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The Impact of Postoperative Complications on Short- and Long-Term Health-Related Quality of Life After Total Mesorectal Excision for Rectal Cancer

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Abstract

This study focuses on the impact of complications after rectal cancer surgery on the short- and long-term Health-related Quality of Life (HRQoL). The results show that. short-term HRQoL was affected by complications. Twelve months postoperative HRQoL had returned to the preoperative level regardless of complications. In patients that survived 14-years, there was no effect of complications on HRQoL detected.

Background: Survival for rectal cancer patients has improved over the past decades. In parallel, long-term health-related quality of life (HRQoL) is gaining interest. This study focuses on the effect of complications following rectal cancer surgery on HRQoL and survival. **Methods:** The TME-trial (1996-1999) randomized patients with operable rectal cancer between surgery with preoperative short-course radiotherapy and surgery. Questionnaires including the Rotterdam Symptom Checklist were sent at 6 time points within the first 24 months and after 14 years the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires. Differences in HRQoL and survival between patients with and without complications were analyzed. **Results:** A total of 1207 patients were included, of which 482 (39.9%) patients experienced complications, surgical complications occurred in 177 (14.6%) patients, non-surgical complications in 197 (16.3%) and 108 patients (8.9%) had a combination of both types of complications. Three months after surgery, patients with a combination of surgical- and non-surgical complications, especially patients with anastomotic leakage, had the worst HRQoL. Twelve months postoperative HRQoL returned to a similar level as before surgery, regardless of complications. In patients who survived 14 years, no significant differences in HRQoL were seen between patients with and without complications. However, patients with complications did have lower overall survival. **Conclusion:** This study shows that survival and short-term HRQoL are negatively affected by complications. Twelve months after surgery HRQoL had returned to the preoperative level regardless, of complications. Also, in patients that survived 14 years, there was no effect of complications on HRQoL detected.

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Introduction

Colorectal cancer is one of the most common types of cancer in western countries with increasing incidence, of which approximately a third is located in the rectum. Fortunately, survival has improved substantially.[1-3] The cornerstone of rectal cancer treatment is surgery, which is a complex procedure and is associated with a high rate of overall postoperative complications, 36 to 59 %.[4,5] Postoperative complications are associated with increased morbid-

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core; HRQoL, Health-Related Quality of Life; RSCL, Rotterdam Symptom Checklist; TME, Total Mesorectal Excision; ERAS, Enhanced Recovery After Surgery; APR, Abdominoperineal Resection.

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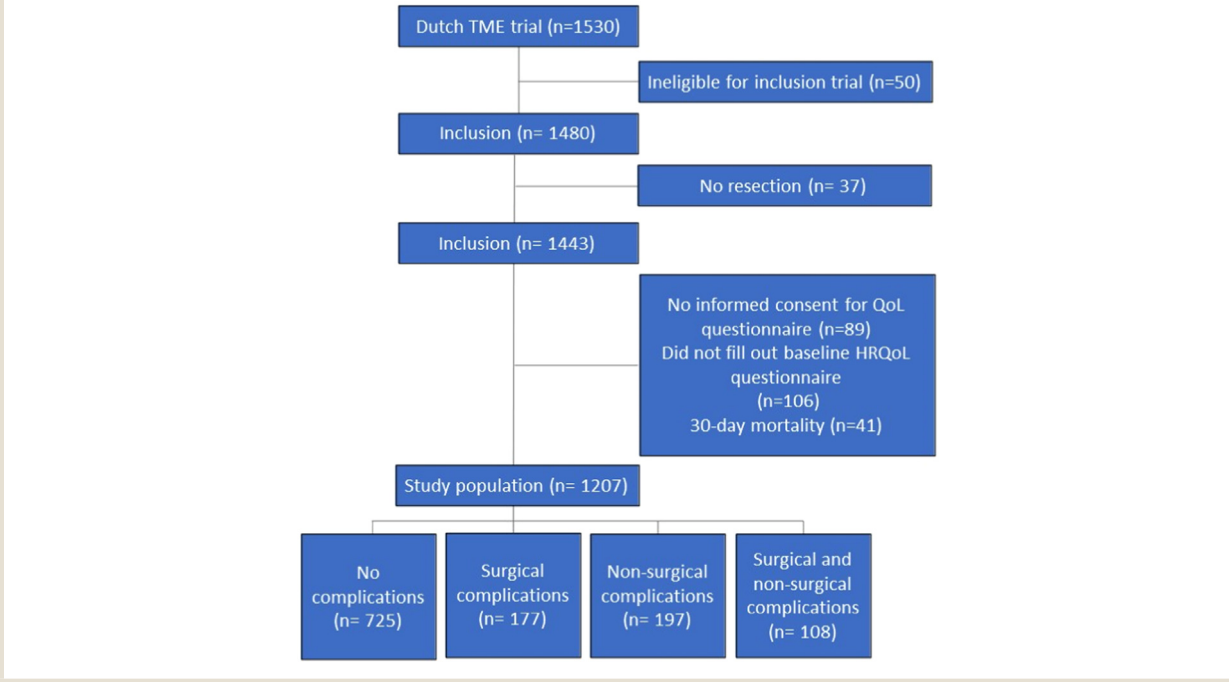
Figure 1 Flowchart of patient selection for study



ity and mortality, as well as increased hospital length of stay and health care costs. Another major issue in rectal cancer treatment is local recurrence. The Dutch TME-trial demonstrated that reduction from 10.9% to 5.6% of local recurrence rates was achieved by adding short-course preoperative radiotherapy to the standard treatment.[6] Preoperative radiotherapy may increase postoperative complications,[7] although the addition of preoperative radiotherapy does not seem to lead to a decreased health-related quality of life (HRQoL).[8]

Currently, the overall 5-year survival of rectal cancer lies around 75% to 80%.[9] Together with an increasing trend towards value-based health care and shared decision-making, recurrence-free – and long-term survival are not the only important factors that have to be considered during treatment planning, but also other factors such as quality of life. Furthermore, studies indicate that patients are only willing to risk an inferior functional outcome for better survival to a certain extent.[10] This impacts decision-making regarding treatment options, eg, watching and waiting after clinical complete response to neoadjuvant therapy.[11] Therefore, HRQoL after rectal cancer should be investigated as well as factors influencing this, both to inform patients and to gain insight into possible improvements of perioperative care.

