Systematic Review and Meta-Analysis

Medicine®

OPEN

Physical activity programmes for patients undergoing neo-adjuvant chemoradiotherapy for rectal cancer

A systematic review and meta-analysis

Marianne Latrille, MS[a], Nicolas C. Buchs, MD[b], Frédéric Ris, MD[b], Thibaud Koessler, MD, PhD[c,d,*]

Abstract

Background: Patients diagnosed with localized rectal cancer should undergo Neoadjuvant Radio-Chemotherapy (NACRT) followed, a few weeks later, by surgical resection. NACRT is known to cause significant decline in the physical and psychological health of patients. This literature review aims to summarize the effects of a prehabilitation programme during and/or after NACRT but before surgery.

Methods: Articles included in this review have been selected by two independent researchers on Pubmed, Google Scholar, and Cochrane databases with the following terms: "Rectal Cancer AND Physical Activity" and "Exercise AND Rectal Cancer."

Results: We obtained 560 articles. We selected 12 of these, representing 7 series but only one randomized study, constituting 153 patients in total. Most studies included have considerable variation in their prehabilitation programmes, in terms of supervision, training content, frequency, intensity, duration, and temporality, in regard to NACRT and surgery. Implementing a prehabilitation programme during NACRT seems feasible and safe, with adherence ranging from 58% to 100%. VO_{2max} (maximal oxygen consumption during incremental exercise) was improved in three of the studies during the prehabilitation programme. No significant difference in the step count, 6-minute-walk test, or quality of life was seen.

Conclusions: Prehabilitation programmes during NACRT for localized rectal cancer patients are safe and feasible; however, due to considerable variation in the prehabilitation programmes and their small size, impact on fitness, quality of life, and surgical outcome are unknown. Larger randomized studies are needed.

Abbreviations: θ_L = lactate threshold, ASA score = American Society of Anesthesiologists score, BDI-II = Becks Depression Inventory, BMI = body mass index, CPET = Cardio Pulmonary Exercise Testing, EORTC QLQ CR = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal, FACT-C = Functional Assessment of Cancer Therapy-Colorectal, MFI = Multidimensional Fatigue Index, NACRT = Neoadjuvant Radio-Chemotherapy, PA = physical activity, PANAS = Positive and Negative Affect Schedule, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation, SF-36 = short form (36) Health Survey, VO_{2max} = Maximal oxygen consumption during incremental exercise.

Keywords: exercise, neo-adjuvant radiochemotherapy treatment, physical activity, prehabilitation, rectal cancer

1. Introduction

Patients diagnosed with locally advanced rectal cancer should be offered Neoadjuvant Radio-Chemotherapy (NACRT) (T3/T4, N+, Cancer Resection Margin +), followed by a treatment-free interval of 8 to 12 weeks before surgery, according to the European Society for Medical Oncology Guidelines. The aims of NACRT are to decrease the risk of local recurrence, to downstage locally advanced tumors, to increase the rate of sphincter-preserving surgery to increase circumferential margin and, sometimes, to achieve a complete clinical and pathological response. However, so far, NACRT has not been shown to improve overall survival.[1]

Although the clinical benefits of NACRT are clear, it has negative effects on patient's quality of life (QoL) and physical condition. Using two European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal (EORTC QLQ-CR) questionnaires, Herman et al showed a significant decrease in QoL during NACRT (−9.50, $P = .0024$) with return to baseline a month after the end of treatment (−0.33, $P = .92$).[2] In a small prospective study, West et al showed that NACRT significantly decreases whole-body physical condition.[3]

Prehabilitation is defined as an intervention to enhance functional capacity in anticipation of a forthcoming physiological

Editor: Jianxun Ding.

The authors have received no funding for the realization of the review.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Data sharing is not applicable to this article as no datasets were generated or analyzed during the present study.

[a] Geneva Medical School, Geneva, Switzerland, [b] Division of Visceral Surgery, Geneva University Hospital, Geneva, Switzerland, [c] Oncology Department, Geneva University Hospital, Geneva, Switzerland, [d] Geneva University, Geneva, Switzerland.

[*] Correspondence: Thibaud Koessler, Hopitaux Universitaires de Genève, 4 Rue Gabrielle Perret-Gentil, 1205 Genève, Switzerland (e-mail: Thibaud.kossler@hcuge.ch).

How to cite this article: Latrille M, Buchs NC, Ris F, Koessler T. Physical activity programmes for patients undergoing neo-adjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis. Medicine 2021;100:51(e27754).

Received: 26 March 2021 / Received in final form: 10 August 2021 / Accepted: 27 October 2021

http://dx.doi.org/10.1097/MD.0000000000027754

stressor. In cancer care, it involves a series of multidisciplinary interventions such as physical exercises, physiotherapy, nutritional support, and psychological counselling that aims to improve patient health before starting acute treatment. In the case of rectal cancer, prehabilitation will take place before surgery in order to improve patients' fitness and well-being. Standardized protocol for prehabilitation in cancer care does not exist and therefore the exercise regimen used in the literature often differ.

Hughes et al's meta-analysis showed that prehabilitation before major abdominal surgery decreases overall morbidity by 37%. However, the literature on the subject is still young, with very few randomized studies, only a small number of multimodality studies—combining nutrition, psychological and physical activity—and no clear guidance on the optimal characteristics of the intervention.[4]

In breast cancer, physical activity programmes during neoadjuvant chemotherapy have been shown to be safe and feasible and translate into an improved VO_2 peak.[5] In prostate cancer, resistance exercise, during radiotherapy improved QoL, aerobic fitness, and upper and lower-body strength, and decreased body fat.[6]

Little is known about the feasibility, impact and benefits of prehabilitation during and/or after NACRT for localized rectal cancer. This literature review aims to summarize the feasibility and the effects of a physical activity programme during NACRT in patients diagnosed with rectal cancer.

