Physical Fitness and Skeletal Muscle Mass During Neoadjuvant Chemoradiotherapy in Patients with Locally Advanced Rectal Cancer: An Observational Study

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Background: Patients with locally advanced rectal cancer are often considered for neoadjuvant chemoradiotherapy before resection. This presurgical treatment can have negative effects on physical fitness, muscle mass, and treatment compliance, which can negatively influence clinical outcomes. **Objective:** The aim of this study was to evaluate physical fitness and skeletal muscle mass before and after neoadjuvant chemoradiotherapy in single subjects with locally advanced rectal cancer. **Design:** An observational longitudinal study of single subjects. **Methods:** Routine care data were retrospectively analyzed. Data consisted of tumor characteristics, clinical data (eg, side effects and toxicity of the neoadjuvant chemoradiotherapy, loss of body mass), data on performance-based physical fitness, and computed tomography–derived skeletal muscle mass. An independent-samples *t* test or its nonparametric equivalent was performed on outcome measures to test for significant differences between T_0 and T_1. For comparing several subgroups in this cohort, the Mann-Whitney

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U test was performed and correlations were studied using the Pearson or Spearman correlation coefficient, as appropriate. **Results:** Data from 25 single subjects were available. Aerobic capacity (n = 25, $P = .033$) and skeletal muscle mass (n = 16, $P = .005$) were significantly reduced after neoadjuvant chemoradiotherapy. Although not statistically significant, a large number of patients demonstrated a decrease in muscle strength and functional mobility after completing neoadjuvant chemoradiotherapy. In 14 patients (56%), adverse events, dose-limiting toxicity, or early termination of treatment occurred. **Conclusions:** Aerobic capacity and skeletal muscle mass decreased following neoadjuvant chemoradiotherapy, with large interindividual differences concerning the changes in physical fitness and muscle mass. This between-subject variability indicates the importance of a personalized treatment approach. **(Rehab Oncol 2021;39:E73–E82)** *Key words: aerobic capacity, computed tomography, neoadjuvant treatment, physical fitness, preoperative care*

Colorectal cancer is the third most common type of cancer in the Netherlands,[1] with a total incidence of 14 438 in 2017, which is 12.8% of the total number of new cancer diagnoses in the Netherlands in 2017.[1] Of these 14 438 new cases of colorectal cancer, 4676 were rectal cancer, which is 32.4%.[1] In 2011, the 5-year survival rate for rectal cancer was 67.0%.[1] Patients with established high risk based on resectability and locally advanced rectal cancer (tumor, node, metastasis [TNM] stage cT4 or cT3 with a distance to the mesorectal fascia ≤1 mm and/or cN2 or extramesorectal pathological nodes)[2] are considered for an extensive treatment protocol of neoadjuvant chemoradiotherapy (nCRT).[3-7] In 2017, 48.0% of patients with rectal cancer in the Netherlands received neoadjuvant therapy (radiotherapy and/or chemotherapy) prior to elective surgery, of which 26.2% received a combination of both.[8] In rectal cancer, nCRT aims to control local disease and improve surgical resectability by downsizing the tumor.[6,9] However, this chemoradiotherapy is a therapy with significant toxic side effects, which can lead to comorbidities such as extensive diarrhea, hand-foot syndrome, cardiotoxicity, and anorexia.[10] In addition, chemoradiotherapy can have negative physical side effects, such as fatigue[11] and a decrease in aerobic capacity.[3-5,12]

A consistent positive relation has been reported between preoperative aerobic capacity and postoperative outcomes following major abdominal surgery.[4,13-17] Furthermore, literature shows an independent association between low skeletal muscle mass and a poor overall survival after resection for advanced rectal cancer.[18]

Previous studies (Table 1) investigated the effect of neoadjuvant therapy on physical fitness and skeletal muscle mass in different patient populations. Studies by West et al[3-5] investigated the effect of nCRT on aerobic capacity in patients with locally advanced resectable rectal cancer. They showed a decrease in aerobic capacity (oxygen uptake at the ventilatory anaerobic threshold and oxygen uptake at peak exercise) following nCRT. In addition, these studies demonstrated dose-limiting toxicity in some patients[3] and a decrease in muscle mitochondrial capacity.[5] Skeletal muscle mass, estimated at the level of the third lumbar vertebra from an abdominal computed tomographic (CT) scan, was also investigated in patients with different types of cancer of the gastrointestinal tract. Dalal et al[19] showed a decrease in skeletal muscle mass and body mass in patients with inoperable locally advanced pancreatic cancer after neoadjuvant chemotherapy. Daly et al[20] and Palmela et al[21] showed a decrease in skeletal muscle mass after nCRT in patients with foregut cancer and locally advanced gastric cancer, respectively. The latter study also showed dose-limiting toxicity and early termination of treatment in a large part of the patients. In contrast, the study by Heus et al[22] showed an increase in skeletal muscle mass after nCRT in patients with locally advanced rectal cancer.

