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**Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

**Department of Surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands

Department of Surgery, Meander Medical Center, Amersfoort, The Netherlands

Department of Surgery, Diakonessenhuis, Utrecht, The Netherlands

Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

Department of Surgery, Rivierenland Hospital, Tiel, The Netherlands

Department of Medical Oncology, University Medical Center, Utrecht, The Netherlands

Department of Surgery, University Medical Center, Utrecht, The Netherlands

Imaging Division, University Medical Center, Utrecht, The Netherlands

Utrecht University, Utrecht, The Netherlands

CONTACT Alice M. Couwenberg a.m.couwenberg-2@umcutrecht.nl Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

**Authors contributed equally to the manuscript.

**Supplemental data for this article can be accessed here.

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ABSTRACT

Background: Neoadjuvant chemoradiation with delayed surgery (CRT-DS) and short-course radiotherapy with immediate surgery (SCRT-IS) are two commonly used treatment strategies for rectal cancer. However, the optimal treatment strategy for patients with intermediate-risk rectal cancer remains a discussion. This study compares quality of life (QOL) between SCRT-IS and CRT-DS from diagnosis until 24 months after treatment.

Methods: In a prospective colorectal cancer cohort, rectal cancer patients with clinical stage T2-3N0-2M0 undergoing SCRT-IS or CRT-DS between 2013 and 2017 were identified. QOL was assessed using EORTC-C30 and EORTC-CR29 questionnaires before the start of neoadjuvant treatment (baseline) and at 3, 6, 12, 18 and 24 months after. Patients were 1:1 matched using propensity score matching. Between- and within-group differences in QOL domains were analyzed with linear mixed-effects models. Symptoms and sexual interest at 12 and 24 months were compared using logistic regression models.

Results: 156 of 225 patients (69%) remained after matching. The CRT-DS group reported poorer emotional functioning at 3, 6, 12, 18 and 24 months (mean difference with SCRT-IS: −9.4, −12.1, −7.3, −8.0 and −7.9 respectively), and poorer global health, physical-, role-, social- and cognitive functioning at 6 months (mean difference with SCRT-IS: −9.1, −9.8, −14.0, −9.2 and −12.6, respectively). Besides emotional functioning, all QOL domains were comparable at 12, 18 and 24 months. Within-group changes showed a significant improvement of emotional functioning after baseline in the SCRT-IS group, whereas only a minor improvement was observed in the CRT-DS group. Symptoms and sexual interest in male patients at 12 and 24 months were comparable between the groups.

Conclusions: In rectal cancer patients, CRT-DS may induce a stronger decline in short-term QOL than SCRT-IS. From 12 months onwards, QOL domains, symptoms and sexual interest in male patients were comparable between the groups. However, emotional functioning remained higher after SCRT-IS than after CRT-DS.

Introduction

Neoadjuvant therapy followed by surgery is the cornerstone of treatment in most patients with rectal cancer [1]. According to the Dutch rectal cancer guideline, patients with high-risk, locally advanced rectal cancer (including irresectable tumors, four or more suspicious regional lymph node metastases and/or suspicious extramesorectal lymph nodes) undergo chemoradiation – 45–50 Gy in fractions of 1.8–2 Gy in 5 weeks with concurrent chemotherapy – followed by delayed surgery (CRT-DS) usually after 8–12 weeks [2]. CRT-DS was designed to downsize high-risk rectal tumors and so to achieve curative resection and to decrease the risk of local recurrence [3–5]. Patients with intermediate-risk, resectable rectal cancer, receive short-course radiotherapy – 25 Gy in 5
including chemotherapy and a longer treatment duration with delayed surgery (without concurrent chemotherapy), showed a higher, although non-significant, postoperative complication rate in the SCRT-IS group (50% versus 39% in the SCRT group) and comparable oncological outcomes [14].

Nevertheless, CRT-DS involves a more extensive treatment with a longer treatment duration than SCRT-IS. On the other hand, CRT may give the opportunity to opt for organ-sparing treatment approaches in case of a cCR [9,15,16], which would be suitable in approximately 15–20% of the LARC patients (based on pathological complete response rates) [17]. Patients undergoing SCRT-IS do not have the chance to achieve cCR and to proceed to organ-preservation because of the short time interval between neoadjuvant therapy and resection. Replacement of SCRT-IS by CRT-DS in patients with intermediate-risk rectal cancer may render patients with a complete response to become eligible for organ-sparing treatment. However, this may have implications for patients’ health-related quality of life (QOL) during and after rectal cancer treatment.