2. Objectives

The primary objective of this systematic review is to evaluate the safety and feasibility of prehabilitation programmes in patients with localized rectal cancer undergoing NACRT before surgery. The secondary objective is to give an overview of the existing programs: timing, frequency, type, intensity. We will also discuss QoL and interventional outcomes when data are available.

3. Materials and methods

This is a systematic review of literature that aims to analyze all the studies that investigate the benefits of exercise programmes implemented during NACRT, or during the treatment-free interval preceding surgery, or both. Since the articles included have been published, an ethical review was not necessary.

3.1. Literature search

We selected the articles included in this review by searching the Pubmed, Google Scholar, and Cochrane databases using the keywords "Physical Activity AND Rectal Cancer" or "Exercise AND Rectal Cancer." The search was conducted in March 2020. We did not defined a timeframe with regards to publication dates as prehabilitation literature in rectal cancer is a recent research field. Abstracts were screened and reviewed against pre-defined inclusion and exclusion criteria by two independent assessors (Marianne Latrille and Thibaud Koessler). Data were extracted by both investigators in accordance with pre-defined criteria. Reasons for the exclusion of studies were documented in the "Description of the studies" paragraph. The study selection process is presented in an adapted PRISMA flow diagram (Fig. 1).

3.2. Inclusion criteria

3.2.1. Study design. Studies considered in this review had to implement a designated physical activity programme during the time between the start of NACRT and the time of surgery. Studies had to be prospective randomized controlled trials (RCTs) or non-RCTs. The exercise programmes could be supervised or not,

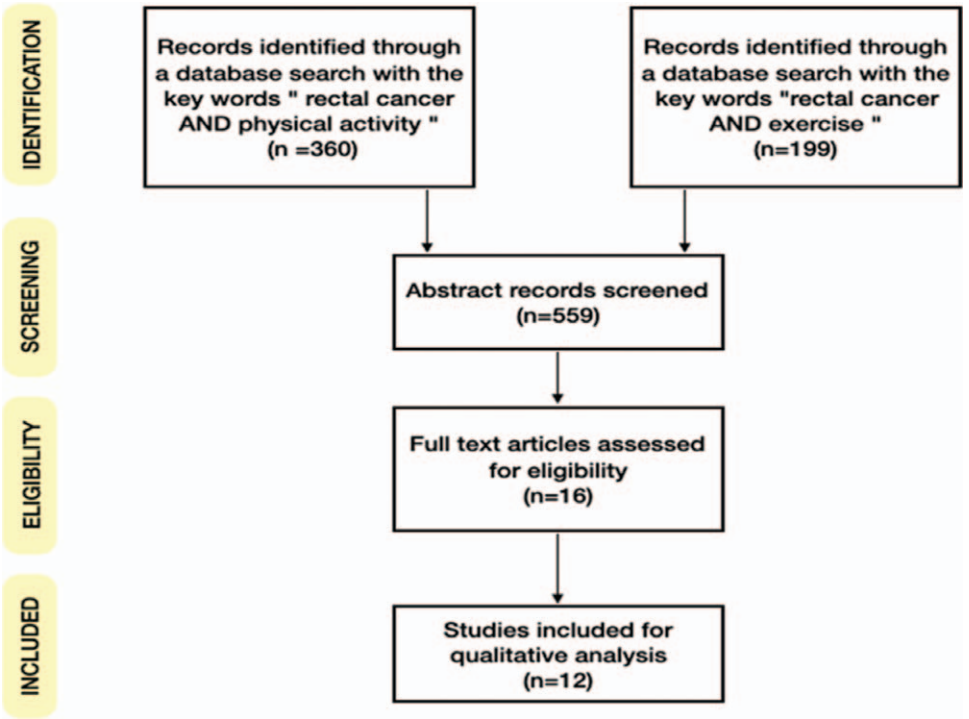

Figure 1. The article selection process.

Table 1

Study characteristics.

	West et al[9]	Singh et al[10]	Singh et al[17]	Morielli et al[11]	Heldens et al[13]	Moug et al[16]	Alejo et al[18]
National Clinical Trial (NCT)	NCT 01325909	Not registered	Not registered	Not registered	Not registered	Not registered	Not registered
Prospective	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Randomization	Non-randomized	Non-randomized	Non-randomized	Non-randomized	Non-randomized	Randomized 1:1	Non-randomized
Number of groups	2	1	1	1	1	2	1
Study design	Parallel groups, interventional, controlled trial	Single arm	Single arm	Single arm	Single arm	Randomized controlled study	Single arm
Data reporting	Data reported blind	Not available	Not available	Not available	Nor available	Not available	Not available
Adverse events	Reported	Reported	Reported	Reported	Reported	Reported	Reported
Outcome measurement	Objective	Objective	Objective	Objective	Objective	Objective	Objective
Description of patient treatment and disease	Complete	Incomplete	Incomplete	Incomplete	Complete	Incomplete	Incomplete

activity measurement with accelerometers is not considered as a form of supervision.

3.2.2. Participants. Studies included those recruiting adult (>18 years) patients with localized rectal cancer undergoing an exercise intervention during and/or after NACRT but which started before surgery. Studies were excluded if they assessed exercise interventions for: cancer survivors, patients with rectal cancer receiving palliative treatment, and exercise interventions during the NACRT phase only.

3.3. Data extraction and analysis

All studies that met the inclusion criteria were independently assessed for descriptive characteristics, such as study characteristics, participant characteristics, prehabilitation programme composition (type of exercise, duration, and frequency), compliance, outcomes measures used to quantify the impact of prehabilitation programmes (changes in functional capacity, cardiopulmonary fitness, psychological assessments, postoperative complications, and health-related QoL).

