Original titel (dansk)
EDFI-Kohorten: Et kohortestudie om udviklingen af afføringsinkontinens og endetarmens lukkemuskelsfunktion, hos personer opereret for endetarmskræft.

Project title
The EDFI-Cohort: Determining early development of faecal incontinence and anorectal muscle function after curative surgery for rectal cancer.

Background
Patients who have been diagnosed with rectal cancer and treated with curative rectal surgery (low anterior resection (LAR)) have a high chance of survival (about 60% are alive after 5 years). [1] There is increasing focus on quality of life for these survivors. A stigmatized problem that more than a third of patients surgically treated for rectal cancer develop is faecal incontinence also known as the low anterior resection syndrome (LARS) [2-7], that has significant impact on quality of life. [8, 9] There is limited knowledge on why some patients develop major LARS. Some of the known exposures that increases the risk of developing major LARS are; age at surgery, gender, tumor height, pre-operative radiotherapy and surgical technique. The choice of surgical procedure is likely to play an important role in developing LARS, but has primarily been evaluated in smaller longitudinal studies with few patients (mean n ≈ 18 patients, range 3-100 patients). [10, 11]
Other factors that are likely to play a role in developing major LARS, has to our knowledge not yet been studied. In order to evaluate the underlying mechanisms of LARS, and in the future provide effective treatments, it is central to evaluate the anorectal muscle function. Anorectal muscle function has been evaluated with anorectal manometry in patients who have been treated with low anterior resection at a median of 6 weeks (range 4-40 weeks) [12] and at a mean of 23 months (range 6-106 months) [13, 14] after surgery. Despite variations in methodology, these studies had similar findings with anorectal resting pressure of 20-40 mmHg and maximal squeeze pressure of 80-140 mmHg, which is half the pressure performed by continent controls [12-16]. These studies have also measured rectal capacity. They found a maximal tolerated volume of 95-140 mL and around 200 mL measured in continent controls. Additionally, a conscious rectal sensitivity threshold of 35-44 mL was measured in both patients and continent controls. [12-16] Despite these findings, there is limited knowledge of the relationship between severity of faecal incontinence and pelvic floor muscle function in patients surgically treated for rectal cancer [17].
Despite LARS being a central factor for reducing quality of life, other factors are likely to play an important role as well. Dysfunctions such as sexual dysfunction, urinary incontinence and feacal incontinence are present in patients with rectal cancer as long after surgery as 4 years, therefore it is important to determine when these symptoms develop and how they are related to each other in patients treated for rectal cancer. [18] Other factors likely to reduce quality of life are problems with fatique, physical inactivity and finding meaning in life. To our knowledge, no records exist on these relationships from prior to surgery to 2 years after. These softer factors are central to include when developing effective treatments strategies for this patient group.

To guide the choice of surgical technique outcomes of mortality, adverse events and self-reported quality of life are important to report. As before mentioned LARS has significant impact on quality of life and is thus important to study. In order to evaluate the underlying mechanisms of LARS, and in the future provide effective treatments, it is central to evaluate the anorectal muscle function. Anorectal muscle function has been evaluated with anorectal manometry in patients who have been treated with low anterior resection at a median of 6 weeks (range 4-40 weeks) [12] and at a mean of 23 months (range 6-106 months) [13, 14] after surgery
Sexual dysfunction, urinary incontinence and feacal incontinence are present in patients with rectal cancer as long after surgery as 4 years, therefore it is important to determine if when these symptoms develop and how they are related to each other in patients treated for rectal cancer. [18] To our knowledge, no records exist on these relationships from prior to surgery to 2 years after low anterior resection. This type of information is central to the future design and conduct of expensive randomized trials.

Purpose
The primary purpose of the EDFI-Cohort study is to determine how several baseline variables (surgical technique, anorectal muscle function, faecal incontinence, urinary incontinence, sexual dysfunction, fatigue, physical activity, meaning in life and physical functioning) develop over time and predicts quality of life, and secondary how it predicts LARS-score in patients with rectal cancer from prior to surgery to 2 years after primary treatment.