This study aims to objectify the difference in short- and long-term HRQoL between uncomplicated and complicated postoperative recovery after total mesorectal excision (TME) surgery for rectal cancer. The hypothesis is that postoperative complications lead to a decreased HRQoL. Furthermore, the differences in overall survival between patients with- and without postoperative complications are studied.

Methods

Study Population and Treatment

Between January 1996 and December 1999 patients with resectable rectal cancer were enrolled in the Dutch multicenter TME-Trial.[12-15] The trial was approved by the medical ethics committees of all the participating hospitals. During this trial, patients were randomly allocated to TME surgery or preoperative radiotherapy followed by TME surgery. Eligibility criteria were a clinically resectable adenocarcinoma with an inferior tumor margin below the level of S1/S2 and within 15 cm from the anal verge, without evidence of distant metastases. Patients were excluded from analysis when not having filled out the baseline HRQoL questionnaire or when deceased within 30 days after surgery. Patients assigned to preoperative radiotherapy received a total dose of 25 Gy in 5 fractions delivered by a 3- or 4-field technique over 5 to 7 days. The clinical target volume included the primary tumor and the mesentery containing the sacral, perirectal, and internal iliac nodes up to the S1/S2 junction. The perineum was also included in this volume if an abdominoperineal resection (APR) was planned. Otherwise, the lower field border was 3 cm above the anal verge. All patients underwent surgery following the TME principle.[12,16] Following our previous report, survival was calculated from the day of surgery.[12] The status, alive, of patients, was censored at the time of the last follow-up.

Health-Related Quality of Life (HRQoL) Assessment

HRQoL was measured using different questionnaires on 7 different time points. Preoperatively and 3, 6, 12, 18 and 24 months after surgery the Rotterdam Symptom Checklist (RSCL) was used

Table 1 Patient, Tumor- and Treatment Characteristics

Characteristics(n = 1248)	No Complications(n = 725 (60.1%))	Surgical Complications(n = 177 (14.6%))	Non-Surgical Complications(n = 197 (16.3%))	Surgical and Non-Surgical Complications(n= 108 (8.9%))	*P*-value
Median age [range]	64 [23-88]	65 [41-86]	66 [26-92]	67 [43-88]	< .01
Male	447 (61.7%)	123 (69.5%)	121 (61.4%)	76 (70.4%)	.09
Mean BMI at baseline	25.4 [16.2-53.1]	26.1 [18.4-45.9]	25.4 [17.1-45.4]	25.4 [17.7-35.3]	.13
Comorbidities					
Any comorbidity	195 (26.9%)	39 (22.0%)	55 (27.9%)	20 (18.5%)	.36
Hypertension	104 (14.3%)	24 (13.6%)	27 (13.7%)	6 (5.5%)	.38
Cardiac comorbidity	35 (4.8%)	8 (4.5%)	7 (3.3%)	7 (6.5%)	.21
Pulmonary comorbidity	23 (3.2%)	4 (2.3%)	6 (3.0%)	4 (3.7%)	.65
Diabetes	46 (6.3%)	14 (7.9%)	6 (3.0%)	4 (3.7%)	.15
Previous abdominal surgery	50 (6.9%)	10 (5.6%)	11 (5.6%)	7 (6.5%)	.66
Chronic drug use	164 (22.6%)	36 (20.3%)	44 (22.3%)	17 (15.7%)	.50
TNM stage					.80
0	14 (1.9%)	5 (2.8%)	4 (2.0%)	0 (0.0%)	
I	221 (30.5%)	52 (29.4%)	67 (34.0%)	33 (30.6%)	
II	193 (26.6%)	48 (27.1%)	43 (21.8%)	32 (29.6%)	
III	262 (36.1%)	60 (33.9%)	74 (37.6%)	36 (33.3%)	
IV	35 (4.8%)	12 (6.8%)	9 (4.6%)	7 (6.5%)	
Distance to anal verge					.01
<5	203 (28.0%)	69 (39.0%)	54 (27.4%)	41 (38.0%)	
5-10	303 (41.8%)	72 (40.7%)	76 (38.5%)	40 (37.0%)	
>10	219 (30.2%)	35 (19.8%)	67 (34.0%)	27(25.0%)	
Unknown	0 (0,0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Neo-adjuvant RT					.32
Yes	345 (47.6%)	89 (50.3%)	104 (52.8%)	60 (55.6%)	
No	380 (52.4%)	88 (47.7%)	93 (47.2%)	48 (44.4%)	
Operation type					<.01
LAR	490 (67.6%)	92 (52.0%)	135 (68.5%)	64 (59.3%)	
APR	203 (28.0%)	82 (46.3%)	41 (20.8%)	41 (38.0%)	
Hartmann	32 (4.4%)	3 (1.7%)	21 (10.7%)	3 (2.8%)	
Stoma					<.01
None	210 (29.0%)	45 (25.4%)	48 (24.4%)	35 (32.4%)	
Diverting	312 (43.0%)	50 (28.2%)	107 (54.3%)	32 (29.6%)	
Permanent	203 (28.0%)	82 (46.3%)	41 (20.8%)	41 (38.0%)	
Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	

supplemented with questions concerning sexual functioning as reported previously (Table A.1).[13,14,17,18] In July - August 2012, after a median follow-up of 14.4 years after surgery the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC) questionnaires: cancer-specific QLQ-C30 and colorectal- cancer-specific QLQ-CR29 was sent by mail to the surviving patients.[19,20] In all questionnaires, a 4-point Likert scale was used and subsequently all responses were linearly converted to 0 to 100 scales.

Complications

All complications that occurred during admission were registered and reviewed, of which the following definitions were used. Surgical complications are considered complications directly related to the surgical intervention (eg, anastomotic leakage. Non-surgical complications are complications not directly related to the surgical intervention (eg, urinary tract infection). Anastomotic leakage included all leakages clinically diagnosed or confirmed by contrast enema, furthermore, an abscess around the anastomosis was also recorded as anastomotic leakage. Rare complications were classified as other.