3.4. Quality assessment

RCTs included in this systematic review were checked for the method of randomization, blinding, similarity of groups at baseline, dropout rate, adherence, outcome measure assessment, sample size, and pre-specified outcomes. For the non-RCTs, the quality assessment checked for blinding (whether there was a blinded outcome assessor and whether either the care provider or patients were blinded) and for adequate description of the control/comparison group. Two reviewers independently undertook the quality assessment (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G544).

4. Results

4.1. Database search

The database search yielded 559 candidate abstracts (Fig. 1). After reviewing these and applying inclusion and exclusion criteria, 12 articles were selected.[9–20]

Out of the 12 articles, two are prospective studies protocols: the "EXERT trial" [NCT03082495] by Morielli et al[19]; and the "EMPOWER" trial [NCT01914068] by Loughney et al.[20] Those protocols were excluded from our analysis. Ten references were extracted for full text review.

After full text screening, we found only 7 original studies.[9–11,13,16–18] One independent research group used their patient dataset to publish several articles (West et al, 4 times,[9,12,14,17] with different outcomes). It is possible that Singh et al[10,17] might have done the same but, given that the characteristics of the population are different in the publications, we treated them as 2 separate studies. Given the small number of studies available, and in an effort to maximize the yield of information, studies using the same dataset but reporting different outcomes in different publications will hereafter be aggregated and analyzed as a single study.

4.2. Study characteristics

We summarized the characteristics of the 7 studies in Table 1. All studies were prospective, 1 was randomized[16]while the other 6 were non-randomized.[9–11,13,17,18] Five were single-arm studies[10,11,13,17,18] and two had two arms.[9,16] Data were reported as blind in one study[9]; this information was not given in the other 6.[10,11,13,16–18] Adverse events due to the fitness programme were reported in all studies. Out of the 12 articles, 9 reported objective [quantitative] outcomes[9–13,15–18] only one reported subjective [qualitative] outcomes.[14] Finally, out of the 7 studies, NACRT was described in detail in 2, and information was missing in 5.[9,13]

4.3. Study aims

The aims of the studies are presented in Table 2. Out of the 7 studies, 6 aimed to assess the feasibility of an exercise intervention in the neo-adjuvant setting.[10,11,13,16–18] The 4 articles by West and colleagues looked at changes in O_2 uptake,[9] physical activity levels,[12] experiences of QoL,[14] and QoL[15] as outcomes. In one study,[18] the exercise training programme took place during NACRT only (Fig. 2); in one (West), it took place after NACRT but before surgery[12,14,15]; and in 5, during and after NACRT but prior to surgery.[10,11,13,16,17]

4.4. Participants

All studies were mixed gender, with males representing 60% of the patients. Age was available for all the studies, and the mean

Table 2

Summary of study aims and outcome measures.

	Cancer stage	Cancer treatment	Exercise programme	Study aim	Primary outcome measure	Secondary outcome measure
West et al[9]	> T2/N+	NACRT	6-week supervised aerobic exercise intervention	To evaluate how physical fitness changes with NACRT and a preoperative structured responsive exercise training programme.	Changes in θL between baseline, week 0, and week 6	○ Changes in number of steps with NACRT ○ Changes in number of steps in the exercise and control groups ○ Changes in VO2 at θL and at peak until at week 15 ○ Safety and feasibility of the exercise intervention
Loughney, West et al[12]	> T2/N+	NACRT	6-week supervised aerobic exercise intervention	To evaluate changes in daily step count (numbers of steps taken) and overall physical activity level pre- and post-NACRT	Measure changes in daily PAL	○ Changes in daily step count ○ Overall PAL at the start and end of the pre-operative programme
Burke, West et al[14]	> T2/N+	NACRT	6-week supervised aerobic exercise intervention	To understand patients' experiences of QoL during a structured exercise programme	Experiences of QoL [qualitative research]	
Brunet, West et al[15]	> T2/N+	NACRT	6-week supervised aerobic exercise intervention	To assess the effects of the exercise intervention on indicators of QoL in comparison to usual care	EORTC QLQ-C30	RAND 36 – Item Health Survey
Singh et al[10]	Localized	NACRT	10-week supervised aerobic and resistance exercise intervention	To assess if the supervised aerobic and resistance exercise programme implemented during NACRT was feasible and produced any beneficial effects	Feasibility	○ Muscle strength and endurance ○ Physical performance ○ Body composition ○ Cancer-specific QoL ○ Cancer-specific fatigue
Singh et al[17]	Localized	NACRT	16-week supervised aerobic and resistance exercise intervention	To assess feasibility and potential effectiveness of a supervised presurgical exercise programme, consisting of combined resistance and aerobic training in patients with rectal cancer scheduled to receive rectal resection	Feasibility	○ Muscle strength and endurance ○ Physical performance ○ Body composition ○ Cancer-specific QoL ○ Cancer-specific fatigue
Morielli et al[11]	Stages IIA to IVA	NACRT	6-week supervised aerobic exercise intervention	To test the feasibility and safety of an aerobic exercise intervention in patients with rectal cancer, during and immediately after NACRT	Feasibility	Health-related fitness outcomes Patient-reported outcomes
Heldens et al[13]	> T2/N0 or N+	NACRT	9–17 weeks supervised resistance aerobic exercise interventions	To determine the feasibility of a supervised outpatient physical exercise training programme during NACRT in patients with rectal cancer	Feasibility	○ Functional exercise capacity ○ Muscle strength ○ Perception of fatigue ○ QoL
Moug et al[16]	Localized	NACRT	13-week unsupervised aerobic exercise intervention	To assess the feasibility of performing a physical activity intervention prior to, during and after NACRT	Feasibility	○ Physical variables ○ Psychological variables ○ QoL
Alejo et al[18]	Stages II and III	NACRT	1 educational session and 5 practical classes on aerobic, resistance and flexibility exercises	To assess adherence to the intervention	Feasibility	○ QoL ○ Psychological distress ○ Physical fitness ○ Physical activity

θL = estimated lactate threshold, $\dot{V}O_2$ = oxygen uptake, NACRT = Neo-adjuvant chemoradiotherapy, PAL = physical activity level, QoL = quality of life.