Hypothesis
A priori, we determined the following major hypotheses for this study to be (with corresponding null hypotheses):

1. We expect to see poorer quality of life in patients with a higher LARS-score
2. Overall we expect to see poorer quality of life in patients with poor anorectal muscle function, faecal incontinence, urinary incontinence, sexual dysfunction, fatigue, low physical activity, low meaning in life and physical functioning.
3. We expect to a difference in quality of life and LARS-scores between surgical technique. We expect that PME will lead to fewer symptoms and TA-TME to worse symptoms compared with other techniques.
4. We expect to see no differences in mortality rate and adverse events between the different baseline variables.

Method
Subjects for the EDFI-Cohort study will be recruited during 2019 and 2020 from Department of Surgery, Slagelse, and Zealand University Hospital, Køge. Subjects need to be diagnosed with rectal cancer and have received curative surgery (low anterior resection) with/without adjuvant (radiation/chemo) therapy. Subjects for this study are to meet the following inclusion criteria: Low anterior resection (e.g. not limited to total mesorectal excision (TME) or partial mesorectal excision (PME)), ability to communicate in Danish, adults (> 18 years of age), and American Society of Anaesthesiologists (ASA) score: I-IV. Exclusion criteria are: ASA score of: V-VI.

Prior to inclusion, subjects must provide written informed consent to participate in this study.
Subjects for the EDFI-Cohort study will be identified through surgical codes at Slagelse Hospital and Zealand University Hospital, Køge, Denmark. Eligible subjects will primarily be invited to participate in this study prior to discharge with oral and written information, provided in person by a health professional from the research group. Alternatively eligible subjects will be sent a letter after discharge. The letter and written information contain information on the study, the right to say no to the study, the right to 24 hours reflection time and the right to bring next of kin or another person of the subject's choice with him/her to the inclusion meeting. Potential subjects that are only invited by letter are asked to contact the research group for further information. A second letter will be sent to potential subjects whom have not contacted the research group within two weeks, and 2-3 weeks after the second letter has been sent, subjects will be contacted once by phone. Verbal and written information will be provided by a health professional from the research group at a meeting in an undisturbed examination room at Slagelse Hospital or Zealand University Hospital, Køge, Denmark.

Sample size:

The cohort will recruit all eligible patients from summer 2019 to April 2020. I this time period we estimate to recruit 70 patients to the EDFI cohort. A total of 86 patients were surgically treated for rectum cancer in 2017 at Slagelse Hospital and Zealand University Hospital, Køge.

The minimal clinically important difference on the EORTC QLQ-C30 subscale Global Health Status is considered to be 7-12 points for a variety of cancer types (rectal cancer not studied). [19-22] Thus, with the estimated recruitment flow; we will have a power of 0.98 for a two-sample pooled t-test of a normal mean difference with two-sided significance level of 0.05 ($p \leq 0.05$), assuming a common SD of 22 EORTS QLQ-C30 points to detect a mean difference of 10 points between groups with different surgical techniques or with high or low anorectal muscle function (primary study purpose 1).

Additionally, we will have a power of 0.99 for a two-sample pooled t-test of a normal mean difference with two-sided significance level of 0.05 ($p \leq 0.05$), assuming a common SD of 12 LARS points [3] to detect a mean difference of 6 LARS points between groups with different surgical techniques or with high or low anorectal muscle function (study purpose 2).

Whether or not we are able to reach sufficient numbers within the 1 year timeframe, recruitment will end in April 2020.

Outcomes:

Outcomes is to be obtained from patient records, self-reported questionnaires and objective measures. For full list of outcomes to be collected and time points, see table 1.

