for patients' quality of life.

Anatomical basis for physical dysfunction

Sexual and urinary dysfunction is mainly the result of damage to pelvic autonomic nervous structures by preoperative radiotherapy or surgery[7, 110, 111]. The sympathetic innervation may be damaged during dissecting at the pelvic brim or during ligation of the inferior mesenteric artery on the aorta, while parasympathetic nerves may be injured during perineal or lateral pelvic wall dissection. If the superior hypogastric plexus and hypogastric nerves are damaged, this leads to urinary incontinence, ejaculatory dysfunction in men and reduced lubrication in women. Damage to the pelvic splanchnic nerves and the inferior hypogastric plexus results in urinary retention, erectile disorders in men and reduced labial and vaginal swelling in women (Figure 5).

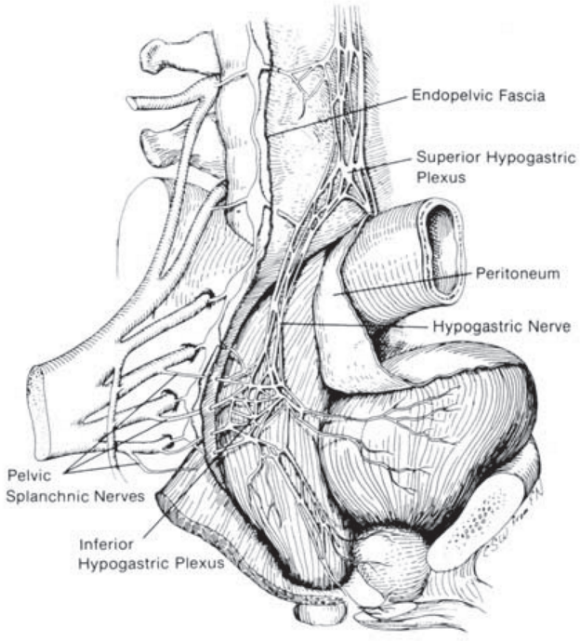


Figure 5. *Autonomic innervation of the pelvis.*

Keating, J.P. ANZ J Surg 2004[110]. Reprinted with permission from the author.

Radiotherapy may injure nervous structures directly or increase the risk of surgical nerve damage by making dissection planes unclear. In addition, radiotherapy may damage other tissues and organs[112]. In men, radiation damage to the seminal vesicles and small blood vessels may lead to ejaculatory and erectile dysfunction, respectively[7,

[113]. Furthermore, radiation damage to the testes may lead to decreased serum testosterone which may contribute to erectile dysfunction[114]. Many patients operated by anterior resection experience bowel dysfunction as a consequence of the low anastomosis[115, 116], which will be discussed in more detail below. Radiation damage to the anal sphincter may contribute to bowel dysfunction in these cases[117-120]. A radical resection of the cancer sometimes necessitates partial or complete resection of surrounding organs and distortions of the natural anatomy with risk for functional consequences. In case a stoma is created, stoma related problems may occur[121, 122].

Sexual dysfunction

The frequency of sexual dysfunction has been reported to range from 10-35 % [111], but some studies have reported higher figures[100, 123, 124]. This may be explained by the fact that sexual dysfunction lacks a standardized definition, which makes comparison between studies difficult[125]. Sexual dysfunction may include ejaculatory and erectile dysfunction, vaginal dryness and dyspareunia as well as decreased sexual activity, desire or satisfaction and other aspects. Radiation therapy is considered a major risk factor for sexual dysfunction in both men and women[102, 111, 113, 124]. It is often difficult to know if the sexual dysfunction was caused by treatment or if problems were present before treatment[100]. Among the cohort of 545 Swedish men and women described in paper IV, 47 % reported a decreased ability to achieve an orgasm after surgery and 74 % of all men reported decreased erectile function following their operation[126]. Sexual dysfunction is more common after abdominoperineal excision compared to anterior resection[100, 102, 127, 128]. This may be explained by the higher risk of nerve damage associated with abdominoperineal excision, especially during the perineal phase[7]. Sexual function is, however, multifactorial and some dysfunctions may be related to psychosocial factors, e.g. a psychological reaction to the stoma[100, 110, 129, 130]. While McGlone et al described better outcome after laparoscopy regarding erectile function and all aspects of sexual function in women[131], the laparoscopic technique did not reduce genitourinary problems in the COLOR II trial[132]. Age and perhaps sex influence the way patients perceive their quality of life in relation to a sexual dysfunction[110]. Younger patients and men seem to be more bothered by their sexual dysfunction[128, 133, 134].

Urinary dysfunction

Urinary dysfunction following treatment involves voiding difficulties, nocturia and incontinence and seem especially common in women. In comparison with sexual dysfunction reported frequencies are generally lower[111], but this apparently depends on what is measured and how. Among the patients included in paper IV, 41 % of women used incontinence pads three years after abdominoperineal excision while only 7 % reported being incontinent before surgery. For men, the figures were 10 and 2 %, respectively[126]. Urgency was experienced by 77 % and incontinence by 63 % among

516 female patients operated in Denmark by low anterior resection or abdominoperineal excision about four and a half years earlier[123].

Bowel and stoma-related dysfunction

Bowel dysfunction is common following anterior resection with a low anastomosis and may be experienced by as many as 50-90 % of patients[116, 117, 135, 136]. Symptoms include increased stool frequency, urgency, clustering and incontinence. The combination of these symptoms is referred to as the low anterior resection syndrome (LARS). Symptoms often arise immediately after surgery and may decrease after a few months. While some patients eventually recover almost normal function, others suffer life-long disability[137]. The severity of the low anterior resection syndrome may be investigated by the LARS score[115], which was developed by Emmertsen and Laurberg and is based on five questions that are weighted according to their estimated impact on quality of life. Further studies have indicated that the severity of the low anterior resection syndrome is closely associated with the patients' quality of life[138].

Many studies have examined the impact of a stoma on quality of life[78, 122, 139-143]. The assumption that a permanent colostomy is associated with lower quality of life compared with anterior resection has been challenged[144, 145]. Among the patients included in paper III, 90 % were able to live their life to the full and could engage in leisure activities of their choice about four years after abdominoperineal excision[146]. Cultural differences may be significant, with poor acceptance of stomas in some parts of the world, where many patients may accept poor bowel function in preference to a stoma[7]. Possibly this is in part related to the availability of stoma therapists and to the cost of stoma appliances.

Patients who receive a permanent colostomy may develop a parastomal hernia, resulting in a bulge around the stoma which may be inconvenient, painful and cause leakage of the appliance. A hernia incidence as high as 30-50 % has been reported [121, 122], although the prevalence of symptomatic parastomal hernias three years after abdominoperineal excision was only 11 % in the national cohort described in paper IV[147]. Although stoma patients as a group do not seem to have inferior quality of life compared to patients operated by anterior resection, patients with a dysfunctional stoma, including those who develop a parastomal hernia, may have a risk of a decreased quality of life[148].

Perineal morbidity

Following an abdominoperineal excision, the healing of the perineal wound may be lengthy and distressful and chronic symptoms from the perineum may be common[149]. Chronic perineal pain has been reported in as many as half of patients after extralevator abdominoperineal excision[108, 109]. Walking and sitting disability has also been

reported[108, 150, 151]. The development of a perineal hernia has been considered a rare complication with an incidence of less than one to a few percent[68, 152]. However, the incidence may have been underestimated and may be increased following extralevator abdominoperineal excision[153].

Psychological determinants of quality of life

When interpreting the effect of a treatment on health-related quality of life it should be remembered that quality of life is multifactorial and not only related to somatic morbidity. Two interesting psychological factors are intrusive thoughts and the concept of sense of coherence.

Intrusive thoughts

Intrusive thoughts differ from ordinary thoughts in that they are unwelcome, unintentional, repetitive and hard to fight off. Such thoughts constitute one component of post-traumatic stress disorder[154, 155]. They also occur in conditions such as depression and obsessive-compulsive disorder as well as in patients with cancer[156, 157]. Cancer-related intrusive thoughts have been reported to be associated with quality of life in patients with prostate cancer[158]. Only a few studies have explored intrusive thoughts in patients with colorectal cancer[159, 160]. Intrusive thoughts have often been evaluated by the Impact of events scale[155, 161], which contains questions on intrusions. Others have performed structured interviews to explore the nature and content of intrusive thoughts in depth[156] or used single global questions relating to the occurrence and severity of intrusions[158]. Studies have indicated that intrusive thought may be possible to treat with cognitive[162-164] as well as pharmacological[160] interventions, as will be discussed in more detail later (p. 40).

Sense of coherence

The concept of sense of coherence (SOC) was developed by Aaron Antonovsky in the seventies[165]. Sense of coherence mirrors the extent to which we perceive life as comprehensible, manageable and meaningful[166]. It may be regarded as a personality trait or coping disposition. Sense of coherence is evaluated by SOC-29, a validated instrument with 29 questions (see Appendix). A shorter version of the original 29-item scale has also been developed[167]. An association between sense of coherence and quality of life has been reported in several studies[168]. Some have investigated this association in patients with colorectal cancer[169, 170]. While Antonovsky viewed sense of coherence as a relatively stable trait, some reports indicate that it may be accessible for intervention[171-173].

AIM

The overall aim of this thesis was to explore treatment outcome in patients with rectal cancer, with specific focus on morbidity and quality of life.

