Quality of life in patients with resectable rectal cancer during the first 24 months following diagnosis

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Abstract

Aim An increasing number of patients survive rectal cancer, resulting in more patients living with the side-effects of the treatment. Exploring quality of life before and after treatment enables follow-up and additional treatment to be adjusted to the patient's needs. The aim of the study was to describe the quality of life during the 24 months following diagnosis and to identify risk factors for poor quality of life.

Method This is a prospective cohort study of patients with rectal cancer followed up by extensive questionnaires. Patients from 16 surgical departments in Denmark and Sweden from 2012 to 2015 were included. The self-assessed quality of life was measured with a seven-point Likert scale.

Results A total of 1110 patients treated with curative intent were included, and the response rate at the 24-month follow-up was 71%. Patients with rectal cancer assessed their quality of life before start of treatment as poorer than that of a reference population. At the

12- and 24-month follow-up, the quality of life on group level had recovered to the same level as for the reference population. Risk factors for poor quality of life included bother with urinary, bowel and stoma function. A reference population was used for comparison.

Conclusion The quality of life of patients with resectable rectal cancer recovered to levels comparable to a reference population 12 and 24 months after diagnosis. Our results indicate that the urinary, bowel and stoma function has an impact on quality of life.

Keywords rectal neoplasm, quality of life, patient-reported outcome measures

What does this paper add to the literature?
The treatment for rectal cancer can result in side-effects which may have an impact on the patient's quality of life. The aim of this study was to describe the quality of life after diagnosis and to explore if there are factors increasing the risk of poor quality of life.

Introduction

An increasing number of patients survive rectal cancer, resulting in more survivors living with the side-effects of treatment. Exploring the patients' self-assessed quality

of life before and after treatment and detecting patient and healthcare related factors associated with poor quality of life enables the follow-up and additional treatment to be adjusted to the patient.

Prospective studies of patients with rectal cancer reporting on generic quality of life before and after treatment are scarce. However, there have been reports of quality of life remaining unchanged over time, when preoperative assessments were compared to follow-up at 12 months [1] and at 15–18 months [2]. Other studies found that the quality of life was restored or even improved 12 months after surgery [3]. However, recurrence of disease has been shown to impact the quality of life negatively [4].

Treatment for rectal cancer can alter urinary, sexual and bowel function. For example, in this cohort we have previously found that patients may become urinary incontinent [5,6] or experience impaired sexual function [6,7]. Some patients with bowel continuity experience poor bowel function [8]. The change in physical functions can impact well-being and quality of life [1,9].

The influence of a stoma on quality of life has been discussed but was found not to have an impact in a Cochrane review [10]. In a previous study by our research group, a majority of patients stated that they could live a full life with their stoma [11]. However, a recent report indicated that the presence of a stoma had a negative impact on quality of life [12] and the functional aspects have been reported to affect quality of life negatively [13].

The aim of this study was to describe the quality of life of patients with rectal cancer during the first 24 months following diagnosis. An additional aim was to identify risk factors that could predict low quality of life during this time.

Method

Study design and study population

This study reports the results of a prospective cohort multicentre study of patients with rectal cancer and self-assessed quality of life, the QoLiRECT (Quality of Life in RECTal cancer) study [14]. All patients presenting with a biopsy-confirmed rectal adenocarcinoma within 15 cm from the anal verge were invited to participate, irrespective of tumour stage. The patients were included at 16 surgical departments in Denmark and Sweden from 2012 to 2015. In the present analysis, all patients planned for treatment with a curative intent were eligible for inclusion in the study.

The methodology is based on extensive questionnaires, developed according to an established clinimetric method [15,16], including questions on symptoms, socioeconomics, personality, comorbidity and lifestyle. The questionnaires consisted of about 200 questions each; not all of them were used in this particular study. To supplement the data retrieved in the questionnaires, clinical data such as tumour stage, treatment characteristics and clinical details were collected from the national quality registries for rectal cancer in Denmark (the Danish Colorectal Cancer Group) and Sweden (the Swedish Colorectal Cancer Registry). The first questionnaire was administered at diagnosis, before start of treatment, and at follow-up 12, 24 and 60 months later. This study reports data from baseline and the 12- and 24-month follow-ups. Future studies will report the results of the 60-month follow-up.