Figure 2. Structure of exercise protocol in the different studies. Latency period = period of time where the patients neither receive treatments nor does physical exercise, NACRT = neo-adjuvant chemoradiotherapy, PA = physical activity.

age was 61.7 years old. Body mass index (BMI) was available for 6 studies,[10,11,13,16–18] with an average BMI of 28.2 kg/m^2. The ASA score was available for 3 studies[9,13,16] (N: 54 patients): 30% of them were ASA1, 55% were ASA2, and 15% were ASA3.

4.5. Cancer stage and treatment

Of the 7 studies, all patients had localized rectal cancer with an indication for NACRT (153 in total). Metastatic patients are excluded, except from Morielli et al,[11] which included one metastatic patient. TNM staging at diagnosis was available in only one study[13]; and there was stage grouping in one other.[11] Details regarding NACRT were available for 4 studies only,[9,11,13,16] with radiotherapy consisting of 45 to 54 Gy in 25 to 30 fractions on weekdays with capecitabine (625–900 mg/m^2) twice daily on radiotherapy days. Of note, two studies also gave the option of using 5-Fluorouracil.[11,16] Heldens et al[13] added two cycles of XELOX (oxaliplatin 130 mg/m^2 intravenously on day 1, in combination with capecitabine 1000 mg/m^2 twice daily orally on days 1–14), 3 weekly cycle during the waiting period before surger.

4.6. Exercise intervention characteristics and outcomes

4.6.1. Exercise intervention. Out of the 7 programmes, 3 were aerobic only,[9,11,16] 3 combined aerobic and resistance,[10,13,17] and one combined aerobic, resistance and flexibility.[18]Table 3 summarizes exercise interventions characteristics.

4.6.2. Exercise intervention adherence. Adherence rates varied from 58% to 100%. They ranged in supervised programmes from 70% to 100%; and in unsupervised programmes from 58% to 83%.

4.6.3. Exercise intervention frequency and duration. Six programmes[9–11,13,16,17] had a frequency of 2 to 5 sessions per week, each session lasting 30 to 60 minutes. The seventh programme consisted of 6 educational and exercise demonstration sessions, lasting 35 to 60 minutes each.[18] Programme lasted from 6 to 16 weeks.

4.6.4. Exercise intervention intensity. For aerobic exercises, monitoring of intensity were used. In several studies, researchers used a percentage (ranging from 50% to 95%) of the estimated maximal heart rate.[10,13,17,18] In another study, patients alternated exercise at 80% and 50%, at oxygen uptake at estimated lactate threshold.[9] Morielli et al used 40% to 60% of the estimated volume of oxygen consumption reserve.[11] Lastly, Moug et al saw an incremental increase in the number of steps.[16]

Four programmes[10,13,17,18] incorporated resistance training. Intensity was modulated by modifying the number of sets (2–4) and the number of repetitions (6–15) per muscle group. To further adjust exercise intensity and training duration, two programmes used the rate of perceived exertion (Borg scale), with variable cut-offs.[13,18]

4.6.5. Exercise intervention time. Aerobic exercise training programmes were designed to last 30 to 60 minutes per session. Heldens et al had a weekly objective of 150 minutes.[13] The studies by Singh et al[10,17] incorporated in-hospital supervised sessions (60 min) as well as at-home unsupervised sessions (at least 2× 15 min/week); lastly, in the programme by Alejo et al,[18] participants were required to wear an accelerometer for a minimum of 5 and a maximum of 10 consecutive days, including 2 weekend days, with a minimum of 10 hours of complete accelerometry data recorded per day, but without exercise objectives.

4.6.6. Exercise intervention type. All 5 supervised programmes undertook an aerobic exercise training programme with cycle ergometer, treadmill or rowing. Of the 2 community-based, unsupervised programmes, one used walking,[16] and the other left it to the participants to decide.[18] Resistance exercises used weight-training exercises, such as leg presses or chest presses.

4.6.7. Exercise intervention supervision. Out of 7 prehabilitation programmes, the 5 in-hospital ones[9–11,13,17] were supervised, with no further details on the supervision frequency, except for Singh et al who reported one-on-one supervision by a qualified and accredited exercise physiologist.[17] The two home-based programmes were unsupervised.[16,18]

4.6.8. Inclusion of control group. Only two studies had a control group[9,16]; however, only one was part of a randomized study design,[16] while the other, by West et al, was a non-randomized, parallel group.[9]

4.7. Exercise intervention outcomes

4.7.1. Safety. All 7 study programmes assessed safety during the intervention, and they all reported no adverse events related to the programme and no delay in surgery due to the it.[9–11,13,16–18]

4.7.2. Physical fitness outcomes. A measure of physical fitness was used as primary outcome in one study,[9] and as a secondary outcome in three studies.[11,13,18] In the study by West et al,[9] after NACRT, both the exercise and the control groups had significantly decreased ($P < .0001$) VO_2 at lactate threshold (θ_L) and VO_2 at peak compared to pre-NACRT. After the 6-week programme, the exercise group improved VO_2 at θ_L by +2.12 mL kg^{-1} min^{-1} (95% CI +1.34–2.90; $P < .0001$), while the control group did not (−0.65 mL kg^{-1} min^{-1}, 95% CI −1.66 to +0.37; $P = .204$). The improvement was also seen in the VO_2 peak at week 6 (post-programme) compared to immediately post-NACRT (week 0), with an increase of 2.65 mL kg^{-1} min^{-1}

Table 3

Summary of exercise interventions.