The specific aims were to:

- Design and initiate a prospective study on quality of life and treatment-associated morbidity in patients with rectal cancer (QoLiRECT).
- Explore possible psychological determinants of pretreatment quality of life within the QoLiRECT study.
- Evaluate a new surgical technique for abdominoperineal excision with regard to short-term morbidity and oncological result.
- Investigate the prevalence of chronic perineal symptoms in patients operated by abdominoperineal excision and to explore potential risk factors and association with quality of life.

PATIENTS AND METHODS

General methodological considerations

In research, one should always aim to use the strongest possible study design in relation to the research question. An *interventional* study is generally considered to be of higher evidence value than an *observational* study. The randomized controlled trial is an interventional study and considered the golden standard in clinical research. The randomization aims to minimize the influence of confounding factors on the outcome so that group level estimates have minimal bias. Consequently, observed differences between treatments may be interpreted in terms of causality. The value of randomized controlled trials is sometimes limited by small sample size and selection of patients, which may decrease generalizability of results. Low response rates and participant drop-out (loss to follow-up) may be a concern in interventional as well as in observational studies, as this can introduce bias, which will be discussed below (p. 28-29). The studies included in this thesis are all observational.

Observational studies

Unlike randomized trials, observational studies generally do not allow for assessment of causality but only reveal associations between variables. In a typical *cohort study* one or several exposures are studied in a cohort of patients that are followed over time. The observational period may be prospective, as in the QoLiRECT study (paper I-II) but it may also be retrospective, as in the consecutive case series described in paper III. Furthermore, retrospectively retrieved data may have been prospectively registered as is the case with the national registry data that were analysed within this thesis. Because patients have not been assigned to exposure groups by randomization in observational studies, confounding factors need to be accounted for in the analysis. Even though there is no intervention, data collection itself may affect the behaviour of the study population. For example, patients who are regularly asked about their physical activity may start questioning their life style and perhaps increase their level of exercise. In addition to comparing groups within the study cohort, comparisons can also be made with an external reference population, as was done in paper II. National quality registries greatly facilitate data collection and increase the external validity of cohort studies[72], as discussed in more detail below (p.27).

As opposed to a prospective cohort study, a *cross-sectional study* is carried out at one time-point. It allows for prevalence estimation in a sample of a population, e.g. the prevalence of chronic perineal symptoms in patients operated by abdominoperineal excision three years earlier as in paper IV – although in this study, questionnaire send-out was in fact not undertaken at a fixed time-point but instead scheduled so that each patient was assessed three years after surgery. Notably the result of a cross-sectional

study is only a snap-shot; if another time frame had been chosen, e.g. perineal symptoms one instead of three years postoperatively, the results may have been different.

Studies and sources of data

This thesis is based on three methodologically different clinical studies (Table 3) as well as a questionnaire review in a sample of the Swedish population to obtain population reference data, as described in paper II.

Paper	Study name	Study design	Patients	Endpoints	Data sources
I- II	QoLiRECT	Prospective, observational multicentre study	1248 Swedish and Danish patients (1085 patients analysed in paper II)	Quality of life, treatment-related morbidity	Questionnaire, SCRCR[1], DCCG[2] national database, clinical record forms, reference population survey
III	-	Retrospective cohort study	156 patients operated by conventional or extralevator abdominoperineal excision in one institution 2004-2009	Perineal wound complications, short-term oncological outcome	Medical records, SCRCR[1]
IV	APER	Cross-sectional questionnaire survey	Three-year survivors of a national cohort of patients operated by abdominoperineal excision in Sweden 2007-2009	Perineal symptoms, quality of life	Questionnaire, SCRCR[1], operation notes

Table 3. Studies included in this thesis. Note that the main endpoint of the APER study[174] was three-year local recurrence rate, as reported elsewhere[38]. Here, we describe treatment-related morbidity and quality of life in this national cohort.
[1]The Swedish ColoRectal Cancer Registry
[2]The Danish Colorectal Cancer Group

Clinical data

Within the works of this thesis, clinical data were retrieved from the Swedish ColoRectal Cancer Registry[5, 175] and the national database of the Danish Colorectal Cancer Group[176]. As these registries have almost complete coverage of rectal cancer cases, they allow for excellent control of external validity. Medical records and operation notes provided additional clinical data. Two short clinical record forms were used to collect data that were not covered by the registries, as described below (p. 21).

Patient-reported data

Patient-reported data were retrieved by way of study-specific questionnaires. Two main questionnaires were developed, one to be used in the APER study (paper IV) and one to be used in the QoLiRECT study (paper I-II). In addition, questionnaires for the collection of follow-up data in the QoLiRECT study were produced (Figure 6).

The APER study questionnaire included questions on patient demographics, comorbidities, socioeconomic data and detailed exploration of quality of life, symptoms and treatment-associated functional impairments. The QoLiRECT study questionnaire was similar, with the exception that the base-line questionnaire focused on pretreatment functional status and the follow-up questionnaires included questions on functional impairments intended for all patients treated for rectal cancer, not only those operated by abdominoperineal excision.

Included in all questionnaires was the EQ-5D-3L, which is a short generic health-related quality of life instrument[85, 177]. It consists of five questions covering different aspects of health as well as a visual analogue scale where respondents indicate their current health state, as described in more detail below (p. 31). The Sense of Coherence scale (SOC-29, see Appendix), which has been described above, was included in the questionnaire used in the QoLiRECT study (paper I-II).

Questionnaire development

In the development of the study questionnaires we used the methods described by Steineck et al[178-180]. Patients with rectal cancer were involved in the process of developing novel questions on functional impairments through semi-structured interviews. These were word by word transcribed and the resulting texts underwent content analysis with a qualitative methodology[181]. Questions were developed and refined and the content was validated in a multidisciplinary group of professionals, as described elsewhere[182]. This process resulted in a questionnaire draft, which also included questions previously used in studies of men with prostate cancer[178, 183, 184]. The questionnaire draft was reviewed by patients regarding acceptability, relevance, clarity and ambiguity in a process referred to as face-to-face validation (Table 2). This was followed by a second content validation and the process was repeated until no ambiguities remained. The questionnaire was used in a pre-study among survivors of the cohort described in paper III to test the questionnaire as well as the data collection procedure and response frequency[146]. In the case of the QoLiRECT questionnaires, this was followed by translation into Danish according to commonly accepted principles[185, 186].

In order to obtain reference data for the questionnaires, a cross-sectional population survey was conducted among 1078 persons (median age 63 years, range 31-90; 53 %

female) who were randomly selected from the general population through the Swedish Tax Agency. The study protocol is available at www.ssorg.net.

Paper I

This paper describes the design of the prospective QoLiRECT study[182]. The aim of this study was to explore treatment-associated morbidity and quality of life in an unselected population of patients with rectal cancer. Patients were included at 16 participating hospitals in Sweden (n=977) and Denmark (n=271). Inclusion took place when the rectal cancer diagnosis had been confirmed by a biopsy, the multidisciplinary team conference had reviewed the case and the patient had been informed about the recommended treatment. There were no exclusion criteria except age below 18 and inability to understand the questionnaire because of language difficulties, cognitive failure or other reasons.

Inclusion started in February 2012 and was terminated in September 2015. The study is running and patients will be followed for five years. A study-specific questionnaire, which has been described above (p. 20), is completed at base-line and at three additional time points during follow-up (Figure 6).

Figure 6. In the QoLiRECT study, patients complete a base-line and three follow-up questionnaires.

Clinical data are retrieved repeatedly during the course of the study from the Swedish ColoRectal Cancer Registry[5] and the national database of the Danish Colorectal Cancer Group[176]. As the registries differ slightly from one other, two short clinical record forms were produced to make up for those differences: one pertaining to the surgical technique of abdominoperineal excision (Sweden) and the other mainly to details of neoadjuvant and adjuvant treatment (Denmark).

Paper II

In this paper, the first results from the QoLiRECT study[182] are reported. This was an analysis of baseline data that aimed to explore psychological and clinical determinants

of pretreatment quality of life. The analysis included 1085 patients scheduled for curative (n=1012) or palliative (n=73) treatment of their newly diagnosed rectal cancer (Figure 7). Median age was 69 (25-100) and 55 % were male.

Data were retrieved from the baseline questionnaire of the QoLiRECT study (Figure 6) and from the Swedish ColoRectal Cancer Registry[5] and the national database of the Danish Colorectal Cancer Group[176].

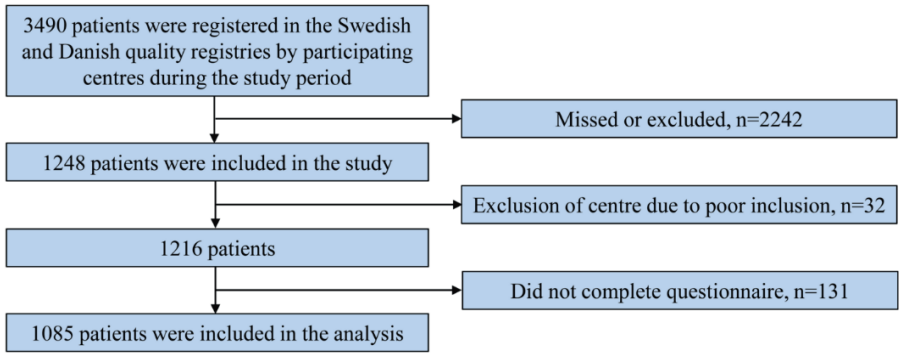


Figure 7. Flow chart of patients included in the analysis of pretreatment quality of life.