Since the initial power calculation for the size of the study cohort was based on quality of life at the 60-month follow-up as primary outcome, no a priori calculation of power was performed specifically for this study. Nevertheless, the available sample size was considered large enough to ensure sufficient statistical power for the study objective, e.g. to describe the quality of life of patients with rectal cancer and to identify risk factors that could predict poor quality of life.

The study was preregistered at www.clinicaltrials.gov (NCT01477229). Permission was obtained from the Danish Data Protection Agency (HEH.750.89-21; HGH-2016-016) and the Regional Ethical Review Board in Sweden (EPN 595-11) and Denmark (H-3-2012-FSP26).

Study outcomes

The primary outcome was the patients' self-assessed quality of life, measured by a seven-point Likert scale and dichotomized as low (0–4) or high (5–6). The cut-off for the quality of life question has been used in previous studies [17]. The repeated measures of quality of life in the study population were compared to a reference population, a random sample of the Swedish general population of 1078 individuals [18]. This was a cross-sectional study including patients from 2014 to 2015, the participants retrieved from the Swedish Inland Revenue. In the risk factor analysis, the outcome was the quality of life assessment at 24 months' follow-up. To increase the comparability with the results of previous reports and to supplement the results of the quality of life analyses, the five domains of the Euro-Qol's EQ-5D-3L [19] are also presented. The domains of the EQ-5D-3L include mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Statistical analysis

The longitudinal characteristics of the prevalence of a high quality of life were estimated by a generalized linear mixed effects model with a logit link and a Bernoulli distribution [20]. A random intercept accounted for the within-patient correlation. Sex and time were included as fixed effects and age as a continuous covariate [21], as well as two- and three-way interaction effects. Individual random effect (conditional) predictions as well as least-squares mean fixed effect (marginal) predictions with 95% confidence intervals (CI) were presented graphically. The mean effects were evaluated in the first and third quartiles of age at inclusion, 62 and 75 years, respectively. The prevalence in the reference population was presented as crude rates with 95% CI. The

prevalence was compared between the study population and the reference population separately for each follow-up using a generalized linear model with binomial distribution and log-link and is presented as ratios, 95% CI and P values.

A risk factor analysis was performed to assess patient characteristics and clinical factors that could predict low quality of life 24 months after rectal cancer diagnosis. In the statistical model, the following questionnaire-derived baseline variables were included: sex [21], age [21], comorbidity, the sense of coherence (SOC-29) [22], marital status, physical activity according to the Saltin–Grimby scale [23], negative intrusive thoughts [24], depression [25], alcohol consumption and bother related to sexual [6], urine [5], bowel [26], stoma function [11,12,27] and recurrence of cancer[4]. The following variables were included from the registries: metastatic disease at diagnosis [28,29], neoadjuvant chemotherapy and neoadjuvant radiation therapy.

The risk factor analysis consisted of three subsequent steps. First, the univariate relationship between the quality of life and each of the variables was explored by simple log-binomial. Second, variable selection was performed by least absolute shrinkage and selection operator (LASSO) logistic regression[30] using 10-fold cross-validation where the shrinkage factor used for the selection was chosen according to the 'one standard error rule' [30,31]. After the variable selection, 50 datasets were generated with missing values imputed for the five selected variables using predictive mean matching [32].

In the third and final step, the parameters of a multiple regression featuring the selected variables were estimated for each of the 50 datasets and pooled in a single set of parameter estimates. The estimation of log-binomial models may not converge due to sparseness of data and a Poisson distribution is then an option. This situation applied to the present model and therefore a Poisson distribution was used. Results were presented as risk ratios, 95% CIs and P values. To what degree the predictors could explain the variability in quality of life was described according to McFadden's R^2. Descriptive data were calculated by IBM SPSS Statistics version 25 and the longitudinal model was estimated using PROC GLIMMIX in SAS v9.4 (SAS Institute Inc., Cary, North Carolina, USA). Variable selection and imputations were made using the glmnet and mice packages in R version 3.2.3 [33].

