



Effect of Neoadjuvant Therapy and Rectal Surgery on Health-related Quality of Life in Patients With Rectal Cancer During the First 2 Years After Diagnosis

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Abstract

The present study describes the trends in quality of life (QOL) of 272 rectal cancer patients treated with neoadjuvant therapy and surgery ≤ 2 years after diagnosis. During and shortly after treatment, QOL declined substantially and recovered toward pretreatment levels thereafter. However, the functioning scores remained lower compared with the Dutch general population, with postoperative treatment-related symptoms frequently reported.

Introduction: Rectal cancer surgery with neoadjuvant therapy is associated with substantial morbidity. The present study describes the course of quality of life (QOL) in rectal cancer patients in the first 2 years after the start of treatment. **Patients and Methods:** We performed a prospective study within a colorectal cancer cohort including rectal cancer patients who were referred for neoadjuvant chemoradiation or short-course radiotherapy and underwent rectal surgery. QOL was assessed using the European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) and colorectal cancer questionnaire (EORTC QLQ-CR29) before treatment and after 3, 6, 12, 18, and 24 months. The outcomes were compared with the QOL scores from the Dutch general population and stratified by low anterior resection and abdominoperineal resection. Postoperative bowel dysfunction after low anterior resection was measured using the low anterior resection syndrome score.

Results: Of the 324 patients, 272 (84%) responded to at least 2 questionnaires and were included in the present study. Compared with pretreatment levels, the strongest decline was observed in physical, role, and social functioning at 3 and 6 months after the start of treatment. Global health and cognitive functioning declined to a lesser extent, and emotional functioning gradually improved over the time. Within 24 months, the QOL scores had recovered toward the pretreatment levels in most patients. Compared with the general population, physical, role, social, and cognitive functioning and symptoms of fatigue and insomnia remained significantly worse in patients on longer-term. After low anterior resection, major bowel dysfunction was reported by 44% to 60% of the patients. Increasing urinary incontinence and severe complaints of impotence were observed in patients who had undergone abdominoperineal resection. **Conclusion:** Rectal cancer treatment is associated with a significant decline in QOL during the first 6 months after the diagnosis. Within 2 years, most patients return toward

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pretreatment functioning but could still experience poorer functioning and treatment-related symptoms compared with the general population. These findings support shared decision-making and emphasize the need for post-operative supportive care and novel treatment approaches.

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Introduction

During the past decades, improvements in the diagnosis and treatment of rectal cancer have led to better survival and local disease control.¹⁻³ However, treatment of intermediate- and high-risk rectal cancer, involving neoadjuvant radiotherapy with or without chemotherapy followed by total mesorectal excision (TME), is invasive and associated with significant postoperative short- and long-term morbidity.⁴⁻⁶ As more patients live with the consequences of treatment, resulting from both the increasing rectal cancer incidence and the improving survival rate,⁷ patients' quality of life (QOL) has increasingly become a focus of attention.

Surgery is the cornerstone of rectal cancer treatment and is usually performed by sphincter-preserving low anterior resection (LAR), abdominoperineal resection (APR) with formation of a permanent colostomy, or, less often, proctosigmoidectomy with permanent colostomy (Hartmann resection).^{1,8} The choice of which of these procedures to use mainly depends on the tumor location. In addition, patient performance status, predicted bowel function and continence, and personal preference play important roles in the decision process.⁹ Often a LAR procedure is preferred because of the preserved rectal function and avoidance of a permanent stoma. Nonetheless, LAR has been associated with a substantial risk of acute and chronic anastomotic complications¹⁰ and long-term bowel dysfunction.^{11,12} On the other hand, after APR, perineal wound infection and delayed wound closure are common complications.¹³ In addition, a permanent stoma can cause stoma-related problems¹⁴ and can have a negative effect on psychosocial functioning.¹⁵ It is therefore essential to inform patients of the treatment-related risks and the effect of treatment on QOL to manage patients' expectations and to allow for shared decision-making.⁹

The QOL of rectal cancer patients has been reported previously but often using a cross-sectional study design, without a reference population or without pretreatment measurements.¹⁶⁻¹⁸ In the present longitudinal study, we have described the trends in QOL of patients with rectal cancer to evaluate the effect of neoadjuvant therapy and rectal surgery in the first 2 years after the start of treatment. We compared the QOL scores of patients with those of the Dutch general population and stratified the outcomes by LAR and APR.

Patients and Methods

The Dutch multicenter prospective data collection initiative on colorectal cancer (PLCRC) cohort¹⁹ includes adult patients with histologically proven colorectal cancer and has been approved by the Medical Research Ethics Committee of the University Medical Center Utrecht (the Netherlands). All PLCRC participants

provided informed consent for the collection of their clinical data and optional consent for the collection of biomaterial and patient-reported outcome measures. For the present study, we made use of the PLCRC Utrecht rectal cancer subcohort (PLCRC-URECT), which includes patients with a diagnosis of rectal cancer, who were referred for neoadjuvant radiotherapy to the radiation-oncology department of the University Medical Center Utrecht. All selected patients were enrolled between 2013 and 2016, underwent TME, and responded to the patient-reported outcome measures ≥ 2 times. Patients referred for radiotherapy for recurrent rectal cancer, after radical local excision, or for palliative care and patients who did not undergo TME were excluded.

Neoadjuvant treatment was administered in accordance with the Dutch guidelines for colorectal cancer.²⁰ Patients with intermediate-risk disease (cT1-3N1 or cT3c-dN0 without involvement of the mesorectal fascia or T2-3N0 before incorporation of the most recent guidelines in 2014) received short-course radiotherapy (SCRT). SCRT included 5×5 Gy, followed by TME, usually within 10 days (immediate surgery). Patients with high-risk rectal cancer (cT3 with involvement of the mesorectal fascia, cT4 and/or cN2) underwent chemoradiation (CRT), including 25×2 Gy in 5 weeks with concurrent oral capecitabine (825 mg/m^2 twice daily), followed by TME after 6 to 12 weeks (delayed surgery). Patients unfit for CRT or patients requiring direct resection for oligometastatic disease underwent SCRT with delayed surgery. TME included LAR with or without diverting stoma, APR with permanent colostomy or Hartmann resection with permanent colostomy. LAR with a temporary diverting stoma was performed at the discretion of the surgeon and was usually reversed 3 months after primary surgery. A Hartmann resection was performed as an alternative to LAR in patients with an increased risk of anastomotic leakage and/or with poor preoperative sphincter function.

QOL was assessed using the questionnaires of the European Organization for Research and Treatment of Cancer (EORTC), including the cancer QOL core questionnaire (EORTC QLQ-C30)²¹ and the colorectal cancer questionnaire (EORTC QLQ-CR29).²² The EORTC QLQ-C30 includes 5 functional domains (physical, role, emotional, cognitive, and social functioning), a global health score, and 9 cancer-related symptoms.²¹ The EORTC QLQ-CR29 comprises colorectal cancer-specific domains and symptoms, including sexual function-, stoma-, and bowel function-related items.²² Bowel dysfunction after LAR was assessed using the LAR syndrome (LARS) score in patients without a stoma at the time of assessment. The LARS score is an internationally validated questionnaire to evaluate bowel dysfunction after LAR and contains 5 questions regarding the frequency of incontinence for flatus, incontinence for liquid stool, frequency of bowel movements,

Table 1 Baseline Characteristics of Rectal Cancer Patients Stratified by Questionnaire Responders and Nonresponders