First author	Study design	N (int/Ctl)	Exercise programme	Supervision, location	Frequency	Intensity	Duration	Type	Adherence (%)	Significant outcomes
West et al[9]	Pilot	39 (22/17)	Aerobic	Supervised, in-hospital	3/week for 6 weeks	*Prog*: Mod-high (% of VO_2 at θ_L peak)	30–40 min	*Aerobic*: cycle ergometer	100†	*VO_2 at θL *Physical activity
Singh et al[10]	Pilot	10 (10/0)	Aerobic and resistance	Supervised, hospital and home	2/week for 10 weeks in hospital 2 or more/week at home	*Resistance*: 2–4 sets per exercise at a 6- to 12-repetition maximum. At 70% of the one repetition maximum. *Aerobic*: 20 min, at an intensity of 60%–80% of estimated maximum heart rate	60 min in hospital and 15 min at home	*Resistance*: chest press, seated rowing, lateral pull-down, leg press, leg extension, and leg curl *Aerobic*: Treadmill, cycling, rowing ergometer	70	*Muscular strength *Muscular endurance *Physical performance *Body composition *QoL *Fatigue
Singh et al[17]	Pilot	12 (12/0)	Aerobic and resistance	Supervised, hospital and home	2/week for 16 weeks in hospital 2 or more/week at home	*Resistance*: 2–4 sets per exercise, at a 6- to 12-repetition maximum. At 70% of the one repetition maximum. *Aerobic*: 20 min, at an intensity of 60%–80% of estimated maximum heart rate	60 min in hospital and 15 min at home	*Resistance*: chest press, seated rowing, lateral pull-down, leg press, leg extension, and leg curl *Aerobic*: Treadmill, cycling, rowing ergometer	75	*Muscular strength *Physical performance *Body composition
Morielli et al[11]	Phase 1	18 (18/0)	Aerobic	Supervised, hospital	3/week for 6 weeks minimum. Optional continuation	*Aerobic*: 40%–60% of estimated volume of oxygen consumption [VO_2] reserve	50 min	*Aerobic*: Treadmill, upright bike, recumbent bike, elliptical trainer, and rowing machine	83	*Feasibility *Health-related QoL *Cancer-specific QoL *Psychosocial functioning
Heldens et al[13]	Pilot	13 (13/0)	Aerobic and resistance	Supervised, hospital	2/week for 6 weeks	*Resistance*: three series of 15 repetitions, targeting RPE: 13–14 *Aerobic*: 15 min at 50%–60% of the estimated maximal heart rate Adjusted using Borg scale from week 2	45–60 min	*Aerobic*: treadmill and cycle ergometer	70	*Feasibility *Muscular strength
Moug et al[16]	RCT	48 (24/24)	Aerobic	Unsupervised, home-based	5/week for 13 weeks	*Aerobic*: Progressive targeted stepping counts	150 min/week	*Aerobic*: Walking	83‡	*Feasibility
Alejo et al[18]	Pilot	13 (13/0)	Aerobic, resistance, flexibility	Unsupervised, home-based	5–10 consecutive days, including 2 weekend days	*Resistance*: 2 sets per exercise, at a 10- to 15-repetition maximum. RPE6–7. *Aerobic*: incremental time at an intensity of 70%–95% of maximum heart rate.	NR	Six educational sessions of exercise	58	*Feasibility *Cardiorespiratory fitness (VO_2 peak) *Health-related QoL *Psychological distress

* Significant results ($P < .05$).

† In the intervention group only.

‡ In the intervention arm.

Int/Ctl = intervention group and control group, Min = minute, NR = not reported, Prog = progressive, RCT = randomized controlled trial, RPE = rate of perceived exertion or Borg scale, VO_2 at θL = oxygen uptake at lactate threshold.

($P < .0005$) in the exercise intervention group compared to a decrease of 1.25 mL kg^{-1} min^{-1} ($P = .19$) in the control group.

The study by Morielli et al[11] had no control group. They showed a decrease of the mean VO_2 max (mean change = –1.3 mL kg^{-1} min^{-1}; 95% CI [–3.6, 1.7]) and an increase from post-NACRT to pre-surgery (mean change = +2.4 mL kg^{-1} min^{-1}; 95% CI [–0.9, 5.7]), resulting in a slight improvement from pre-NACRT to pre-surgery (mean change = +1.1 mL kg^{-1} min^{-1}; 95% CI [–1.7, 3.9]).

Lastly, 6 to 8 weeks after completing NACRT concomitantly with the educational exercise programme, patients in the Alejo et al study showed an improved VO_2 peak from a mean 24.4 to 29.6 mL kg^{-1} min^{-1} ($P = .015$).[18]

4.7.3. Surgical complications. Moug and colleagues showed that prehabilitation reduced the risk of post-surgical complication: they reported a complication rate of 67% in their study whereas in similar patients who did not undergo prehabilitation it reached 85%.

4.7.4. Step count. Moug et al,[16] in the only randomized trial, showed a decrease in the number of steps per day during NACRT and during the programme, with no significant difference between the control and the experimental groups, or before and after the programme in the experimental group. West et al,[9] in a two-arm non-randomized trial, showed a significant drop in the step count during NACRT, and a significant increase during the 6 weeks of the programme after completion of NACRT; however, this significant increase is seen in the control and in the experimental group, with no significant difference between the two groups.