Patient records:

In order to identify and invite eligible subjects, information on diagnosis, type of surgery, admission and contact information will be collected from patient records and given to the research group, prior to acceptance to participate in the study. After acceptance to participate in this study the following descriptive information will be collected from patient records (including electronic patient journals): Age at surgery (years), time of surgery (weeks), type of surgery, surgical complications, gender (male/female), tumor height (cm from anal verge), tumor stage (UICC), involvement of lymph nodes (N stage), additional radiotherapy/chemotherapy, surgical technique, anastomosis, ASA grade (I-IV), time with temporary stoma, and if available data from pre-surgery manometric examination, digital examination, Six-Minute Walk test (6MWT) and mortality status. This information will be used to adequately describe patient characteristics, cancer treatment, surgical outcome and mortality status. Additionally the acceptance to participate in this study allows the research group and relevant control agency direct access to collect information on health status in relation to quality control.

Self-reported outcomes:

Information on education level, work status and civil status will be obtained through self-reported questionnaires at 3 weeks. The remaining self-reported outcomes is collected with a series of validated questionnaires that subjects will be asked to complete 6 times during the two year study, see table 1.

Quality of life of cancer patients (primary outcome) is assessed with questionnaires developed by the European Organisation for Research and Treatment of Cancer (EORTC). EORTC has developed and validated a generic core set (EORTC QLQ-C30) for assessing quality of life. [23] [24] As recommended by the EORTC, have added symptom specific module (EORTC QLQ-CR29) [23] and fatique module (EORTC QLQ-FA12). [25] [26]

Bowel related quality of life (secondary outcome) is quantified with the Low Anterior Resection Symptom score (LARS-score), which is a validated score to group subjects into either no/low LARS or major LARS. [9] The items included in the LARS-score have been selected and weighted to reflect bowel related quality of life. [9] [27]

Faecal incontinence is also quantified with the St. Marks Incontinence score (also known as the Vaizey score), which is a validated instrument for assessing severity of faecal incontinence. [28]

Urinary incontinence is assessed with questionnaires developed by the workgroup International Consultation on Incontinence Modular Questionnaire (ICIQ). ICIQ has developed and validated a generic core set (ICIQ-UI) for assessing urinary incontinence. [29] Additionally, we use symptom specific modules also developed and validated by ICIQ. The modules assess urinary symptoms in males and females and sexual matters in males and females.

Physical activity level is quantified as done in the Danish National Health Profile – Health of the Danish People, which is a nationwide questionnaire answered by more than 180.000 Danish people in 2017. [30, 31]

Sources of meaning and meaningfulness is assessed with Sources of Meaning and Meaning in Life Questionnaire (SoMe), which is a self-reported measure of meaningfulness and crisis of meaning reported on two separate scales, enabling further analysis and comparisons of positive and negative aspects of meaning in life. The questionnaire has been validated in a Danish population. [32] [33]

Objective measures
All objective measures are to be collected at Slagelse Hospital and Zealand University Hospital, Køge, at 6 weeks, 6 months, 12 months and 24 months.

Digital examination of anorectal muscle function is an easy-to-use and cheap assessment tool readily available in a clinical setting. When using the Digital Rectal Examination Scoring System (DRESS) that ranges 0-5 (lowest to highest), the digital examination showed very high agreement with manometry pressures (Spearman rank correlation coefficients 0.81-0.82). [34] Digital examination involves inserting a finger in the anal canal.

High-Resolution AnoRectal Manometry (HR-ARM) is considered state of art in measuring anorectal muscle function and has shown to have moderate to high reliability in adults with or without faecal incontinence, with intra-individual correlations (ICC) for resting pressure (ICC 0.60-0.91) [35] [36] [16], squeezing pressure (ICC 0.49-0.95) [35] [36] [16] and rectal perception (ICC 0.75-0.92) [36] [16]. HR-ARM involves a narrow catheter being inserted in the anal canal that measures pressure with strain gauges several times throughout the anal canal. Rectal perception is measured by inflating a balloon in the rectal canal.

The Six-Minute Walk test (6MWT) is a widely used measure of submaximal exercise capacity in populations with and without pathology. [37] The 6MWT has shown to be correlated to maximum exercise capacity ($r=0.67$) and to perceived physical function (EORTC QLQ-C30 physical function subscale) ($r=0.55$) in cancer patients. [38] A systematic review has recommended that a minimal clinically important difference of ≥ 30.5 m for the 6MWT can be considered clinically meaningful for patients with a variety of pathology. [39] 6MWT involves the patient walking as far as possible in 6 minutes indoor.