Literature on the effect of SCRT-IS versus CRT-DS on patients’ QOL during treatment is scarce [18]. A randomized trial from Australia compared SCRT with CRT up to 12 months after surgery and observed no differences [18]. Nevertheless, in this study, the longer treatment duration of CRT-DS was not considered because date of surgery was set as baseline. Based on our previous observational study on QOL during rectal cancer treatment, we noticed worse QOL in patients undergoing CRT-DS compared with SCRT-IS at 6 and 12 months after the start of treatment [19]. However, these findings were based on univariable analyses. In the present study, we, therefore, aimed to compare QOL between SCRT-IS and CRT-DS from start of treatment until 24 months after in a cohort using propensity score matching.

Material and methods

The Dutch Prospective Data Collection Initiative on Colorectal Cancer (PLCRC) cohort includes adult patients with colorectal cancer and has been approved by the Medical Research Ethics Committee of the University Medical Centre (UMC) Utrecht, the Netherlands [20]. Within PLCRC, participants gave informed consent to the collection of clinical outcomes and optionally consented to questionnaires on patient reported outcomes (PROs). For the present study, we selected PLCRC participants of the Utrecht RECTal cancer (U-RECT) sub cohort, that includes patients referred for radiotherapy of rectal cancer to the Radiation-Oncology Department of the UMC Utrecht. We included patients with a cT2-3N0-2M0 enrolled between February 2013 and August 2017, who underwent routine SCRT-IS or CRT-DS with curative intent, who gave informed consent for PROs and who responded to at least one questionnaire (Figure 1). Patients diagnosed with a cT4 stage (N = 34) or with synchronous distant metastases (N = 11) were excluded because these patients may have poorer short-term prognosis which could influence QOL.

All patients were treated in accordance with the Dutch guideline and underwent intensity-modulated radiotherapy (IMRT) [2]. CRT is delivered to patients with LARC (cT4 or cT3 with a distance to the mesorectal fascia (MRF) of ≤ 1 mm, and/or cN2 and/or suspicious extramesorectal lymph node metastases) and consists of 25 × 2 Gy with concurrent oral Capecitabine (825 mg/m² twice a day) followed by delayed surgery. SCRT is administered in patients with intermediate-
risk disease (cT3c-dN0 or cT1-3N1 with a distance to the MRF of >1 mm, and cT2-3N0 before the implementation of the current guideline in 2014) and consists of 5 × 5 Gy followed by immediate surgery. Surgery is performed by the principles of a total mesorectal excision (TME), including low anterior resection (LAR) with or without temporary deviating stoma, abdomino-perineal resection (APR) with permanent colostomy or rectosigmoid resection with permanent colostomy (Hartmann’s procedure). Adjuvant therapy is not routinely administered.

QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) core QOL questionnaire (QLQ-C30) [21] and colorectal-specific questionnaire (QLQ-CR29) [22] before the start of neoadjuvant treatment (baseline) and at 3, 6, 12, 18 and 24 months after. The EORTC QLQ-C30 consists of 5 functioning domains (physical, role, emotional, cognitive and social functioning), a global health score and cancer-related symptoms [21]. The EORTC QLQ-CR29 comprises colorectal cancer-specific scales and symptoms [22]. For this study, we presented prevalent rectal cancer treatment-related symptoms [19] including fatigue, insomnia and pain of the EORTC QLQ-C30 and bowel-related items (stool frequency, flatulence and fecal incontinence) and genitourinary-related items (urinary frequency, urine incontinence, impotence and sexual interest) of the EORTC QLQ-CR29. Questionnaires were provided online or on paper and collected within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry [23]. Patient and treatment characteristics were collected from patients’ medical files.