These previous findings demonstrate the negative side effects of chemoradiotherapy and emphasize the importance of sufficient aerobic capacity and skeletal muscle mass for the continuation and completion of neoadjuvant treatment. Hence, these studies show that there is a decrease in aerobic capacity and/or skeletal muscle mass and early termination of nCRT in these patients, of which early termination of treatment has a negative influence on the prognosis. These parameters are important for the consideration of preoperative intervention options, such as prehabilitation, as well as for postoperative outcomes and survival in patients with gastrointestinal malignancies. To the best of our knowledge, there are currently no studies describing the effects of nCRT on physical fitness and skeletal muscle measurements in patients with rectal cancer. The aim of this study was therefore to evaluate changes in performance-based physical fitness and CT-derived skeletal muscle measurements, before and after nCRT, in single subjects with locally advanced rectal cancer scheduled for elective resection.

METHODS

Participants

Data evaluated in this observational longitudinal study consisted of routine care data of patients with locally advanced rectal cancer scheduled for nCRT at the Maastricht University Medical Center (Maastricht UMC+). Patients were referred to the physical therapy department for a screening of physical fitness before and after nCRT as part of the usual preoperative follow-up. From January 2016 until June 2018, all patients with locally advanced rectal cancer 18 years who underwent nCRT were included. This study was conducted in accordance with International Conference on Harmonization-Good

TABLE 1

Summary of Previous Literature Investigating the Effect of Neoadjuvant Treatment in Patients With Gastrointestinal Malignancies

Authors	Cancer Type	N	T	M	Results
West et al (2014)[3]	Locally advanced resectable rectal cancer	25 17♂	nCRT	CPET	↓ Oxygen uptake at ventilatory anaerobic threshold ↓ Oxygen uptake at peak exercise Dose-limiting toxicity (n = 3)
West et al (2014)[4]	Locally advanced resectable rectal cancer	12 10♂	nCRT	CPET	↓ Oxygen uptake at ventilatory anaerobic threshold ↓ Oxygen uptake at peak exercise ↓ Muscle mitochondrial capacity in vivo
West et al (2015)[5]	Locally advanced resectable rectal cancer	35 23♂	nCRT	CPET	↓ Oxygen uptake at ventilatory anaerobic threshold
Dalal et al (2012)[19]	Inoperable locally advanced pancreatic cancer	41 18♂	nCRT	CT L3	↓ Skeletal muscle mass ↓ Body mass (n = 33), median loss 4.7% + Correlation loss muscle mass and loss body mass
Daly et al (2018)[20]	Foregut cancer	225 150♂	nCT	CT L3	↓ Skeletal muscle mass ↑ Prevalence of sarcopenia (40.5%-49.1%)
Palmela et al (2017)[21]	Locally advanced gastric cancer	48 33♂	nCRT	CT L3	↓ Skeletal muscle mass Association of sarcopenia and early termination nCT Dose-limiting toxicity (n = 22) Early treatment termination (n = 17)
Heus et al (2016)[22]	Locally advanced resectable rectal cancer	74 39♂	nCRT	CT L3	↑ Skeletal muscle mass

Abbreviations: CPET, cardiopulmonary exercise testing; CT, computed tomography; L3, third lumbar vertebra; M, measurement method; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; T, treatment.

Clinical Practice guidelines, and the medical ethical committee of the Maastricht UMC+ decided (15-4-234) that this study met the ethical policies of the Maastricht UMC+ and the regulations of the Dutch government. Patients gave written informed consent for the use of routine care data for research purposes. This article is reported according to the STROBE guidelines for observational studies.

Neoadjuvant Chemoradiotherapy

All patients received standardized nCRT during a period of 5.5 weeks. Radiotherapy consisted of 45 Gy in 28 fractions of 1.8 Gy. Capecitabine (825-1000 mg/m^2 twice a day), an oral fluoropyrimidine chemotherapeutic agent, was administered on the same days that radiotherapy was performed.[2] Data of toxicity and side effects of nCRT were collected from the electronic patient files, documented according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5). In addition, the World Health Organization performance score was collected from patient files. This score is used to quantify the general well-being from patients and ranges from 0 (functioning without restriction) to 5 (deceased).[23]

Performance-Based Physical Fitness

As part of usual care, patients visited the hospital physical therapist for a preoperative screening of physical fitness before the start of nCRT (T_0) and after completing nCRT (T_1). Following nCRT, patients were scheduled for surgery; however, in case of a clinical complete response after nCRT, patients were admitted to a "wait and see policy," which consists of omission of surgery, with close clinical and radiological follow-up.[24]