Table 1: Full list of outcomes.

Patient records at hospital	**Items that is obtained**	**Time point**
Descriptive information:	Age at surgery (years) Time of surgery (weeks) Gender (male/female) Tumor height (cm from anal verge) Tumor stage (UICC) Involvement of lymph nodes (N stage) Additional radiotherapy/chemotherapy Surgical technique Anastomosis ASA grade (I-IV) Time with temporary stoma Manometric examination (if available) Digital examination (if available) Six-Minute Walk test (if available)	At identification of relevant patients
Adverse events from surgery	Hospitalisation 30 days after surgery Surgical complications	30 days after surgery
Mortality (and at the National Patient Registry)	Is the subject deceased?	If no answer is obtained through questionnaires or no show at clinical examination.

Self-reported outcomes:	**Questionnaire**	**Time point**
Education level, work status and civil status	Non standardized questionnaire	3 weeks
Bowel related quality of life	Low anterior resection symptom – score (LARS-score)	3, 6, 12, 26, 52 and 104 weeks
Faecal incontinence	St. Marks Incontinence score (Vaizey-score)	3, 6, 12, 26, 52 and 104 weeks
Quality of life of cancer patients:	EORTC QLC-C30	3, 6, 12, 26, 52 and 104 weeks
Colorectal	EORTC QLQ-CR29	3, 6, 12, 26, 52 and 104 weeks
Fatique	EORTC QLQ-FA12	3, 6, 12, 26, 52 and 104 weeks
Information about disease and treatment	EORTC QLQ-INFO25	3, 6, 12, 26, 52 and 104 weeks
Urinary Incontinence	International Consultation on Incontinence Modular Questionnaire (ICIQ) - Urinary Incontinence Short Form (ICIQ-UI SF)	3, 6, 12, 26, 52 and 104 weeks
Urinary symptoms, males	ICIQ-Male Lower Urinary Tract Symptoms (ICIQ-UI MLUTS)	3, 6, 12, 26, 52 and 104 weeks
Urinary symptoms, females	ICIQ-Female Lower Urinary Tract Symptoms (ICIQ-UI FLUTS)	3, 6, 12, 26, 52 and 104 weeks
Sexual dysfunction		

	Sexual dysfunction, males	ICIQ-Male Sexual Matters associated with Lower Urinary Tract Symptoms (ICIQ-UI MLUTSsex)	3, 6, 12, 26, 52 and 104 weeks
	Sexual dysfunction, females	ICIQ-Female Sexual Matters associated with Lower Urinary Tract Symptoms (ICIQ-UI FLUTSsex)	3, 6, 12, 26, 52 and 104 weeks
Physical activity level		physical activity section of the Danish National Health Profile	3, 6, 12, 26, 52 and 104 weeks
Sources of meaning and meaningfulness		Sources of Meaning and Meaning in Life Questionnaire (SoMe)	3, 6, 12, 26, 52 and 104 weeks

Objective measure:	**Units:**	**Time point**
Anorectal muscle function (digital examination)		
Maximal resting pressure Maximal squeeze pressure Endurance squeeze - max squeeze pressure or longest time Latency (rate of force development), number of rectal muscle contractions/squeezes in 15 sec test.	0-5 (DRESS) (lowest to highest) 0-5 (DRESS) (lowest to highest) 0-5 (DRESS) and s, maximum of 60 s. n	6, 26, 52 and 104 weeks
Anorectal muscle function (High-Resolution AnoRectal Manometry)		
<u>Pressure measurements:</u> Maximal resting pressure Maximal squeeze pressure Maximal squeeze pressure duration	 mmHg mmHg s	6, 26, 52 and 104 weeks
<u>Volume capacity measurements:</u> Maximal tolerated volume Conscious rectal sensitivity threshold Conscious rectal sensitivity Constant sensation	 mL mL % of maximal volume mL	6, 26, 52 and 104 weeks
Physical Performance		
6-Minute Walk test	M	6, 26, 52 and 104 weeks

<u>Statistical analysis</u>

We plan to analyze the EDFI-Cohort study as repeated measures with both simple and multiple linear regression models for the continuous data. We plan to adjust for the following known confounders: patient characteristics: age at surgery, gender, tumor height, tumor stages and variables related to treatment: surgical complications (e.g. nerve damage, sphincter rupture), additional radiotherapy/chemotherapy, time with stoma.