4.7.5. Six-minute-walk test and other walking tests. Five studies evaluated the impact of the NACRT and their programme on walking tests. Singh et al[17] showed a significant decrease in the 400 m walk and the 6-minute backward walk during NACRT and prior to surgery. However, between baseline (16 weeks pre-surgery) and the end of the exercise programme, no significant difference in the standard 6-minute-walk or the 400 m walk was seen. A significant decrease in the 6-minute fast (2.9 ± 0.3 *vs* 2.7 ± 0.4, $P = .047$) and backward (14.2 ± 3.5 *vs* 12.0 ± 2.8, $P = .012$) walks was observed.[10] Similarly, the standard 6-minute walk was not significantly impacted in the Morielli[11] or Heldens[13] studies or in Moug's randomized trial.[16]

4.7.6. Muscular strength. Two studies evaluated muscular strength using a leg-press assessment at different points in time. Singh et al's study showed a significant improvement in leg press (kg) [121.0 ± 48.4 *vs* 153.9 ± 65.8, $P = .030$] and leg extension (kg) [56.0 ± 22.5 *vs* 68.7 ± 31.4, $P = 0.046$], pre- and post-exercise, conducted during NACRT but before surgery, and no impact on the chest press or seated rowing.[10] Heldens et al also showed a significant improvement of leg muscle strength between baseline (1st week of NACRT) and after 5 weeks of training [104.0 ± 32.3 kg *vs* 120.7 ± 34.0 kg, $P = .035$], between 5 and 10 weeks of training [120.7 ± 34.0 kg *vs* 144.8 ± 45.6 kg, $P = .019$] and between baseline and 10 weeks of training [144.8 ± 45.6 kg *vs* 104.0 ± 32.3 kg, $P < .001$].[13]

4.7.7. Muscular endurance. Only Singh et al's study looked at muscular endurance. This was done by assessing the number of repetitions on a leg press, showing a significant improvement in the number [12.0 ± 7.1 *vs* 21.2 ± 11.2, $P = .007$] after a 10-week programme conducted during NACRT but before surgery, but there was no significant improvement with the chest press.[10]

4.8. Quality-of-life outcomes

Quality-of-life (QoL) was assessed in 6 studies.[10,11,13,15,16,18] In 4, the European Organization for Research and Treatment of Cancer 30-item core Quality of Life questionnaire (EORTC QOL-C30) was used,[10,15,16,18] and two studies used the Short Form (36) Health Survey (SF-36).[11,13]

Using the EORTC QOL-C30, Singh et al showed a significant improvement in the emotional functioning (75.0 ± 14.2 [pre-exercise] *vs* 84.9 ± 26.4 [post-exercise], $P = .048$) and a significant decrease in diarrhea (36.7 ± 29.2 [pre-exercise] *vs* 21.6 ± 25.7 [post-exercise], $P = .027$) and financial difficulties (33.3 ± 27.2 [pre-exercise] *vs* 23.8 ± 30.2 [post-exercise], $P = .038$).[10] In contrast, Alejo et al showed as unique significant parameter decrease in emotional function after the intervention (88 [SD:16] *vs* 79 [SD: 18], $P = .027$). Moug et al showed no difference in the EORTC QOL-C30 fatigue item between the two arms at 12 weeks; the other items were not reported.[16]

Using the SF-36, Morielli et al showed a decrease in patients' QoL between pre- and post-NACRT, with 6 (physical functioning, role-physical, general health, vitality, social functioning, and physical health components) out of 10 items showing a significant decrease. All items significantly improved in the post-NACRT to pre-surgery time-periods. Comparing pre-NACRT to pre-surgery time points—representing the effect of the programme- emotional and mental health component were the only two items with significant (increase) variation.[11] Using SF-36, Heldens et al showed no difference at any of the four time points.[13]

4.8.1. Cancer-specific QoL. Cancer-specific QoL was measured by the Functional Assessment of Cancer Therapy—Colorectal (FACT-C) scales in two studies.[11,16] Morielli et al showed a significant decrease, pre- to post-NACRT [–13.7 (–20.9, –6.6)] but a significant increase post-NACRT to pre-surgery [20.7 (10.9, 30.5)] and pre-NACRT to pre-surgery [6.5 (0.2, 12.8)].[11] However, in their randomized trial, Moug et al showed no difference in the FACT-C total score at 12 weeks between both arms.[16]

4.8.2. Fatigue. Fatigue assessed by the multidimensional fatigue index (MFI) remained stable in the study by Heldens et al.[13]

4.8.3. Depression and affect. Using the Becks Depression Inventory (BDI-II) and the Positive and Negative Affect Schedule (PANAS), Moug et al showed no difference, at 12 weeks, between the two arms of their randomized trial.[16] Using the Hospital Anxiety and Depression Scale, Alejo et al showed a significant decrease in depression post-intervention, but no anxiety difference.

5. Discussion

To the best of our knowledge, this is the first systematic review of exercise training interventions in patients with localized rectal cancer undergoing NACRT before surgery.

All studies reported the intervention to be safe, with no adverse events linked to the intervention reported. This is especially important, as all the patients are in a curative setting and will undergo surgery. These good results are also reported by other authors[21–23] in breast cancer. In this review, adherence rates

vary from 58% to 100%. These figures are in line with what is reported by other programmes in other settings. In breast cancer prehabilitation, adherence rates range from 70% to 90%[23] and, in prehabilitation programmes for gastrointestinal cancer surgery, the mean compliance rate recorded is 78.1%, with wide variation from one study to another (16%–97%).[27,28] We notice a difference in adherence between patients enrolled in supervised programmes (mean: 80%) and those in unsupervised programmes (mean: 70%). This point did not stand out in other prehabilitation RCTs for other tumor types.[21–23] Looking at factors that maximize adherence to prehabilitation programmes, Ferreira et al showed that the biggest barrier to participation is transportation.[24] None of the studies recorded distance travelled.

5.1. Quality of the studies

However, the quality of the included studies is poor. In term of design, only one study is randomized,[16] one was two-armed but non-randomized[9] and the rest are single-arm studies.[10,11,13,17,18] The studies have a small sample size (10–48 patients). The population used is different from the average rectal population. First, male subjects are over-represented, accounting for 61% of the participants, while rectal cancer is (almost) equally represented among men and women. Secondly the participating population is younger (61.7 years old) compared to the median age of occurrence, at 70 years old, in the general population. It is possible that these two parameters have altered the studies outcomes, toward making prehabilitation less effective.