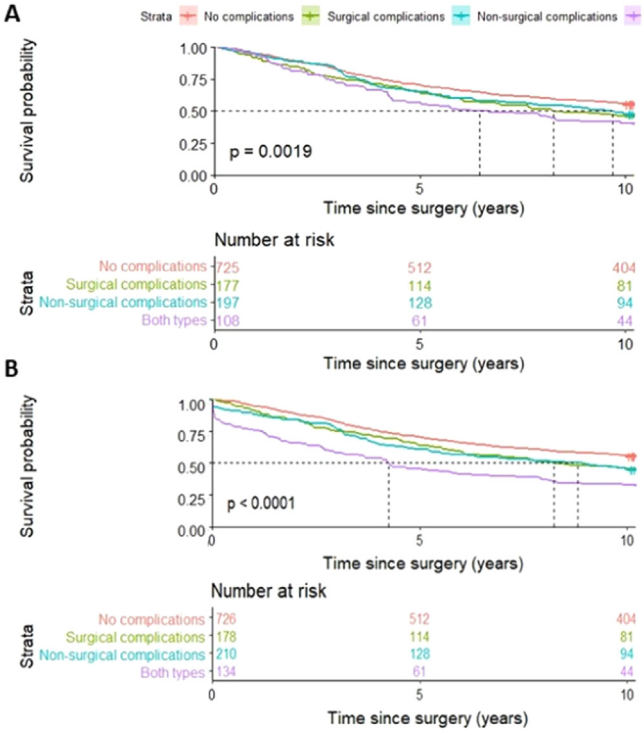
Statistics

Linear mixed models with random patient intercepts and time (categoric) and treatment group as fixed factors were used to obtain estimates for the subscales of the RSCL of each of the scheduled time points, to account for drop-out. At each time point, the difference in quality of life between groups was tested by Wald's tests, using linear mixed-effects model the "lme" package. A univariable

Table 2 Questionnaire Response Per Time Point. Percentages are Calculated Using the Patients That Were Alive at the Time of the Questionnaire

	No Complications	Surgical Complications	Non-Surgical Complications	Surgical and Non-surgical Complications	Overall	*P*-value
Completed questionnaires						
Baseline	725 (100.0%)	177 (100.0%)	197 (100.0%)	108 (100.0%)	1207 (100.0%)	
3 months	672 (93.1%)	161 (92.0%)	182 (92.9%)	101 (90.2%)	1205 (92.6%)	.22
6 months	662 (92.3%)	157 (91.3%)	174 (90.6%)	93 (86.1%)	1086 (91.3%)	.20
12 months	623 (90.2%)	145 (88.4%)	167 (88.8%)	87 (85.3%)	1022 (89.3%)	.31
18 months	590 (87.7%)	137 (89.0%)	155 (86.6%)	77 (81.1%)	959 (87.1%)	.34
24 months	543 (83.8%)	129 (86.0%)	146 (83.0%)	74 (84.1%)	892 (84.0%)	.81
14 years	251 (76.3%)	57 (82.9%)	66 (82.5%)	25 (71.4%)	400 (77.8%)	.44

Figure 2 Overall survival probability analysis using Cox regression, subgroups are patient without complications, with surgical complications, non-surgical complications, and patients with a combination of surgical- and non-surgical complications. (A) represents survival cure of patients included in HRQoL analyses, (B) represents the survival curve without conditional-survival. HRQoL = Health-related Quality of Life.



Poisson regression analysis was carried out using the "lme" package to analyze the effect of individual variables on HRQoL. Cox regression analysis were carried out using the "survival" and "survminer" packages. Analysis were performed in R Version 3.6.3.

Results

Patient Characteristics

A total of 1530 patients were selected of which 323 were excluded because of the following reasons: ineligible at randomization (n = 50), no resection (n = 37), no informed consent for HRQL questionnaires (n = 89), 30-day mortality (n = 41) and no baseline HRQL forms returned (n = 106), leaving 1207 patients for analysis (Figure 1). Patient, tumor and treatment characteristics are listed in Table 1. In total 482 (39.9%) patients suffered from complications, of which urinary tract infection (n = 106) was the most common followed by pulmonary complication (n = 85), anastomotic leakage (n = 79) and abdominal wound infection (n = 75) (Table A.2). Patients were divided into 4 separate groups

Table 3 Survival Analysis of Using Cox Regression. *Adjusted for Age, Sex, TNM-Stage

	Univariate Cox	Multivariate Cox		
	HR (95%CI)	P-value	HR (95%CI)	P-value
Age	1.03 (1.02-1.04)	<0.01		
Male sex	0.76 (0.64-0.91)	<0.01		
BMI	0.99 (0.97-1)	0.67		
Level of education	0.79 (0.49-1.27)	0.34		
Type of complications				
No complications	ref		ref	
Surgical complications	1.33 (1.06-1.67)	0.01	1.23* (0.92-1.55	0.07
Non-surgical complications	1.24 (0.99-1.55)	0.06	1.18* (0.95-1.48)	0.14
Both surgical and non-surgical complications	1.56 (1.19-2.03)	<0.01	1.37* (1.043-1.78)	0.02
Anastomotic leakage	1.10 (0.80-1.52)	0.54	1.12* (0.81-1.54)	0.49
Type of surgery				
LAR	ref		ref	
APR	1.23 (1.03-1.46)	0.02	1.20* (1.00-1.43)	<0.05
Hartmann	1.86 (1.33-2.60)	<0.01	1.45* (1.04-2.04)	0.03
TNM-stage	1.91 (1.74-2.10)	<0.01		
Stoma				
No stoma	ref		ref	
Diverting	1.23 (1.00-1.51)	<0.05	1.12* (0.92-1.38)	0.27
Permanent	1.33 (1.07-1.65)	0.01	1.25* (1.0-1.56)	<0.05
Neoadjuvant RT	0.99 (0.85-1.17)	0.98		
Any comorbidity	1.00 (1.00-1.00)	0.99		
Previous malignancy	3.67 (0.38-35.2)	0.26		
Chronic medication	0.55 (0.09-3.3)	0.51		

based on the type of complications: no complications, surgical complications, non-surgical complications or a combination of surgical and non-surgical complications. There was a significant difference between the different groups in age, the distance of the tumor to the anal verge and stoma formation during primary surgery. There were no significant differences observed in comorbidities (Table 1). Response to the HRQoL questionnaires did not significantly differ between the groups at any time point (Table 2).