<u>Patient involvement</u>

Prior to planning of the EDFI-Cohort study, we have performed a single case-study (spring 2016) on examination procedure, questionnaires and pelvic floor muscle rehabilitation. This case provided us with valuable information on testing and possible evaluation of treatment effect. In the winter of 2017-18, we

interviewed subjects on their perspective on this study design and examination load. In the same time-period, we did pilot testing on the clinical examinations.

Research ethics

Examinations included in this study are all associated with very few, if any, adverse events, except from the mild discomfort related to the clinical anorectal examination itself. Subjects included in this study will receive four examinations, whereas care as usual at Slagelse and Køge Hospital usually include one examination/contact to the local LARS clinic with no anorectal examination. This, included subjects are more closely monitored and, if need be, might receive relevant treatment earlier compared to care as usual patients.

Future implications

Results from the EDFI-Cohort study will help guide the design of randomized controlled trials on treatments of faecal incontinence in subjects who have been surgically treated for rectal cancer. With emphasis on establishing the role of anorectal muscle function in the development of faecal incontinence.

Applicability of registrations and approvals

A prior version of the EDFI-Cohort study protocol has been approved by the regional research ethics committee of Region Zealand and The Data Protection Agency journal number: REG-130-2017. This project adhere to the General Data Protection Regulation and Data Protection Act. The regional research ethics committee and data protection agency will need to approve the new version of the study protocol prior to project start. Finally, the project will, prior to start, be registered at ClinicalTrials.gov. This study is part of the patient compensation scheme (patienterstatningsordningen).

Study economy

This study is partially funded. Funding has so far come from the local research fund of NSR hospitals (DKK 968,000) and The Association of Danish Physiotherapists (DKK 82,000). The Department of Physiotherapy and Occupational Therapy at Slagelse Hospital provides access to facilities and offices. None of the funding agencies have any influence on study design or reporting of data. Further funding will be applied for from public and private foundations.

To reduce unnecessary inconvenience for subjects, we have planned the study test sessions on same days as subjects are to meet in the LARS outpatient clinics.

Dissemination of study results:

The EDFI-Cohort study is expected to be presented at several conferences for health professionals and the public and to provide 4 international peer-reviewed scientific papers on the findings whether they are positive, negative or inconclusive. All reporting of the EDFI-Cohort study will comply with the STROBE-guidelines [40, 41].

The first publication (paper 1) will report on associations between quality of life and LARS-score, adjusted for baseline variables (surgical technique, anorectal muscle function, faecal incontinence, urinary incontinence, sexual dysfunction, fatigue, physical activity, meaning in life and physical functioning) from prior to curative surgery until 12 weeks after surgery.

The second publication (paper 2) will report on the development of quality of life and LARS-score, stratified based on choice of surgical technique prior to curative surgery until 6 months after surgery.

The third publication (paper 3) will report on associations between quality of life and LARS-score, adjusted for baseline variables (surgical technique, anorectal muscle function, faecal incontinence, urinary incontinence, sexual dysfunction, fatigue, physical activity, meaning in life and physical functioning) from prior to curative surgery until 2 years after surgery.

The fourth publication (paper 4) will report on mortality rate and adverse events adjusted for baseline variables (surgical technique, anorectal muscle function, faecal incontinence, urinary incontinence, sexual dysfunction, fatigue, physical activity, meaning in life and physical functioning) from prior to curative surgery until 2 years after surgery.

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