Results

Patients were recruited at 16 surgical departments in Denmark and Sweden from 2012 to 2015. In total,

1110 patients planned for treatment with curative intent were included and constitute the study population. The response rates for the questionnaires at baseline and the 12- and 24-month follow-ups were 90%, 79% and 71%, respectively (Fig. 1). At the 12-month follow-up 37 patients were deceased and 12 months later that number had increased to 47. Of the entire study population, 70 (6.3%) did not return any of the three questionnaires (Table 1).

Patient characteristics

The median age of the study population at baseline was 69 years (range 19–92) (Table 2). There were more men than women. About two-thirds were married and one-third were employed. Half of the study participants had comorbidity such as pulmonary disease, cardiovascular disease or diabetes and 16% reported self-assessed depression. Among the study population, 18% were classified as ASA III or IV (American Society of Anesthesiologists' physical status classification). Regarding preoperative tumour stage, 15% were classified as T4, 54% as N1 or N2, and 12% as M1 or M status not known. Thirty-five per cent of the patients underwent abdominoperineal resection, 53% anterior resection and 9% Hartmann's procedure. Preoperative radiotherapy was given to 62% and 23% received preoperative chemotherapy.

Outcomes

The longitudinal self-assessed quality of life is shown in Fig. 2 and detailed data are given inTable S1. The patients with rectal cancer assessed their quality of life as poorer than the reference population at baseline. At the 12- and 24-month follow-up, the quality of life on group level had recovered to levels comparable to those of the reference population [18]. The quality of life was not affected by sex or age.

Results from the EQ-5D-3L are shown in Fig. 3. At baseline, every second study participant indicated that they had pain or discomfort. This was maintained throughout the follow-up period. Ten per cent of the study population indicated problems with mobility at baseline and the proportion was 20% at the 12- and 24-month follow-up. At baseline, after they had received information on the diagnosis and the planned treatment, 38% indicated anxiety or depression. At the 12- and 24-month follow-up, this was reduced to 29%.