Characteristic	Responders (n = 272)	Nonresponders (n = 52)
Age, y		
Median	65	67
Range	26-87	35-87
Male sex	197 (72.4)	40 (76.9)
Comorbidity (yes)	164 (60.3)	36 (69.2)
Previous abdominal surgery (yes)	90 (33.1)	15 (28.8)
Tumor location		
Low (<6 cm)	130 (47.8)	29 (55.8)
Mid (6-10 cm)	103 (37.8)	18 (34.6)
High (>10 cm)	39 (14.3)	5 (9.6)
Clinical T stage		
cT1	1 (0.4)	0 (0.0)
cT2	32 (11.8)	8 (15.4)
cT3	202 (74.3)	32 (61.5)
cT4	37 (13.6)	12 (23.1)
Mesorectal fascia involvement		
Yes	136 (50.0)	29 (55.8)
No	135 (49.6)	22 (42.3)
Unknown	1 (0.4)	1 (1.9)
Clinical N stage		
cN0	41 (15.1)	4 (7.7)
cN1	116 (42.6)	25 (48.1)
cN2	115 (42.3)	23 (44.2)
Clinical M stage		
cM0	251 (92.3)	42 (80.8)
cM1	17 (6.3)	8 (15.4)
Unknown	4 (1.5)	2 (3.8)
Neoadjuvant therapy		
SCRT, immediate surgery	93 (34.2)	14 (26.9)
SCRT, delayed surgery	20 (7.4)	9 (17.3)
CRT	157 (57.7)	26 (50.0)
Long-course radiotherapy	1 (0.4)	0
None	1 (0.4)	2 (3.8)
Surgical procedure		
Low anterior resection	134 (49.3)	23 (44.2)
Abdominoperineal resection	119 (43.8)	23 (44.2)
Hartmann resection	19 (7.0)	6 (11.5)
Stoma type		
Temporary stoma	98 (36.1)	23 (44.2)
Permanent stoma	138 (50.7)	29 (55.8)
None	36 (13.2)	0
Surgical approach		
Open	47 (17.3)	6 (11.5)
Laparoscopic	224 (82.4)	45 (86.5)
Unknown	1 (0.4)	1 (1.9)

Table 1 Continued

Characteristic	Responders (n = 272)	Nonresponders (n = 52)
Follow-up period, mo		
Median	29	24
Range	5-50	8-48
Mortality during follow-up	22 (8.1)	11 (21.2)

Data presented as n (%) or median and range. Abbreviations: CRT = chemoradiation; SCRT = short-course radiotherapy.

clustering of stools, and urgency.^{23,24} The weighted scores of the individual answers are summed to a total score with a range of 0 to 42 and interpreted as “no LARS” (range, 0-20), “minor LARS” (range, 21-29), or “major LARS” (range, 30-42).

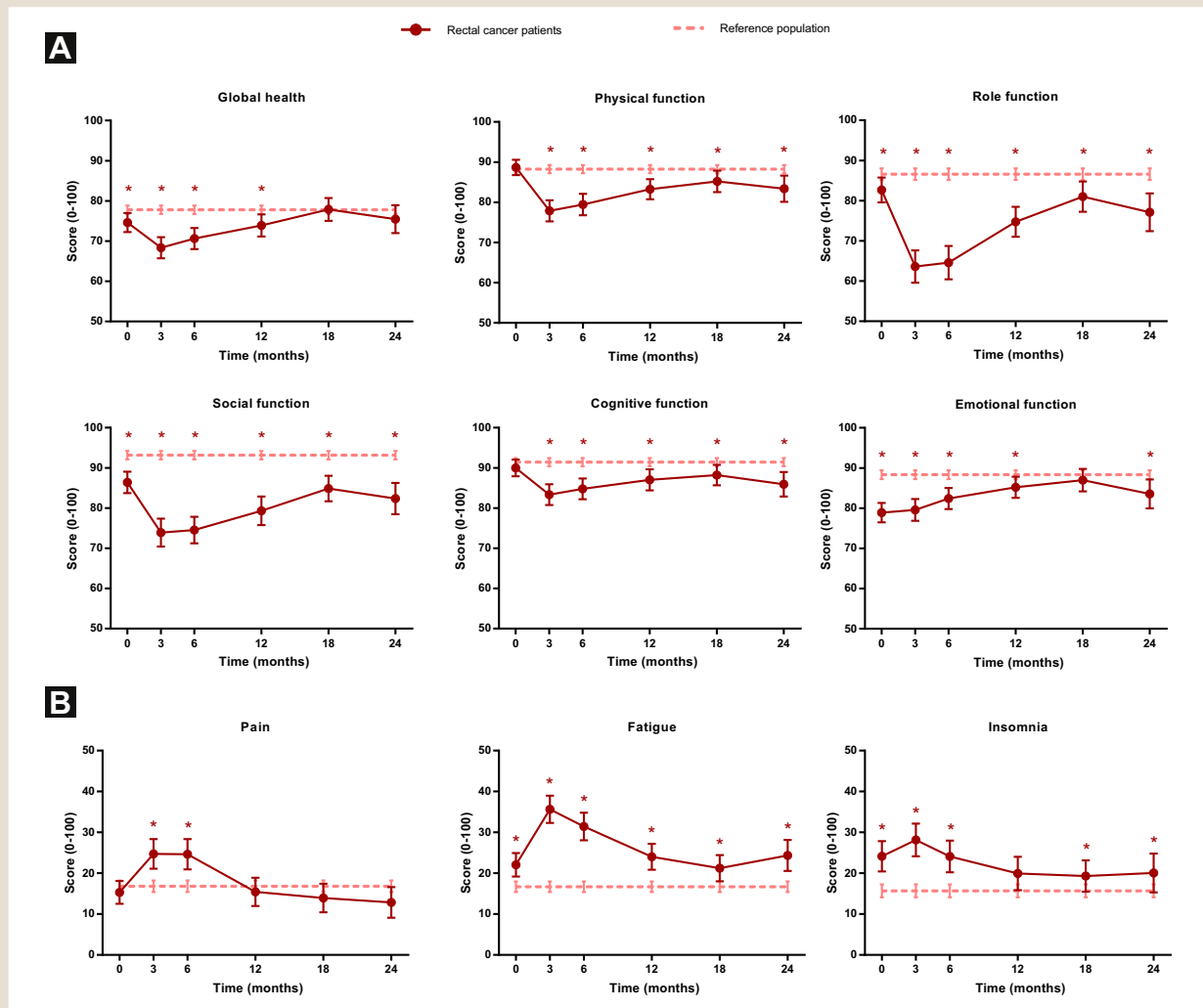
QOL was assessed at fixed points: before neoadjuvant therapy (baseline) and at 3, 6, 12, 18, and 24 months after the start of therapy. Because the LARS score is designed to evaluate bowel function after surgery, the LARS outcomes were rearranged, with the date of surgery as time 0 (baseline) and the follow-up measurements grouped in months after surgery, including 1 to 4, 5 to 10, 11 to 15, and 17 to 22 months. The EORTC QLQ-C30 and QLQ-CR29 questionnaires were administered at the start of the cohort study. The LARS questionnaire was only administered after March 2015. The questionnaires were provided online or on paper and were collected within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship registry.²⁵ The QOL scores of the patients were compared with scores of an age-matched Dutch general population (n = 915; age range, 55-75 years; 57.4% male). The patient and treatment characteristics were collected from patients’ medical files.

Statistical Analysis

The questionnaires were processed according to their manuals.^{22,24,26} Scores of the EORTC QLQ-C30 and QLQ-CR29 ranged from 0 to 100 with higher scores representing better functioning or global health or greater level of symptoms. The functioning domains, global health, and symptoms assessed with the EORTC QLQ-C30 are presented as the mean scores and compared between patients and the general population using Mann-Whitney *U* tests. Functioning domains and global health were stratified by LAR and APR (because the Hartmann group was small, no separate analysis was performed). Changes in QOL within the LAR and APR group were analyzed with linear mixed-effects models to account for the correlation within subjects between the repeated measurements and included a random intercept, time (as factor), and an autoregressive covariance structure of the first order, assuming correlations would be greater between measurements that were closer together in time compared with those further apart.²⁷ QOL changes are presented as the mean differences (MDs) with 95% confidence intervals (CIs), reflecting the difference between the mean score at baseline and the follow-up measurements. As a measure of clinically meaningful change in QOL, the standardized effect size (ES) was calculated (MD

Quality of Life During Rectal Cancer Treatment

Figure 1 European Organization for Research and Treatment of Cancer Quality of Life (QOL) Core Questionnaire (EORTC-QLQ-C30) QOL Domains (A) and Symptoms of Pain, Fatigue, and Insomnia (B) in Rectal Cancer Patients and the Dutch General Population (Reference). Scores Presented as Mean With 95% Confidence Intervals. A Higher Score Indicates Better Functioning, Better Global Health, and a Greater Level of Symptoms.



