Scandinavian Surgical Outcomes Research Group
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QoLiRECT

Protocol

Quality **o**f **L**ife in **RECT**al cancer
A study within the Scandinavian Surgical Outcomes Research Group

CONTENTS

ORGANISATION

This study is registered at ClinicalTrials.gov. The principal investigator (PI) and deputy PI together must decide on any analyses of results prior to full inclusion. A plan for data analyses will be made by the steering committee well in advance of reaching full accrual of the study. After reaching accrual, all analyses, results and conclusions will be discussed in the steering committee, as will any publication issues.

PRINCIPAL INVESTIGATOR

Principal Investigator: Eva Angenete, MD, PhD.
Deputy Principal Investigators: Eva Haglind, MD, adj. Professor of Surgery and Jacob Rosenberg, MD, Professor of Surgery, Herlev Hospital/University of Copenhagen.

COMMITTEES

Protocol committee

The Scandinavian Surgical Outcomes Research Group (SSORG).

Steering committee

Protocol committee and the local investigator at each participating hospital, if not a member of SSORG.

Writing committee

Members of the protocol and steering committees who fulfil established criteria for "authorship" as well as doctoral/post.doc students working with the study.

Data monitoring committee

Eva Haglind and Jane Heath, SSORG/Gothenburg.

COORDINATING CENTER

Department of Surgery, Sahlgrenska University Hospital/Östra.

DOCTORAL STUDENT

Dan Asplund, MD.

STUDY SECRETARIAT

The study secretariat is located at SSORG, Sahlgrenska University Hospital/Östra.
Contact persons: Elisabeth González, Eva Angenete.
The data collection and the data base will be at SSORG, Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg and using the INCA system at *Regionalt Cancercentrum Väst*. The SSORG/ Gothenburg secretariat will send the questionnaires to all patients, for details see below.

LOCAL SECRETARIATS

In each participating hospital, a local investigator will be responsible for inclusion, control of internal validity, and participate in the steering committee.

PARTICIPATING HOSPITALS

Surgical departments outside the SSORG network are welcome to join in the study. Participating hospitals should have an established unit for colorectal surgery, including rectal cancer surgery. A process should be instituted that ensures that all patients eligible for inclusion are asked about participation.

PROTOCOL SUMMARY

All patients presenting at participating hospitals during the recruitment period (two years) with a newly diagnosed rectal cancer, regardless of stage and planned treatment, will be eligible for inclusion. They will answer a questionnaire on health related quality of life, physical symptoms, functional impairments and socioeconomic status at diagnosis and after 12, 24 and 60 months. Clinical data including recurrence, survival, surgical treatment, oncologic result (pathology report) and adjuvant treatment will be collected from the national quality registry for rectal cancer.

BACKGROUND

RECTAL CANCER

Colorectal cancer is the second most common cancer in Swedish women (after breast cancer) and the third most common cancer in Swedish men (after prostate cancer and skin cancer)[1]. About one third of all colorectal cancers are situated in the rectum. Rectal cancer is more frequent in men than in women and is relatively uncommon before the age of 50. The prognosis for rectal cancer has improved over the last decades[2]. Almost 60% of all patients survive more than five years, and because of advances in early detection and treatment, this number is expected to increase in the future[1]. Treatment of rectal cancer varies depending on the stage of the disease at diagnosis. For some patients, operation is the only treatment. For others, surgery is combined with radiotherapy, chemotherapy or both. The two most common operative procedures are the sphincter-preserving anterior resection (AR) and the abdominoperineal excision (APE) – the latter results in a permanent colostomy. Patients with generalised disease at diagnosis receive palliative treatment, which may include chemotherapy and radiotherapy as well as surgery.

Rectal cancer comes with a high risk of local recurrence, i.e. return of the tumour within the pelvis after a presumed curative resection. Local recurrence is difficult to treat and often very painful and distressing for the patient. Some local recurrences will be candidates for second line surgery, as is also true for some distant metastases.