Survival After TME Surgery

The 5-year overall survival was 67.5%, the 10-year overall survival was 51.6% in the study cohort (Figure 2A). When leaving out the condition for 30-day survival the 5-year survival was lower in the patients with both surgical- and non-surgical complications, 5-year survival was 45.5% and 56.5% respectively (Figure 2B). Decreased survival after surgery was associated with postoperative complications, the 5-year and 10-year overall survival were poorest in patients with both surgical- and non-surgical complications 56.5% and 40.7% respectively (adjusted HR: 1.37, 95%CI 1.04-1.78) (Table 3).

Health-Related Quality of life (0-24 Months)

The HRQoL measured by the global health status, activity level and physical level was lower after 3 months compared to the preoperative measurements but after approximately 12 months the levels were back to the preoperative level for all groups (Table A.3, Figure 3). In the patients with a combination of both surgical and non-surgical complications the impact of surgery was significantly larger ($P < .05$) in the first 12 months after surgery. Likewise, patients that suffered from anastomotic leakage had a significantly decreased global health status and activity level (Table A.4, Figure A.1). A decrease in male sexual functioning and psychological distress was seen after surgery, these changes were comparable in all subgroups.

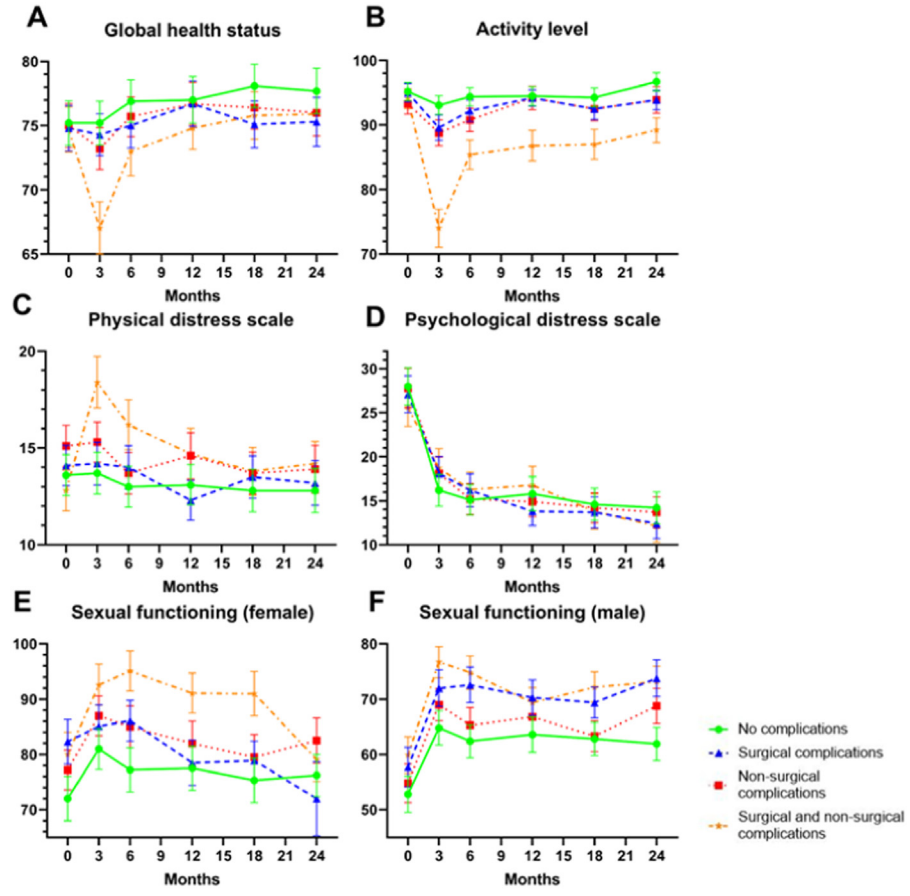
Impact of Individual Variables

Univariate regression analysis was performed to identify influential factors for postoperative overall health and the activity level at the 3-month, 12 month and 24 month time point (Table 4). A combination of surgical and non-surgical complications was significantly associated with a decreased global health (RR: 0.88, 95%CI 0.80-0.97) and activity level (RR: 0.84, 95%CI 0.70-0.98) 3 months after TME surgery. Anastomotic leakage was also significantly associated with a decreased global health status 3 months after surgery (RR: 0.91, 95%CI 0.82-1.00). Additionally, a more advanced tumor stage (RR: 0.98, 95%CI 0.95-0.99) and Hartmann resection (RR: 0.82, 95C%CI 0.70-0.95) were associated with a decreased global health status 12 months after surgery.

Health-Related Quality of Life (14 Years)

After a median follow-up of 14 years, 429 patients filled out the quality-of-life questionnaires, which entails 84.0% of the patients that survived. Global health status was not significantly different between the different (sub)groups with and without complications (Table A.5). We do see significant changes in constipation, urinary

Figure 3 Health-related quality of life measured by the Rotterdam Symptoms Check List questionnaire on 6 time points, preoperatively, 3, 6, 12, 18 and 24 months postoperative. Overall health, a higher score is a better health, for all other scores a higher score is more problems. (A) Global health status, (B) Activity level, (C) Physical distress scale, (D) Psychological distress scale, (E) Sexual functioning (female), (F) Sexual functioning (male). The scores of Overall health and Activity Scale are 0 to 100, a higher score means a better health. For the other subscale the scores are linearly transformed (0-100) a higher score is indicating more distress. Raw results are shown in Table A.3.



frequency, which are more common in the patients after both surgical and non-surgical complications.