*Significant Difference Between Patients and the Reference Group, Based on a Mann-Whitney *U* test

divided by the standard deviation of the difference in scores) and classified as “no change” ($ES < 0.2$), “small change” ($ES, 0.2-0.4$), “moderate change” ($ES, 0.5-0.7$), and “considerable change” ($ES \geq 0.8$), according to Cohen.²⁸ Also, we have presented the proportion of patients with clinically relevant worsened QOL domain scores of the EORTC QLQ-C30 relative to their baseline score. This was defined as a decrease of > 10 points (10% of the scale breadth) as suggested Osoba et al.²⁹ To evaluate the effect of baseline characteristics on QOL worsening during and shortly after treatment, we applied logistic regression models to estimate the association between worsening in > 2 QOL domains and age, sex, clinical tumor stage, presence of synchronous metastases, tumor location, type of neoadjuvant therapy, and type of surgery at 3, 6, and 12 months. The outcomes are presented as odds ratios (ORs) and 95% CIs.

The scores of the EORTC QLQ-CR29 (derived from 4-level Likert scale answer options) were categorized as “no” (score 0), “mild” (score 1-49), “moderate” (score 50-99), and “severe” (score 100) complaints for symptoms and “not at all” (score 0), “a little” (score 1-49), “quite a bit” (score 50-99), and “very much” (score 100) for sexual interest. Trends are described using descriptive statistics, stratified by LAR and APR. Sexual interest, stratified by sex, and impotence are presented with the outcomes of the Dutch general population.

The level of statistical significance was $P < .05$. Statistical analyses were performed using SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY).

Results

A total of 324 rectal cancer patients were identified. Of the 324 patients, 272 (84%) completed 2 or more questionnaires and were

Table 2 Baseline Characteristics of Rectal Cancer Patients Stratified Surgical Procedure

Characteristic	LAR (n = 134)	APR (n = 119)
Age, y		
Median	64	66
Range	38-83	26-87
Male sex	93 (69.4)	91 (76.5)
Comorbidity (yes)	71 (53.0)	78 (65.5)
Tumor location		
Low (<6 cm)	23 (17.2)	103 (85.8)
Mid (6-10 cm)	46 (56.7)	15 (12.5)
High (>10 cm)	35 (26.1)	0 (0.0)
Clinical T stage		
cT1	0 (0.0)	1 (0.8)
cT2	16 (11.9)	15 (12.6)
cT3	104 (77.6)	83 (69.7)
cT4	14 (10.4)	20 (16.8)
Clinical N stage		
cN0	16 (11.9)	21 (17.6)
cN1	55 (41.0)	51 (42.9)
cN2	63 (47.0)	47 (39.5)
Clinical M stage		
cM0	121 (90.3)	113 (95.0)
cM1	12 (9.0)	4 (3.4)
Unknown	1 (0.7)	2 (1.7)
Neoadjuvant therapy		
SCRT, immediate surgery	51 (38.1)	32 (26.9)
SCRT, delayed surgery	6 (4.5)	7 (5.9)
CRT	76 (56.7)	79 (66.4)
Other/none	1 (0.7)	1 (0.8)
Surgical approach		
Open	25 (18.7)	15 (12.6)
Laparoscopic	109 (81.3)	103 (86.6)
Unknown	0 (0.0)	1 (0.8)
Follow-up period, mo		
Median	28	29
Range	5-49	5-50
Mortality during follow-up	11 (8.2)	10 (8.4)

Data presented as n (%) or median and range.

Abbreviations: APR = abdominoperineal resection; CRT = chemoradiation; LAR = low anterior resection; SCRT = short-course radiotherapy.

included in the present study. The response rates at baseline and 3, 6, 12, 18, and 24 months were 91% (247 of 272), 86% (235 of 272), 83% (225 of 272), 82% (190 of 231), 74% (152 of 206), and 75% (123 of 165), respectively.

The questionnaire responders had a median age of 65 years, 197 (72%) were men, 138 (60%) had ≥ 1 comorbid condition, and 90 (33%) had undergone previous abdominal surgery (Table 1). In most patients, a low or mid-rectal tumor (48% and 38%, respectively) had been diagnosed. Also, most patients had clinical T3 stage (74%) and clinical N+ stage (85%) and did not have synchronous distant metastases (92%). Of the 272 patients, 157 (58%) received neoadjuvant CRT, 93 (34%) received SCRT with immediate

surgery, and 20 (7%) underwent SCRT with delayed surgery. LAR was performed in 134 patients (49%), APR in 119 patients (44%), and a Hartmann procedure in 19 patients (7%). Ninety-eight patients (36%) received a temporary deviating stoma, corresponding to 73% of the LAR patients. Most patients (82%) underwent surgery with a laparoscopic approach. The characteristics of the patients who did not complete 2 or more questionnaires (n = 52; 19%) were comparable to the responders in terms of age, sex, comorbidity, tumor location, clinical N stage, surgical treatment, and surgical approach. However, the nonresponders more often had a diagnosis with a clinical T4 stage (23% vs. 14%, respectively), synchronous distant metastases (15% vs. 6%), a greater mortality rate (21% vs. 8%, respectively) and more often underwent SCRT with delayed surgery (17% vs. 7%, respectively; Table 1).

QOL of Rectal Cancer Patients Versus the General Population

Before the start of treatment, the patients reported physical and cognitive functioning comparable to that of the general (reference) population (Figure 1A; Supplemental Table 1; available in the online version). In contrast, global health, social, role, and emotional functioning were significantly lower. After 3 and 6 months, all scores were significantly lower compared with those from the general population. Emotional functioning showed an increasing trend toward the reference level; however, it was still significantly lower at 24 months (83 vs. 88 in the general population). Global health was similar to the reference level at 18 months (78 vs. 78, respectively). Up to 24 months, physical, role, social, and cognitive functioning remained lower compared with the general population (83 vs. 88, 77 vs. 87, 82 vs. 93, and 86 vs. 91, respectively).

Fatigue, pain, and insomnia were the most prevalent reported symptom items of the EORTC-QLQ-C30 (Figure 1B; Supplemental Table 1; available in the online version). At baseline, pain was comparable to that of the general population, and fatigue and insomnia were more common in the patients. All symptoms had increased at 3 and/or 6 months and decreased thereafter. Pain was comparable to the reference level after 12 months, but fatigue and insomnia remained significantly more prevalent in patients than in the general population.

Change in QOL Stratified by Surgical Procedure

Patients in the LAR group (n = 134) had a median age of 64 years (range, 38-83 years), and 69% was male (Table 2). At 3 and 6 months, physical, role, and social functioning had significantly decreased, with moderate ESs relative to baseline (Table 3). At 6 months, 57% of the patients reported worsened role functioning, 53% worsened social functioning, and 34% worsened physical functioning compared with the baseline score. Cognitive functioning and global health had significantly decreased, with small ESs at 3 and 6 months. At 12 months, role functioning and global health were comparable with the pretreatment scores and emotional functioning had significantly improved, with small ESs. At 12, 18, and 24 months, physical, social, and cognitive functioning remained significantly lower compared with the baseline score, but with small ESs. At 24 months, 26%, 28%, and 20% of the patients reported worsened physical, social, and cognitive functioning compared with baseline, respectively.