Poor sexual function, depressed mood, negative intrusive thoughts and neoadjuvant radiation had a statistically significant effect on the risk of low quality of
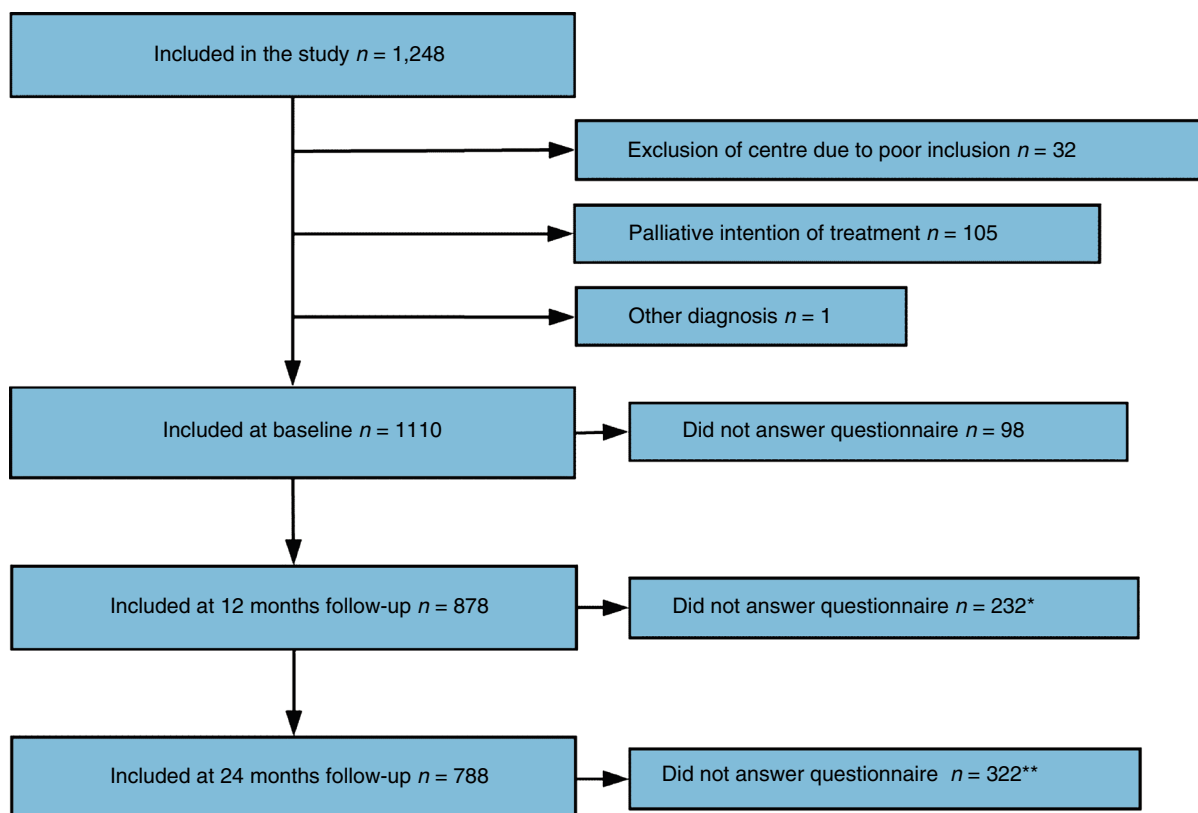
Figure 1 Flow chart of patients included in the study. Among the 1110 patients included, 70 did not return any of the three questionnaires. *Of which $n = 37$ were deceased. **Of which $n = 47$ were deceased

life at 24 months in the univariate analysis but none was selected for the multiple regression (Table 3). A low score for sense of coherence at diagnosis was a risk factor for poor quality of life 24 months later (Table 4). Functional problems such as urinary function, as well as stoma or bowel function, were also risk factors for poor quality of life 24 months after diagnosis. Comorbidity at diagnosis and recurrence of rectal cancer, as stated by the patient in the questionnaire 24 months after diagnosis, were also risk factors. McFadden's R2 for the multivariate model was 6.0% (Table 4).

Discussion and conclusions

The most important finding was the recovery of quality of life 12 months after diagnosis to levels comparable to a reference population. Another finding was that poor urinary, bowel and stoma function were risk factors for poor quality of life after treatment for rectal cancer.

Our study implies that the quality of life of patients with resectable rectal cancer recovers to the same level as that of a reference population 12 and 24 months