Discussion

The HRQoL, as measured by our approach, of patients that survived 12 months after TME surgery for rectal cancer is comparable with the preoperative status and no significant differences were witnessed between patients with an uncomplicated and complicated recovery. However, short-term postoperative recovery was affected in patients with complicated TME surgery, especially when there was a combination of surgical and non-surgical complications and in case of anastomotic leakage. Nevertheless, in patients who survived 1 year up to 14 years after surgery no significant HRQoL differences were seen between uncomplicated and complicated surgery, suggesting the deficit of HRQoL as a result of complications is temporary. Nonetheless, this study showed that postoperative complications negatively impact overall survival, this effect was the highest in patients that suffered a combination of surgical and non-surgical complications.

The results of the short-term postoperative HRQoL are in line with a previously conducted study about patients undergoing oncological colorectal surgery, as they did observe a decrease in physical functioning after complications requiring reoperation.[21] However, they showed no effect of postoperative complications on the global health status, while in our study there was a significant difference shown between patients without complications and patients with both surgical- and non-surgical complications in the first year after surgery. A similar pattern was reported after surgery for diverticular disease: a significant decrease of physical functioning was associated with postoperative complications, while no significant effects on global health perception were seen.[22] As reported by Sharma et al. postoperative complications were significantly associated with increased anxiety, depression and poorer functional wellbeing.[23] This is not supported by our study, since

Table 4 Univariable Regression Analysis of the Effect of Variables on Global Health Status and Activity Level, Measured by the Rotterdam Symptom Checklist at 3 Months, 12 Months, and 24 Months After Surgery. * Ileostoma of Colostoma Present at Time of the Questionnaire

	3 Months		12 Months		24 Months	
Global Health Status						
	Unadjusted RR (95%CI)	*P*-value	Unadjusted RR (95%CI)	*P*-value	Unadjusted RR (95%CI)	*P*-value
Age	1.00 (1.00-1.00)	.27	1.00 (1.00-1.00)	.39	1.00 (1.00-1.00)	.20
Sex	0.99 (0.94-1.04)	.66	0.97 (0.93-1.02)	.27	0.97 (0.92-1.02)	.28
BMI at baseline	1.00 (0.99 -1.01)	.73	0.99 (0.99-1.00)	.08	0.99 (0.98-1.00)	< .05
Level of education	1.01 (0.99-1.02)	.41	1.01 (0.99-1.02)	.28	1.01 (0.99-1.02)	.49
Type of complications						
No complications	1.00		1.00		1.00	
Surgical complications	0.99 (0.92-1.05)	.72	1.00 (0.93-1.06)	.92	0.97 (0.90-1.00)	.39
Non-surgical complications	0.97 (0.91-1.04)	.40	1.00 (0.93-1.06)	.92	0.98 (0.91-1.04)	.52
Both surgical and non-surgical complications	0.88 (0.80-0.97)	< .01	0.97 (0.89-1.06)	.51	0.98 (0.89-1.07)	.61
Anastomotic leakage	0.91 (0.82-1.00)	.04	0.95 (0.86-1.04)	.32	0.94 (0.84-1.04)	.21
Type of surgery						
LAR	1.00		1.00		1.00	
APR	1.04 (0.99-1.09)	.08	0.99 (0.94-1.04)	.78	0.99 (0.94-1.05)	.84
Hartmann	0.91 (0.80-1.02)	.13	0.82 (0.70-0.95)	< .01	0.89 (0.76-1.03)	.13
TNM-stage	0.98 (0.96-1.00)	.07	0.98 (0.95-0.99)	< .05	0.98 (0.96-1.01)	.20
Stoma*	1.02 (0.99-1.05)	.13	1.00 (0.97-1.03)	.87	1.00 (0.97-1.03)	.98
Neoadjuvant RT	1.02 (0.98-1.07)	.34	1.01 (0.97-1.06)	.55	1.00 (0.95-1.05)	.97
Activity level						
Age	1.00 (0.99-1.00)	.07	1.00 (0.99-1.00)	.06	1.00 (0.99-1.00)	.13
Sex	0.96 (0.88-1.03)	.28	0.97 (0.89-1.05)	.39	0.95 (0.87-1.04)	.25
BMI at baseline	1.00 (0.99-1.01)	.83	1.00 (0.99-1.01)	.71	1.00 (0.98-1.01)	.64
Level of education	1.01 (0.99-1.03)	.34	1.01 (0.99-1.03)	.43	1.01 (0.99-1.03)	.29
Type of complications						
No complications	1.00		1.00		1.00	
Surgical complications	0.97 (0.86-1.08)	.61	1.00 (0.89-1.11)	0.97	0.99 (0.88-1.11)	.92
Non-surgical complications	0.97 (0.86-1.07)	.51	0.98 (0.87-1.09)	.72	0.97 (0.85-1.08)	.60
Both surgical and non-surgical complications	0.84 (0.70-0.98)	< .05	0.94 (0.79-1.08)	.40	0.96 (0.80-1.11)	.58
Anastomotic leakage	0.92 (0.77-1.07)	.32	0.96 (0.81-1.12)	.96	0.99 (0.82-1.15)	.87
Type of surgery						
LAR	1.00		1.00		1.00	
APR	1.00 (0.92-1.08)	.99	1.00 (0.92-1.09)	.93	0.99 (0.90-1.08)	.90
Hartmann	0.95 (0.77-1.13)	.57	0.94 (0.75-1.13	.55	0.95 (0.74-1.17)	.67
TNM-stage	0.99 (0.96-1.03)	.73	0.99 (0.95-1.03)	.76	0.99 (0.95-1.04)	.73
Stoma*	1.00 (0.95-1.05)	.97	1.00 (0.95-1.05)	.97	1.00 (0.94-1.05)	.92
Neoadjuvant RT	1.02 (0.94-1.09)	.67	1.00 (0.93-1.08)	.95	1.00 (0.92-1.08)	.94

we see a high preoperative psychological distress and a decrease in psychological distress after surgery which is comparable in both patients with and without postoperative complications. This might be the result of improved preoperative informing and counseling of patients over the past decades, leading to patients having lower preoperative anxiety.[23] Additionally, a study on HRQoL after oncological esophagectomy showed no significant difference on short- or long-term HRQoL after postoperative complications or anastomotic leakage compared to an uncomplicated postoperative course.[24] However, in a study measuring HRQoL after restorative proctocolectomy a difference in HRQoL in patients with and without postoperative pelvic sepsis was observed.[25] The differences in outcome between these studies might be subjected to the patient population, especially benign versus malignant, or the different questionnaires used in the studies. It might be related to the coping style which might differ between different patient populations, since patients with malignant diseases might be more resilient and cope differently with health deficits following postoperative complications, leading to a relative underestimation of the effect of complications on HRQoL.[26,27] Time points of measuring HRQoL were not equal in all studies, however, most studies measured HRQoL within the first 2 years after surgery. Only Constantinides et al. measured HRQoL at 3 to 6 years after surgery.[22] This may lead to different outcomes as this study shows that HRQoL is subjected to time.