Before data analysis, it was decided to exclude all patients from any hospital with an inclusion rate less than 20 % in order to avoid an obvious risk of selection bias. As illustrated in Figure 7, this resulted in the exclusion of 32 patients from one hospital.

Variables and statistical analyses were strictly defined in a statistical analysis plan prior to data retrieval from the study database. In addition to the two psychological variables (cancer-related intrusive thoughts and sense of coherence, see p. 16) we decided to include the treatment plan (curative or palliative) as a potential determinant of pretreatment quality of life. An alternative option would have been to include clinical tumour stage. Obviously the treatment plan and clinical tumour stage are strongly associated, which prevents the inclusion of both in a statistical model as this would infer problems of collinearity. The decision to include the treatment plan instead of tumour stage seemed justified since results probably mirror a psychological reaction to the treatment plan rather than the clinical tumour stage *per se*. The important issue was to adjust for the impact of the clinical situation in the analysis of other potential determinants of quality of life.

This analysis was concerned with pretreatment data only. Thus, regarding the treatment plan, this was literally an intention-to-treat analysis. To take into consideration the treatment that was eventually received was beyond the scope of this analysis.

Paper III

This paper reports the results of a retrospective study that aimed to evaluate short-term clinical outcome of a new surgical technique for abdominoperineal excision. Patients operated by abdominoperineal excision because of a primary rectal cancer at Sahlgrenska University Hospital/Östra between 2004 and 2009 were identified by search of the operation planning software (Operätt), the hospital administrative system and the Swedish ColoRectal Cancer Registry. Patients with previous rectal surgery (local excision by transanal endoscopic microsurgery in most cases) or palliative treatment were excluded, as the inclusion of these patients in the analysis of oncological outcome would be misleading. Seventy-nine cases of conventional abdominoperineal excision and 79 cases of extralevator abdominoperineal excision were included in the analysis. Median age was 68 (35-89) and 63 % of patients were male. 82 % were ASA 1-2 and pathological tumour stage was pT I-II in 30 % of patients.

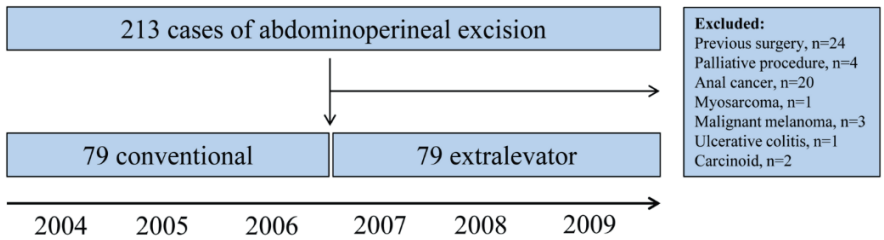


Figure 8. Following its introduction in the beginning of 2007, the extralevator technique was employed for all cases of abdominoperineal excision at Sahlgrenska University Hospital/Östra for the remainder of the study period.

Medical records and operation notes were scrutinized for data regarding operative technique and perineal wound infection, wound revision, wound healing and other clinical data. Additional data were retrieved from the Swedish ColoRectal Cancer Registry[5].

Groups were compared by the chi-square test for categorical data and non-parametric methods (Mann-Whitney) for continuous data.

Paper IV

In this paper, aspects on treatment-related morbidity and quality of life three years after surgery are reported in a national cohort of patients operated by abdominoperineal excision between 2007 and 2009. Oncological results in this cohort have been reported previously[38, 39]. Patients were identified through the Swedish ColoRectal Cancer Registry[5]. The cohort was cross-checked with the Swedish Population Register in order

to avoid misplaced contacts with patients who had died during the intervening period. An introductory letter was sent to the patients followed by a phone call. Eligible patients who consented to take part in the quality of life part of the study received a questionnaire by mail and returned it to the study secretariat by way of a prepaid envelope. Questionnaire send-out was followed two weeks later by a reminder/thank you note in the form of a postcard. The development and content of the study-specific questionnaire was described above (p. 20). Clinical data were retrieved from the Swedish ColoRectal Cancer Registry[5] and included patient demographics, neoadjuvant treatment, distance from the distal tumour border to the anal verge, American Society of Anesthesiologists (ASA) physical status classification and pathological tumour stage. Whether patients were operated by conventional or extralevator abdominoperineal excision was determined from operation notes together with details of perineal dissection and reconstruction, as the registry does not include this information. Notably, operation notes did not reveal which technique had been used in a fairly large proportion of patients. In this study, data were thus retrieved from three different sources: a questionnaire, a national registry and operation notes.

Of the 1319 patients of the original cohort, 545 patients (60 % male) with a median age of 66 at the time of surgery were included in the quality of life analysis (Figure 9).

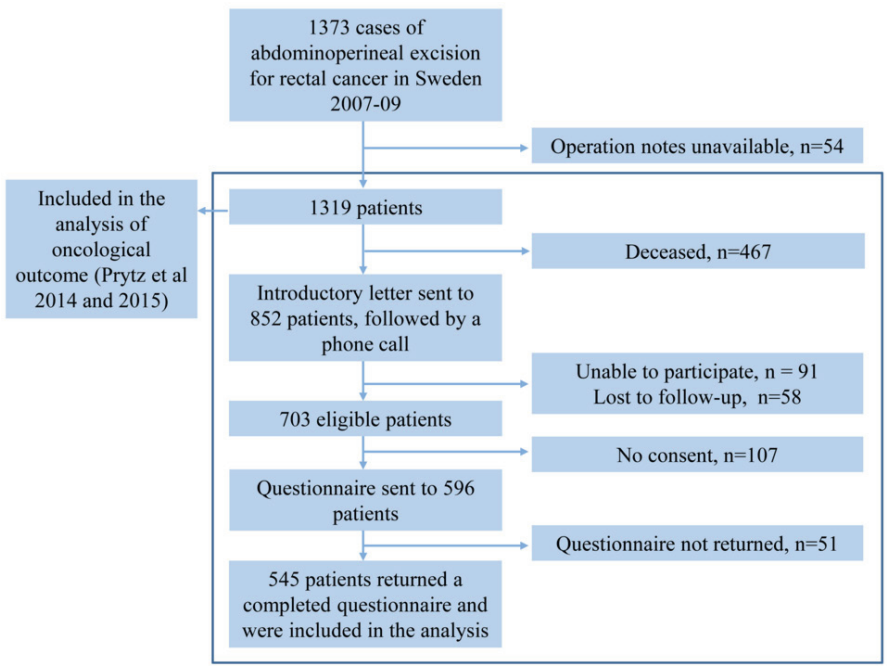


Figure 9. Flow chart of patents included in the cross-sectional questionnaire survey.

Prior to analysis, a detailed analysis plan was developed. One aim was to investigate the frequency of chronic perineal symptoms and another was to identify patients with pronounced symptoms and to explore what they had in common. Six questions were analysed in relation to perineal symptoms (Table 4).

Have you had pain between the buttocks in the past month?
Have you had difficulties to sit in the past month?
Have you had loss of sensation/numbness in the buttocks in the past month?
Have you experienced tension in the buttocks in the past month?
Have you experienced a tingling/stinging sensation in the buttocks in the past month?
Have you experienced cramps/urgency that you perceived came from the previous location of your rectum in the past month?

Table 4. Questions on perineal symptoms.
Response options: Not at all/a little/quite a bit/very much.

Pronounced or "severe" symptoms were defined by response options *quite a bit* or *very much*. In turn, *severe perineal morbidity* was defined as the experienced of at least one symptom of severe degree. Delayed healing and surgical technique were identified as the exploratory variables of interest. Age, sex, preoperative radiotherapy and distance from the distal tumour border to the anal verge were considered relevant confounders. The intention was to investigate the association of these factors with the compound outcome *severe perineal morbidity* by regression analysis and to explore the association of chronic perineal symptoms with health-related quality of life. Additional aims were to evaluate the patients' recollection of the perineal wound healing after the index operation, and to investigate the potential impact of different reconstruction techniques on chronic symptoms in patients operated by extralevator abdominoperineal excision.

Methodological aspects

Comparability

In observational studies where patients are not randomized between groups, it is important to consider any confounding factors that may influence the outcome. Examples of such confounding factors are age, sex, comorbidity, lifestyle and socioeconomic factors as well as disease characteristics and treatment-related variables. All these factors may partly explain observed differences between groups, e.g. regarding surgical complications or quality of life.

In paper III, the comparability of groups was evaluated by comparison of baseline characteristics and potential confounding was handled by performing a number of prespecified subgroup analyses, as will be described below (p. 35 and 37). Although

cautious conclusions may be drawn from such methods, adjusting for confounding factors by regression analysis is more flexible and may strengthen the evidence. This approach was taken in paper II and IV, where a wide range of potential confounding factors that could influence patients' perception of quality of life and the experience of chronic perineal symptoms, respectively, were considered.

Comparing conventional and extralevator abdominoperineal excision with regard to oncological outcome can be challenging in a non-randomized setting. If the choice of surgical technique is dependent on tumour stage, this would obviously make comparisons difficult. Furthermore, as a result of differing tumour stage other clinical differences would be likely to exist as well. It is important to know that following the introduction of extralevator abdominoperineal excision in the beginning of 2007, the new technique was perceived to be recommended as a replacement for the conventional technique for all cases of abdominoperineal excision[34]. The decision to perform an extralevator abdominoperineal excision was more a question of hospital policy or the surgeons own conviction than of tumour stage in the initial years following the introduction of the technique.