after diagnosis, which is in accordance with some previous studies and differs from others. A study using the Quality of Life in Adult Cancer Survivors Generic Summary Score (QLACS-GSS) [34] concluded that the scores of patients with colorectal cancer were comparable with other cancer survivors [35]. In another prospective trial [3] of patients with rectal cancer, it was shown that global quality of life according to the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) [36] was restored to preoperative scores 12 months after surgery. A cross-sectional study [37] of patients with colorectal cancer 12 months after surgery reported almost identical mean scores of global health/quality of life and physical functioning according to the same questionnaire. This is in contrast to another study using the questionnaire EORTC QLQ-C30 and comparing patients with rectal cancer at the 4-year follow-up with a sample of the general German population; it was concluded that they had poorer function and more problems [38]. Hypothetically, the result might differ from the results of this study due to the clinical setting, that the patients were included

Table 1 Demographics for the study cohort at baseline, before start of treatment

	Baseline n = 1110	Missing
Age, median (range)	69 (19–92)	0
Sex, M:F	694:416	0
Married	745 (68)	10
University education (yes)	368 (33)	0
Working	306 (28)	0
Comorbidity (yes)	539 (49)	0
Depression (yes/don't know)	165 (16)	106
Alcohol consumption last month (yes)	723 (73)	120
Low physical activity (Saltin–Grimby scale)	135	140
Sense of coherence, mean (SD; range)*	159 (19.6; 85–203)	127
Negative intrusive thoughts (yes)	242 (24)	119

Values in parenthesis are percentages, unless indicated otherwise.
* Sense of coherence scale score (SOC-29).