Aerobic Capacity

The Steep Ramp Test (SRT) is a short and practical maximal exercise test,[25] of which its primary outcome measure (the achieved maximal work rate [WR_{peak}], in watt [W]) has been reported to be strongly correlated to objectively measured aerobic capacity (peak oxygen uptake) during maximal cardiopulmonary exercise testing in different populations, including adult cancer survivors.[26,27] An adjusted protocol of the original SRT was used, in which patients started with 2 minutes of unloaded cycling (warm-up phase), followed by a rapidly increase in work rate of 10 W every 10 seconds until voluntary exhaustion despite strong verbal encouragement. Patients were instructed and verbally coached to maintain at a pedaling frequency of 70 to 80 rotations per minute (rpm) throughout the test. When a patient was not able to maintain the pedaling speed of 60 rpm or more, the test was ended. WR_{peak} at which the pedaling frequency definitely dropped to less than 60 rpm was the primary outcome measure. Heart rate and peripherally measured oxygen saturation were measured continuously throughout the test. Before and directly after finishing the test, rating of perceived exertion (Borg score 1-10) was measured.

Functional Mobility

Functional mobility was measured with the Timed Up and Go (TUG) test and the 2-Minute Walk Test (2MWT). With the TUG test, the time needed to rise from a chair, walk 3 m, turn, walk back to the chair, and sit down again was measured in seconds.[28] In the 2MWT, the patient was instructed to walk as far as possible in 2 minutes (running was not allowed) on an equal surface of 15 m (hallway). Patients were allowed to take 1 or more rests during the test. The use of a walking aid or orthoses was accepted. Patients were instructed to stop walking at 2 minutes, and the walking distance was measured in meters.

Muscle Strength

Hand grip strength (in kg) as measured with a handheld dynamometer (JAMAR Hydraulic Hand Dynamometer, JAMAR, Patterson Medical Holdings, Inc, Warrenville, Illinois) was measured to provide an indication of the patient's overall muscle strength. Patients were seated in a chair with their elbow flexed at 90° and the forearm in a neutral position without any arm support from the chair. Patients performed the test 3 times with the dominant hand, of which the highest value (kg) was reported.[29]

Self-reported Functional Capacity in Performing Activities of Daily Living

The patient's perception of functional capacity in performing activities of daily living was measured using the Duke Activity Status Index (DASI). The DASI is a questionnaire with 12 items, corresponding with common activities of daily living linked to a particular metabolic equivalent of task (MET) score.[30]

Computed Tomography–Derived Skeletal Muscle Measurements

A contrast-enhanced CT scan of the abdomen was obtained before the start of nCRT and after completion of nCRT as part of routine preoperative cancer staging. On these images, the cross-sectional skeletal muscle area (SMA, in cm^2) at the level of the third lumbar vertebra (L3) was determined. SMA at this level is highly correlated (Pearson correlation, $r = 0.71$-0.92) with total body skeletal muscle mass.[31,32] SMA (in cm^2) was normalized for body height, which results in the skeletal muscle index (SMI, in cm^2/m^2), a measure for relative muscle mass.[33] Furthermore, SMI can be used to classify sarcopenia, for which several cancer-specific cutoff values have been published.[21,34,35]

For analysis, a single axial slide at the level of L3 was selected and the total skeletal muscle was demarcated by using predefined validated boundaries based on the number of Hounsfield units (HU), with the following thresholds: −29 to +150 HU. Selection and demarcation were performed by one trained assessor and at the moment of assessment by an independent assessor (I.M.-R.) who was unaware of the study objectives and blinded for all other patient data. Following demarcation, SMA was automatically quantified (in cm^2) using a software program (SliceOmatic; TomoVision, Montreal, Quebec, Canada). The change in SMI between the CT scans was calculated as a percentage per 100 days (percentage change divided by the number of days between the CT scans, multiplied by 100).[36] Taking into account a measurement error of 2% based on previous literature about the accuracy of CT analysis,[33] a change in SMI of less than 2% (−2% to +2%) was considered as maintenance of muscle. Loss of SMI larger than 2% was defined as clinically relevant. Finally, changes in SMI were dichotomized into loss of skeletal muscle tissue (>2% decrease) and maintenance/gain of skeletal muscle tissue (an increase or ≤2% decrease), according to recommendations of Rutten et al.[36]

Statistical Analysis

The Statistical Package for the Social Sciences for Windows (version 23.0; IBM, SPSS Inc, Chicago, Illinois) was used for statistical analysis. Shapiro-Wilk tests for normality were performed in order to evaluate the data distribution of all outcome measures. Data are presented as mean and standard deviation (SD) and as median and interquartile range (IQR). As appropriate, an independent-samples *t* test or its nonparametric equivalent, the Mann-Whitney *U* test, was performed on outcome measures to test for significant differences between T_0 (pre-nCRT) and T_1 (post-nCRT). For comparing several subgroups in this cohort, the Mann-Whitney *U* test was performed and correlations were studied using the Pearson or Spearman correlation coefficient, as appropriate. A P value of less than .05 was considered statistically significant. Where applicable, Bonferroni corrections were made to overcome the problem of multiple comparisons.