This study has shown that patients with postoperative complications have lower overall survival. These outcomes are in line with previous studies.[28-30] Furthermore, anastomotic leakage has been shown to be associated with increased local recurrence which impacts survival as well.[28] Several mechanisms might explain this, first the overall survival might be affected by postoperative complications causing an impaired health status.[31] Additionally, it is thought that a systemic inflammatory response after complications leads to decreased (recurrence-free) survival. This inflammatory response is responsible for the release of pro-inflammatory cytokines and growth factors that subsequently might stimulate the growth of residual cancer cells.[32,33]

This study is based on data obtained during a multicenter randomized-controlled trial on preoperative short-course radiotherapy and TME surgery versus TME surgery alone. Since there was no significant difference in the postoperative complication rate between irradiated- and non-irradiated patients, making this study data is representable for this research question as well. However, our study was not designed to answer whether radiotherapy does increase postoperative complications. Furthermore, previous studies have shown that patients with preoperative radiotherapy may have an impaired activity level in the first 2 years after surgery, no effect on HRQoL was shown 14 years postoperative [13,17] Additionally, the more recent RAPIDO trial, reported no influence of (neo-)adjuvant therapy on long term HRQoL in rectal cancer patients.[34]

The current improvements in overall survival of rectal cancer patients result in a larger population that has to live with the physical-, psychological- and societal consequences of rectal cancer surgery, such as having a stoma, bowel dysfunction, physical and psychological stress.[35,36]. The results of this study give insights in the impact of postoperative complications after rectal cancer surgery on the development of HRQoL overtime after postoperative compilations. This information may serve in optimizing patient information and shared decision-making before engaging treatment.[37] Additionally, information on the postoperative HRQoL development can be used for preparatory education of patients planned for surgery on what to expect in the short- and long-term. Preoperative education of patients has been shown to reduce postoperative anxiety and postoperative pain.[38,39] Furthermore, this study gives leads for alteration of (p)rehabilitation programs that should be focusing on enhancing activity and physical fitness and in case of postoperative complications rehabilitation programs might be directed on regaining activity level and physical fitness. The use of prehabilitation programs seems to be especially effective in high-risk patients, therefore preoperative detection of high-risk patients will be needed.[40,41]

A limitation of this study is that postoperative complications are significantly associated with lower survival. This may cause bias in HRQoL measurements, especially 14 years after surgery. Furthermore, between surgery and the 14-year postoperative HRQoL questionnaires other events may have occurred which may have influenced the HRQoL, leading to a possible underestimation of the effect of complications. Furthermore, rectal cancer care has evolved over the past years leading to improvements in treatment, advanced diagnostics and early detection by screening contributing to improved survival. Also, treatment and detection of postoperative complications have been improved, which may lead to a lower burden of postoperative complications. The strength of this study is the high response (77.8%) of long-term follow-up (14 years) HRQoL questionnaires. To our knowledge, this study has currently the longest follow-up of all studies on the impact of complications after rectal surgery. However, although the TME trial is a well-designed and documented RCT, this study has been conducted in 1996-1999 and since then perioperative care and surgical techniques have been improved. Currently, postoperative outcomes after colorectal surgery are improved due to progress in surgical techniques and perioperative care. A major improvement in perioperative care is the introduction of Enhanced Recovery After Surgery (ERAS) protocols. ERAS protocols have been proven to reduce postoperative complications and mortality.[42-44] Preadmission exercise interventions, incorporated in ERAS protocols, are associated with a positive impact on HRQoL.[45] The progress in surgical techniques is marked by the introduction of minimally-invasive surgery. However, in a meta-analysis no clinically significant difference was found in postoperative HRQoL between laparoscopic surgery and open colorectal surgery.[46] Despite, the absence of a significant effect on HRQoL, minimally invasive surgery is thought to lead to a faster postoperative recovery and less use of parenteral and oral analgesics.[47,48] There are no significant differences between laparoscopic and open surgery regarding intra-operative or postoperative complications.[49,50]

In conclusion, this study did show a decreased overall survival after postoperative complications. Furthermore, this study presents that short-term HRQoL is affected in patients with a combination of surgical and non-surgical complications and in patients with anastomotic leakage. Moreover, after 12 months HRQoL in all patients returned to the pretreatment level. No significant effects of postoperative complications were seen on long-term HRQoL (24 months and 14 years) in patients with- and without postoperative complications. These results suggest that the effects of postoperative complications on the HRQoL are temporary.

Clinical Practice Points

- Postoperative complications lead to a decreased overall survival.
- Short-terms health-related quality of life was negatively affected by postoperative complications.
- Twelve months after surgery health-related quality of life returned to the preoperative level regardless, of complications.
- Fourteen years after rectal cancer surgery there was no effect of postoperative complications on health-related quality of life detected.

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Disclosure

The authors have stated that they have no conflicts of interest.

APPENDIX 1

Figure A.1, Tables A.1 -A.5

Figure A.1 Health-related quality of life in patients with anastomotic leakage and without anastomotic leakage. Measured by the Rotterdam Symptoms Check List questionnaire on 6-time points, preoperative, 3, 6, 12, 18 and 24 months postoperative. Overall health, a higher score is better health, for all other scores a higher score is more problems. (A) Global health status, (B) Activity level, (C) Physical distress scale, (D) Psychological distress scale. The scores of overall health and Activity Scale are 0 to 100, a higher score means better health. For the other subscale, the scores are linearly transformed (0-100) a higher score is indicating more distress.