The aim of the QoLiRECT study is to increase the knowledge about symptoms, functional impairments, quality of life (QoL) and psychological and socioeconomic burden in an unselected population of rectal cancer patients. Symptoms such as incontinence, pain, fatigue and impaired sexual function[3] are common with this disease. Bodily changes, caused by the treatment or the disease itself, may lead to functional impairments and psychological, social, emotional and economical restraints. Conventional outcome measures such as morbidity and survival reveal little about these things. Measuring health related quality of life is today a common and well established means to gain such information[4-7]. A large number of different instruments (questionnaires) have been developed for this purpose. Some of the most well-known are the EQ-5D, the SF-36 and the EORTC QLQ-C30[5]. Our knowledge about the symptoms, functional impairments and QoL of rectal cancer patients is insufficient, especially in the longer perspective. Studies have often included only a selected part of the patient population, sample sizes have been small, compliance low and the QoL instruments used have typically produced results that are not intuitive or easy to grasp[8]. The questionnaires to be

used in this study are based on the principles developed by Steineck et al[9-11]. They include detailed and very specific questions about bowel, urinary, sexual and stoma-related function, daily activities, pain, fatigue and psychological symptoms. Besides newly constructed questions on symptoms and QoL, the questionnaires include the EQ-5D and the Sense of Coherence (SOC) scale (KASAM in Swedish)[12].
Today, new surgical techniques are being explored in the treatment of rectal cancer[13,14], and their effects on QoL, long term symptoms and functional results are unknown. The costs resulting from decreased QoL and defective functional results of treatment is another unexplored area. Treatment decisions are largely based on considerations of prolonged survival. Less attention is given to expected changes in QoL of the individual patient in relation to a suggested treatment. Patients may feel very differently about aspects on quality of life versus longevity and it may be that prolonged survival at any cost is not what the patient wants[15]. This is something that needs to be addressed preoperatively to individualize treatment decisions. If the advances in rectal cancer treatment result in a significantly decreased QoL, it may have implications for our treatment strategies. The QoLiRECT study may generate new and deeper knowledge about the experiences of this patient population that may have implications for the fashioning of treatment and palliative care.

INTRUSIVE THOUGHTS AND EXPRESSIVE WRITING

Psychosocial factors are essential determinants of a person's QoL. In this context, the concept of intrusive thoughts has received increasing attention. Intrusive thoughts are unwelcome, involuntary thoughts, images or ideas that are difficult to manage or suppress and may cause serious anxiety and distress. It is a well-known phenomenon in depression, obsessive-compulsive disorder, post-traumatic stress syndrome and other conditions. In cancer patients, intrusive thoughts about the cancer diagnosis and treatment have been found to be associated with a decreased QoL[16]. Most studies on this subject have focused on prostate and breast cancer patients. Recently we found that intrusive negative thoughts were associated with worse quality of life among a group of Swedish men undergoing radical prostatectomy[17].
Expressive writing is an intervention where individuals write privately about an event with emotional impact for a limited period of time (15-30 minutes) and repeat this for several days (e.g. 3 to 5 days). This brief intervention has been found to improve psychological and health outcomes in medical populations[18,19]. A few studies of expressive writing intervention has examined its effects on cancer patients[20]. To explore the presence of intrusive thoughts in rectal cancer patients and their implications in relation to QoL will be a secondary objective of the QoLiRECT study.

STUDY DESIGN

QoLiRECT is an explorative, prospective, longitudinal, non-interventional, international, multicenter study of health-related quality of life, physical symptoms, functional impairments and socioeconomic burden in rectal cancer patients. All patients presenting at participating hospitals during the recruitment period (estimated two years) with a newly diagnosed rectal cancer, regardless of stage and planned treatment, will be eligible for inclusion. Patients will be followed for 5 years. They will be asked to answer questionnaires at four different time points during follow-up: at diagnosis and after 12, 24 and 60 months. Clinical data, including recurrence, surgical treatment, oncologic result (pathology report) and adjuvant treatment will be collected from the national quality registry for rectal cancer in Denmark and Sweden. As these registries differ in some areas between the countries, additional data will be collected through short CRF:s (see below).