The study reported in paper III was not only a comparison of surgical techniques, but also in a sense a comparison of two different time periods (Figure 8). This could introduce bias, as clinical practise may change over time. However, in comparison to a much cited study on the same subject[43] the time frame was short, both types of operations were performed largely by the same surgeons and cases were consecutive. The finding that chemoradiotherapy was more common in the extralevator group, i.e. during the latter part of the study, may mirror a shift in clinical practice rather than a change in tumour stage over time. To our knowledge, referral patterns in the region did not change during the study period. Still, as chemoradiation has the potential to downstage tumours, the uneven distribution of chemoradiotherapy between conventional and extralevator abdominoperineal excision is a potential source of bias in this study. In the evaluation of comparability between groups, analysis of clinical instead of pathological T-stage may have been more conclusive but as pretreatment staging during the first half of the study did not include magnetic resonance imaging or endorectal ultrasound for most patients, clinical T-stage would have been unreliable in this setting. According to the pathology report the only significant tumour-related difference between patients operated by conventional and extralevator abdominoperineal excision was the number of retrieved lymph nodes (but not the lymph node ratio). Distance from the distal tumour border to the anal verge as determined by preoperative rectoscopy was no different between groups. Interestingly we found a small number of patients with mid-rectal tumours in the cohort. This may seem odd, as abdominoperineal excision is generally not considered for tumours located more than 6 cm from the anal verge. However, sphincter-sparing surgery may have been avoided in these patients due to poor sphincter function or other reasons.

External validity

External validity refers to whether results are generalizable beyond the study group and apply to the entire population in question. For instance, is the frequency of chronic perineal symptoms reported in paper IV generalizable to all three-year survivors following abdominoperineal excision for rectal cancer in Sweden? The assessment of external validity of our results was greatly facilitated by the national quality registries in Sweden and Denmark that cover 99 and 95 % of all rectal cancer cases, respectively[175, 187]. This allowed for comparison of clinical and demographic data between included and non-included patients and of responders and non-responders to the study questionnaires, as will be discussed below. The external validity of results may also be increased by the fact that patients were not excluded from the QoLiRECT study (paper I-II) based on tumour or treatment characteristics, as is often the case in clinical studies.

In the analysis of pretreatment quality of life in an unselected population of patients with rectal cancer (paper II), non-included patients were one year older (median age), less healthy according to the ASA physical status classification and had a higher clinical T and M stage. Clinical N stage was not included in the Danish registry, resulting in a high number of missing values among non-included patients, which makes this variable less informative. There were fewer women among non-included compared to included patients. How these differences between non-included and included patients affect the generalizability of results is not immediately apparent. Intrusive thoughts may be more common among non-included patients as they may be more burdened by disease, but how this would affect the predictive value of intrusive thoughts and sense of coherence on pretreatment quality of life is uncertain. In relation to what was said about clinical N-stage above, it could be mentioned here that the clinical N-stage of included Danish patients was retrieved by use of a clinical record form as described on p. 21.

In the cross-sectional questionnaire survey among patients operated by abdominoperineal excision (paper IV), non-included patients were five years older (median age), less healthy according to the ASA physical status classification, received less preoperative radiotherapy and had a higher frequency of circumferential resection margin involvement than included patients. Again, the implication of these differences for the prevalence of chronic perineal symptoms may not be obvious, but the data give no clear reason to suspect a difference between non-included and included patients. Thus, with reference to the question at the beginning of this section, this analysis may give a fair estimate of the frequency of perineal symptoms in the total population of three-year survivors.

Inclusion rate and compliance

A high rate of non-included patients or non-responders to a questionnaire may introduce bias to a study, given that the reason for their non-participation is not completely random. The overall inclusion rate of the QoLiRECT study (paper I-II) was estimated by the retrieval of data on non-included patients from the national registries. As illustrated in Figure 7, participating centres reported 2242 new cases of rectal cancer to the registries during their time of recruitment that were not included in the study. Thus, the overall inclusion rate, which does not take consciously excluded patients in consideration, was 36 %. The number of included patients at participating hospitals ranged from 20 to 237, primarily depending on hospital size and differing inclusion periods (some hospitals joined the study later than others) but also on differing inclusion rates. To minimize the number of missed patients and increase the inclusion rate, the inclusion process at participating hospitals was continually supported and monitored. The response rate to the baseline questionnaire among the 1216 patients eligible for analysis in paper II was 89 % (Figure 7). This means that 131 patients never returned the questionnaire that was sent to them by mail a few days after inclusion, preceded by a phone call.

The percentage of patients scheduled for palliative treatment included in paper II was 7 %, which is lower than the reported rate of palliative treatment in Sweden of about 20%[13]. This was not unexpected but still disappointing, as efforts were made to specifically include these patients into the QoLiRECT study. Part of the explanation may be a reluctance in some surgeons and/or nurses to inform patients who were not scheduled for curative treatment about a five year prospective study – although in our experience many of these patients appreciated our interest in their situation and were encouraged by the fact that we included them in a study with the intent to stay in touch for five years. Importantly, however, the classification of patients as curative or palliative was done prospectively at the time of inclusion into the study. As some patients scheduled for curative treatment may not have been operated, the number of missed palliative patients may actually not be as large as it looks. A lower inclusion rate among palliative patients would possibly introduce a selection bias, as it may be suspected that it is the most severely ill or emotionally affected patients who would be excluded. This would lead to an overestimation of quality of life among palliative patients, and in that way the potential bias is conservative.

In the cross-sectional survey (paper IV), the questionnaire was completed by 60 % of all patients operated by abdominoperineal excision in Sweden 2007-2009, patients who had died not included (Figure 9). Considering that the study was conducted three years after surgery, this inclusion rate seems acceptable. As opposed to the inclusion rate, which is in this case is influenced by the rate of non-eligible or unreachable patients, the response rate to the questionnaire among those who received it was 91 %.

To increase response rates to postal questionnaires a strategy involving repeated contacts by mail and telephone has been recommended[188]. The routine that we used for the send-out of questionnaire was described above (p. 24) and involved such repeated contacts. This routine has been used in previous studies with similar response rates[134, 146, 158, 178]. It is also used in the follow-up of patients within the QoLiRECT-study (Figure 6). Although loss to follow-up occurs in most longitudinal studies, this routine may enable us to keep the number of drop-outs to a minimum and limit the bias that may be introduced if drop-out is systematic.

Validity of data

In a study where data are collected retrospectively from medical records, results and conclusions partly depend on the quality of the registered information. In the retrospective case series of patients operated by conventional or extralevator abdominoperineal excision (paper III), a perineal wound infection was considered to be present if this was stated in the records during admission or follow-up or if the perineal wound was described in such a way that a wound infection was likely. This process was facilitated by the fact that patients were evaluated for signs of infection by trained nurses during admission and that this information was routinely documented under a specific entry term in the medical record. However, whether the infection was abdominal or perineal was not evident and this information had to be found elsewhere. As discussed below (p. 36), the estimation of perineal wound healing was complicated by the fact that documentation was non-systematic and sometimes absent. A prospective study design would have increased the validity of the data on perineal wound infection and healing. It would also have allowed for the distinction between superficial and deep infections according to established criteria, which was not possible in our retrospective study.

The validity of quality registry data is dependent on correct reporting by administrative staff at individual hospitals and correct registration into the registry database. The internal validity of the Swedish ColoRectal Cancer Registry has been reported to be good[189]. As already mentioned, the external validity of both the Swedish and Danish national registries is excellent because of their high coverage[175, 189]. The Swedish ColoRectal Cancer Registry is continuously linked to the Swedish Cancer Registry and the Causes of Death Registry to ensure that no cases have been missed[175, 189]. It should be mentioned that the Danish registry only includes patients diagnosed and treated in surgical departments, which means that palliative patients are not included. Notably coverage in Sweden can never be 100 %, as cases diagnosed at autopsy are reported to the Swedish Cancer Registry but not to the Swedish ColoRectal Cancer Registry.

The validity of quality of life data is related to the validity of the questions and questionnaires with which data were retrieved, as has been discussed above (p. 12). It

is also affected by the pattern and frequency of missing data, e.g. questions left unanswered in an otherwise filled-out and returned questionnaire. As has already been discussed in the context of inclusion rate and compliance, data missing in a systematic fashion may introduce bias whereas data missing at random is less of a problem[82]. Thus, results may be biased if a particular question is associated with a low response frequency. Efforts should be made to identify problematic questions already during questionnaire development and validation, so that they may be rephrased and refined to increase acceptability, as discussed above (p. 12 and 20). There are many ways to handle missing data statistically[190]. In the calculation of the SOC-29 total sum score (paper II) an imputation method was used as described in the paper. Otherwise, as missing values were generally unusual and appeared to be random, frequencies were reported but not handled statistically in the analyses.

Statistical considerations

Prespecification and multiplicity

To ensure a high scientific credibility it is important to prespecify variables and analysis methods prior to data retrieval[190] and to avoid a "fishing expedition" in search of statistically significant results. Prior to any data analyses within this thesis detailed analysis plans were developed as described in detail above (p. 22 and 24-25). The analysis plans were adhered to with few exceptions, one of which was the estimation of local recurrence rate in paper III. In this way the number of analyses was kept to a minimum. The testing of several hypotheses within a single study may raise concern about inflation of the familywise error rate (the risk of incorrectly rejecting at least one null hypothesis). As the aims of paper II and IV may be characterized as exploratory and hypothesis-generating, and as the number of analyses in paper III was reasonably low, a less conservative approach was taken within the works of this thesis and no correction for multiplicity was performed.