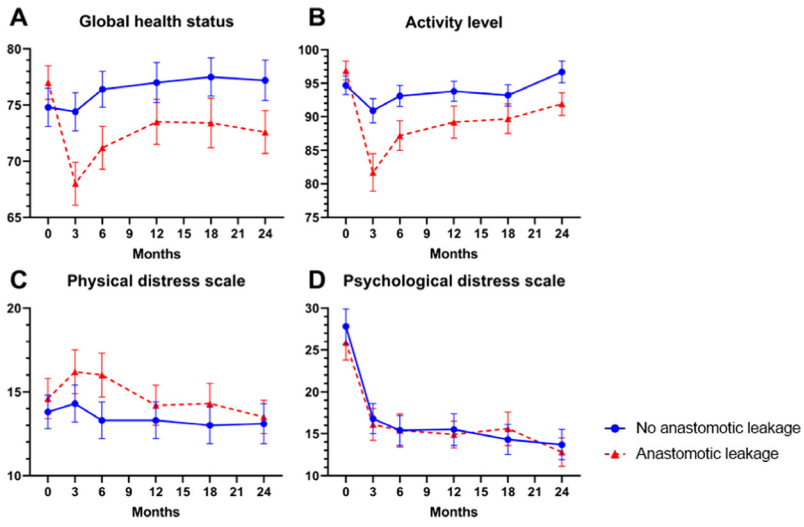

Table A.1 Overview of the Items Included in the Rotterdam Symptom Checklist (RSCL) and the Sexual Functioning Scale [13]

Items Containing HRQoL Questionnaires
RSCL physical symptom distress (23 items)
1 Lack of appetite
2 Tiredness
3 Sore muscle
4 Lack of energy
5 Low back pain
6 Nausea
7 Difficulty sleeping
8 Headaches
9 Vomiting
10 Dizziness
11 Decreased sexual interest
12 Abdominal (stomach) aches
13 Constipation
14 Diarrhea
15 Acid indigestion
16 Shivering
17 Tingling of hands or feet
18 Difficulty concentrating
19 Sore mouth/pain when swallowing
20 Loss of hair
21 Burning/sore eyes
22 Shortness of breath
23 Dry mouth
RSCL psychologic distress scale (7 items)

(*continued on next page*)

Table A.1 (*continued*)

Items Containing HRQoL Questionnaires
1 Irritability
2 Worrying
3 Depressed mood
4 Nervousness
5 Despairing about future
6 Tension
7 Anxiety
RSCL activity level scale (8 items)
1 Care for myself (wash, etc.)
2 Walk about the house
3 Light housework/household jobs
4 Climb stairs
5 Heavy housework/household jobs
6 Walk out of doors
7 Go shopping
8 Go to work
Sexual Functioning (4 items)
1 Feeling sexual attractive
2 Sexually interested
3 Sexual pleasure
4 Sexual satisfaction

Table A.2 Overview of Complications

	Surgical Complications(n = 177 (14.6%))	Non-Surgical Complications(n = 197 (16.3%))	Surgical and Non-Surgical Complications(n = 108 (8.9%))
Surgical complications			
Abdominal wound dehiscence	13	-	16
Perineal wound dehiscence	31	-	11
Wound infection abdomen	48	-	27
Wound infection perineal	26	-	11
Intestinal necrosis	2	-	3
Anastomotic leakage	41	-	38
Hemorrhage	23	-	12
Intestinal fistula	7	-	9
Stoma complication	11	-	7
Intestinal perforation	1	-	6
Non-surgical complications			
Urinary tract infection	-	65	41
Abdominal abscess	-	27	16
Sepsis	-	17	34
Infected hematoma	-	5	3
Pulmonary complication	-	50	35
Renal complication	-	1	5
Neurological complication	-	11	8
Thromboembolism	-	8	9
Cardiac complications	-	22	10
Delirium	-	18	8
Multi-organ failure	-	1	2
Tension complication	-	4	0
Line sepsis	-	12	3
Cholecystitis	-	5	7

Table A.3 Raw results of health-related quality of life (HRQoL) measured by the Rotterdam Symptoms Check List (RSCL) questionnaire on 6 time points, preoperative, 3, 6, 12, 18 and 24 months postoperative, graphical presentation of results is shown in Figure 3

	No Complications(n = 725 (60.1%))	Surgical Complications(n = 177 (14.6%))	Non-Surgical Complications(n = 197 (16.3%))	Surgical and Non-Surgical Complications(n = 108 (8.9%))	*P*-value
Overall health					0.48 α
Preoperative	75.2	74.8	75.0	74.7	
3 Mo	75.2	74.3	73.2	67.0	
6 Mo	76.9	75.0	75.7	73.0	
12 Mo	77.0	76.7	76.7	74.8	
18 Mo	78.1	75.1	76.4	75.8	
24 Mo	77.7	75.3	76.0	75.9	
Activity level					< 0.01 α, γ, δ, ε
Preoperative	95.2	95.0	93.3	94.1	
3 Mo	93.1	89.6	88.8	74.0	
6 Mo	94.4	92.2	90.8	85.4	
12 Mo	94.5	94.2	92.0	86.8	
18 Mo	94.3	92.5	91.6	87.0	
24 Mo	96.7	93.9	90.8	89.2	
Physical distress scale					< 0.01
Preoperative	13.6	14.1	15.1	12.8	
3 Mo	13.7	14.2	15.3	18.4	
6 Mo	13.0	14.0	13.7	16.2	
12 Mo	13.1	12.3	14.6	14.7	
18 Mo	12.8	13.5	13.7	13.8	
24 Mo	12.8	13.2	13.9	14.2	
Psychological distress scale					0.77
Preoperative	28.0	27.1	27.8	25.6	
3 Mo	16.2	18.1	18.1	18.7	
6 Mo	15.1	16.2	15.2	16.3	
12 Mo	15.8	13.8	14.9	16.8	
18 Mo	14.6	13.7	14.2	13.8	
24 Mo	14.2	12.4	13.7	12.1	
Sexual functioning (male)					0.43 α
Preoperative	52.8	57.7	54.8	59.9	
3 Mo	64.8	72.0	69.0	76.7	
6 Mo	62.4	72.6	65.3	74.8	
12 Mo	63.6	70.3	66.8	69.4	
18 Mo	62.8	69.4	63.3	72.2	
24 Mo	61.9	73.8	68.8	73.2	
Sexual functioning (female)					0.66
Preoperative	72.0	82.3	77.2	80.0	
3 Mo	81.0	85.1	87.0	92.6	
6 Mo	77.2	86.1	85.0	95.1	
12 Mo	77.6	78.5	82.0	91.1	
18 Mo	75.3	78.9	79.5	91.0	
24 Mo	76.2	72.0	82.5	79.1	