### Statistics

To decrease the risk of confounding bias in this observational study, patients in the SCRT-IS and CRT-DS group were matched using propensity score matching (PSM). PSM is a statistical matching technique using the probability of treatment assignment conditional on observed covariates [24]. Propensity scores were estimated by logistic regression, with treatment strategy group (CRT-DS versus SCRT-IS) as dependent variable and age (continuous), sex, presence of at least one comorbidity, and tumor location as independent variables. Matching was performed according to the ‘nearest neighbour’ method using a caliper width of 0.55 times the standard deviation of the logit of the propensity score and 1:1 ratio. Patients were not matched on cT-stage, cN-stage, and MRF involvement as these variables are used as selection criteria for SCRT-IS and CRT-DS. Baseline characteristics

### Table 1. Baseline characteristics before and after propensity score matching of rectal cancer patients treated with neoadjuvant short-course radiotherapy with immediate surgery (SCRT-IS) or neoadjuvant chemoradiation with delayed surgery (CRT-DS).

|                          | Original cohort | Matched cohort* |
|--------------------------|-----------------|-----------------|
|                          | SCRT-IS N = 106 (%) | CRT-DS N = 119 (%) | SCRT-IS N = 78 (%) | CRT-DS N = 78 (%) |
| Age, median (range)      | 66 (40–85)      | 64 (42–83)      | 65 (40–83)      | 66 (47–83)      |
| Sex                      |                 |                 |                 |                 |
| Male                     | 77 (72.6)       | 85 (71.4)       | 55 (70.5)       | 54 (69.2)       |
| Female                   | 29 (27.4)       | 34 (28.6)       | 23 (29.5)       | 24 (30.8)       |
| Comorbidity              |                 |                 |                 |                 |
| >1 condition             | 66 (62.3)       | 74 (62.2)       | 43 (55.1)       | 45 (57.7)       |
| None                     | 40 (37.7)       | 45 (37.8)       | 35 (44.9)       | 33 (42.3)       |
| Tumour location          |                 |                 |                 |                 |
| <6cm                     | 36 (34.0)       | 62 (52.1)       | 31 (39.7)       | 34 (43.6)       |
| 6-10cm                   | 48 (45.3)       | 42 (35.3)       | 35 (44.9)       | 32 (41.0)       |
| >10cm                    | 22 (20.8)       | 15 (12.6)       | 12 (15.4)       | 12 (15.4)       |
| Clinical tumor stage     |                 |                 |                 |                 |
| cT2                      | 34 (32.1)       | 4 (3.4)         | 28 (35.9)       | 3 (3.8)         |
| cT3                      | 72 (67.9)       | 115 (96.6)      | 50 (64.1)       | 75 (96.2)       |
| Clinical nodal stage     |                 |                 |                 |                 |
| cN0                      | 28 (26.4)       | 8 (6.7)         | 19 (24.4)       | 4 (5.1)         |
| cN1                      | 77 (72.6)       | 32 (26.9)       | 58 (74.4)       | 17 (21.8)       |
| cN2                      | 1 (0.9)         | 79 (66.4)       | 1 (1.3)         | 57 (73.1)       |
| MRF threatened           |                 |                 |                 |                 |
| Yes                      | 1 (0.9)         | 77 (64.7)       | 1 (1.3)         | 51 (65.4)       |
| No                       | 102 (96.2)      | 39 (32.8)       | 75 (96.2)       | 25 (32.0)       |
| Unknown                  | 3 (2.8)         | 3 (2.5)         | 2 (2.6)         | 2 (2.6)         |
| Surgical procedure       |                 |                 |                 |                 |
| LAR                      | 63 (59.4)       | 61 (51.3)       | 45 (57.7)       | 45 (57.7)       |
| Hartmann                 | 10 (9.4)        | 3 (2.5)         | 7 (9.0)         | 2 (2.6)         |
| APR                      | 33 (31.1)       | 55 (46.2)       | 26 (33.3)       | 31 (39.7)       |
| Postoperative stoma      |                 |                 |                 |                 |
| No stoma                 | 22 (20.8)       | 12 (10.1)       | 18 (23.1)       | 10 (12.8)       |
| Temporary                | 41 (38.7)       | 50 (42.0)       | 27 (34.6)       | 35 (44.9)       |
| Permanent                | 43 (40.6)       | 57 (47.9)       | 33 (42.3)       | 33 (42.3)       |
| Days to surgery*         | 4 (3–5)         | 76 (62–86)      | 3 (3–5)         | 76 (62–85)      |
| Months follow-up*        | 32 (21–49)      | 39 (25–53)      | 32 (21–48)      | 40 (25–51)      |
| Treatment year*          | 2015 (2014–2016) | 2014 (2013–2015) | 2015 (2014–2016) | 2014 (2013–2015) |

Cohort matched on age, sex, comorbidity and tumor location.