Sample size

At the planning stage of a clinical study the number of subjects required to reach a sufficient statistical power (the chance of rejecting the null hypothesis when the alternative hypothesis is true) needs to be determined. Depending on the objective and outcome measures of the study, the sample size calculation requires pre-specification of values for a set of parameters. If, for instance, the aim is to test a difference between two incidence rates, two parameters need to be specified: the expected incidence in the control group and the difference between groups that we would not like to miss provided that the alternative hypothesis is true. In exploratory studies in particular, assumptions regarding the incidence of the outcome of interest may often be uncertain. Furthermore, the pre-specified difference between groups under the alternative hypothesis should be clinically relevant, as discussed above (p. 10-11). The minimal important difference may, however, be unknown or difficult to estimate. Nevertheless,

we made an attempt to formulate a sample size calculation in paper I that was based on our knowledge of the incidence of rectal cancer, the expected distribution among clinically relevant groups and the desired time frame of the study.

Quality of life

Quality of life was assessed in this thesis by global single questions on overall and health-related quality of life. The question on overall quality of life was phrased *"How would you describe your quality of life during the past month?*" with a 7-point Likert scale response format anchored by 0 (*"No quality of life"*) and 6 (*"Best possible quality of life"*). Health-related quality of life was measured by the EQ-5D-3L visual analogue scale, a vertical thermometer-like scale anchored by 0 (worst imaginable health state) and 100 (best imaginable health state)[85]. While overall quality of life is a broad term that includes many aspects of quality of life in addition to health, health-related quality of life is a narrower concept. We have used the term *global* health-related quality of life, as this variable was evaluated by a single question (the EQ-5D-3L visual analogue scale) and therefore represents a summation of many factors. As the EQ-5D-3L visual analogue scale requests patients to indicate their current health state, we might just as well have used the term health status.

RESULTS AND COMMENTS

Main results

Paper I

This paper described the protocol of a large, prospective, multicenter study on quality of life and morbidity in patients with rectal cancer (QoLiRECT)[182] and the development of the study questionnaire. No results were reported.

Paper II

Among patients included in the QoLiRECT study, pretreatment quality of life was negatively affected by intrusive thoughts (odds ratio 0.3, 95 % confidence interval 0.2-0.5) and a low sense of coherence (odds ratio 0.4, 95 % confidence interval 0.4-0.5) regardless of the clinical setting (curative or palliative intent of treatment). Eighty-three percent of included patients experienced intrusive thoughts about the rectal cancer, with no significant difference between curative and palliative patients. The higher the frequency and perceived intrusiveness of these thoughts, the greater was the impact on quality of life. Patients facing palliative treatment had lower overall quality of life (odds ratio 0.6, 95 % confidence interval 0.4 to 0.9) and global health-related quality of life (median 53 versus 80 on the EQ-5D-3L visual analogue scale[85], $p < 0.001$) compared to those scheduled for curative treatment. Ninety-seven percent of patients planned for curative treatment considered themselves well informed about their diagnosis and treatment plan versus 85% of patients planned for palliative treatment ($p<0.001$).

Paper III

In this retrospective case series in one institution, the incidence of postoperative perineal wound infection was high after abdominoperineal excision and higher following extralevator than conventional abdominoperineal excision (Table 5). The number of patients who required revision of the perineal wound increased with the extralevator technique (Table 5). The perineal wound healing process exceeded one month in the majority of patients (median 40 days, range 12-400) with no significant difference between groups. The proportion of patients with involved circumferential resection margins did not differ significantly (Table 5).

	Conventional abdominoperineal excision, n=79	Extralevator abdominoperineal excision, n=79	P-value
Perineal wound infection	28 %	46 %	<0.05
Perineal wound revision	8 %	22 %	<0.05
Length of hospital stay (median)	11 days	12 days	<0.05
Circumferential resection margin involvement	20 %	17 %	n.s.

Table 5. Perineal wound complications increased following the introduction of extralevator abdominoperineal excision, but oncological results were no better.

Paper IV

In this cross-sectional questionnaire survey in a national cohort of patients operated by abdominoperineal excision three years earlier, 50 % of patients experienced chronic perineal symptoms that included pain, sitting disability, tension, tingling or numbness between the buttocks and perineal cramps or a sense of urgency to defecate. A quarter of all patients experienced pronounced symptoms. Symptoms were more common in women (58 % vs 44 %, p=0.001). Surgical technique (conventional versus extralevator abdominoperineal excision) and preoperative radiotherapy were not associated with the occurrence or degree of perineal symptoms. Overall 25 % of the patients had a delayed (> 1 month) perineal wound healing after surgery. The risk of a delayed wound healing was increased after extralevator abdominoperineal excision (relative risk 3.5, 95 % confidence interval 1.5-8.2). A delayed perineal wound healing emerged as a risk factor for pronounced perineal symptoms (relative risk 1.6, 95 % confidence interval 1.1-2.1). In patients operated by extralevator abdominoperineal excision the use of mesh reconstruction, as opposed to plain suturing or the use of a myocutaneous flap, was associated with a decreased risk of pronounced perineal symptoms. Pronounced perineal symptoms were associated with a lower global health-related quality of life (median 75 versus 83 points on the EQ-5D-3L visual analogue scale[85], p <0.001).

Comments and discussion

Quality of life

Determinants of quality of life in patients with colorectal cancer have been explored in several studies[191-194], but only a few have investigated the role of psychological variables[169, 170, 195]. To our knowledge, there are no previous studies on the impact of psychological variables on quality of life in patients with rectal cancer only. In our analysis, intrusive thoughts and sense of coherence both turned out to be strong and

independent predictors of pretreatment quality of life (paper II). Notably, intrusive thoughts were more strongly associated with *global* than *health-related* quality of life. As discussed above (p.31), health-related quality of life in this study was equivalent to health status. In most people's minds health status probably refers to physical health. As intrusive thoughts are likely to affect a person's psychological wellbeing rather than physical health, the differing strengths of association seem plausible. Interestingly, the predictive ability of pretreatment quality of life on survival has been investigated in patients with primary rectal cancer in one small prospective study[196], which found that some dimensions of quality of life**,** together with age**,** predicted one-year survival with an accuracy of 76.8 %.

In paper IV, the impact of chronic perineal symptoms on quality of life was investigated among patients operated by abdominoperineal excision three years earlier. The association of perineal symptoms with quality of life has not been reported before. We found a statistically significant association of pronounced chronic perineal symptoms with health-related quality of life. However, the difference in quality of life between patients with and without pronounced perineal symptoms was smaller than the reported minimal important difference of the EQ-5D-3L visual analogue scale, which is estimated to be about 10 units[197]. Regardless of the magnitude of the effect, the fact that the experience of chronic perineal symptoms was at all mirrored by the EQ-5D-3L visual analogue scale is interesting and should lead to further investigations.

Intrusive thoughts

The high prevalence of intrusive thoughts among patients with a newly diagnosed rectal cancer (paper II) is comparable to the findings of Thorsteinsdottir et al, who reported a prevalence of 73 % in 883 men with prostate cancer before surgery[158]. As a reference the prevalence was 63% in the population of 1078 "healthy" Swedish individuals described in paper II. Importantly, the same questions were used in these three studies. The prevalence of intrusive thoughts among patients with breast cancer has been reported to be lower[198], but because of the use of different instruments with different recollection period and wording of questions, detailed comparisons are difficult. In our study, the experience of intrusive thoughts about the rectal cancer was found to be a strong predictor of pretreatment quality of life. As will be discussed below, intrusive thoughts may be accessible for simple clinical interventions, which may be one way to improve quality of life among these patients.

Sense of coherence

We demonstrated a significant and independent association between patients' sense of coherence and pretreatment quality of life (paper II). The mean value of sense of coherence in the study cohort was 158 (standard deviation 20, range 85-203) as

estimated by the SOC-29 scale. There was a difference between curative and palliative patients by 6 units, which was statistically significant but hardly clinically relevant. In the reference population of Swedish individuals mentioned above the SOC-29 mean value was 151 (standard deviation 22, range 68-197). A systematic review reported a range of mean SOC-29 values from 101 to 164 among 124 studies of diverse patient populations worldwide[167]. Although considered to be relatively stable during adulthood, sense of coherence is reported to increase with age, which may lower comparability between studies. Furthermore there are no general instructions on how to handle missing data, so this may be a source of variation as well.

Perineal wound infection

The rate of perineal wound complications after any type of abdominoperineal excision seems to be high[68, 70, 199, 200]. An increased rate has been reported following extralevator APE [43, 71]. This was supported by a recent meta-analysis[201] but questioned by another, which found that radiotherapy rather than the extralevator technique itself may account for the differences[68]. There was no difference in the rate of preoperative radiotherapy between surgical techniques in our retrospective case series (paper III) which would suggest that surgical technique was indeed responsible for the increased infection rate following extralevator abdominoperineal excision. However, when patients treated with a combination of chemotherapy and radiotherapy were excluded, the difference between groups was not statistically significant (p=0.092). As chemotherapy increases the sensitivity of cells to radiotherapy[58] and as radiation is delivered at a higher dose and during a longer period of time in chemoradiotherapy compared to short-course radiotherapy – both of which may theoretically increase the risk of postoperative wound complications – the differing rates of chemoradiotherapy between groups may have biased the results on the perineal infection rate in our study.