Table 3 Within-group Changes Between Baseline and Follow-up Assessments in Quality of Life Domains of the EORTC QLQ-C30 Using Linear Mixed Models Stratified by Surgical Procedure, Presented With the Standardized Effect Size of the Mean Difference, and Proportion of Patients With Worse Score (>10 Points) Compared With Baseline

Domain	Patients, n	Baseline	3 mo				6 mo				12 mo				18 mo				24 mo			
			MD ^a	95% CI	ES ^b	Worse QOL, ^c n (%)	MD ^a	95% CI	ES ^b	Worse QOL, ^c n (%)	MD ^a	95% CI	ES ^b	Worse QOL, ^c n (%)	MD ^a	95% CI	ES ^b	Worse QOL, ^c n (%)	MD ^a	95% CI	ES ^b	Worse QOL, ^c n (%)
LAR																						
Global health	120	75.6 ± 18.6	-6.5 ^d	-10.0 to -3.0	-0.3	38/106 (35.8)	-5.8 ^d	-9.7 to -2.0	-0.3	31/99 (31.3)	0.4	-3.7 to 4.5	0.0	17/82 (20.7)	0.9	-3.4 to 5.3	0.0	19/72 (26.4)	-0.1	-5.0 to 4.8	-0.0	13/50 (26.0)
Physical function	122	90.6 ± 14.4	-10.9 ^d	-13.6 to -8.1	-0.7	47/108 (43.5)	-9.0 ^d	-12.0 to -6.0	-0.5	35/102 (34.3)	-3.9 ^d	-7.1 to -0.6	-0.2	19/83 (22.9)	-4.0 ^d	-7.4 to -0.4	-0.2	18/73 (24.7)	-5.6 ^d	-9.5 to -1.7	-0.3	13/50 (26.0)
Role function	122	84.3 ± 24.0	-18.2 ^d	-23.5 to -12.9	-0.6	63/108 (58.3)	-20.0 ^d	-26.0 to -14.1	-0.6	58/102 (56.9)	-5.3	-11.7 to 1.1	-0.2	29/83 (34.9)	-4.3	-11.2 to 2.6	-0.1	20/73 (27.4)	-5.0	-12.7 to 2.6	-0.1	15/50 (20.0)
Social function	120	87.5 ± 19.9	-12.7 ^d	-17.1 to -8.3	-0.5	49/106 (46.2)	-16.5 ^d	-21.4 to -11.6	-0.6	52/99 (52.5)	-7.8 ^d	-13.0 to -2.5	-0.3	33/82 (40.2)	-4.5	-10.1 to 1.1	-0.1	22/72 (30.6)	-6.6 ^d	-12.8 to -0.3	-0.2	14/50 (28.0)
Cognitive function	120	89.7 ± 17.2	-6.7 ^d	-10.0 to -3.4	-0.4	42/106 (39.6)	-6.8 ^d	-10.1 to -3.5	-0.4	41/99 (41.4)	-4.3 ^d	-7.9 to -0.8	-0.2	25/82 (30.5)	-4.6 ^d	-8.3 to -0.8	-0.2	24/72 (33.3)	-6.1 ^d	-10.2 to -1.9	-0.3	15/50 (20.0)
Emotional function	120	78.1 ± 20.3	2.4	-0.6 to 5.5	0.1	19/106 (17.9)	1.2	-2.3 to 4.8	0.1	19/99 (19.2)	6.1 ^d	2.2 to 10.0	0.3	13/82 (15.9)	6.8 ^d	2.6 to 11.0	0.3	8/72 (11.1)	4.7	0.0 to 9.4	0.2	9/50 (18.0)
APR																						
Global health	107	72.9 ± 20.0	-7.3 ^d	-11.3 to -3.3	-0.3	38/90 (42.2)	-3.7	-7.9 to 0.4	-0.2	32/88 (36.4)	-1.6	-6.0 to 2.8	-0.1	21/75 (28.0)	3.7	-1.2 to 8.6	0.2	12/65 (18.5)	1.9	-3.2 to 7.0	0.1	13/51 (25.5)
Physical function	107	87.2 ± 19.5	-13.4 ^d	-17.3 to -9.5	-0.7	45/91 (49.5)	-12.0 ^d	-15.8 to -8.1	-0.6	44/88 (50.0)	-7.9 ^d	-11.9 to -3.8	-0.4	31/75 (41.3)	-4.3	-8.7 to 0.2	-0.2	22/65 (33.8)	-5.6 ^d	-10.3 to -1.0	-0.2	21/51 (41.2)
Role function	107	80.0 ± 28.2	-21.5 ^d	-28.2 to -14.9	-0.6	51/91 (56.0)	-18.8 ^d	-25.6 to -11.9	-0.5	53/88 (60.2)	-8.5 ^d	-15.7 to -1.3	-0.2	35/75 (46.7)	0.2	-7.7 to 8.1	0.0	23/65 (35.4)	-5.1	-13.4 to 3.2	-0.1	19/51 (37.3)
Social function	107	84.1 ± 23.3	-13.1 ^d	-18.3 to -3.0	-0.5	46/90 (51.1)	-8.5 ^d	-13.9 to -3.0	-0.3	42/88 (47.7)	-5.4	-11.1 to 0.3	-0.2	29/75(38.7)	-1.0	-7.3 to 5.3	-0.0	24/65 (36.9)	-3.8	-10.4 to 2.8	-0.1	19/51 (37.3)
Cognitive function	107	89.7 ± 17.1	-7.3 ^d	-10.9 to -3.7	-0.4	37/90 (41.1)	-4.8 ^d	-8.4 to -1.1	-0.3	31/88 (35.2)	-1.4	-5.2 to 2.5	-0.1	17/75 (22.7)	1.8	-2.5 to 6.0	0.1	12/65 (18.5)	-0.7	-5.1 to 3.8	-0.0	15/51 (29.4)
Emotional function	107	79.0 ± 18.5	-1.1	-4.5 to 2.4	0.1	21/90 (23.3)	3.3	-0.6 to 7.2	0.2	12/88 (13.6)	6.3 ^d	2.1 to 10.6	0.3	10/75 (13.3)	9.1 ^d	4.4 to 13.7	0.4	7/65 (10.8)	7.3 ^d	2.4 to 12.3	0.3	4/51 (7.8)

Abbreviations: APR = abdominoperineal resection; CI = confidence interval; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; ES = effect size; LAR = low anterior resection; MD = mean difference; QOL = quality of life.

^aMD between baseline score and indicated follow-up score using linear mixed effect models.

^bStandardized ES as a measure for minimal important difference for change in QOL, classified as no change (ES < 0.2), small change (ES, 0.2-0.4), moderate change (ES, 0.5-0.7), and considerable change (ES ≥ 0.8).

^cProportion of patients with worse QOL score of > 10 points since baseline for patients who responded to both baseline and follow-up questionnaire.

^dStatistically significant difference between mean baseline score and indicated mean follow-up score using linear mixed effect models ($P < .05$).

Table 4 Univariable Logistic Regression of Association Between Baseline Characteristics and Rectal Cancer Patients Reporting Worse Score (>10 Points) Compared With Baseline for > 2 QOL Domains of the EORTC QLQ-C30

Characteristic	QOL Worsening		
	3 mo (n = 87/215) ^a	6 mo (n = 74/205) ^a	12 mo (n = 49/169) ^a
Age	1.02 (0.99-1.05); .182	1.00 (0.98-1.03); .842	1.01 (0.98-1.05); .554
Sex			
Female	Ref	Ref	Ref
Male	0.92 (0.50-1.67); .780	1.42 (0.74-2.71); .291	0.87 (0.41-1.83); .715
Clinical tumor stage			
cT1-3	Ref	Ref	Ref
cT4	1.30 (0.57-2.97); .529	2.52 (1.11-5.73); .027	1.85 (0.74-4.67); .191
Clinical M stage			
cM0	Ref	Ref	Ref
cM1	1.02 (0.31-3.32); .975	1.84 (0.57-5.92); .309	1.90 (0.62-5.80); .259
Tumor location			
Low (≤5 cm)	Ref	Ref	Ref
Mid/high (>5 cm)	1.04 (0.60-1.79); .897	0.80 (0.45-1.41); .430	1.21 (0.62-2.36); .583
Neoadjuvant therapy			
SCRT, immediate TME	Ref	Ref	Ref
SCRT, delayed TME	2.16 (0.77-6.03); .141	5.01 (1.69-14.84); .004	3.00 (0.85-10.63); .089
CRT	0.99 (0.55-1.80); .980	2.48 (1.24-4.96); .010	2.50 (1.06-5.91); .037
Surgical procedure			
LAR	Ref	Ref	Ref
Hartmann resection	1.45 (0.49-4.30); .501	0.76 (0.23-2.57); .659	2.21 (0.63-7.76); .214
APR	1.24 (0.71-2.20); .451	1.52 (0.84-2.74); .168	1.46 (0.73-2.94); .290

Data presented as ORs (95% CIs) for probability of worse QOL; *P* value.