*Presented as median (interquartile range).

APR: abdomino-perineal resection; CRT-DS: chemoradiation with delayed surgery; LAR: low anterior resection; MRF: mesorectal fascia; SCRT-IS: short-course radiotherapy with immediate surgery.
Table 2. Differences in quality of life domains of the EORTC QLQ-C30 questionnaire between neoadjuvant short-course radiotherapy with immediate surgery (SCRT-IS) and neoadjuvant chemoradiation with delayed surgery (CRT-DS) in a matched cohort of rectal cancer patients.

| EORTC QLQ-C30                  | Group     | baseline Mean (SD) | 3 months       | 6 months       | 12 months      | 18 months      | 24 months      |
|--------------------------------|-----------|--------------------|----------------|----------------|----------------|----------------|----------------|
|                                |           |                    | MD 95% CI      | ES3            | MD 95% CI      | ES3            | MD 95% CI      | ES3            |
| Global health                  | CRT-DS    | 72.7 (20.9)        | -2.2           | -8.7 to 4.3    | -0.1           | -15.7 to -2.5  | -0.5           | -10.2 to 3.8   | -0.2           | -3.5           | -11.0 to 3.8   | -0.2           | 3.1            | -4.7 to 11.0   | 0.2            |
|                                | SCRT-IS   | 77.3 (16.1)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |
| Physical functioning           | CRT-DS    | 88.3 (15.4)        | -2.1           | -8.2 to 3.9    | -0.1           | -9.8 to -3.6   | -0.6           | -11.0 to 2.0   | -0.3           | -2.7           | -4.0 to 9.4    | -0.2           | -1.9           | -8.9 to 5.1    | -0.1           |
|                                | SCRT-IS   | 91.4 (15.3)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |
| Role functioning               | CRT-DS    | 80.4 (26.0)        | -3.2           | -13.0 to 6.6   | -0.1           | -14.0 to -4.1  | -0.6           | -16.0 to 5.1   | -0.2           | -2.0           | -13.1 to 9.1   | -0.1           | 0.7            | -11.2 to 12.5  | 0.0            |
|                                | SCRT-IS   | 87.2 (22.4)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |
| Social functioning             | CRT-DS    | 83.8 (23.7)        | -7.9           | -2.2 to -13.8  | -0.0           | -17.5 to -0.8  | -0.4           | -9.8 to 7.9    | 0.0            | 2.6            | -6.5 to 11.8   | 0.1            | 0.3            | -9.3 to 10.0   | 0.0            |
|                                | SCRT-IS   | 88.9 (18.2)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |
| Cognitive functioning          | CRT-DS    | 90.0 (16.9)        | -3.2           | -9.5 to 3.1    | -0.2           | -12.6 to -6.2  | -0.7           | -9.4 to 4.1    | -0.2           | -4.9           | -11.9 to 2.2   | -0.3           | -5.7           | -13.1 to 1.7   | -0.3           |
|                                | SCRT-IS   | 88.2 (17.4)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |
| Emotional functioning          | CRT-DS    | 78.0 (19.6)        | -9.4           | -15.7 to -3.1  | -0.5           | -12.1 to -5.8  | -0.6           | -14.0 to -0.6  | -0.3           | -8.0           | -15.1 to -1.0  | -0.4           | -7.9           | -15.5 to -0.3  | -0.4           |
|                                | SCRT-IS   | 77.5 (22.1)        | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            | Ref            |

Italic: significant difference between SCRT-IS and CRT-DS based on linear mixed-effects models adjusted for baseline score, surgical procedure and stoma presence.

CI: confidence interval; EORTC: European Organization for Research and Treatment of Cancer; ES: standardized effect size; MD: mean difference; SD: standard deviation. Ref: reference group.