As no defined prehabilitation protocol has been established yet, the studies' exercise regimen varies a lot from one another. The period of intervention are different, as physical activity took place either during NACRT only,[18] or during NACRT and during the period before surgery[10,11,13,16,17] or only after NACRT but preceding surgery.[12,14,15] The type of exercise training varied as well. It was mainly aerobic [cycle ergometer] and resistance exercises, supervised in hospital, lasting 6 to 17 weeks. Programmes had 2 to 5 sessions per week, usually at moderate intensity, for a duration of from 30 to 60 minutes per session. This is similar to breast and prostate cancer prehabilitation programmes.[8,21] With such a heterogeneity it is currently difficult to determine when prehabilitation programmes should take place and how it should be built.

5.2. Outcomes

5.2.1. VO_2 max. Improvement in VO_2 max is an outcome of particular importance in the neo-adjuvant setting, as it is associated with surgical complication rates, late effects of therapy, and survival in breast cancer patients.[7] Cardiopulmonary Exercise Testing (CPET) outcomes, such as VO_2 max, identify patients with an increased risk of adverse perioperative outcomes.[29] Lower anaerobic thresholds and peak oxygen consumption predict increased post-operative morbidity and mortality.[30] In our review, only the non-randomized but controlled study by West et al showed an improvement in the VO_2 at θL and in the VO_2 peak after the 6-week programme. Two other studies[11,18] showed improvement in VO_2. The only randomized study, from Moug et al, did not measure VO_2. In patients undergoing major abdominal surgery, prehabilitation group with enhanced aerobic capacity [ΔET 135 (218) %; $P < .001$) reduced the number of patients with post-operative complications by 51% (relative risk 0.5; 95% confidence interval, 0.3–0.8; $P = .001$), and the intervention group showed a lower rate of complications, 31% *vs* 62%, than the control group ($P = .001$).[31] In breast cancer prehabilitation, several studies have shown an improvement in VO_2 after a 12-week exercise programme.[21,23]

5.2.2. Six-minute-walk test. The results of the six-minute-walk test did not significatively differ from control to intervention group.[16,17,11,13] This test is a valid measurement of health in cancer patients, with correlation with VO_2 peak ($r = 0.67$) and perceived physical function (EORTC QLQ-C30 physical function subscale).[25] It is a predictor of post-operative pulmonary complications for cancer patients undergoing elective abdominal or thoracic oncosurgery under general anesthesia with a cut-off at 390 m.[26] Only one study[11] measured VO_2 and the six-minute-walk test during two time periods (post-NACRT to pre-surgery and pre-NACRT to pre-surgery). These two measurements evolve in the same direction; however, only the six-minute-walk test during pre-NACRT to pre-surgery changed significantly, rendering any correlation hazardous. Two studies[10,13] showed increased patient strength during prehabilitation programmes. However, the impact of these measurements is unknown, particularly the impact on QoL or surgery outcome in a cancer population.

5.2.3. QoL. In the neoadjuvant setting, QoL can be altered in multiple ways. Six studies reported general QoL; most used the EORTC QOL-C30 questionnaire but two used the SF-36.[11,13] Two studies reported an improvement in emotional function after the intervention.[10,18] This emotional improvement was also noticed by one study using the SF-36[11]; however, the only randomized trial showed no difference in general QoL or in cancer-specific QoL using the FACT-C in the two arms.[16] This is non improvement in QoL is also reported in breast or prostate cancer prehabilitation studies.[8,21] This observation is somehow counter intuitive. We can only hypothesize that timing of measurement might be inadequate or that QoL measured trough a patient reported outcome platform could give a better grasp of the true QoL evolution. To the best of our knowledge, none such data exist for rectal cancer yet.

5.2.4. Strength and limitations of the review. The main strength of this review is that it provides an up-to-date comprehensive review of all studies using an exercise programme in patients with localized rectal cancer during or after NACRT but before surgery. This review has several important limitations. First, only a limited number of studies were published (7) and only one of them was randomized[16]; and second, important heterogeneities exist in the duration of each intervention, the period at which the prehabilitation programmes occur (before NACRT and/or during NACRT and/or after NACRT), their composition, the measured outcomes, and the time points of measured outcomes.

6. Conclusion

In conclusion, apart from being safe and feasible, little is known regarding the value of prehabilitation programmes during neoadjuvant treatment for localized rectal cancer. Currently, the benefit of prehabilitation program in this setting is largely unproved. Well designed, large, randomized trials are needed before we will able to draw any conclusion. However, given the

benefits shown by similar programmes in RCTs in other tumor types, it is plausible to expect analog results from the two large RCTs currently underway: the EXERT trial [NCT03082495] and the EMPOWER trial [NCT01914068] in localized rectal cancer.

Author contributions

Conceptualization: Marianne Latrille, Thibaud Koessler Data curation: Marianne Latrille, Thibaud Koessler Formal analysis: Marianne Latrille, Thibaud Koessler Methodology: Marianne Latrille Supervision: Thibaud Koessler Validation: Thibaud Koessler Nicolas C. Buchs, Frédéric Ris Writing – original draft: Marianne Latrille, Thibaud Koessler Writing – review & editing: Marianne Latrille, Thibaud Koessler Nicolas C. Buchs, Frédéric Ris

All authors approved the conclusions of our study.

Formal analysis: Marianne Latrille.
Investigation: Marianne Latrille.
Supervision: Thibaud Kössler.
Validation: Thibaud Kössler.
Writing – original draft: Marianne Latrille.
Writing – review & editing: Marianne Latrille, Nicolas C. Buchs, Frédéric Ris, Thibaud Kössler.