The perineal infection rates were somewhat higher in our study compared to other reported data[68, 70, 199, 200]. This may be explained by the fact that this was a primary endpoint in our study and great efforts were made to identify all cases of infection, as discussed above (p. 29). The fact that neither myocutaneous flap reconstruction nor mesh reconstruction was used to close the perineal wound in any of the patients may also have contributed. However, the use of myocutaneous flap reconstruction has been associated with high rates of perineal wound complications as well[43]. As mentioned above (p. 29), we did not differentiate between superficial and deep infections. However, as most deep infections would require surgical wound revision the frequency of wound revisions should represent a fair estimate. The percentage of patients requiring a perineal wound revision was 8 and 22 % following conventional and extralevator abdominoperineal excision, respectively. As a reference, Bullard et al reported a rate of wound revisions of 7 % among 160 consecutive patients operated by conventional abdominoperineal excision between 1988 and 2002[70].

Perineal wound healing

In our retrospective case series (paper III), the median healing time was 40 days (mean 59) with no difference between conventional and extralevator abdominoperineal excision. This figure seems high but Bullard et al reported an even longer healing time following conventional abdominoperineal excision in another retrospective analysis (mean 3.8 months, although the median value may have been more informative)[70]. Sixty-two % of all patients in our study (paper III) had a delayed perineal healing, defined as a healing time in excess of one month. Among the patients included in the cross-sectional questionnaire survey (paper IV), a delayed healing was experienced by 25 % with a very pronounced difference between conventional (9 %) and extralevator (22 %) abdominoperineal excision. The differences between studies III and IV regarding the frequency of a delayed healing is possibly explained by differing study designs and methodology. It is probable that the wound healing time was underestimated in paper III, as we did not have access to medical records of primary care facilities, to which many patients were referred for wound care after the initial follow-up visit(s).

Surgical technique was not associated with a delayed healing in paper III and neither was radiotherapy in paper IV. The explanation in both cases may be a lack of power to detect significant differences regarding this secondary outcome, or methodological problems in determining the correct healing time in a non-prospective setting as discussed above.

Perineal wound reconstruction

The perineal defect following abdominoperineal excision may be closed by plain suturing or reconstructed by the use of a biological mesh or a myocutaneous flap[150, 202-205]. All patients in the retrospective case series (paper III) were handled with plain suturing. This means that the recommendations[36] to reconstruct the perineal wound by way of myocutaneous flaps – preferably with the aid of plastic surgeons – were not adhered to, which may or may not have contributed to a higher wound complication rate, as discussed above. Myocutaneous flap reconstruction was carried out in some patients at Sahlgrenska University/Östra during the study period, but the technique was reserved for cases of local recurrence, which were excluded from this study as they would have interfered with the analysis of short-term oncological results as already mentioned (p. 23).

Among the 545 patients included in paper IV, the perineal defect was closed by plain suturing in 78 % of cases. All patients operated by conventional abdominoperineal excision were sutured, while mesh and flap reconstruction was used in 25 and 21 % of patients operated by extralevator abdominoperineal excision, respectively. Mesh reconstruction decreased the rate of perineal wound complications in a recent meta-

analysis[68]. Interestingly, we also found mesh reconstruction to be associated with favourable outcome with regard to chronic perineal symptoms.

Circumferential resection margin involvement

The oncological advantage of extralevator compared to conventional abdominoperineal excision has been debated in recent years[37-45, 199-201, 206-208]. At least six meta-analyses have compared the rate of an involved circumferential resection margin following the respective techniques. Three of them reported no significant differences[40, 206, 207], while three favored extralevator abdominoperineal excision [199, 201, 208]. No advantage of the extralevator technique regarding circumferential resection margin involvement was found in the large, registry-based APER study[39]. In our retrospective case series (paper III) the frequency of an involved circumferential resection margin following conventional abdominoperineal excision was 20 %, which is comparable to results from another single-centre retrospective series[209]. The extralevator technique was associated with an involvement rate of 17 % in our study, which is similar to the rate reported by West et al[43]. Keeping the limitations of our retrospective case series in mind (see p. 26), our data seem plausible and do not support an oncological advantage of the extralevator technique (Table 5).

Extralevator abdominoperineal excision is not likely to be of any advantage in cases where the distal tumour border is located above the region of the anorectal junction. As discussed in paper III, a subgroup analysis of tumours within 4 cm from the anal verge was performed, excluding roughly half of the patients, which did not change the results regarding circumferential resection margin involvement.

It has been suggested that there is an increased risk of circumferential resection margin involvement in anterior tumours[209, 210]. This may be related to a more difficult dissection plane in anterior tumours, as well as to the fact that tumours located above the peritoneal reflection lack a mesorectal envelope anteriorly so that any T4 tumour will have an involved circumferential resection margin. However, data regarding this aspect of tumour location was not available to us for most patients, as it is not included in the registry, and was left out of the analysis.

Chronic perineal symptoms

Before our investigation the prevalence of chronic perineal symptoms following abdominoperineal excision has been largely unknown. One symptom that has been reported is perineal pain, presumably because it is covered by the frequently used quality of life questionnaires developed for colorectal cancer by the European Organization for Research and Treatment of Cancer (EORTC)[86, 90, 91]. Chronic perineal pain was reported in 51 % of patients after extralevator abdominoperineal excision versus 6 % after conventional abdominoperineal excision in a prospective randomized

study[109]. One study found chronic perineal pain in half of all patients two years after extralevator abdominoperineal excision[108] while another indicated that patients may experience difficulties to sit because of pain following extralevator abdominoperineal excision with myocutaneous flap reconstruction[151]. All three studies were limited by a small sample size.

We reported prevalence rates of six chronic perineal symptoms among 545 patients operated by abdominoperineal excision three years earlier (paper IV). Half of all patients reported the experience of at least one symptom. Symptoms were more common in women and women were at increased risk of more severe symptoms. This is possibly related to differences in pelvic anatomy between sexes which may affect the way surgery is performed. As an example, when the perineal defect is closed in women it may include or put tension on parts of the vaginal wall in some cases. Furthermore, the vagina and uterus tilt backwards following rectal resection, which may have functional consequences and lead to changed perceptions. Other and so far unrecognized factors may play a role.

While Han et al reported an increased rate of chronic perineal pain following the extralevator technique[109] we found no association between extralevator abdominoperineal excision and our compound outcome measure *severe perineal morbidity*. This needs to be discussed from a methodological point of view. During analysis, extralevator abdominoperineal excision was found to be strongly associated with a delayed healing. This means that the consideration of surgical technique and wound healing together as explanatory variables in relation to perineal morbidity would infer problems of collinearity. Thus, the impact of a delayed healing on perineal morbidity was determined in the adjusted regression analysis, while the impact of surgical technique was analysed in bivariate analysis. Importantly, the result of the bivariate analysis was possibly biased by the fact that women were overrepresented among patients operated by conventional abdominoperineal excision (54 versus 39 %, $p<0.05$), as female sex was a risk factor for perineal symptoms. In view of these methodological issues, cautious conclusions are advised regarding the association between surgical technique and chronic perineal symptoms in this study.

Errata

The relative risk presented in the abstract of paper IV is slightly incorrect; correct values are presented in Table 7 of paper IV.

In Table 3 of paper IV, the variable *Microscopic radicality* does not refer to circumferential resection margin involvement but to whether or not an R0 resection was achieved. There are two variables related to the radicality of a resection in the Swedish ColoRectal Cancer Registry, c*ircumferential resection margin in mm* and

microscopically radical. By mistake the wrong variable was presented and Table 3 gives the rates of R2 resections and not of an involved circumferential resection margin. The rates of circumferential resection margin involvement for included, diseased and non-included patients, respectively, were 7.4 %, 27.2 % and 9.6 %, and differences were statistically significant.

In paper IV, mean values were presented for age and BMI in Table 3 and for tumour height in Table 3 and 4. Median values would have been a more appropriate means of presenting the centre of these distributions, as they are skewed.

None of the errors above change the results or conclusions in any way.

GENERAL DISCUSSION AND CLINICAL RELEVANCE

When a person is diagnosed with rectal cancer, there is generally a good chance that treatment will lead to cure and that life subsequently will return to almost normal. However, as has been discussed throughout this thesis, treatment is sometimes associated with impairments and symptoms which may limit patients' ability to live life to the full but may also lead to daily suffering in some patients. To explore such consequences of treatment and investigate how they affect patients' quality of life has been the overall aim of this work.

There are many difficulties associated with the measurement and interpretation of a patient-reported outcome like quality of life, as has been discussed in some detail. On the other hand, the interpretation of "objective", clinical measures is often not as straightforward as it may appear. For instance, selection of patients to treatment will affect almost any clinical outcome. In the evaluation of treatment effects this may be an important source of bias and emphasises the need to assess external validity in clinical studies. Furthermore, many methodological issues apply to clinical and patient-reported outcomes alike, such as the internal validity of measures and the clinical relevance of findings.