3Effect size defined as the mean difference divided by the pooled standard deviation of the baseline score and interpreted as 'no difference' (ES < 0.2), 'small difference' (ES = 0.2–0.4), 'moderate difference' (ES = 0.5–0.7), and 'large difference' (ES > 0.8).

Results

Of the 225 patients whom met the inclusion criteria, 196 (87.2%) were included in the analysis (Figure 1). The CRT-DS group included 113 (57.6%) of 196 patients with lower rectal tumors, higher cT-stages, higher cN-stages, and more positive lymph nodes (cN0 = 92.6% in the CRT-DS group). Patients in the CRT-DS and SCRT-IS group were well balanced in terms of the matched variables and surgical procedure (Table 1). As expected, patients in the CRT-DS group had more positive lymph nodes (cN0 = 92.6% in the CRT-DS group) than in the SCRT-IS group (cN0 = 73.7% in the SCRT-IS group), and distance to the MRF was shorter (7.5 mm in the CRT-DS group and 13.5 mm in the SCRT-IS group). The overall survival of the matched cohort of rectal cancer patients was 76.2% in the CRT-DS group and 77.6% in the SCRT-IS group, and distance to the MRF was shorter (7.5 mm in the CRT-DS group and 13.5 mm in the SCRT-IS group). The overall survival of the matched cohort of rectal cancer patients was 76.2% in the CRT-DS group and 77.6% in the SCRT-IS group, and distance to the MRF was shorter (7.5 mm in the CRT-DS group and 13.5 mm in the SCRT-IS group).
more patients in the CRT-DS group received a LAR with deviating stoma than in the SCRT-IS group (44.9% versus 34.6%). Median delay from completion of neoadjuvant treatment to surgery was 3 days in the SCRT-IS group and 76 days (10 weeks) in the CRT-DS group. Median follow-up time and median year of treatment in the SCRT-IS group was 32 months and 2015 respectively, and in the CRT-DS group 40 months and 2014 respectively.

Questionnaire response rates at baseline, 3, 6, 12, 18 and 24 months, accounted for follow-up time and mortality, in the SCRT-IS group were 69/78 (89%), 65/78 (84%), 58/76 (76%), 49/70 (70%), 44/65 (68%) and 35/52 (67%) respectively and in the CRT-DS group were 73/78 (94%), 66/77 (86%), 64/76 (84%), 60/72 (83%), 51/68 (75%) and 48/61 (79%) respectively. The number of responses for all individual items are presented in Supplementary Data Table S1.

Between-group differences in QOL

Compared with the SCRT-IS group, patients in the CRT-DS group reported significantly poorer emotional functioning at 3 and 6 months with moderate ES (MDs $-9.4$ and $-12.1$, respectively) and at 12, 18, and 24 months with small ES (MDs $-7.3$, $-8.0$ and $-7.9$, respectively) (Table 2). At 6 months, global health, physical-, role-, and cognitive functioning were significantly poorer in the CRT-DS group than in the SCRT-IS group with moderate ES (MDs $-8.9$, $-9.9$, $-13.6$ and $-12.3$, respectively) and social functioning was poorer with a small ES (MD $-9.2$). Besides emotional functioning, all functioning scores were comparable between the groups at 12, 18 and 24 months after the start of treatment.

Within-group differences in QOL

Within-group changes in quality of life domains of the EORTC QLQ-C30 in a matched cohort of rectal cancer patients receiving short-course radiotherapy with immediate surgery (SCRT-IS) or chemoradiation with delayed surgery (CRT-DS). Scores are presented in mean differences with the 95% confidence intervals (dashed lines). Duration of neoadjuvant treatment and approximate timing of surgery are indicated in the boxes below the graphs and the line respectively.

*Significant mean difference between baseline score and follow-up score within the SCRT-IS and CRT-DS group.

Figure 2. Within-group changes in quality of life domains of the EORTC QLQ-C30 in a matched cohort of rectal cancer patients receiving short-course radiotherapy with immediate surgery (SCRT-IS) or chemoradiation with delayed surgery (CRT-DS). Scores are presented in mean differences with the 95% confidence intervals (dashed lines). Duration of neoadjuvant treatment and approximate timing of surgery are indicated in the boxes below the graphs and the line respectively.
level after 6 months. Emotional functioning showed an increasing trend but was only significantly improved since baseline at 18 months. In both groups, physical functioning remained significantly poorer up to 24 months compared with baseline level.