Abbreviations: APR = abdominoperineal resection; CI = confidence interval; CRT = chemoradiotherapy; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; LAR = low anterior resection; OR = odds ratio; Ref = reference group; SCRT = short-course radiotherapy; TME = total mesorectal excision.

^aNumber of patients with worse score in > 2 QOL domains of EORTC QLQ-C30/total number of eligible patients.

Patients undergoing APR (n = 119) had a median age of 66 years (range, 26-87 years), and 77% were male (Table 2). At 3 months, the largest decline was observed in physical, role, and social functioning, including significant changes with moderate ESs (Table 3). Global health and cognitive functioning had significantly declined with small ESs. Also at 6 months, physical and role functioning were significantly lower compared with baseline, with moderate ESs and worsening in 50% and 60% of the patients, respectively. Social and cognitive functioning were significantly lower than baseline, with small ESs, and global health was nonsignificantly changed. At 12 months, emotional functioning had significantly improved. Physical and role functioning were still significantly lower, but with small ESs. At 18 months, all scores were comparable with the pretreatment scores, except for significantly improved emotional functioning. At 24 months, physical functioning was again significantly lower than the baseline score, but with a small ES, and 41% of the patients reported worsened functioning compared with baseline. Social and role functioning at 24 months were worse than at baseline for 37% of the patients.

Effect of Baseline Characteristics on Worsening in QOL

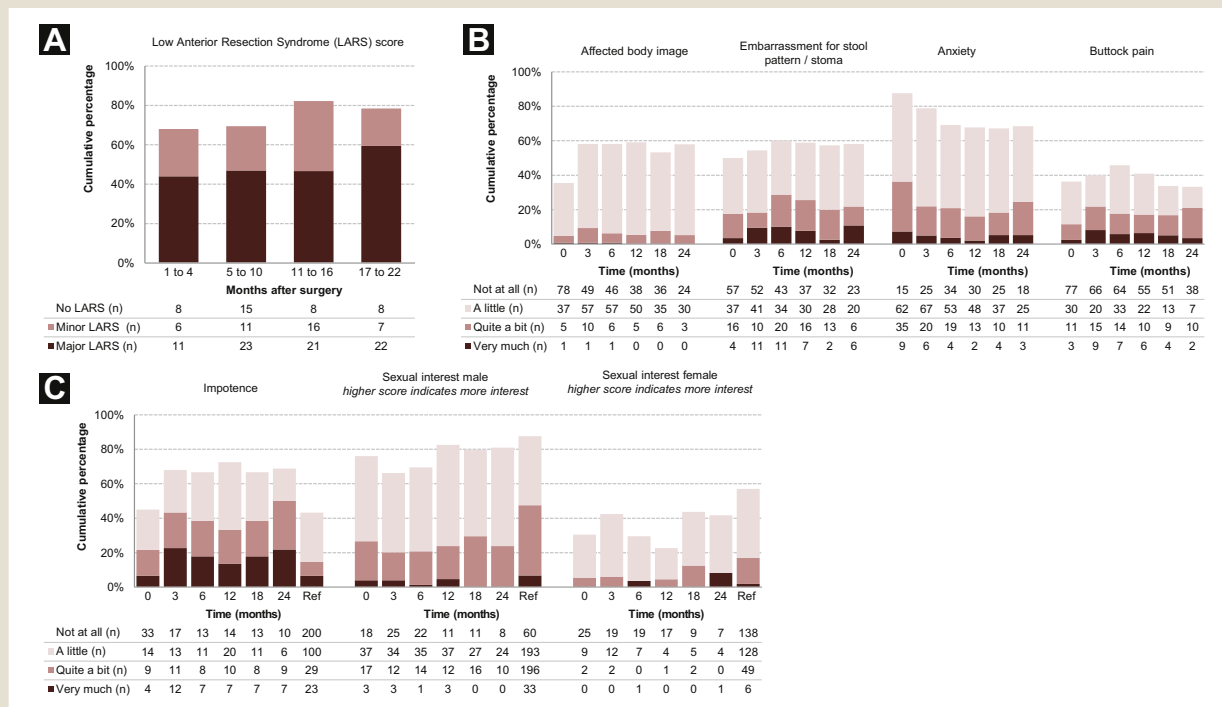
Univariable analyses of the association between the baseline characteristics and worsening in > 2 QOL domains in the first year after diagnosis showed that patients treated with CRT or SCRT and

delayed surgery had a significantly greater probability of worsening at 6 months after baseline compared with those who underwent SCRT with immediate surgery and patients with clinical T4 stage compared with clinical T1-T3 stage (Table 4). CRT was also significantly associated with worsening in > 2 QOL domains at 12 months after baseline. On multivariable analysis that included clinical T stage and neoadjuvant therapy regimen (data not shown), CRT and SCRT with delayed surgery remained significantly associated with worsening > 2 QOL domains at 6 months compared with SCRT with immediate surgery (OR, 2.2; 95% CI, 1.08-4.5; and OR, 4.3; 95% CI, 1.4-13.1, respectively). In contrast, the effect of clinical T4 stage was not significant anymore (OR, 1.8; 95% CI, 0.78-4.30). Age, sex, the presence of synchronous metastases at diagnosis, tumor location, and type of surgery were not significantly associated with worsening of QOL in > 2 domains at 3, 6, and 12 months.

Symptoms Stratified by Surgical Procedure

In the LAR group, major LARS was reported in 44% of the patients at 1 to 4 months after surgery, 47% at 5 to 10 months, 47% at 11 to 15 months, and 60% at 17 to 22 months (Figure 2A). Minor LARS was present in 19% to 36% of the patients during the follow-up period. Prevalent reported symptoms using the EORTC QLQ-CR29 in the LAR group included affected body image, embarrassment for stool pattern, anxiety, and buttock pain (any

Figure 2 Outcomes of the Low Anterior Resection Syndrome (LARS) Score (A), and Prevalent Symptom Items (B) and Sexual Interest (C) of the EORTC QLQ-CR29 in Rectal Cancer Patients Undergoing Low Anterior Resection.



Ref = Outcomes of the Dutch General Population as Reference Group.

level of severity at 24 months in 58%, 58%, 68%, and 33% of the patients, respectively; Figure 2B; Supplemental Table 2; available in the online version). Impotence was often reported during and after treatment (at 12 months, 73%) and was more common than in the general population (Figure 2C). Sexual interest in male and female patients showed an approximately stable trend but was lower than that of the reference population.

In the APR group, bowel/stoma-related symptoms (ie, flatulence, fecal incontinence, embarrassment for stool pattern/stoma, and problems with stoma care), anxiety, and buttock pain were commonly reported at diagnosis and during treatment, but showed a decreasing trend thereafter (Figure 3A; Supplemental Table 2; available in the online version). At 24 months, complaints of affected body image and embarrassment for stoma were reported by 67% and 49% of the patients, respectively, and one third of the patients complained of buttock pain. Urinary incontinence had increased gradually from 7% at baseline to 49% of the patients at 24 months. Impotence strongly increased after baseline and was greater than that in the male reference population (at 24 months, 81% vs. 15%, respectively; Figure 3B). Sexual interest in male and female patients deteriorated during treatment and was lower than that of the reference population for ≤ 24 months.