HYPOTHESES

- Rectal cancer and its treatment lead to decreased QoL
- Some treatment strategies causes lower QoL than others
- Rectal cancer-specific symptoms and treatment-specific effects influence QoL
- Some effects and symptoms have greater impact on QoL than others
- Functional impairments of rectal cancer patients influence QoL
- Psychological symptoms including intrusive thoughts influence QoL
- Stage of disease at diagnosis influences QoL during treatment and follow-up
- Patient expectations/experiences at diagnosis influence QoL during treatment and follow-up
- Patient expectation of cure of the rectal cancer influences QoL
- Gender, age and education level influence QoL during treatment and follow up
- High occurrence and intensity of intrusive thoughts about the rectal cancer diagnosis and its treatment is associated with lower QoL
- Early closure of temporary loop ileostomy after anterior resection is associated with higher QoL than late closure
- Pre-treatment QoL influences QoL during follow-up as well as survival
- Significant changes in symptoms and function may not be detected with conventional QoL instruments
- Our questionnaire may result in deeper understanding of the factors determining QoL than conventional QoL instruments and may lead to identification of areas for improvement in treatment and patient care

AIMS

PRIMARY AIM

- To describe QoL, symptoms and functional impairments in an unselected population of rectal cancer patients

SECONDARY AIMS

- To explore potential differences in QoL, symptoms and functional impairments between subgroups of the population
- To identify symptoms, functional impairments and other risk factors that have great impact on QoL
- To identify patient and environmental factors with an impact on QoL
- To analyse how clinical factors like oncologic result of operation, morbidity, recurrence and survival influence QoL
- To identify areas of improvement in treatment and patient care
- To initiate interventional studies when appropriate

- To generate basic descriptive data of the patient population, such as demography, socioeconomic data, disease stage at diagnosis, type of treatment, recurrence, survival etc
- To analyse health economy aspects of QoL and morbidity in the patient population
- To explore the presence and impact of intrusive thoughts on QoL in the patient population

DATA ANALYSIS PLAN

- Demographic data (age, gender, education etc)
- Descriptive data (time from first symptom to diagnosis, disease stage at diagnosis, palliative treatment, anterior resection, abdominoperineal excision, stoma, radiation, adjuvant treatment, circumferential resection margin (CRM), radical operation, recurrence, survival etc.)
- Analysis of symptoms and functional impairments
- Analysis of QoL in relation to physical and psychological symptoms including intrusive thoughts and functional impairments
- Comparison of QoL, symptoms and functional impairments in subgroups of the population:

  -Type of treatment

  -Disease stage at diagnosis

  -Palliative operation vs. non-operative palliation

  -Stoma vs. no stoma

  -Early vs. late closure of ileostomy
- Analysis of QoL in relation to preoperative expectations/experiences
- Health economy analysis of QoL and functional impairments

ETHICS

This study has been approved by the Central Ethical Review Board in Sweden (EPN Dnr 595-11). In Denmark, no ethical permission is needed for this study.
Eligible patients receive written and oral information about the study. Informed consent is obtained from each patient prior to inclusion. Patients remain free to withdraw their consent to participate in the study at will and at any time without giving their reasons.

ELIGIBILITY

INCLUSION CRITERIA

All patients presenting at the participating hospitals with a newly diagnosed rectal cancer, regardless of stage at diagnosis and plans for treatment, will be eligible for inclusion.

EXCLUSION CRITERIA

Age below18 years at diagnosis. No informed consent received or withdrawal of informed consent.

EXTERNAL VALIDITY

External validity is secured by the fact that virtually all rectal cancer patients in Sweden and Denmark are registered in the national quality registries for rectal cancer and through registration of all non-included patients in a "screening log" at each participating hospital.

