Cover page

Title:

Individual Follow-up after Rectal Cancer - Focus on the Needs of the Patient (FURCA)

[NCT-number not assigned yet]

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Content

1 Introduction

Colorectal cancer is the third most common cancer worldwide. Rectal cancer amounts for about one third of colorectal cancers, with a small male predominance (1,2). A total of 1674 new rectal cancer patients (62 ,1 % males) were diagnosed in Denmark in 2014 (3). The overall 5-year survival rate is 62 %, although mortality is decreasing due to improvement in treatment (3).

Among the patients undergoing treatment with a curative intent, the standard treatment is surgery. The two predominant resectional techniques in Europe are abdomino-perineal resection (APR) and low anterior resection (LAR). APR leaves the patient with a permanent stoma, while LAR is a sphincter-sparing procedure that restores bowel continuity.

Surgery is in some cases combined with pre- and/or postoperative chemo-radiotherapy (4,5). The risk of local recurrence after rectal cancer has been estimated to 7-9 % and possibly lowers with the addition of preoperative radiotherapy and improved surgery techniques. Local recurrence is a severe condition, and markedly increases mortality (6,7). It is therefore crucial to identify these individuals at a very early stage. Most local recurrenses occur within the first three years past diagnosis, and 65-70 % of the cases will present clinical symptoms (rectal bleeding, pain, sudden change in bowel function, weight loss). In other cases, the recurrence is asymptomatic (8-10).

A large proportion of rectal cancer patients suffer from severe physical and psychological adverse effects from treatment .

Recent studies have shown that almost half of the LAR patients suffer from severe bowel dysfunction one year after their operation (11,12). The symptoms consist of fecal/gas incontinence, fecal urgency, frequent bowel movements and fragmentation/clustering of stools, which collectively is referred to as “the low anterior resection syndrome” – or LARS . Other physical adverse effects from the treatment can be urinary dysfunction, sexual dysfunction, pain and fatigue (13-15). Psychological distress and fear of recurrence are known psychological adverse effects following treatment for rectal cancer (8,16). All of which, can influence negatively on the patients’ symptom burden, everyday functioning and quality of life (17,18).

The follow-up regimen currently offered to Danish rectal cancer patients is rigidly constructed with standardised controls in the outpatient clinic, has a low level of patient involvement and is based on a poor level of evidence.

The primary focus is detection of local recurrence and methastases. The follow-up regimen consists of rectoscopy and clinical control 6,12,18,24 and 36 months after surgery (APR-patients receive less clinical controls and no rectoscopies). Furthermore, a CT-scan of the thorax and abdomen is performed one and three years postoperatively and a colonoscopy is offered every fifth year until the age of 75 (19).

There is some evidence that frequent follow-up to detect distant methastases reduces mortality, but evidence on the effect from frequent routine controls and endoscopies on detecting local recurrences, and the general methodology of follow up programmes is scarce (20,21). Thus, a large number of Danish patients are each year enrolled in comprehensive follow up programs based on dubious levels of evidence.

Based on several years of clinical experience we know that the specific needs after rectal cancer surgery differ substantially from patient to patient. Patients and clinicians request more patient-centred follow up, also focusing on physiological and psychological aspects – in combination with monitoring potential recurrence of the cancer (20,22).
The Danish Health Authorities recommend a more individualised follow-up, in order to detect both recurring cancers and to treat the adverse effects of rectal cancer surgery (20).
As a new alternative we propose a patient-led follow-up program with a higher degree of patient involvement.
The patient-led follow-up programme is based on a standardized education program in order to enforce the patients' ability to assess and respond sufficiently to symptoms and health problems, by consulting a health professional for adequate assistance and intervention.
Patient education, supporting the patients' self-efficacy and health litteracy, together with standardised and evidence based response algorithms to self-referrals form the basis for patient-led follow-up program.

1.1 Objectives

This project aims at improving the follow-up program after rectal cancer by:
1. Developing and implementing a new patient led follow-up program, based on patient education and involvement, and self-referral by direct access to project nurse
2. Examining the effect of the new follow-up program on symptom burden and health related quality of life
3. Examining the effect of the new follow-up program on specific physiological and psychological symptoms and late adverse effects from treatment, event-free survival, patient experienced satisfaction, information and involvement
4. Evaluating cost-effectiveness of the new follow-up program

2 Hypotheses

We hypothesize, that early identification and treatment of late adverse effects after rectal cancer surgery, and earlier detection of local recurrence is possible if the patients are empowered to actively play a role in their own care pathway. This, by means of the new patient-led follow-up programme, based on standardised education and thorough patient information regarding relevant symptoms, patients' access to direct self-referral to an affiliated nurse, and standardised response algorithms to patient reported data.
We believe that this will reduce the symptom burden from physical and psychological symptoms and greatly improve the quality of life of each individual patient. And that this new follow-up program will improve other patient-reported outcomes such as patient satisfaction, patient involvement and information.
Furthermore, we hypothesise that the patient led follow-up program will lead to earlier detection and treatment of local recurrences, although no effect on overall survival is expected. We expect that the new program will optimise the use of economic resources.