**Symptoms and sexual interest**

In Figure 3, longitudinal outcomes for the selected symptoms and for sexual interest in male patients are presented stratified by SCRT-IS and CRT-DS (differences not tested for...
was observed in both treatment groups shortly after surgery randomization [18]. Similar to our findings, a decline in QOL chemotherapy at seven time points up to 12 months after adjuvant chemotherapy and CRT-DS plus 4 courses of (cT3N0-2M0) randomized between SCRT-IS plus 6 courses of trial longitudinally assessed QOL in 297 rectal cancer patients and CRT-DS [18,28]

Several other studies compared QOL between SCRT-IS and CRT-DS [18,28-30]. As mentioned earlier, an Australian trial longitudinally assessed QOL in 297 rectal cancer patients (ct3N0-2M0) randomized between SCRT-IS plus 6 courses of adjuvant chemotherapy and CRT-DS plus 4 courses of chemotherapy at seven time points up to 12 months after randomization [18]. Similar to our findings, a decline in QOL was observed in both treatment groups shortly after surgery with gradually improvement up to 12 months with the most severely affected domains/symptoms including physical- and role functioning, fatigue, pain, impotence and sexual functioning. In contrast to our study, no significant differences in short-term QOL were observed between SCRT-IS and CRT-DS. This could be explained by the re-arrangement of QOL measurements in the Australian study with date of surgery taken as baseline to align treatment duration. However, in our view, the difference in treatment duration is inherent to SCRT-IS and CRT-DS and forms an essential difference between the treatment strategies that, as suggested by our results, may affect QOL. Our aim was therefore to compare the treatment strategies including surgery and not solely radiotherapy regimens. Besides, in contrast to our study, patients in the Australian trial received adjuvant chemotherapy which may likely affect QOL.

A Dutch cross-sectional study compared QOL at a median follow-up of 58 months after diagnosis between 85 patients routinely treated with CRT-DS and 306 patients treated with SCRT-IS in the TME trial [30]. No significant differences were found in global health and functioning. A Polish cross-sectional study neither observed significant differences in QOL and sexual functioning in 222 ct3-4 rectal cancer patients randomized to SCRT-IS or CRT-DS at 12 months after surgery [28]. In a German cross-sectional study with a median follow-up of 67 months after diagnosis, no difference was found in QOL between 108 patients treated with SCRT-IS and 117 patients with CRT-DS, except for better physical functioning in the CRT-DS group [29]. These studies support our conclusion that longer-term QOL is comparable between SCRT-IS and CRT-DS.

As shown by the within-group QOL changes, patients undergoing CRT-DS took longer time to recover to pretreatment levels than patients undergoing SCRT-IS. This could be related to the longer neoadjuvant treatment duration, significance). At 12 and 24 months after the start of treatment, no significant differences in moderate/severe symptoms between the treatment strategy groups were observed (Table 3). Also, the probability for having no sexual interest was comparable between SCRT-IS and CRT-DS in male patients at 12 and 24 months after the start of treatment. For female patients, sexual interest was not presented because of the insufficient number of responses.

### Discussion

This study showed that global health, physical-, role-, cognitive- and emotional functioning were poorer in the CRT-DS group than in the SCRT-IS group at 6 months after the start of neoadjuvant treatment with moderate effect sizes. Social functioning at 6 months and emotional functioning at 12, 18 and 24 months were poorer in CRT-DS with small effect sizes. Besides better emotional functioning in the SCRT-IS group, all other QOL domains were comparable with CRT-DS on longer-term. Within-group QOL changes showed that in both groups physical functioning was significantly lower at all follow-up measurements compared with baseline. Symptoms of fatigue, insomnia, pain, stool frequency, flatulence, fecal incontinence, urinary frequency, urine incontinence and impotence as well as sexual interest in male patients were comparable between the groups at 12 and 24 months after the start of treatment.