Table 2 Clinical data of the study cohort at baseline, before start of treatment

|	Study cohort n = 1040	Missing	Drop-out n = 70	Missing
Age*	69 (19-92)	0	70 (19-86)	0
ASA† physical status classification		82		8
1	250 (26)		16	
2	609 (64)		31	
3–4	169 (18)		15	
Clinical TNM stage				4
T1–T2	295 (30)	47	13	
T3	598 (60)	47	40	
T4	153 (15)	47	12	
TX	17 (2)	47	1	
N0	460 (47)	53	32	
N1–N2	534 (54)	53	32	
NX	63 (6)	53	2	
M0	935 (95)	57	59	
M1	82 (8)	57	7	
MX	36 (4)	57	0	
Surgical technique		66		8
Abdominoperineal excision	340 (35)		25	
Anterior resection	518 (53)		28	
Hartmann's procedure	88 (9)		6	
Other surgical procedure	28 (3)		3	
Preoperative radiotherapy	626 (62)	33	38	4
Preoperative chemotherapy	234 (23)	35	16	4

The patients who did not answer any of the three questionnaires are presented separately (Drop-out). Values in parenthesis are percentages unless indicated otherwise.
* Years in median (range).
† American Society of Anesthesiologists.

some 20 years ago and in another country where the general acceptance of stomas might differ from that in Scandinavia.

Recurrence of rectal cancer was correlated to poor quality of life, which has also been shown in previous studies [4,28]. Our results indicate that it is the
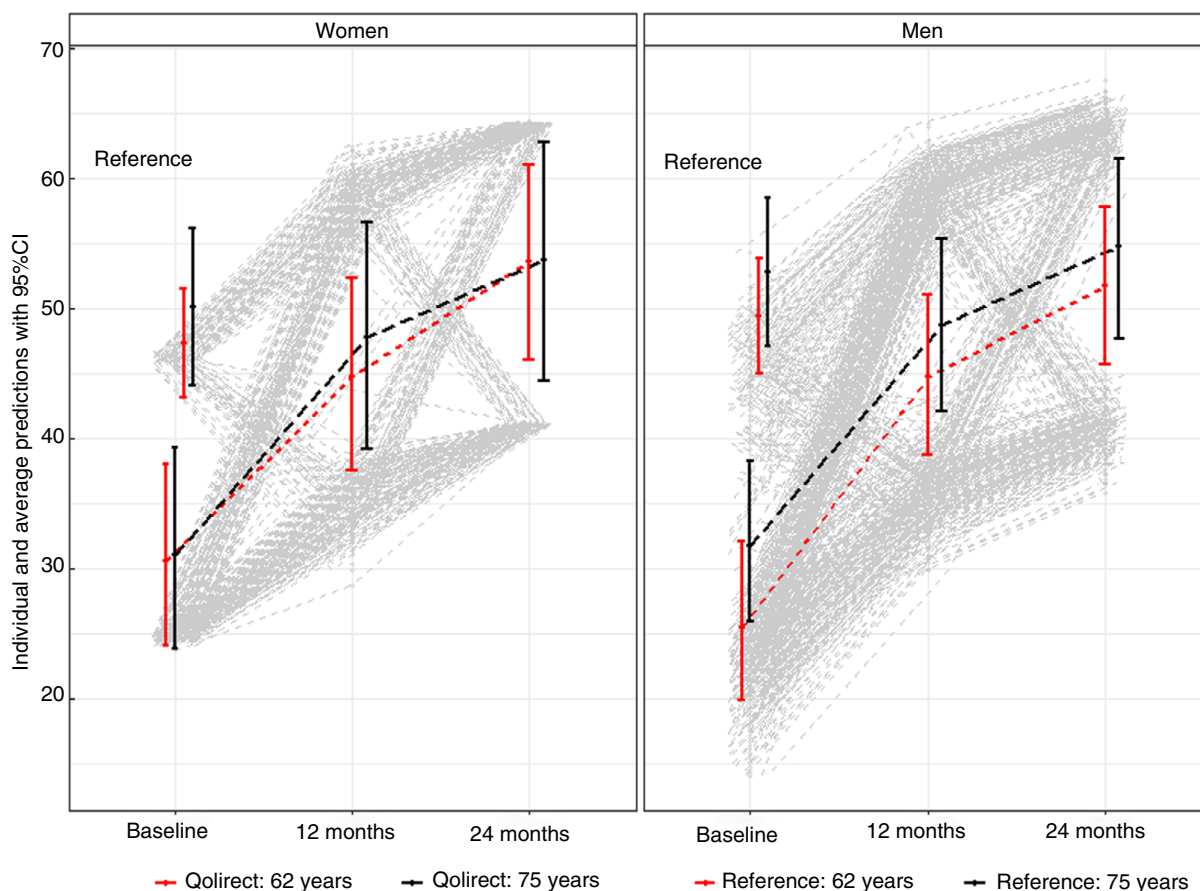
Figure 2 Estimated prevalence of high quality of life during the first 24 months following rectal cancer diagnosis. The reference population is presented at the left-hand side of the figures. Detailed data are given in Table S1