RESULTS

During the study period, 205 patients with colorectal cancer were diagnosed at the Maastricht UMC+, of which 25 patients (12.2%) were diagnosed with advanced rectal cancer and scheduled for nCRT. All these patients were screened by the hospital physical therapist prior to nCRT (T_0) and after completing nCRT (T_1). The median and IQR time between the physical therapy screening at T_0 and first nCRT session was 13.0 and 7.5 days, respectively, whereas the median and IQR time between the last nCRT session and the physical therapy screening at T_1 was 9.0 and 16.0 days, respectively. Figure 1 shows the flowchart of the study.

A total of 25 patients were included for analysis concerning preoperative data, including 19 men (76.0%) and 6 women (24.0%) with a median and IQR age of 66.0 and

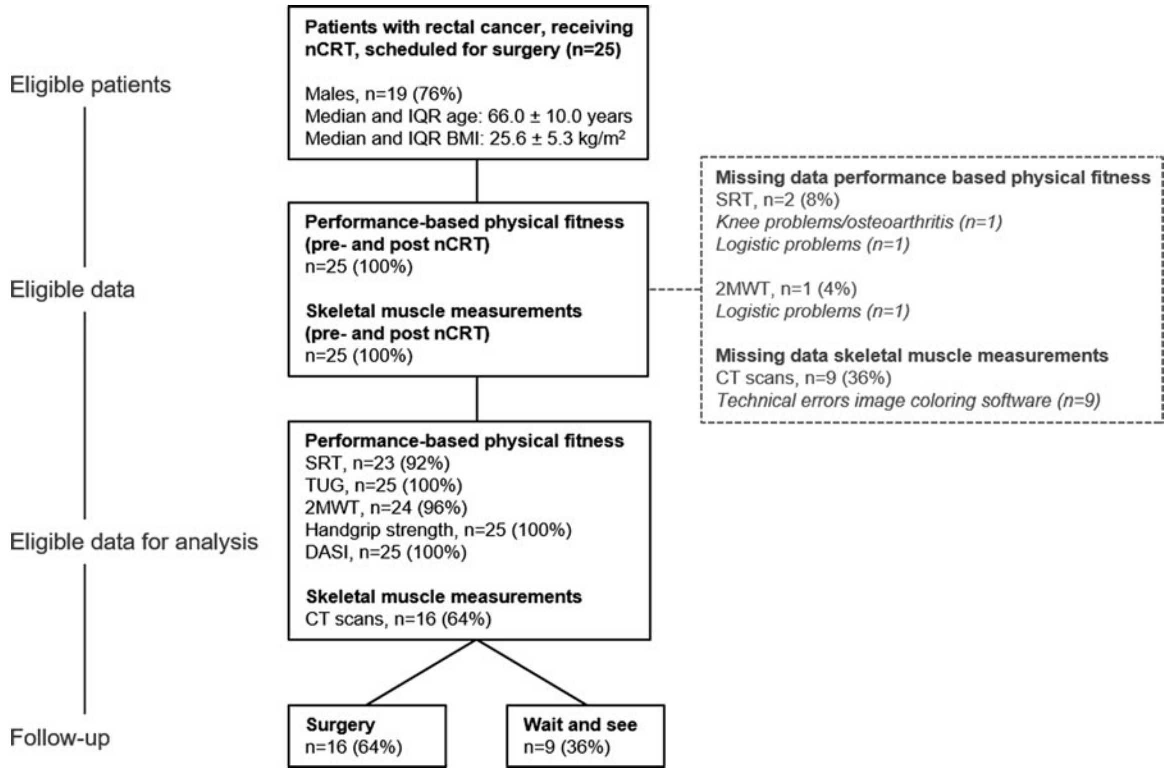

Fig. 1. Flowchart of the study. BMI, indicates body mass index; CT, computed tomography; DASI, Duke Activity Status Index; IQR, interquartile range; nCRT, neoadjuvant chemoradiotherapy; SRT, Steep Ramp Test; TUG, Timed Up and Go; 2MWT, 2-Minute Walk Test.