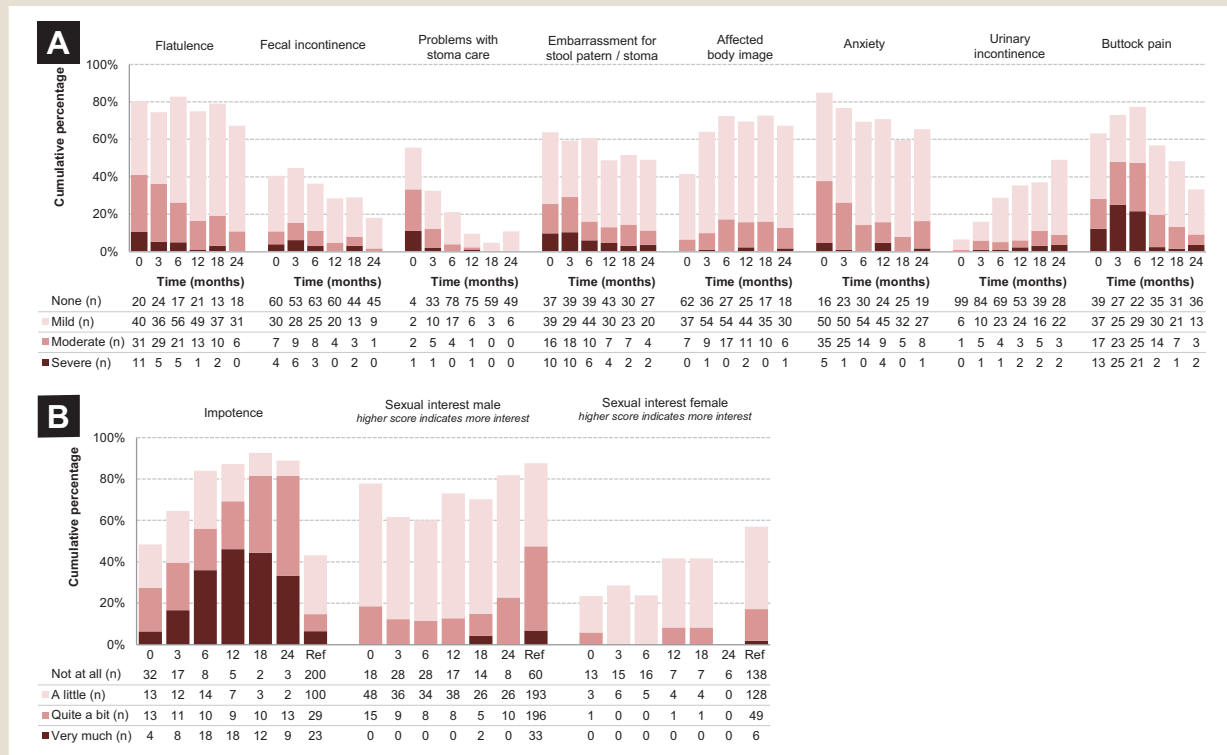
Discussion

In the present study, we evaluated the trends in QOL during the first 2 years after the start of rectal cancer treatment in relation to the general population and described treatment-related morbidity

stratified by sphincter-sparing LAR and APR with a permanent stoma. Also, we estimated the association of several baseline characteristics on worsening of QOL during and shortly after treatment. Of all QOL domains, physical, role, and social functioning declined the strongest during and shortly after treatment. Global health and cognitive functioning declined to a lesser extent, and emotional function gradually improved over time. The type of neoadjuvant regimen was associated with QOL worsening, and CRT and SCRT with delayed surgery had a greater impact on the QOL decline compared with SCRT with immediate surgery. Within 2 years, however, QOL scores of most patients had normalized toward the pretreatment levels. Nevertheless, compared with the Dutch general population, patients experienced lower physical, role, social, and cognitive functioning and more insomnia and fatigue during the first 2 years after the start of treatment.

Lower functioning scores and greater levels of symptoms in the patients compared with the general population have been reported previously and were well-described in a systematic review of QOL in rectal cancer patients compared with general populations.¹⁶ To the best of our knowledge, our study is the first to compare longer term longitudinal QOL scores between rectal cancer patients and a reference population. A Swedish study compared longitudinal QOL with a 6-month follow-up period between rectal cancer patients receiving a stoma and population norms using the 36-item Short Form Health Survey and also observed significant differences in the physical and emotional role function, social function, and mental health domains and reported fatigue, pain, illness-induced

Figure 3 Prevalent Symptom Items (A) and Sexual Interest (B) of the EORTC QLQ-CR29 in Rectal Cancer Patients Undergoing Abdominoperineal Resection.



Ref = Outcomes of the Dutch General Population as Reference Group.

limitations in life activities, and worries about the future as the main obstacles to maintaining QOL.³⁰ In contrast to many studies, we observed significantly lower global health for the patients compared with the reference population up to 12 months after the start of treatment. Most studies found no differences¹⁶ or only found differences in specific subcohorts of rectal cancer patients.^{16,31,32} In some studies, global health status was even better than that in the reference population.³³⁻³⁵ It is well-known that a change in global health status is often less pronounced compared with the changes in specific functioning scales and symptom items.³⁶⁻³⁸ It should, therefore, not be seen as a sum score for QOL but might, rather, reflect patients' adaptation to their disease and a change in priorities and expectations: the phenomenon of the "response shift."³⁹

We presented standardized effect sizes as measure for clinically meaningful changes in QOL using the interpretation proposed by Cohen²⁸ and observed that physical, role, and social functioning changed with moderate ESs. In contrast, global health, cognitive functioning, and emotional functioning changed with small ESs during treatment. Nevertheless, the clinical implications of ESs in QOL are unclear and cutoffs to define a change clinically meaningful remain arbitrary.⁴⁰ Therefore, they should not be interpreted rigidly.⁴¹ However, ESs are useful to quantify the effect of a treatment or intervention within subjects over time and to compare outcomes across studies. To interpret changes in QOL at the patient level, we also reported the proportion of patients in whom QOL worsened relative to their baseline score.

Unlike many studies,¹⁷ we have not compared the QOL between LAR and APR because of the selection criteria used for patients receiving sphincter-sparing surgery or a permanent stoma. A general comparison of these groups would, therefore, not be informative for most patients and includes a considerable risk of selection bias. In both groups, however, we observed comparable trends in QOL scores during treatment. In contrast, differences between APR and LAR were found in the postoperative symptoms related to preserved bowel function or placement of a permanent stoma.

We observed major LARS in a range of 44% to 60% of the patients who underwent LAR from 1 to 22 months after surgery. In a Danish study of 938 patients, major LARS was reported by 41% after a median interval of 54 months.⁴² In the Dutch TME trial, 46% of the patients reported major LARS after a median interval of 14.6 years, with a greater proportion observed in the neoadjuvant radiotherapy group than in the nonirradiated group (56% vs. 35%, respectively).⁴³ Neoadjuvant radiotherapy with or without chemotherapy is one of the largest risk factors for the development of major LARS.^{44,45} In our study, all patients had received neoadjuvant therapy, which might explain why we observed a relatively high proportion of patients reporting major LARS. This emphasizes the need for effective treatment of LARS. Sacral nerve stimulation, pelvic floor rehabilitation, transanal irrigation, and percutaneous tibial nerve stimulation have been described as potential LARS treatments; however, randomized trials comparing the effects of these interventions are lacking.⁴⁶ Martellucci⁴⁷ proposed a LARS

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treatment algorithm that included pelvic floor muscle training for all patients at discharge and clinical evaluation using validated scores, such as the LARS score, to identify patients who might require more advanced treatments. Furthermore, more precise radiation of the tumor, margin reduction, or dose restriction to the organs at risk, such as the anal sphincter, could be potential factors to reduce the risk of LARS in patients undergoing neoadjuvant therapy.

Low sexual interest and increasing genitourinary symptoms are frequently reported in rectal cancer patients.^{48,49} Genitourinary symptoms are likely to be mainly related to autonomic pelvic nerve injury or, indirectly, by vascular damage⁴⁹ and might be more pronounced after APR owing to the deeper resection plane in the pelvis. Techniques for autonomic nerve preservation could potentially reduce the risk of genitourinary symptoms,⁴⁹ such as intraoperative neurostimulation⁵⁰ or robot-assisted rectal cancer surgery.⁵¹ The high frequency of sexual problems highlights the need for discussing and documenting sexual dysfunction as a surgical risk.⁴⁸ Studies have shown, however, that many rectal cancer patients do not believe they are sufficiently informed before surgery regarding the potential postoperative sexual problems.^{48,52}

Organ-sparing treatments, such as wait-and-see and local excision, are the most promising approaches to reduce and/or prevent treatment-related morbidity in rectal cancer patients with a good or complete response to neoadjuvant therapy.^{53,54} Better physical and cognitive function, better physical and emotional roles, better global health, and fewer symptoms have been observed in patients with a wait-and-see approach compared with patients who underwent neoadjuvant CRT and surgery.⁵⁵ Nevertheless, organ preservation is at present only feasible in highly selected patients constituting a small fraction of the total number of rectal cancer patients.