Psychological factors as predictors of quality of life

Our finding that psychological factors were stronger predictors of pretreatment quality of life than the clinical situation (curative or palliative) among patients with a newly diagnosed rectal cancer (paper II) is important and has theoretical as well as practical implications. Firstly, the results emphasize the need to consider psychological factors as relevant confounding factors in studies that aim to describe quality of life in patients with rectal cancer, as has already been discussed. Intrusive thoughts and sense of coherence are two such psychological factors, although there may be many others. Secondly and more importantly, the distressful experience of intrusive thoughts about cancer seem to be accessible for intervention by relatively simple measures. One of them is expressive writing, which is a self-administered intervention that lets patients write regularly about their emotions for a limited period of time. A recent meta-analysis found the method to be feasible to use in patients with cancer and concluded that it may be a simple, accessible and inexpensive way to offer the patients relief, although there was no clear evidence of its effects[211]. The benefit seems larger in patients with a recently diagnosed cancer[164]. This intervention has not been tried in patients with rectal cancer and a randomized study in this patient population is warranted. Patients planned for palliative treatment may benefit most from this intervention, as they were found to have a significantly lower quality of life than patients planned for curative treatment (paper II).

Extralevator abdominoperineal excision

When the results of the retrospective case series (paper III) was published in 2012, it was the first publication to question the superiority of the extralevator technique with regard to the oncological outcome. The findings led to the initiation of the APER study[38, 39, 174] which to date is one of few national registry-based studies on the topic[212]. The APER study confirmed the results of the retrospective case series[39] and subsequently reported a significant increase in three-year local recurrences with the extralevator technique[38].

The fact that centres in Sweden and abroad failed to demonstrate the superiority of the extralevator technique, despite the excellent results achieved by Dr Holm and colleagues in a small select cohort of 28 patients[36], may be attributable to the way that extralevator abdominoperineal excision was implemented and its use in all tumour stages. Today indications and application of extralevator abdominoperineal excision have changed. A bilateral extralevator dissection is no longer considered necessary in all cases of abdominoperineal excision and the procedure is instead tailored depending on the loco-regional extension of the tumour. The distinction between conventional and extralevator abdominoperineal excision may therefore be less relevant now than it was in the early years following the introduction of the new technique[34]. Our retrospective case series does raise questions, however, about the way that new methods are implemented in the field of surgery. New techniques have often been employed without proper scientific evidence to support them. One recent example is robotic surgery for colorectal cancer, which has already been mentioned. Conversely, the implementation of laparoscopic surgery has been slow in Sweden despite evidence of its benefits compared to open surgery[48]. Extralevator abdominoperineal excision was introduced in response to a perceived urgent need to improve results in the treatment of low rectal tumours[28] which may explain the enthusiasm with which it was implemented in our hospital and all over Sweden. This is illustrated by the fact that in our retrospective case series (paper III), we did not identify one single case of conventional abdominoperineal excision following the introduction of the new technique, as far as could be determined from operation notes: all patients were turned into prone position for the perineal phase and the procedure was described as an extralevator dissection. The way in which the extralevator technique was introduced may have led to an overtreatment of patients with less advanced tumours in the initial years. There is, however, little doubt that the technique contributes to increased quality of surgery when applied on correct indications and to an appropriate extent. Few surgeons would probably consider going back to performing the perineal dissection in the lithotomy position or to apply the conventional dissection technique in a tumour with potential involvement of the pelvic floor.

Perineal wound complications

The high frequency of perineal wound complications following abdominoperineal excision that was demonstrated within the works of this thesis highlights the need for measures aimed to promote an uncomplicated healing process. This need is emphasised by our finding that a delayed wound healing is an independent risk factor for chronic perineal symptoms. A number of changes in perioperative routines have already been introduced in many centres and future studies should evaluate the results. Based on our results, there is probably also a need for better support to patients who suffer a delayed perineal wound healing.

Chronic perineal symptoms

This thesis found that perineal symptoms is a chronic problem for many patients operated by abdominoperineal excision in addition to the more well-described issues of sexual, urinary and stoma dysfunction. The finding that perineal symptoms include not only pain but many other problems as well is novel. Risk factors for chronic symptoms should be further explored in prospective trials. Specifically, the association between reconstruction technique and chronic symptoms should be further investigated. There is definitely a need for increased focus on perineal symptoms in the follow-up of patients after abdominoperineal excision. Furthermore, the risk of chronic perineal symptoms should be discussed with patients preoperatively.

FUTURE PERSPECTIVES

In the coming years, the QoLiRECT study will provide valuable insights into the quality of life and morbidity of patients treated for rectal cancer. One-year follow-up data will be available for analysis in the beginning of 2017 and subsequently, two and five-year data will follow. Our ambition is to identify specific areas of improvement which can then be investigated further in interventional studies and ultimately lead to improvements in patient care.

Sunset over lake Möckeln *in Värmland. Photo by Eva Angenete*.

CONCLUSIONS

As has been discussed throughout this thesis, treatment of rectal cancer is associated with unwanted side effects, some of which may be avoidable. Whether the aim is to cure or palliate, treatment-associated morbidity and its consequences for patients' quality of life must be considered in relation to available treatment options.

The main conclusions of this thesis are as follows:

- Pretreatment quality of life in patients with a newly diagnosed rectal cancer depends in part on psychological factors, particularly on the experience of intrusive thoughts. Such thoughts may be accessible for intervention by simple clinical measures, which may be one way to improve quality of life in these patients. Furthermore, based on our results psychological factors should be considered as relevant confounders in relation to quality of life in clinical studies.

- Based on our short-term oncological data, extralevator abdominoperineal excision was not associated with improved outcome in the first few years following its introduction. This conclusion was later supported by registry-based, national data. However, this may be attributable to the way that the new technique was implemented and with better patient selection and application, results of today may have improved.

- Perineal wound complications following abdominoperineal excision is a clinical problem in the short as well as in the long term. A delayed perineal wound healing may lead to chronic perineal symptoms in many patients, including not only pain but other symptoms as well. Efforts to decrease perineal wound complications following abdominoperineal excision should be a priority.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Ändtarmscancer utgör en tredjedel av all kolorektal cancer. I Sverige drabbas ungefär 2000 personer per år, framför allt den äldre delen av befolkningen och något fler män än kvinnor. Om tumören upptäcks i tid kan botande behandling ges. Grunden för behandlingen är en omfattande operation som i drygt två tredjedelar av fallen kombineras med strålbehandling. I utvalda fall ges även cellgifter för att öka effekten av strålningen. Behandlingsresultaten har förbättrats under senare decennier och femårsöverlevnaden är idag över 60 %. Många patienter drabbas dock av funktionspåverkan efter behandlingen, t.ex. försämrad sexuell funktion, blåsfunktion och tarmfunktion. En ny operationsteknik vid lågt sittande tumörer introducerades för ett par år sedan i syfte att minska återfallen i cancer, men det vetenskapliga underlaget var bristfälligt och sårkomplikationerna tycktes öka.
Syftet med avhandlingen var att studera behandlingsresultat och biverkningar efter behandling av ändtarmscancer, med särskilt fokus på patienter som opererats med så kallad ändtarmsamputation. Vi ville också ta reda på vad som påverkar livskvaliteten hos patienter med nyupptäckt ändtarmscancer, med förhoppning om att kunna identifiera behandlingsbara orsaker till sämre livskvalitet och på sikt förbättra omhändertagandet av dessa patienter.

Metod

Delarbete I beskriver uppstarten av en stor studie (QoLiRECT) som totalt har inkluderat 1248 patienter med nyupptäckt ändtarmscancer vid 16 sjukhus i Sverige och Danmark mellan åren 2012 och 2015. Studien pågår fortfarande. Patienterna följs under fem år och besvarar ett frågeformulär om funktionspåverkan, symptom och livskvalitet vid fyra tillfällen. Kliniska data hämtas från kolorektalcancerregistren i Sverige och Danmark.

I delarbete II analyserades data från det första frågeformuläret i QoLiRECT-studien. 1085 patienter inkluderades i analysen av vilka faktorer som påverkar livskvaliteten innan behandlingsstart.

I delarbete III studerades korttidsresultaten efter införandet av en ny typ av ändtarmsamputation, där större delen av bäckenbotten opereras bort tillsammans med tumören för att minska risken för återfall. 158 patienter som opererats vid Östra Sjukhuset i Göteborg 2004-2009 inkluderades i analysen. Kliniska data hämtades från patientjournalerna och kolorektalcancerregistret.

I delarbete IV identifierades samtliga patienter som opererats med ändtarmsamputation i Sverige 2007-2009 genom kolorektalcancerregistret. Tre år efter operationen

besvarade 545 patienter ett frågeformulär med frågor om symptom och livskvalitet. Kliniska data hämtades från kolorektalcancerregistret och operationsberättelserna.

Resultat

Delarbete I och II: Hos patienter som nyligen fått sin diagnos men ännu inte påbörjat behandling för sin ändtarmscancer var psykologiska faktorer starkt sammankopplade med upplevelsen av livskvalitet. Det handlade dels om s.k. *påträngande tankar* om cancern, dvs. ofrivilliga och repetitiva tankar som är svåra att slå ifrån sig, och dels om *känsla av sammanhang* (KASAM), som avspeglar i vilken grad man uppfattar livet som begripligt, hanterbart och meningsfullt. Både påträngande tankar och låg KASAM var starkt associerade med sämre livskvalitet. Huruvida patienten planerades för botande eller endast lindrande (palliativ) behandling hade också betydelse för livskvaliteten men inte i lika hög grad.