11.0 years, respectively. The median and IQR time between T_0 and T_1 was 107.0 and 15.5 days, respectively. Eventually, 16 patients (64.0%) underwent surgery after nCRT, whereas 9 patients (36.0%) did not undergo surgery as a result of a clinical complete response after nCRT (*wait and see policy*).[24]

Neoadjuvant Chemoradiotherapy Toxicity

Table 2 shows the patient and treatment characteristics of the total population. Thirteen patients (52.0%) experienced no toxicity of the neoadjuvant chemotherapy (CTCAE grade 0). Ten patients (40.0%) experienced mild toxicity (CTCAE grade 1), including loss of body mass, fatigue, and diarrhea, and 2 patients (8.0%) experienced moderate toxicity with hand-foot syndrome grade 2 (CTCAE grade 2). Eight patients (32.0%) experienced loss of body mass during the period of nCRT. Furthermore, in 3 patients (12.0%), dose-limiting toxicity or early termination of treatment during nCRT occurred.

Performance-Based Physical Fitness

The SRT could not be performed by 2 patients (8.0%), whereas the 2MWT was not performed by 1 patient (4.0%) (see Figure 1). All those patients who performed the SRT completed the test until voluntary exhaustion, despite strong verbal encouragement. Table 3 and Figure 2 show detailed data on performance-based physical fitness. Large interindividual variation was observed between T_0 and T_1 concerning performance-based physical fitness. There was a statistically significant decrease in achieved WR_{peak} at the SRT after completing nCRT ($P = .025$). Regarding self-reported functional capacity in performing activities of daily living, 6 patients (24.0%) reported a lower DASI score at T_1, 1 patient (4.0%) reported a higher DASI score at T_1, and 18 patients (72.0%) reported a DASI score at T_1 that was equivalent to T_0.

Computed Tomography–Derived Skeletal Muscle Measurements

CT scans at the 2 time points of all patients were available; however, because of technical issues pre- and/or post-nCRT, CT scans could not be evaluated for SMA in 9 patients (36.0%). The overall scores on performance-based physical fitness of these 9 patients did not differ from the total population. Consequently, pre- and post-nCRT data on SMA of 16 patients (64%) were complete and therefore available for analysis. Table 3 and Figure 2 show detailed data on body mass and SMI. A statistically significant decrease in SMI (>2%) was found after nCRT when compared with baseline values ($P = .01$). In 8 patients (50%), the change in SMI was less than 2% (−2.0% to +2.0%), which is defined as a maintenance of muscle mass. An additional subgroup analysis showed no significant differences in changes in performance-based physical fitness over time (T_1 vs T_0) between patients with an SMI

TABLE 2

Patient and Treatment Characteristics of the Total Population (N = 25)

Variable	n	%	Median (IQR)
Sex (male)	19	76.0	
Age, y			66.0 (10.0)
Body mass, kg			79.0 (22.5)
Body height, m			1.76 (0.15)
BMI, kg/m^2			25.6 (5.3)
Comorbidities (yes)	16	64.0	
Clinical TNM stage			
T			
cT1	0	0.0	
cT2	1	4.0	
cT3	16	64.0	
cT4	8	32.0	
cTx	0	0.0	
N			
cN0	2	8.0	
cN1	9	36.0	
cN2	14	56.0	
cNx	0	0.0	
M			
cM0	22	88.0	
cM1	1	4.0	
cMx	2	8.0	
Prediagnostic loss of body mass, kg			
Yes	9	36.0	5.0 (3.5)
No	16	64.0	
Loss of body mass during nCRT, kg			
Yes	8	32.0	3.0 (2.8)
No	17	68.0	
WHO performance status score			
0	17	68.0	
1	8	32.0	
CTCAE grade			
0	13	52.0	
1	10	40.0	
2	2	8.0	
Surgery after nCRT			
Yes	16	64.0	
Laparoscopic procedure	14	87.5	
Open procedure	2	12.5	
No (wait and see)	9	36.0	

Abbreviations: BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; IQR, interquartile range; nCRT, neoadjuvant chemoradiotherapy; TNM, tumor, node, metastasis; WHO, World Health Organization.

decrease of more than 2.0% (n = 8) and patients with an SMI decrease of 2.0% or less (n = 8). Correlations between the changes in SMI and the changes in performance-based physical fitness ranged between −0.338 and 0.266 (Spearman rho). Figure 3 shows CT scans of 2 individual patients before and after nCRT.

DISCUSSION AND CONCLUSIONS

The aim of this study was to evaluate the differences in performance-based physical fitness and CT-derived skeletal muscle measurements before and after nCRT in 25 single subjects with locally advanced rectal cancer scheduled for elective resection. Furthermore, it was an institution-based evaluation of the patient population as a first observation of events. Large interindividual variation was observed concerning changes in performance-based physical fitness, muscle mass, and the experience of negative side effects during nCRT. Aerobic capacity and skeletal muscle mass decreased significantly following nCRT. Only weak nonsignificant correlations were found between the changes in SMI and changes in performance-based physical fitness.