perceived function of the urinary tract, bowel or stoma that has an impact on quality of life. These results are supported by previous reports [1,9,13]. It is possible that the relationship between the functional outcome and quality of life is mediated through the patient's bother. Thus, it is important to ascertain that patients receive help if they experience that their function is impaired, as this possibly could improve their quality of life. The relatively low values of R2 illustrate the difficulties in explaining variability in, and prediction of, the long-term quality of life. However, R2 is not quite appropriate for evaluating clinical prediction models, and methods for assessing different classes of models and evaluation measures is a scope of future research. When the 60 months' follow-up of the study is completed, further analyses on the long-term outcome will be possible.

The strengths of our study are that the study population consists of a large population-based sample of patients undergoing curative treatment for rectal cancer, regardless of tumour stage. The high response rates, the recruitment of patients from 16 surgical departments in two countries and the similarity of the study population to the non-included patients [24] combine to ensure a high external validity of the results. Further strengths of our study are that the first assessment of quality of life was after diagnosis, before the start of any treatment, and the primary outcome is presented in relation to a reference population.

Despite the inherent loss of information resulting from the dichotomization of the quality of life measure scale, this was chosen to enable a more easily interpreted model. By similar argument, we used the Poisson distribution to manage the non-convergence of the multiple regression.

Studies on quality of life in patients with rectal cancer including pre-treatment values are indeed sparse. Furthermore, to compare our results to other studies is a delicate matter, since the definition of baseline differs. In our study, baseline refers to the time-point before start of any treatment, not only before surgical treatment. A proportion of patients get radiation and/or
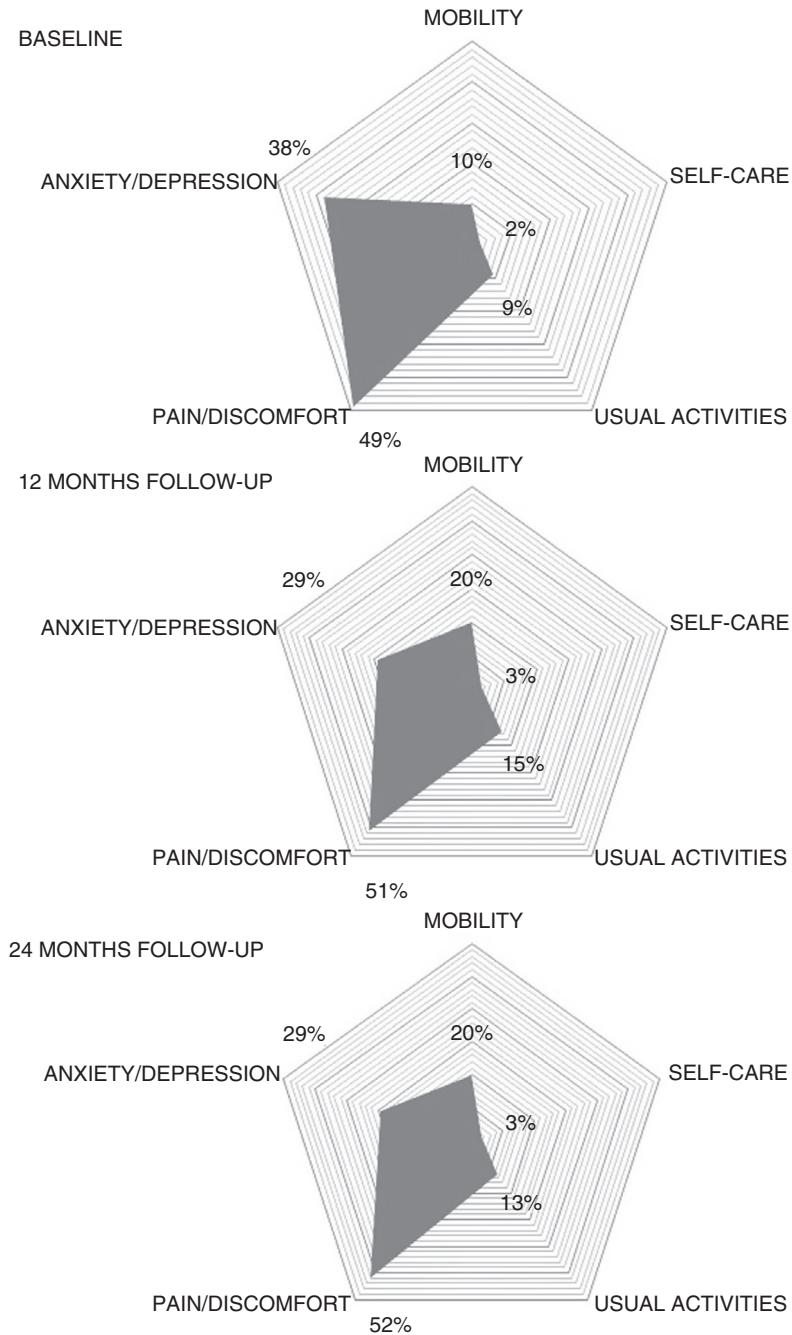
Figure 3 The EQ-5D-3L assessments at baseline (before start of treatment) (n = 996), 12-month follow-up (n = 853) and 24-month follow-up (n = 776). The numbers represent the patients stating any problem with the domain

chemotherapy before surgery and this might influence baseline values registered before surgery. Thus, we emphasize that, when designing future quality of life studies of patients with rectal cancer, the choice of baseline should be carefully considered.

As more patients treated for rectal cancer survive, the numbers of patients living with the side-effects of the treatment are increasing. Poor functional outcome of the urinary tract, bowel or stoma seems to correlate with poor quality of life and these are important aspects of the follow-up after treatment for rectal cancer. Thus, it would be beneficial for patients to monitor their functional recovery after surgery and offer various treatments for those who need it.