3 Material and methods

The study will be designed as a multicentre randomized controlled trial, with follow-up in three years (see Figure 1)

3.1 Patients

Colorectal surgical departments in Aarhus, Randers, Herning and Aalborg will be invited to participate. These centres cover one third of all Danish rectal cancer patients (556 out of 1675 rectal cancers in 2014= 33 %) (3).

Inclusion criteria:

Adult patients operated for a primary adenocarcinoma in the rectum (0-15 cm from the anal verge), with pathology results showing R0/R1 resection – thus treatment with curative intent. The patients must be able to read, speak and understand the Danish language and must not suffer from mental dementia or other mental disorders affecting cognitive functions. Moreover, written informed consent is required from all participants.

Patients treated with local excision of the tumour (without resection of the rectum) are excluded, and likewise if the pathology shows non-radical resection (R2) or known malignant methastases.

Residual life expectancy less than two years and synchronous cancer will lead to exclusion, as will concurrent participation in other research studies with contacts in the follow up periode. Loss to follow-up will be registered as verified recurrence, death, emigration from the participating regions or if a patient requests to interrupt participation.

The three participating centres operate about 550 rectal cancer patients each year and taking the in- and exclusion in regard, this leaves about 330 eligible patients each year.

An estimation of samplesize shows, that a total of 334 participants are needed in order to obtain statistically significant results ($p<0.05$).

3.2 Inclusion

Patients will be approached at the postoperative visit in the outpatient clinic where they are presented for the pathology results from the surgery, approximately 2 weeks after the operation. The doctor will provide short oral information about the study and hand out written information.

A research nurse will contact the patient by telephone a few days later, to help the patient deciding whether or not to participate. If the patient agrees to participate, the research nurse will collect informed written consent and baseline information from the participants before randomisation.

Patients, receiving postoperative chemotherapy, will be contacted by the research nurse after ended treatment.