In line with the current study, previous studies already found that aerobic capacity was decreased after nCRT as measured by cardiopulmonary exercise testing.[3,5] These studies showed that chemotherapy itself can affect cardiorespiratory function, microcirculatory function,[37] and physical activity[38]; however, exact physiological mechanisms remain elusive. There is currently no literature available about the change in physical fitness following nCRT as objectified by other practical performance-based tests (eg, Incremental Shuttle Walk Test, TUG test). This makes it difficult to compare our data with other studies. The decrease in skeletal muscle mass can be explained by cancer-induced cachexia,[38,39] and there is a possible role for oxidative stress damage due to the chemotherapy treatment.[40] The decrease in skeletal muscle is comparable with literature on patients with other gastrointestinal malignancies receiving neoadjuvant chemo(radio)therapy.[19-21] Previous literature about the relation between skeletal muscle mass and disease prognosis showed that the negative change in skeletal muscle mass seems of more importance than muscle mass at one single time point. Liu et al[41] showed that low psoas muscle index at baseline was not associated with a poor prognosis in patients with esophageal cancer whereas a decrease in psoas muscle index had a high correlation with a poor prognosis. Rutten et al[36] showed that patients with ovarian cancer with a decrease in SMI during neoadjuvant chemotherapy had a worse survival, whereas a low SMI at a specific time point was not prognostic for overall survival. Next to SMI, sarcopenia is associated with survival, surgical complications, and treatment-related toxicities in patients with colorectal cancer.[42,43] A post hoc analysis in our cohort showed that the incidence of sarcopenia, according to the criteria from Martin et al,[34] was higher after nCRT than at baseline. These findings emphasize the importance of monitoring (physical) status to guide the patients through their medical treatments and intervene when necessary, for example, with nutrition, medication, or physical therapy. Hence, for patients who develop sarcopenia during nCRT, an intervention during this treatment course can be extra useful.

Elucidating interindividual differences over time in this population was difficult to establish, because there were only 2 time points at which performance-based physical fitness and skeletal muscle mass were measured. In addition, we have no insight into confounding factors as physical activity during nCRT. Monitoring performance-based physical fitness and skeletal muscle mass with a

TABLE 3

Performance-Based Physical Fitness and CT-Derived Skeletal Muscle Measurements Pre- and Post-nCRT

		Pre-nCRT, T_0				Post-nCRT, T_1			Mean Difference	
	n	Median (IQR)	Mean (SD)	Range	n	Median (IQR)	Mean (SD)	Range	T_0 - T_1	*P*
Performance-based physical fitness										
SRT performance, W	24	197.5 (63.3)	195.4 (59.7)	100.0-326.0	23	188.0 (63.0)	181.3 (57.4)	81.0-305.0	*−14.1*	*.026*[a]
SRT performance, W/kg	24	2.5 (1.2)	2.5 (0.7)	1.4-4.1	23	2.3 (0.9)	2.3 (0.7)	1.2-3.9	*−0.2*	*.033*[a]
HR_{peak}, beats/min		127.5 (49.0)	127.4 (30.2)	74.0-186.0		120.0 (40.1)	119.6 (25.8)	71.0-174.0		
SpO_{2rest}, %		96.5 (1.8)	95.8 (1.6)	91.0-99.0		97.0 (2.0)	96.6 (1.7)	93.0-99.0		
SpO_{2peak}, %		96.0 (3.0)	95.0 (4.0)	78.0-98.0		95.0 (3.0)	95.5 (2.0)	91.0-98.0		
Borg $score_{rest}$ (1-10)		0.0 (0.0)	0.2 (0.7)	0.0-3.0		0.0 (0.0)	0.2 (0.7)	0.0-3.0		
Borg $score_{peak}$ (1-10)		7.0 (3.0)	6.5 (1.8)	3.0-9.0		7.0 (3.8)	6.4 (1.8)	3.0-9.0		
TUG test,[b] s	25	5.8 (1.4)	6.1 (1.7)	4.0-10.6	25	6.8 (2.6)	6.5 (1.6)	3.8-9.4	*0.4*	*.095*
2MWT distance, m	25	168.0 (40.5)	172.7 (31.8)	120.0-233.0	24	168.5 (41.8)	172.0 (31.6)	120.0-240.0	*−0.7*	*.975*
Hand grip strength, kg	25	42.0 (14.0)	40.6 (10.8)	12.0-60.0	25	41.0 (17.0)	39.4 (11.9)	16.0-62.0	*−1.2*	*.728*
Self-reported functional capacity in performing activities of daily living										
DASI score (METs)[b]	25	9.0 (1.7)	8.8 (1.1)	5.1-9.9	25	9.0 (2.0)	8.5 (1.3)	5.1-9.9	*−0.3*	*.125*
CT-derived skeletal muscle measurements										
		Pre-nCRT, T_0				Post-nCRT, T_1 (n = 16)			Difference	
	n	Median (IQR)	Mean (SD)	Range	n	Median (IQR)	Mean (SD)	Range	T_0 - T_1	*P*
SMI (cm^2/m^2)[b]	16	50.6 (14.4)	51.5 (9.2)	38.1-71.1	16	49.1 (14.7)	49.4 (8.0)	38.3-64.5	−2.1	.005[c]