Delarbete III: Efter införandet av den nya operationsmetoden vid ändtarmsamputation ökade andelen patienter som drabbades av infektion i såret mellan skinkorna från 28 till 46 %. Andelen som fick genomgå ytterligare en eller flera operationer pga sårinfektionen ökade från 8 till 22 %. Vårdtiden blev längre. 62 % av alla patienter hade fortfarande ett oläkt sår mellan skinkorna efter 4 veckor. Den nya tekniken resulterade inte i att fler patienter blev radikalt opererade.

Delarbete IV: Tre år efter ändtarmsamputation var kroniska symptom från området mellan skinkorna vanligt förekommande. Det rörde sig bland annat om smärta, svårigheter att sitta, stramningar och kramper/trängningar. Hälften av alla patienter, och fler kvinnor än män, upplevde ett eller flera symptom. Patienter som haft en fördröjd sårläkning mellan skinkorna efter sin operation hade en ökad risk att drabbas av uttalade besvär. De patienter som upplevde uttalade besvär hade en lägre hälsorelaterad livskvalitet än övriga.

Slutsats

Livskvaliteten före behandlingsstart påverkades i högre grad av psykologiska faktorer såsom t ex påträngande tankar än av den kliniska situationen, d.v.s. om den planerade behandlingen var botande eller endast palliativ (lindrande). Påträngande tankar om cancer har i andra studier visat sig vara möjliga att påverka med enkla metoder, vilket skulle kunna vara ett sätt att förbättra livskvaliteten för patienter med ändtarmscancer. Den nya operationsmetoden vid ändtarmsamputation bör inte användas rutinmässigt utan endast i utvalda fall, när tumörens läge och utbredning kräver det. Det är viktigt att förebygga infektioner och fördröjd läkning av såret mellan skinkorna, eftersom det kan öka risken för kroniska besvär. Sådana besvär var vanligt förekommande efter ändtarmsamputation och omfattade många andra symptom utöver smärta, vilket inte var känt tidigare.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all friends, colleagues, co-authors and others who have made this work possible. In particular, I would like to thank:

Eva Angenete, for your support, encouragement and endless enthusiasm. Thank you for taking me under your wings and believing in my ability as a researcher. You are simply outstanding and I'm grateful and fortunate to have had you as my supervisor.

Eva Haglind, my co-supervisor, for letting me be part of your extraordinary research group and for your kind, gentle and wise guidance on the journey towards becoming a better scientist. Thank you for your hospitality and generosity and for inspiring me with your integrity and high moral standards.

Elisabeth González, for the tremendous efforts that you have put into the QoLiRECT study and for being such a great person to work with.

Mattias Prytz, for being my good friend and a great travel companion – literally and figuratively – and for your valuable contributions as a co-author.

David Bock, for all your support, statistical guidance and friendship.

Jane Heath, as without you there would be have been no QoLiRECT or APER study and doing research at SSORG would not have been as much fun.

Carina Rosander, **Kira Bröndum** and **Anette Wedin** for everything you have done to keep the studies running. **Carolina Ehrencrona**, for valuable help with the administrative side of the research and for getting my page headers in order at the last minute.

Jacob Rosenberg and **Jakob Burcharth**, for your assistance with the Danish part of the QoLiRECT study and for all those friendly scientific meetings and discussions.

All my other colleagues and friends at SSORG, none mentioned, none forgotten, for all your help, good advice and assistance and for making these years such a precious experience.

All those who have been involved in the recruitment of patients into the QoLiRECT study in Sweden and in Denmark. I am very grateful.

Christina Svärd and **Mattias Block**, head of the surgical and colorectal department at Sahlgrenska University Hospital /Östra, respectively, for giving me the opportunity to do research.

My colleagues at the colorectal department at Sahlgrenska University Hospital/Östra, for your support and patience with my repeated absence from clinical work.

My mother, for your love and for all the times you help us out by taking care of the children; my father, for inspiring me with your endeavour and entrepreneurial mind-set; my sister, because you remind me that things can be done differently; my brother, for your consideration and thoughtfulness and for being someone I can talk to about almost everything, including surgery and science; and my parents-in-law, for always being there for our family.

Maximilian, **Milton** and **Julia**, for helping me remember my priorities in all of this and making me live in the present moment.

And most of all **Annika**, my wonderful wife, for all your loving support and for taking care of everything else in our lives when I have been busy doing this. This would definitely not have been possible without you.

This work was supported by grants from the Swedish Research Council, the Swedish Cancer Society, the Swedish Society of Medicine, the Gothenburg Medical Society, the Health & Medical Care Committee of the Regional Executive Board, Region Västra Götaland, Sahlgrenska University Hospital (ALF grants), Anna-Lisa and Bror Björnsson Foundation, Assar Gabrielsson Foundation, Mary von Sydow Foundation, Bengt Ihre Foundation, Ruth and Richard Julin's Foundation and Lion's Cancer Research Foundation of Western Sweden.

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APPENDIX

Orientation to Life Questionnaire (SOC-29)

Paper I-IV

Sense of Coherence – Orientation to Life Questionnaire – 29 items

Source: Antonovsky, Aaron Unraveling the Mystery of Health. How People Manage Stress and Stay Well. San Francisco 1987.

C = comprehensibility Ma = manageability Me = meaning

R = before calculating the total score this should be reversed.

1. When you talk to people, do you have the feeling that they don't understand you? (C)

R 1 2 3 4 5 6 7

Never Always have this feeling

2. In the past, when you had to do something which depended upon cooperation with others, did you have the feeling that it: (Ma)

1 2 3 4 5 6 7

Surely wouldn't get done Surely would get done

3. Think of the people with whom you come into contact daily, aside from the ones to whom you feel closest. How well do you know most of them? (C)

1 2 3 4 5 6 7

You feel that they're strangers You know them very well

4. Do you have the feeling that you don't really care about what goes on around you? (Me)

R 1 2 3 4 5 6 7

Very seldom or never Very often

5. Has it happened in the past that you were surprised by the behaviour of people whom you
R thought you knew well? (C)

1 2 3 4 5 6 7

Never happened Always happened

6. Has it happened that people whom you counted on disappointed you? (Ma)

R 1 2 3 4 5 6 7

Never happened Always happened

7. Life is: (Me)

R 1 2 3 4 5 6 7

Full of interest Completely routine

8. Until now your life has had: (Me)

1 2 3 4 5 6 7

No clear goals or purpose at all Very clear goals and purpose

9. Do you have the feeling that you're being treated unfairly? (Ma)

1 2 3 4 5 6 7

Very often Very seldom or never

10. In the past ten years your life has been: (C)

1	2	3	4	5	6	7
Full of changes without your knowing what will happen next						Completely consistent and clear

11. Most of the things you do in the future will probably be: (Me)

R	1	2	3	4	5	6	7
	Completely fascinating						Deadly boring

12. Do you have the feeling that you are in an unfamiliar situation and don't know what to do? (C)

1	2	3	4	5	6	7
Very often						Very seldom or never

13. What best describes how you see life: (Ma)

R	1	2	3	4	5	6	7
	One can always find a solution to painful things in life						There is no solution to painful thins in life

14. When you think about your life, you very often: (Me)

R	1	2	3	4	5	6	7
	Feel how good it is to be alive						Ask yourself why you exist at all

15. When you face a difficult problem, the choice of a solution is: (C)

1	2	3	4	5	6	7
Always confusing and hard to find						Always completely clear

16. Doing the things you do every day is: (Me)

R	1	2	3	4	5	6	7
	A source of deep pleasure and satisfaction						A source of pain and boredom

17. Your life in the future will probably be: (C)

1	2	3	4	5	6	7
Full of changes without knowing what will happen next						Completely consistent and clear

18. When something unpleasant happened in the past your tendency was: (Ma)

1	2	3	4	5	6	7
"To eat yourself up" about it						To say "ok that's that, I have to live with it" and go on

19. Do you have very mixed-up feelings and ideas? (C)

1	2	3	4	5	6	7
Very often						Very seldom or never

20. When you do something that gives you a good feeling: (Ma)

R 1 2 3 4 5 6 7

It's certain that you'll go on feeling good — It's certain that something will happen to spoil the feeling

21. Does it happen that you have feelings inside you would rather not feel? (C)

1 2 3 4 5 6 7

Very often — Very seldom or never

22. You anticipate that your personal life in the future will be: (Me)

1 2 3 4 5 6 7

Totally without meaning or purpose — Full of meaning and purpose

23. Do you think that there will always be people whom you'll be able to count on in the future? (Ma)

R

1 2 3 4 5 6 7

You're certain there will be — You doubt there will be

24. Does it happen that you have the feeling that you don't know exactly what's about to happen? (C)

1 2 3 4 5 6 7

Very often — Very seldom or never

25. Many people – even those with a strong character – sometimes feel like sad sacks (losers) in certain situations. How often have you felt this way in the past? (Ma)

R

1 2 3 4 5 6 7

Never — Very often

26. When something happened, have you generally found that: (C)

1 2 3 4 5 6 7

You overestimated or underestimated its importance — You saw things in the right proportion

27. When you think of the difficulties you are likely to face in important aspects of your life, do you have the feeling that: (Ma)

R

1 2 3 4 5 6 7

You will always succeed in overcoming the difficulties — You won't succeed in overcoming the difficulties

28. How often do you have the feeling that there's little meaning in the things you do in your daily life? (Me)

1 2 3 4 5 6 7

Very often — Very seldom or never

29. How often do you have feelings that you're not sure you can keep under control? (Ma)

1 2 3 4 5 6 7

Very often — Very seldom or never