REGISTRATION

All newly diagnosed rectal cancer patients presenting at participating hospitals should be asked about participation. In general, patients should be informed about the study at their first visit to a Department of Surgery and asked for an informed consent at their second visit. The patient should have received full information about the treatment plan before inclusion. Full identity, address and telephone numbers are registered by telephone and fax to *Regionalt cancercentrum väst* (RCCV) in Gothenburg, where the inclusion data base is kept. This data enables SSORG/Gothenburg to contact patients and to send out questionnaires.
All newly diagnosed rectal cancer patients should be registered in the "screening log". The "screening log" is kept at each participating hospital and reported quarterly to the study secretariat. The reason for non-inclusion or exclusion should always be noted. Patients who do not wish to participate are registered as "no consent" by initials, clinical stage at presentation, age and gender. Missed patients are registered as "missed" in the same manner, i.e. by initials etc. The study secretariat will keep a list of all patients with rectal cancer who do not fulfil inclusion criteria or have been excluded or missed. Lists of patients included at each participating hospital will be sent to the respective local investigator. If the patient wants to withdraw her/his earlier consent, all data regarding her/him will be deleted. Patients who do not answer questionnaires are asked if they want to quit the study. If so, no further information will be collected and the patient will be asked if all data collected so far should be deleted or can be kept.
All included patients should be registered in the respective national quality registry for rectal cancer.

QUESTIONNAIRES

Patients will answer questionnaires:

- At diagnosis, i.e. at presentation of a plan for the treatment
- At 12 months after start of the treatment
- At 24 months after start of the treatment
- At 60 months after start of the treatment

The questionnaire has been constructed based on a concept developed by Steineck et al[9-11]. It contains detailed questions about the quality, frequency, intensity and duration of rectal cancer-specific symptoms as well as questions on functional impairments, psychological symptoms, socioeconomic status and demography. The questionnaire is based on in-depth interviews with rectal cancer patients and has been tested for face validity.
To facilitate health economy analyses and comparison with the general population, a commonly used generic instrument, EQ-5D, has been included in the questionnaire. It also includes the Sense of Coherence (SOC) scale (KASAM in Swedish)[12].
We believe that this questionnaire may provide a deeper understanding of a person's QoL than many of the established instruments[9], and make possible the analysis of QoL in relation to rectal cancer-specific symptoms.

DATA COLLECTION

The study secretariat at SSORG/Gothenburg, Sahlgrenska University Hospital/Östra handles routines for sending out of all questionnaires: 0, 12, 24 and 60 months after inclusion and reminders. The first questionnaire will be sent out as soon as the patient has been registered in the inclusion data base. Each questionnaire is given a patient specific code. The questionnaires are returned to the study secretariat and collected data is stored within the Sahlgrenska University Hospital, on a server within the hospital IT system, using the inherent security system. Data from the national quality registries for rectal cancer will be retrieved and added. Data may be used for analysis and publication from time "0" as soon as full accrual has been reached, from time "12 months" when all included patients have passed that time point etc. Data can only be analysed or copied from the database by decision of the principal investigator and the deputy principal investigators together. All such decisions should be discussed by the steering committee. The database is registered at "personuppgiftsombudet", Sahlgrenska University Hospital (register-id 29724). Monitoring of collected data and compliance to the study protocol is achieved through contacts with the local investigators and annual visits to participating departments.
Clinical and oncologic data is collected from the national quality registries in Sweden and Denmark. In Sweden, the quality registry does not include any details about the perineal part of the abdominoperineal excision procedure; for this reason, a very short CRF will be completed by the operating surgeon at the time of operation in Sweden. Data that is not included in the Danish registry will be collected quarterly from patient charts at each participating Danish hospital by an external examiner.

STATISTICAL CONSIDERATIONS

Depending on tumour stage at presentation, the study population of 1500 patients will fall into the following subgroups: palliative treatment, long preoperative chemo-radiation treatment, abdominoperineal excision and anterior resection. The estimated number of patients in each group is 300, 100, 250 and 850, respectively. This will allow for prevalence estimation of health related factors with differences between groups down to 15 percent, even between the smaller subgroups, with a statistical power of 80 percent. This estimate is based on binominal distribution approximation with a prevalence of 50 percent and significance of 5 percent.

PERMISSIONS & REGISTRATIONS

Ethical approval: EPN Dnr 595-11
PUL register-id: 29724
Permission to use EQ-5D and SOC (KASAM) has been obtained.

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