Abbreviations: CT, computed tomography; HR, heart rate; IQR, interquartile range; MET, metabolic equivalent task; nCRT, neoadjuvant chemoradiotherapy; SD, standard deviation; SMI, skeletal muscle index; SpO_2, peripherally measured oxygen saturation; SRT, Steep Ramp Test; TUG, Timed Up and Go; 2MWT, 2-Minute Walk Test.

[a]$P < .05$

[b]Nonparametric distribution, Wilcoxon signed rank test.

[c]$P < .01$.

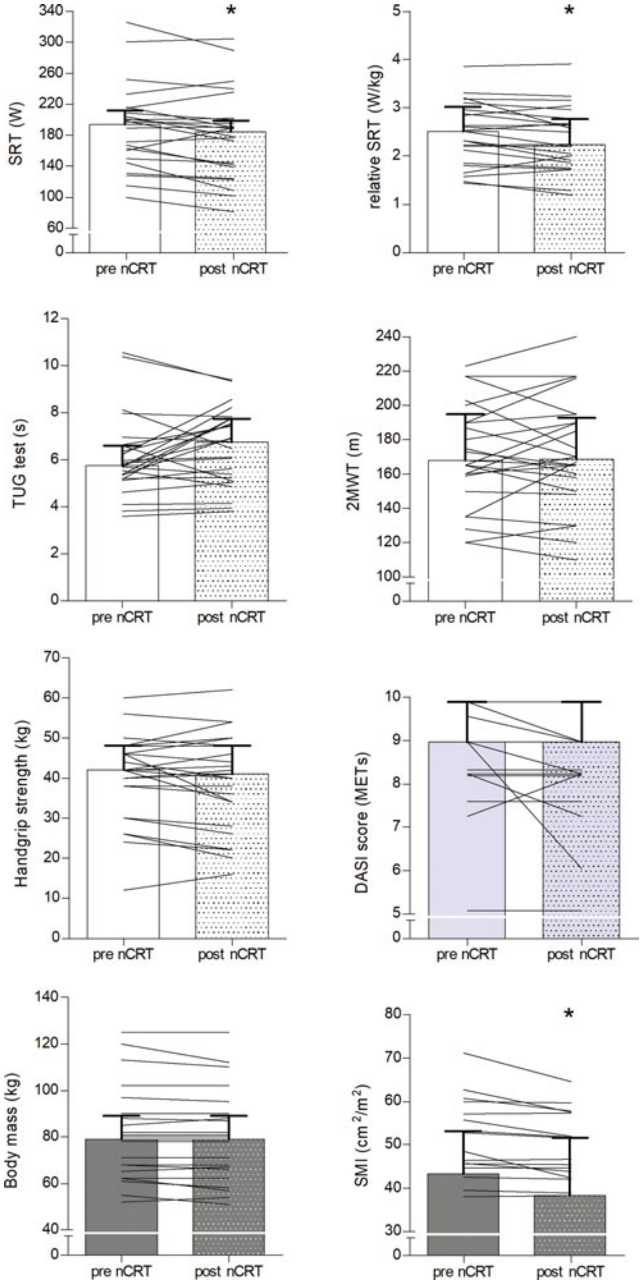

Fig. 2. Pre- and post-nCRT differences in 25 single subjects with data on physical fitness (n = 25), body mass (n = 25), and SMI (n = 16). White bars: Performance-based physical fitness. Light gray bars: Self-reported functional capacity in performing activities of daily living. Dark gray bars: Body mass and CT-derived skeletal muscle measurements. CT indicates computed tomography; DASI, Duke Activity Status Index; METs, metabolic equivalent tasks; nCRT, neoadjuvant chemoradiotherapy; SMI, skeletal muscle index; SRT, Steep Ramp Test; TUG, Timed Up and Go; 2MWT, 2-Minute Walk Test. *Statistically significant difference.

higher frequency over time in combination with wearables for physical activity can be helpful to overcome this problem. Furthermore, the current study was a monocenter study with a rather small sample size. Although clinically relevant reductions in achieved WR_{peak} at the SRT and SMI were found at the group level, a larger patient population might have led to more statistically significant reductions in physical fitness over time. Despite the small study sample, this study was conducted in real-life practice and therefore contributes to unique individual information on (the change of) estimated aerobic capacity (SRT performance) and skeletal muscle mass in patients with locally advanced rectal cancer during nCRT in a university medical center in the Netherlands. This information can help health care professionals to guide patients in their treatment course and advise them about physical activity, nutrition, and prehabilitation to improve patient satisfaction and other patient outcomes as quality of life and (long-term) clinical outcomes.[44,45]