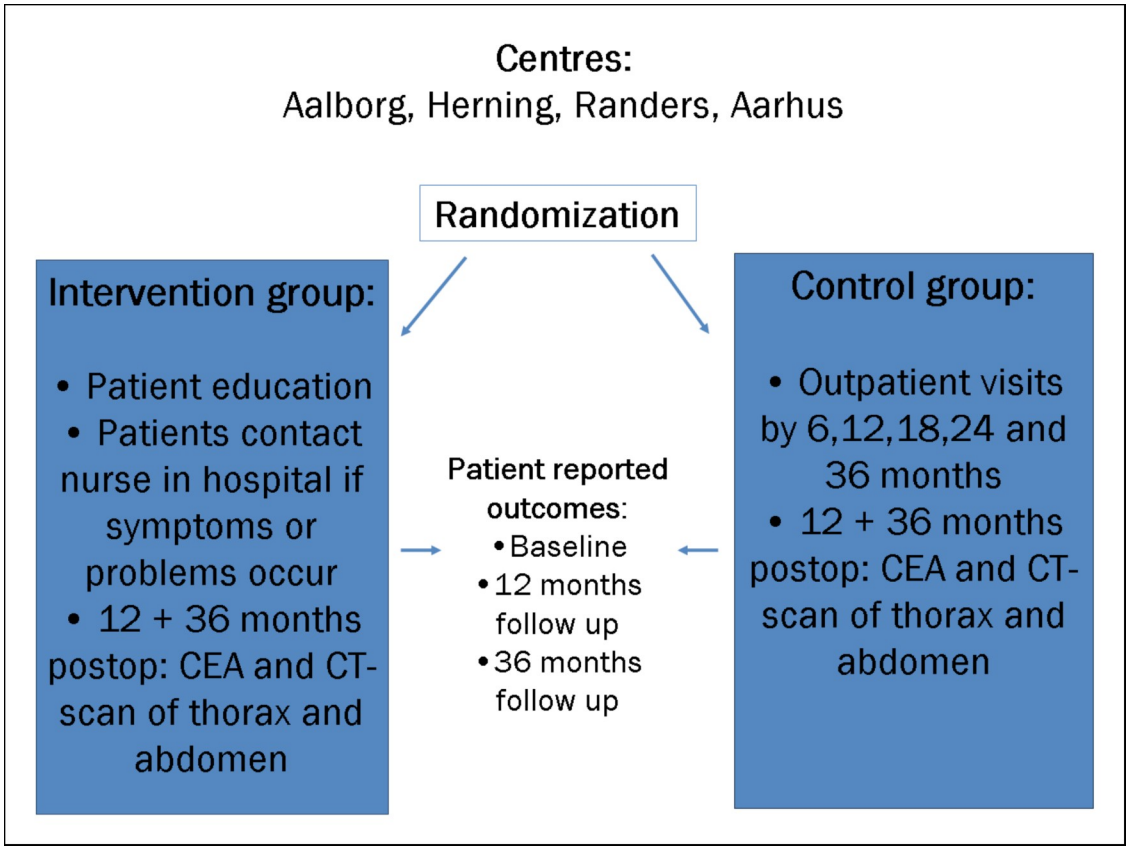
3.3 Randomisation

Participants are randomised into A) an intervention group, where patients will receive standardised education, and are encouraged to contact the assigned project nurse if they experience symptoms of adverse effects or cancer recurrence a control group, and B) following the current FU-programme with routine check-ups. Follow-up time in both groups is 3 years.

Non-participants are asked to complete a baseline questionnaire similar to the one partcipants fill in.

The block-randomization is set op to stratify by centre, sex and treatment type (+/- postoperative oncological treatment and +/- temporary illeal stoma)

Figure 1: randomisation



Group A:

The intervention groups, following the patient-led follow-up programme will not attend regular visits in the outpatient clinic.

They will receive structured education by a nurse regarding early signs of recurrence of the cancer and symptoms of adverse effects, and how to respond adequately.

The education will be performed by the affiliated research nurse, and based on a protocolled manual. The education is supported by a website providing more detailed information on the symptoms and adverse effects. The website is exclusive for the patients in the intervention group. Methods and content for the patient education is developed by the group of affiliated research nurses. Patients are involved in the process, by means of two focus group interviews.

Participants will be instructed to approach the research nurse in case of symptoms and are informed of the necessity of contacting the research nurse immediately in case of pre-defined alarm symptoms (self-referral).

The research nurse will respond to patient's self-referral according to a pre-defined, standardised response-algorithm. The algorithm is developed in close cooperation between participating health professionals, and representatives from other specialities and the primary sector.

Patients can contact the research nurse by telephone and e-mail on a daily basis.

The patients will have a CT scan after 12 and 36 months, and a colonoscopy with five years interval until the age of 75.

Group B:
The control group will follow regular visits with a doctor in the outpatient clinic (+ rectoscopy) at 6, 12, 18, 24 and 36 months postoperatively, have a CEA-test and a CT scan after 12 and 36 months, and a colonoscopy with five years interval until the age of 75.

3.4 Data

Outcomes

A Symptom burden and health related quality of life, together with late adverse effects from rectal cancer surgery: bowel dysfunction, urinary and sexual dysfunction, pain, fatigue, fear of recurrence, anxiety and depression
B Self-efficacy and patient activation, patientinvolvement, and patient's experience of information and sense of security.
C QALY's
D Time to recurrence, 3- year survival

Most data will be collected using patient reported outcome measures (PROM's).
Patients are asked to complete a questionnaire at baseline (time of inclusion), 12 and 36 months postoperatively. The questionnaire will focus on symptom burden and quality of life, specific symptoms, patient activation and self-efficacy, patient involvement and information, needs in the follow-up period and how they have been handled.
Data regarding recurrence of cancer, mortality and socioeconomic factors will be extracted from national registers. While data on comorbidity is extracted from the national clinical database for colorectal cancer surgery.
Data on health care utilisation in the follow-up period will be collected from national registers, in combination with information from patient records (limited access).

3.5 Patient reported outcome measures PROM's

1. **Symptom burden:** 'Functional Assessment of Cancer Treatment – Colorectal' (FACT-C). 36 items
2. **Bowel function**: Patients without a stoma: 'Low Anterior Resection Syndrome Score' (LARS) and Bristol Stool Scale (together 7 items). Patients with a stoma: The Colostomy bother score. 8 items
3. **Urinary function**: 'Male/Female Lower Urinary Tract Symptoms' (ICIQ-MFLUTS/ICIQ-FLUTS). 12 and 13 items respectively
4. **Sexual function, female**: 'The sexual function – Vaginal Changes Questionnaire' (SVQ). 27 items/17 items (shortform)
   Sexual function, male: 'International Index for Erectile Function' (IIEF). 15 items/5 items (shortform)
5. **Pain**: 'Brief Pain Inventory Short Form' (BPI). 15 items
6. **Fatigue**: The Multidimensional Fatigue Inventory (MFI). 20 items
7. **Fear of Recurrence**: 'Fear of Cancer Recurrence Inventory' (FCRI). 43 items
8. **Psychological distress: '**Hospital Anxiety and Depression Scale' (HADS). 14 items.
9. **Quality of Life**: 'EuroQol 5-dimensional health state measure' (EQ-5D). 5 items (+ VAS)
10. **Self-efficacy:** 'Patient Activation Measure' (PAM). 13 items