Several other studies compared QOL between SCRT-IS and CRT-DS [18,28-30]. As mentioned earlier, an Australian trial longitudinally assessed QOL in 297 rectal cancer patients (ct3N0-2M0) randomized between SCRT-IS plus 6 courses of adjuvant chemotherapy and CRT-DS plus 4 courses of chemotherapy at seven time points up to 12 months after randomization [18]. Similar to our findings, a decline in QOL was observed in both treatment groups shortly after surgery

| Item                        | Group  | 12 months | 24 months |
|-----------------------------|--------|-----------|-----------|
| Moderate/severe:            |        |           |           |
| Fatigue                     | CRT-DS | 10/59 (16.9) | 1.8 | 0.6–5.7 | 9/48 (18.8) | 1.1 | 0.4–3.5 |
|                            | SCRT-IS| 5/49 (10.2) | Ref       |       | 6/35 (17.1) | Ref       |       |
| Insomnia                    | CRT-DS | 10/59 (16.9) | 1.5 | 0.5–4.4 | 7/48 (14.6) | 1.0 | 0.3–3.5 |
|                            | SCRT-IS| 6/49 (12.2) | Ref       |       | 5/35 (14.3) | Ref       |       |
| Pain                        | CRT-DS | 10/59 (16.9) | 1.8 | 0.6–5.7 | 7/48 (14.6) | 1.3 | 0.4–4.9 |
|                            | SCRT-IS| 5/49 (10.2) | Ref       |       | 3/35 (11.4) | Ref       |       |
| Stool frequency             | CRT-DS | 17/57 (29.8) | 1.2 | 0.5–3.0 | 9/47 (19.1) | 1.4 | 0.4–4.5 |
|                            | SCRT-IS| 12/47 (25.5) | Ref       |       | 5/34 (14.7) | Ref       |       |
| Faecal incontinence         | CRT-DS | 3/58 (5.2) | 0.8 | 0.2–4.3 | 4/47 (8.5) | N.A.* |       |
|                            | SCRT-IS| 3/48 (6.3) | Ref       |       | 0/35 (0) | Ref       |       |
| Flatulence                  | CRT-DS | 18/57 (31.6) | 2.0 | 0.8–5.0 | 11/47 (23.4) | 1.2 | 0.4–3.6 |
|                            | SCRT-IS| 9/48 (18.8) | Ref       |       | 7/35 (20.0) | Ref       |       |
| Urinary frequency           | CRT-DS | 18/59 (30.5) | 1.2 | 0.5–2.8 | 15/48 (31.3) | 0.9 | 0.3–2.2 |
|                            | SCRT-IS| 13/49 (26.5) | Ref       |       | 12/35 (34.3) | Ref       |       |
| Urinary incontinence        | CRT-DS | 10/59 (16.9) | 0.5 | 0.1–3.4 | 3/48 (6.3) | 1.1 | 0.2–7.0 |
|                            | SCRT-IS| 3/49 (6.1) | Ref       |       | 2/35 (5.7) | Ref       |       |
| Impotence                   | CRT-DS | 12/32 (37.5) | 0.7 | 0.2–1.9 | 12/21 (57.1) | 0.8 | 0.2–3.1 |
|                            | SCRT-IS| 13/28 (46.4) | Ref       |       | 11/18 (61.1) | Ref       |       |

CI: confidence interval; CRT-DS: chemoradiation with delayed surgery; N: number; NA: not applicable; OR: odds ratio; Ref: reference group; SCRT-IS: short-course radiotherapy with immediate surgery.

*Outcomes on sexual interest in female patients are not presented due to insufficient number of responses.

†No odds ratio was calculated because of zero events in the SCRT-IS group. The difference was non-significant when tested with Fisher’s Exact Test, p = 0.132.
chemotherapy administration and/or the timing of surgery. Within 24 months, however, all QOL domains have returned to baseline level or above, except for physical functioning which remained lower compared with baseline in both groups. This is in line with a study that investigated recovery of physical functioning after hospital discharge in colorectal cancer patients that showed that half of the patients had not recovered to baseline function at 6 months after diagnosis and that this was more common in rectal cancer patients [31]. This study suggested that an increase in physical activity after surgery is associated with enhanced recovery of physical functioning. More research should focus on improving physical functioning in rectal cancer patients after treatment.