When this study cohort was compared with the total cohort of patients with colorectal cancer undergoing colorectal resection at our hospital in the same time period (n = 180), the nCRT cohort had a better performance-based physical fitness at the baseline preoperative screening of physical fitness (T_0). This could suggest some kind of (unconscious) preselection by the health care professional, in which patients with locally advanced rectal cancer with a better physical fitness are more often considered eligible for nCRT than patients with a lower physical fitness. With the current knowledge and evidence about prehabilitation and its effectiveness, it may not be necessary to withhold patients from nCRT. Previous studies have shown that physical exercise training during nCRT is feasible and safe for patients with locally advanced rectal cancer.[46] Like previous studies, it would have been of interest to evaluate the association between preoperative aerobic capacity and muscle mass with postoperative outcomes[13-15,42] and overall survival.[18,43] These possible associations were not investigated in the current study because of the rather small sample size.

Finally, the data in this study contain a first observation of several events in this patient population, in which some individuals (see Figure 2) show a really large decrease in 1 or more of the measured parameters. With this article, we aim to share these observations to see whether other professionals have comparable events happening in their patient population. The next step is to exchange and combine these data in order to discuss the next steps for further research (eg, questions, hypothesis, and aims) and implications for daily clinical practice together.

In conclusion, the current study, an institution-based evaluation, revealed a reduction in aerobic capacity and skeletal muscle mass following nCRT in patients with locally advanced rectal cancer, with large interindividual variation concerning alterations in performance-based physical fitness, muscle mass, and the experience of negative side effects. The variability between subjects requires a personalized treatment approach including frequent monitoring of physical fitness.

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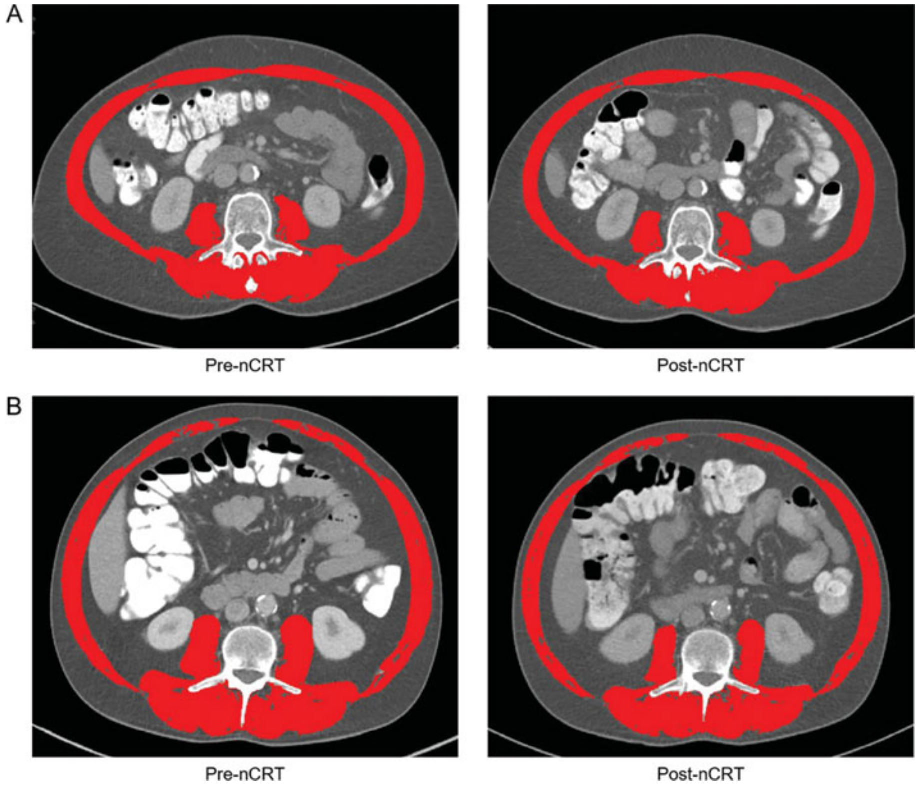

Fig. 3. CT assessment of skeletal muscle with SliceOmatic software of 2 individual patients. Upper graphs (A): 62-year-old man with no changes in SMI (+0.45%) following nCRT; lower graphs (B): a 56-year-old man with a significant decline in SMI (−11.37%) following nCRT. CT indicates computed tomography; nCRT, neoadjuvant chemoradiotherapy; SMI, skeletal muscle index.

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