Table 3 Risk factor assessment for low quality of life at 24 months after diagnosis, univariate analyses

| Covariates | Quality of life | | | Univariate | | McFadden's |
	Low	High	All	Ratio (95% CI)	P value	R2 (%)
Age* (ref: 10 years increase)	68	68		0.98 (0.91–1.06)	0.537	0.03
Women	143/303 (47)	160/303 (53)	303 (38.8)			
Men	227/478 (47)	251/478 (53)	478 (61.2)	0.98 (0.86–1.16)	0.936	<0.001
Married	306/638 (48)	332/638 (52)	638 (82)			
Not married	55/124 (44)	69/124 (56)	124 (16)	0.93 (0.75–1.14)	0.472	0.05
M1 at diagnosis (ref: M0)	28/49 (57)	21/49 (43)	49 (6.27)			
M0 at diagnosis	328/698 (47)	370/698 (53)	698 (89.4)	0.82 (0.637–1.061)	0.1327	0.18
Physical activity	314/661 (48)	347/661 (52)	661 (84.6)			
No physical activity	38/83 (46)	45/83 (54)	83 (10.63)	0.96 (0.75–1.23)	0.770	<0.001
Good sexual function	246/546 (45)	300/546 (55)	546 (70)			
Poor sexual function	110/203 (54)	93/203 (46)	203 (26)	0.831 (0.71–0.97)	0.021	0.47
Depression	71/109 (65)	38/109 (35)	109 (14)			
No depression	287/648 (44)	361/648 (56)	648 (83)	0.68 (0.58–0.8)	<0.0001	1.56
Neoadjuvant chemotherapy	78/157 (50)	79/157 (50)	157 (20)			
No neoadjuvant chemotherapy	283/605 (47)	322/605 (53)	605 (77)	0.942 (0.79–1.13)	0.509	0.04
Neoadjuvant radiation	227/444 (51)	217/444 (49)	444 (57)			
No neoadjuvant radiation	134/319 (42)	185/319 (58)	319 (41)	0.822 (0.70–0.96)	0.015	0.59
Alcohol	265/561 (47)	296/561 (53)	561 (72)			
No alcohol	90/189 (48)	99/189 (52)	189 (24)	1.008 (0.85–1.20)	0.927	<0.001
Negative intrusive thoughts	255/576 (44)	321/576 (56)	576 (73.75)			
No negative intrusive thoughts	106/186 (57)	80/186 (43)	186 (23.8)	1.29 (1.10–1.50)	0.001	0.86

Values in parenthesis are percentages unless indicated otherwise.
*Median.

Table 4 Multivariate model for low quality of life 24 months after diagnosis. The variable selection was according to the LASSO method.

| Covariates | Quality of life | | | Univariate | | Multivariate‡ McFadden's R2 (%) | | |
	Low	High	All	Ratio (95% CI)	P value		Ratio (95% CI)	P value
Poor urinary function	101/140 (72)	39/140 (28)	140 (18)					
Good urinary function	262/628 (42)	366/628 (58)	628 (80)	0.58 (0.50–0.66)	<.00001	4.10	0.70 (0.56–0.89)	0.003
Comorbidity†	118/307 (38)	189/307 (62)	307 (39)					
No comorbidity†	240/450 (53)	210/450 (47)	450 (58)	1.39 (1.18–1.64)	0.0001	1.56	1.29 (1.04–1.61)	0.021
Good bowel/ stoma function	87/300 (0.29)		213/300 (71)	300 (40)				
Poor bowel/ stoma function	272/459 (59)	187/459 (41)	459 (60)	2.04 (1.69–2.49)	<0.0001	6.5	1.77 (1.38–2.27)	<0.0001
Sense of coherence*	154.5	166.0		0.87 (0.82–0.91)	<0.0001	2.5	0.91 (0.86–0.96)	<0.0005
Recurrence at 24 months	45/66 (68)	21/66 (32)	66 (8)					
No recurrence at 24 months	256/546 (47)	290/546 (53)	546 (70)	1.5 (1.23–1.78)	<0.0001	1.22	1.07–2.01	0.017

Values in parenthesis are percentages unless indicated otherwise.
The variable selection was according to the LASSO method.
*Median.
†Cardiovascular disease, diabetes, lung disease, renal failure or joint disease.
‡McFadden's R2 for the multivariate model was 6.0%.

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Conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The generalized linear repeated measures analysis of high quality of life. Ratio (QoLiRECT vs. reference population) of chance of high quality of life at baseline, before start of treatment, and 12 and 24 months later.