The present study had several limitations. We only selected patients referred for neoadjuvant therapy, and our results are therefore not applicable to all rectal cancer patients. Furthermore, the questionnaire nonresponders included a more vulnerable group of patients with larger tumors, more often having synchronous metastases, and experiencing a greater mortality rate. The nonparticipation of these patients and the slightly increasing number of nonresponses during follow-up could have led to biased QOL scores. In addition, because we used a prospective cohort, the number of eligible patients decreased over the time, resulting in smaller sample sizes for time points further from baseline, especially in the strata concerning sexual interest. Moreover, we lacked a sufficient sample size to generate results for patients undergoing a Hartmann resection.

Conclusion

Rectal cancer patients undergoing neoadjuvant (chemo) radiotherapy and rectal surgery are challenged by a decline in QOL and the development of disease- and treatment-related symptoms, of which some are related to the surgical procedure. QOL functioning scores recovered toward pretreatment levels within 2 years but remained lower than the scores of the general population. These results can be used for preoperative patient counseling to manage expectations and allow for shared decision-making. They also emphasize the need for postoperative care and the development of novel interventions and treatment strategies, such as organ-sparing approaches, to reduce treatment-related morbidity.

Clinical Practice Points

- Rectal cancer patients treated with neoadjuvant therapy and surgery have a substantial risk of developing treatment-related morbidity.
- Previous studies have described deterioration in QOL scores after rectal cancer treatment but often lacked a longitudinal design or comparison with a general population.
- The present study showed that the strongest decline is observed in physical, role, and social functioning at 3 to 6 months after the start of treatment.
- Global health and cognitive functioning declined to a lesser extent, and emotional function gradually improved over time.
- Neoadjuvant CRT had a greater effect on the QOL decline during and shortly after treatment compared with neoadjuvant SCRT with immediate surgery.
- Within 2 years, all QOL domains had normalized toward pre-treatment levels in most patients; however, compared with the Dutch general population, patients reported lower physical, role, social, and cognitive functioning and more insomnia and fatigue up to 2 years after the start of treatment.
- Common symptoms after sphincter-sparing LAR included bowel dysfunction, embarrassment for stool pattern, anxiety, buttock pain, impotence, and low sexual interest.
- The common symptoms after APR with a permanent stoma included affected body image, embarrassment for stoma, anxiety, buttock pain, urinary incontinence, severe impotence, and low sexual interest.
- These findings can be used to manage patients' expectations, allow for shared decision-making, and address the need for postoperative supportive care for patients with disease-related symptoms and the development of novel treatment approaches to reduce postoperative morbidity.

Acknowledgments

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Disclosure

The authors declare that they have no competing interests.

Supplemental Data

The supplemental data accompanying this article can be found in the online version at <https://doi.org/10.1016/j.clcc.2018.03.009>.

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Supplemental Table 1 EORTC QLQ-C30 Scores of QOL Domains and Symptom Items Stratified by Measurement Point and Dutch Reference Population Outcomes

EORTC QLQ-C30	Baseline (n = 272)			3 mo (n = 272)			6 mo (n = 272)			12 mo (n = 231)			18 mo (n = 206)			24 mo (n = 165)			Reference Population			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Scale																						
Physical function	247	88.7	15.5	234	77.9 ^a	20.5	224	79.4 ^a	20.3	190	83.3 ^a	17.7	152	85.2 ^a	16.8	123	83.4 ^a	18.4	917	88.2	15.7	
Role function	247	82.7 ^a	24.5	234	63.6 ^a	31.3	224	64.6 ^a	31.4	190	74.7 ^a	26.2	152	81.0 ^a	23.6	123	77.1 ^a	26.5	916	86.6	22.2	
Emotional function	245	78.9 ^a	19.2	233	79.5 ^a	21.2	222	82.4 ^a	19.8	190	85.2 ^a	18.4	151	87.0	17.5	123	83.6	20.2	915	88.3	16.8	
Cognitive function	245	90.0	16.6	233	83.3 ^a	20.0	222	84.8 ^a	19.5	190	87.0 ^a	18.3	151	88.2 ^a	15.9	123	85.9 ^a	17.2	915	91.4	15.5	
Social function	245	86.4 ^a	21.2	233	73.9 ^a	26.9	222	74.5 ^a	25.0	190	79.3 ^a	25.1	151	84.9	19.8	123	82.4 ^a	21.9	915	91.2	16.3	
Global health	245	74.6 ^a	19.1	233	68.3 ^a	20.2	222	70.6 ^a	19.7	190	73.9 ^a	19.2	151	77.9	17.7	123	75.5	19.6	915	77.8	16.7	
Symptoms																						
Fatigue	247	22.1 ^a	23.0	234	35.6 ^a	25.9	224	31.4 ^a	25.4	190	24.0 ^a	22.1	152	21.2 ^a	20.0	123	24.3 ^a	21.2	916	16.7	20.3	
Pain	247	15.3	22.2	234	24.7 ^a	28.1	224	24.6 ^a	28.1	190	15.4	24.3	152	13.9	21.7	123	12.9	21.0	916	16.8	21.9	
Nausea, vomiting	247	3.8 ^a	9.9	234	4.1	13.0	224	4.0 ^a	11.4	190	3.3	9.3	152	3.4	12.4	123	4.7 ^a	11.6	916	2.7	9.9	
Dyspnea	247	5.9	14.7	232	8.0	16.1	224	9.5	19.1	190	11.1	20.0	152	11.4 ^a	18.4	123	12.7 ^a	21.1	916	8.6	18.5	
Insomnia	247	24.2 ^a	29.5	232	28.2 ^a	31.2	224	24.1 ^a	29.1	189	19.9	28.5	152	19.3 ^a	23.9	123	20.1 ^a	26.6	916	15.7	24.6	
Appetite loss	246	8.3 ^a	18.8	234	14.0 ^a	27.0	224	12.2 ^a	22.9	189	6.7 ^a	18.9	152	4.4	15.2	123	7.6 ^a	19.9	916	2.9	11.1	
Diarrhea	242	21.3 ^a	25.4	231	16.5 ^a	27.3	222	9.0 ^a	20.2	189	9.5 ^a	19.8	151	9.5 ^a	18.6	123	10.8 ^a	19.3	915	4.3	13.0	
Obstipation	245	13.3 ^a	23.6	231	10.7 ^a	23.1	219	7.6 ^a	16.9	190	6.5	16.4	150	6.9	16.5	122	6.6	14.6	915	5.4	15.4	
Financial problems	244	6.1 ^a	16.4	233	9.4 ^a	21.1	222	10.1 ^a	20.8	190	9.1 ^a	19.4	151	7.7 ^a	17.4	123	9.5 ^a	21.1	915	3.4	12.5	

Abbreviations: EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire (higher scores indicate better functioning and greater level of symptoms); N = number of responses; n = number of eligible patients; SD = standard deviation.

^aSignificant difference compared with reference population ($P < .05$; Mann-Whitney U test).