11. **Patient involvement, information and sense of security:** Combination of two Danish questionnaires. 11 items
12. **Personality:** 'Life orientation test-revised' (LOT-R). 10 items

4 Organisation and time schedule

The head doctors in four surgical departments in two Danish regions have agreed to participate in the study:

- Mogens Rørbæk Madsen, Head of Surgical Department, Hospitalsenheden Vest, Regionshospitalet Herning.
- Inge Bernstein, Head of Surgical Department, FBE Kirurgi Syd, Aalborg Universitetshospital.
- Knud Thygesen, Head of Surgical Department P, Aarhus University Hospital.
- Lars Maagaard Andersen, Head of Surgical Department, Regionshospitalet Randers.

The participating centres have outstanding research environments and a long research tradition. The collaboration between the centres has in previous studies and projects proven to be irreproachable.
The research group in Aarhus will coordinate the project, and the Ph.D.-student will act as daily project-manager and fill the role as research nurse in the centres Aarhus and Randers. All investigators are responsible for inclusion and the execution of the research project locally.

Time schedule	**Year 1**		**Year 2**		**Year 3**		**Year 4**		**Year 5**	
	Fall 2015	Spring 2016	Fall 2016	Spring 2017	Fall 2017	Spring 2018	Fall 2018	Spring 2019	Fall 2019	Spring 2020
Development and pilot-testing of the intervention										
Systematic literature review										
Instruction of research nurses										
Inclusion RCT										
Follow-up RCT										
Data analysis, publications and completion of Ph.D.-dissertation										

5 Funding

The study is initiated by researchers and clinicians from the participating centres, and thus partially funded from the centres.
Most funding, though, comes from the Danish Cancer Society (3 mio. Dkr).
Funding covers salary for Ph.D.-student, research nurses and consulting statistician, required electronic equipment and other material and resources.
None of the participating investigators have concurrent financial interests in the research study.

6 Ethics

The risks and ethical concerns related to the project are limited. The risk of missing a locally recurrent cancer is minimal, as most recurrences are symptomatic. A local quality report from one of the participating centres showed that out of 33 verified local recurrences over a time

period of six years, only two were detected in connection with a clinical control. The remaining were detected either by patients' self-referral due to symptoms or by CT or MR-scans (unpublished data).
Answering the questionnaire may remind the participant of their disease and therefore to some persons be unpleasant and a stress factor.
The study will empower the participants in the intervention group to be more involved in own health care, desirable to some and the opposite to others. Patients accepting to participate should feel secure whatever group they are randomised to follow. We aim to ensure patients of this by thorough and explicit information by the time of inclusion.
All participants will be asked to provide written informed consent. Data will be handled and stored according to national law and only anonymised results will be published. The study is reported and approved by the Danish Data Protection Agency and The National Committee on Health Research Ethics as required.

7 Publishing strategy

Negative as well as positive results will be published in international peer-reviewed scientific journals. The project will result in at least five scientific publications, and all sources of funding will be acknowledged in the manuscript.
The Ph.d.-student affiliated to the project will draft the manuscripts in collaboration with the supervisors. The investigators from the four centres will besides delivering participants to the study also participate in data management and preparation of manuscripts as co-authors. First author will be the one drafting the initial manuscript, last author will be prof. Søren Laurberg. Other authors will be listed alphabetically.

8 Perspectives

Results from the study will contribute to strengthen the evidence base for RC follow-up, and may impact the future follow-up of RC patients in Denmark and internationally.
If the new follow-up program proves successful, it will be readily implementable in daily clinical practice at a national level. Also, it may attract international attention due to the huge number of affected patients and the high level of costs all over the Western world.

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Addendum for the sample size estimation for the FURCA-trial

Date: June 06, 2018

An initial estimation of sample size showed, that a total of 334 participants were needed in order to obtain statistically significant results (alpha 0.05, beta 0.20, SD 13, minimally important difference 4 points on the TOI-score).
As the end of inclusion draws nearer, a confirmative updated sample size analysis has been performed. The reason for this was mainly that the assumed standard deviation (SD) used for the initial estimation was subject to considerable uncertainty, as it was based on studies where setting and populations differed substantially from ours.
Therefore, an interim analysis of the main-outcome (Trial Outcome Index - TOI) has been performed in order to determine a more precise SD. In the updated sample size estimation, the following preconditions are listed: 10.4 SD, 0.05 alpha-value, 0.20 beta-value, an expected difference of 4 points on the TOI-scale and an expected total drop-out of 30%. Furthermore, additionally 15% are added to the sample size, due to the assumption that the outcome data will be non-parametric. Thus the conclusion from the updated sample size estimation is that a total of 324 participants are needed in order to obtain statistically significant results.