Our findings suggest that emotional functioning is better in patients treated with SCRT-IS than with CRT-DS. Patients in the SCRT-IS group improved to above baseline level, equal to the level of the Dutch normative population (mean score of 89 at 24 months in patients and of 88 in the Dutch population with age of 55–75 years, based on normative population data of Profiles), which was not the case in the CRT-DS group (mean score of 82 at 24 months). The better emotional functioning in the SCRT-IS group could be related to the shorter treatment duration. Nevertheless, this effect warrants further investigation.

This study has several limitations. First, patients were not randomized to one of the neoadjuvant treatment groups. To minimize the risk of confounding bias, we matched the groups based on their propensity score for treatment conditional on baseline characteristics that may have affected treatment choice. However, this could only be performed for known covariates. Residual confounding can, therefore, not be ruled out. Also, the groups were not matched on clinical disease stage as this was highly correlated with treatment indication. We, therefore, excluded patients with most advanced disease (ct4 and/or M1) and corrected the outcomes on QOL domains for baseline scores, surgical procedure and stoma presence. Besides, the study of the Dutch TME trial, earlier discussed, reported that distance to the MRD, tumor and nodal stage were not associated with QOL in their study population [30]. Also, oncological outcomes, such as recurrence rate, are approximately comparable between resectable and locally advanced rectal cancer patients on the short-term [14,32]. We, therefore, assumed that the differences in disease stage between the groups would not influence QOL during the first 24 months after start of treatment to an important extent. Second, to keep sufficient sample size after matching, the caliper width was set at 0.55 which is wider than recommended in literature [33]. Still, matching was considered successful as the differences in baseline characteristics between the groups were small. Third, the proportion of questionnaire non-responders increased over the time and was slightly higher in the SCRT-IS group, which could have introduced non-response bias of the QOL outcomes, meaning that those who respond to the questionnaire differ from those who do not respond.

Besides the use of CRT to become eligible for organ preservation in intermediate risk rectal cancer patients, SCRT with delayed surgery has been proposed as alternative to SCRT-IS and was investigated by the Stockholm III trial [14] and by a prospective non-randomized study in elderly patients [34]. The Stockholm III trial showed comparable oncological outcomes between SCRT with delayed surgery and SCRT-IS [14]. Despite more radiation-induced toxicity after SCRT with delayed surgery, significantly less postoperative complications were observed in this group compared with SCRT-IS. Nonetheless, concerns about delaying surgery after SCRT may include the risk of tumor regrowth [34,35]. Furthermore, the effect of SCRT with delayed surgery on QOL remains yet unknown. Studies investigating the optimal fractionation of neoadjuvant radiotherapy, with or without use of additional chemotherapy, and the optimal time interval to surgery to allow for organ preservation in intermediate risk rectal cancer are warranted. Besides, larger series of QOL following organ-sparing approaches are needed to support the assumption that patients’ QOL after organ preservation is indeed better than after radical surgery [36].

In conclusion, this study suggests that the treatment strategy including CRT with delayed surgery may stronger impair patients’ QOL shortly after the start of rectal cancer treatment than SCRT with immediate surgery. However, long-term QOL seems comparable between both groups, except for a slightly better emotional functioning after SCRT-IS. Furthermore, we showed that patients of both treatment strategies have poorer physical functioning up to 24 months compared with pretreatment status. These results emphasize and stimulate the need for shared- and evidence-based decision making regarding neoadjuvant rectal cancer treatment and its purposes.

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No potential conflict of interest was reported by the authors.

ORCID
Alice M. Couwenberg [http://orcid.org/0000-0002-3547-1895]
Johannes P. M. Burbach [http://orcid.org/0000-0003-0632-9897]
Martijn P. W. Intven [http://orcid.org/0000-0002-5068-5517]
Esther C. J. Consten [http://orcid.org/0000-0002-9447-8181]
Anke B. Smits [http://orcid.org/0000-0002-7484-4244]
Joost T. Heikens [http://orcid.org/0000-0002-0663-1705]
Miriam Koopman [http://orcid.org/0000-0003-1550-1978]
Willemina M. U. van Grevenstein [http://orcid.org/0000-0002-3466-1777]
Helena M. Verkooijen [http://orcid.org/0000-0001-9480-1623]

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