Supplemental Table 2 EORTC QLQ-CR29 Scores Stratified by Measurement Point for Low Anterior Resection Patients

EORTC QLQ-CR29	Baseline (n = 134)			3 mo (n = 134)			6 mo (n = 134)			12 mo (n = 112)			18 mo (n = 100)			24 mo (n = 79)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Scale																		
Blood/mucus in stool	120	66.9	24.1	117	88.9	15.6	109	92.5	12.9	93	94.3	11.4	77	94.4	11.7	57	95.0	9.9
Urinary frequency	121	68.3	25.1	117	66.1	23.3	109	72.3	24.1	92	71.9	23.9	76	72.4	22.5	57	67.0	25.1
Stool frequency	114	69.6	23.2	116	73.3	27.2	106	70.4	27.6	88	63.6	21.4	75	68.4	21.8	54	66.0	27.5
Body image	121	91.1	17.1	117	81.9	21.1	110	82.3	20.8	93	84.3	18.1	77	84.5	19.5	57	83.4	19.1
Sexual interest, male	75	35.6	26.5	74	30.2	27.1	72	30.6	24.9	63	37.0	24.8	54	36.4	23.6	42	34.9	22.0
Sexual interest, female	36	12.0	19.8	34	16.7	20.5	27	12.3	22.9	22	9.1	18.3	17	17.6	23.9	12	19.4	30.0
Symptoms																		
Urinary incontinence	121	4.4	13.6	116	8.3	16.4	109	9.2	19.2	92	7.2	15.5	76	7.9	17.9	56	7.1	16.5
Dysuria	121	3.0	11.4	116	8.3	20.1	109	6.4	16.0	92	6.1	17.1	76	7.0	17.5	56	4.2	11.1
Abdominal pain	120	18.9	22.3	117	17.1	26.1	110	16.1	25.0	92	10.5	19.7	77	10.4	19.7	57	12.9	24.2
Buttock pain	121	16.8	25.5	118	23.2	30.0	110	23.3	33.0	93	21.5	30.6	77	18.6	29.9	57	19.3	30.2
Bloating	121	18.7	23.9	118	18.1	25.7	110	15.5	23.8	92	15.6	21.8	77	14.3	19.1	57	17.0	21.9
Dry mouth	121	14.6	23.1	118	16.4	23.0	110	15.2	23.3	93	16.1	23.9	77	15.2	19.2	57	15.8	20.0
Hair loss	121	0	0	118	3.1	9.7	110	4.8	14.9	93	6.8	8.1	77	6.5	20.3	57	4.7	14.7
Taste change	121	4.4	12.9	118	12.7	25.0	110	10.6	22.5	93	7.5	19.7	77	8.2	18.9	57	8.8	22.3
Anxiety	121	43.8	26.2	118	35.3	25.5	110	31.2	26.4	93	28.7	24.4	76	30.3	27.3	57	32.7	28.5
Weight loss	121	11.8	20.1	118	15.5	22.1	110	17.3	22.9	93	16.1	23.4	77	16.5	23.3	57	20.5	27.3
Flatulence	115	33.9	28.3	115	35.4	30.7	107	28.7	28.4	89	36.3	25.9	74	41.4	28.6	55	42.4	29.7
Fecal incontinence	114	16.1	26.7	114	16.1	26.3	108	22.2	26.2	90	22.6	23.9	75	18.7	23.9	55	20.6	24.4
Sore skin/anus	115	14.2	24.6	115	19.4	27.2	108	32.6	34.0	90	24.8	29.8	75	21.3	29.8	55	20.6	29.7
Embarrassment	114	23.7	27.9	114	27.5	31.7	108	32.9	33.2	90	30.7	31.7	75	26.7	27.4	55	30.3	32.9
Stoma care	11	27.3	36.0	42	12.7	23.2	53	11.9	21.8	12	8.3	15.1	10	0	0	7	9.5	25.2
Impotence	60	24.4	31.8	53	44.7	38.6	51	41.2	36.9	51	39.9	33.3	39	41.0	27.0	32	46.9	38.7
Dyspareunia	14	9.5	20.4	15	24.4	23.5	10	16.7	23.6	9	18.5	33.8	5	20.0	29.8	5	26.7	14.9

Abbreviations: EORTC-QLQ-C29 = European Organization for Research and Treatment of Cancer colorectal cancer questionnaire (higher scores indicate better functioning and greater level of symptoms); N = number of responses; n = number of eligible patients; SD = standard deviation.

Supplemental Table 3 EORTC QLQ-CR29 Scores Stratified by Measurement Point for Abdominoperineal Resection Patients

EORTC QLQ-CR29	Baseline (n = 119)			3 mo (n = 119)			6 mo (n = 119)			12 mo (n = 103)			18 mo (n = 91)			24 mo (n = 73)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Scale																		
Blood/mucus in stool	104	67.9	24.8	100	89.8	16.2	97	96.0	10.7	82	97.8	6.8	62	98.4	5.8	55	98.5	4.8
Urinary frequency	106	68.6	24.8	99	64.0	22.2	97	66.0	23.2	82	66.9	24.1	62	69.4	26.2	55	65.8	26.1
Stool frequency	101	66.8	25.6	96	73.4	25.5	99	85.0	17.4	84	88.7	14.0	61	90.7	12.7	55	90.3	13.1
Body image	106	87.9	25.1	100	80.9	21.5	98	73.9	23.3	82	75.7	24.8	62	75.3	22.0	55	75.6	23.8
Sexual interest, male	81	32.1	31.4	48	40.3	37.0	70	23.8	22.1	63	28.6	20.6	47	29.8	25.3	44	34.8	21.5
Sexual interest, female	18	13.0	23.3	21	9.5	15.4	21	7.9	14.5	12	16.7	22.5	12	16.7	22.5	6	0	0
Symptoms																		
Urinary incontinence	106	2.5	10.0	100	7.7	19.5	97	11.7	20.4	82	14.6	22.9	62	17.2	26.1	55	20.6	25.2
Dysuria	105	4.1	13.6	100	11.7	21.9	96	9.4	17.2	82	5.3	14.3	62	5.4	13.8	54	4.3	14.5
Abdominal pain	105	16.2	25.4	100	14.3	23.8	95	15.8	24.2	82	13.0	21.4	62	8.6	15.9	55	9.7	16.6
Buttock pain	106	34.6	33.8	100	48.7	38.0	97	48.8	35.7	81	26.3	27.2	60	21.1	25.3	54	15.4	25.7
Bloating	106	18.6	25.6	100	19.0	25.2	97	14.4	24.5	82	9.3	18.4	62	11.8	18.2	54	12.3	20.8
Dry mouth	106	16.0	22.6	100	20.7	26.3	98	15.1	23.1	82	18.3	22.3	62	12.9	20.3	55	20.6	24.4
Hair loss	104	0.6	4.6	100	4.3	13.1	97	3.4	12.2	82	3.7	13.9	62	1.6	7.2	55	4.8	13.5
Taste change	106	5.3	15.4	100	14.0	24.2	97	10.3	20.6	82	7.3	17.4	62	7.0	18.2	54	13.6	24.7
Anxiety	106	42.5	25.8	99	34.7	24.2	98	27.9	21.8	82	30.5	25.8	62	22.6	20.7	55	27.9	24.6
Weight loss	106	12.3	23.6	100	15.7	22.5	98	16.0	23.6	82	17.5	23.6	62	13.4	18.6	55	14.5	19.0
Flatulence	102	44.1	30.5	94	38.5	28.9	99	38.0	25.2	84	31.0	22.4	62	33.9	23.8	55	26.1	21.0
Fecal incontinence	101	18.3	26.4	96	22.2	29.7	99	16.8	28.8	84	11.1	18.9	62	13.4	24.5	55	6.7	14.9
Sore skin/anus	102	24.3	30.4	96	29.0	35.5	99	18.5	24.4	83	14.5	20.9	62	12.4	19.3	54	12.3	18.7
Embarrassment	102	33.0	32.0	96	33.0	33.7	99	27.6	28.2	84	22.2	27.5	62	23.1	26.7	53	21.4	26.2
Stoma care	9	33.3	37.3	49	15.6	25.6	99	8.4	17.4	83	4.4	15.4	62	1.6	7.2	55	3.6	10.5
Impotence	62	27.4	32.8	74	24.3	22.3	50	58.7	37.2	39	67.5	36.3	27	72.8	30.7	27	67.9	31.3
Dyspareunia	9	7.4	14.7	8	20.8	30.5	8	12.5	35.4	6	22.2	22.5	6	11.1	17.2	2	0	0

Abbreviations: EORTC-QLQ-C29 = European Organization for Research and Treatment of Cancer colorectal cancer questionnaire (higher scores indicate better functioning and greater level of symptoms); N = number of responses; n = number of eligible patients; SD = standard deviation.