The scores of Overall health and Activity Scale (0-100), a higher score means a better health. For the other subscale the scores are linearly transformed (0-100) a higher score is indicating more distress.
α: statistically difference between no complication and both surgical and non-surgical complications
β: statistically difference between no complication and surgical complications
γ: statistically difference between no complications and non-surgical complications
δ: statistically difference between surgical complications and both surgical and non-surgical complications
ε: statistically difference between non-surgical complications and both surgical and non-surgical complications

Table A.4 Overview of health-related quality of life (HRQoL) Subanalysis of patients with and without anastomotic leakage

Global Health			**<0.01**
Preoperative	75.2	77.0	
3 Mo	75.2	68.0	
12 Months	77.0	73.5	
24 Mo	77.7	72.6	
Activity level			<0.01
Preoperative	95.2	96.8	
3 Mo	93.1	81.7	
12 Mo	93.8	89.3	
24 Mo	96.7	91.9	
Physical scale			0.85
Preoperative	13.6	14.4	
3 Mo	13.7	16.2	
12 Mo	13.1	14.2	
24 Mo	12.8		13.5
Psychological scale		<0.01	
Preoperative	28.0	26.8	
3 Mo	16.2	16.1	
12 Mo	15.8	14.9	
24 Mo	14.2	12.8	

Table A.5 Health-related quality of life (HRQoL) measured by EORTC QLQ-C30 and EORTC QLQ-CR29, 14 years after surgery

	No Complications (n = 251 (49.1%))	**Surgical Complications (n = 57 (11.1%))**	**Non-Surgical Complications (n = 66 (12.9%))**	**Both Surgical and Non-Surgical complications (n = 25 (4.9%))**	***P*-value**
EORTC QLQ-C30					
Global Health status[b]	78.4	81.5	74.3	76.9	.23
Physical functioning[b]	76.7	77.9	74.0	77.6	.35
Role functioning[b]	78.2	78.8	74.2	77.8	.13
Emotional functioning[b]	84.0	89.2	82.9	88.0	.15
Cognitive functioning[b]	86.3	84.4	82.6	82.7	.74
Social functioning[b]	86.0	85.5	83.8	84.6	.54
Fatigue[a]	24.9	25.1	28.5	21.8	.34
Nausea and vomiting[a]	3.3	1.6	4.6	13.3	.25
Pain[a]	15.0	11.6	15.3	12.3	.46
Dyspnea[a]	13.3	11.7	19.1	18.5	.35
Insomnia [a]	24.6	16.9	24.5	25.3	.30
Appetite loss[a]	6.4	2.7	11.9	4.0	.07
Constipation[a]	14.5	8.2	18.8	20.8	.02
Diarrhea[a]	10.5	7.2	14.4	7.3	.21
Financial difficulties[a]	4.6	7.1	7.0	5.1	.26
EORTC QLQ-C29					
Body image[b]	88.1	90.6	88.4	86.4	.94
Anxiety[b]	83.5	81.9	77.3	83.3	.48
Weight[b]	86.9	90.6	85.4	88.9	.51
Sexual interest (male) [b]	57.8	52.1	49.2	69.4	.22
Sexual interest (female) [b]	65.7	85.2	70.1	48.2	.14
Urinary frequency[a]	26.2	30.5	34.6	37.2	.02
Blood and mucus in stool[a]	1.9	4.7	3.5	6.0	.28
Stool frequency (stoma)	12.5	11.8	11.1	10.8	.95
Stool frequency (no stoma) [a]	22.3	24.2	27.8	27.1	.65

(*continued on next page*)

Table A.5 (*continued*)

	No Complications (n = 251 (49.1%))	Surgical Complications (n = 57 (11.1%))	Non-Surgical Complications (n = 66 (12.9%))	Both Surgical and Non-Surgical complications (n = 25 (4.9%))	*P*-value
Urinary incontinence[a]	12.8	10.3	16.4	18.7	.27
Dysuria[a]	1.6	0.0	1.5	1.3	.48
Abdominal pain[a]	4.3	8.5	11.1	5.1	< .01
Buttock pain[a]	7.1	10.9	11.0	15.4	.05
Bloating[a]	9.7	10.9	12.6	8.0	.49
Dry mouth[a]	15.8	18.4	24.9	24.0	.06
Hair loss[a]	1.8	4.0	3.5	3.8	.45
Taste[a]	3.7	3.4	6.5	10.3	.17
Flatulence (stoma) [a]	21.0	24.0	17.9	17.7	.84
Flatulence (no stoma) [a]	31.7	36.8	40.0	29.6	.20
Fecal incontinence (stoma) [a]	14.9	5.4	12.8	12.5	.06
Fecal incontinence (no stoma) [a]	14.0	21.8	23.1	3.7	.08
Sore skin (stoma) [a]	11.6	7.3	14.1	5.9	.61
Sore skin (no stoma)[a]	8.9	6.9	11.7	14.8	.71
Embarrassment (stoma) [a]	10.4	10.4	12.8	3.9	.52
Embarrassment (no stoma) [a]	21.2	26.4	29.2	18.5	.54
Impotence[a]	57.4	59.0	63.8	66.7	.84
Dyspareunia [a]	22.7	22.2	16.7	6.7	.69

[a] a Higher on This Scale Means That Patients Reported More Symptoms
[b] a higher score on this scale means better functioning is reported by the patients. Percentages given in the top row are calculated form the total of patients that were alive (n = 511) at the time of the questionnaire.

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