References

[1] Herman JM, Narang AK, Griffith KA, et al. The quality-of-life effects of neoadjuvant chemoradiation in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2013;85:e15–9.

[2] West MA, Loughney L, Lythgoe D, et al. The effect of neoadjuvant chemoradiotherapy on whole-body physical fitness and skeletal muscle mitochondrial oxidative phosphorylation in vivo in locally advanced rectal cancer patients—an observational pilot study. PLoS One 2014;9: e111526.

[3] Alves A, Panis Y, Mathieu P, Kwiatkowski F, Slim K, Mantion G. Association Française de Chirurgie (AFC). Mortality and morbidity after surgery of mid and low rectal cancer. Results of a French prospective multicentric study. Gastroenterol Clin Biol 2005;29:509–14.

[4] Moran J, Guinan E, McCormick P, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. Surgery 2016;160:1189–201.

[5] Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: a systematic review of randomised controlled trials. Eur J Anaesthesiol 2019;36:933–45.

[6] Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg 2019; 43:1661–8.

[7] Cornette T, Vincent F, Mandigout S, et al. Effects of home-based exercise training on VO2 in breast cancer patients under adjuvant or neoadjuvant chemotherapy (SAPA): a randomized controlled trial. Eur J Phys Rehabil Med 2016;52:223–32.

[8] Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 2009;27:344–51.

[9] West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth 2015;114:244–51.

[10] Singh F, Galvão DA, Newton RU, Spry NA, Baker MK, Taaffe DR. Feasibility and preliminary efficacy of a 10-week resistance and aerobic exercise intervention during neoadjuvant chemoradiation treatment in rectal cancer patients. Integr Cancer Ther 2018;17:952–9.

[11] Morielli AR, Usmani N, Boulé NG, et al. A phase I study examining the feasibility and safety of an aerobic exercise intervention in patients with rectal cancer during and after neoadjuvant chemoradiotherapy. Oncol Nurs Forum 2016;43:352–62.

[12] Loughney L, West MA, Dimitrov BD, Kemp GJ, Grocott MP, Jack S. Physical activity levels in locally advanced rectal cancer patients following neoadjuvant chemoradiotherapy and an exercise training programme before surgery: a pilot study. Perioper Med (Lond) 2017;6:3.

[13] Heldens AF, Bongers BC, de Vos-Geelen J, van Meeteren NL, Lenssen AF. Feasibility and preliminary effectiveness of a physical exercise training program during neoadjuvant chemoradiotherapy in individual patients with rectal cancer prior to major elective surgery. Eur J Surg Oncol 2016;42:1322–30.

[14] Burke SM, Brunet J, Sabiston CM, Jack S, Grocott MP, West MA. Patients' perceptions of quality of life during active treatment for locally advanced rectal cancer: the importance of preoperative exercise. Support Care Cancer 2013;21:3345–53.

[15] Brunet J, Burke S, Grocott MP, West MA, Jack S. The effects of exercise on pain, fatigue, insomnia, and health perceptions in patients with operable advanced stage rectal cancer prior to surgery: a pilot trial. BMC Cancer 2017;17:153.

[16] Moug SJ, Mutrie N, Barry SJE, et al. Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from the REx trial. Colorectal Dis 2019;21:548–62.

[17] Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Galvão DA. Feasibility and efficacy of presurgical exercise in survivors of rectal cancer scheduled to receive curative resection. Clin Colorectal Cancer 2017;16:358–65.

[18] Alejo LB, Pagola-Aldazabal I, Fiuza-Luces C, et al. Exercise prehabilitation program for patients under neoadjuvant treatment for rectal cancer: a pilot study. J Cancer Res Ther 2019;15:20–5.

[19] Morielli AR, Usmani N, Boulé NG, et al. Exercise during and after neoadjuvant rectal cancer treatment (the EXERT trial): study protocol for a randomized controlled trial. Trials 2018;19:35.

[20] Loughney L, West MA, Kemp GJ, et al. The effects of neoadjuvant chemoradiotherapy and an in-hospital exercise training programme on physical fitness and quality of life in locally advanced rectal cancer patients (The EMPOWER Trial): study protocol for a randomised controlled trial. Trials 2016;17:24.

[21] Hornsby WE, Douglas PS, West MJ, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol 2014;53:65–74.

[22] Rao R, Cruz V, Peng Y, et al. Bootcamp during neoadjuvant chemotherapy for breast cancer: a randomized pilot trial. Breast Cancer 2012;6:39–46.

[23] Jones LW, Douglas PS, West M, et al. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. Cancer Prev Res 2013; 6:925–37.

[24] Ramanakumar V, Agnihotram V, Bergdahl R, et al. Maximizing patient adherence to prehabilitation: what do the patients say? Support Care Cancer 2018;26:2717–23.

[25] Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. Int J Sports Med 2013;34:631–6.

[26] Lekshmi Sathyaprasad S, Thomas M, Philip FA, Krishna Km J. Performance in 6-min walk test in prediction of post-operative pulmonary complication in major oncosurgeries: a prospective observational study. Indian J Anaesth 2020;64:55–61.

[27] Ngo-Huang A, Parker NH, Bruera E, et al. Katz home-based exercise prehabilitation during preoperative treatment for pancreatic cancer is associated with improvement in physical function and quality of life. Integr Cancer Ther 2019;18:1–10.

[28] Bolshinsky V, Li MH, Ismail H, Burbury K, Riedel B, Heriot A. Multimodal prehabilitation programs as a bundle of care in gastrointestinal cancer surgery: a systematic review. Dis Colon Rectum 2018; 61:124–38.

[29] Hennis PJ, Meale PM, Grocott MP. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. Postgrad Med J 2011;87:550–7.

[30] Levett DZH, Grocot MPW. Cardiopulmonary exercise testing for risk prediction in major abdominal surgery. Anesthesiol Clin 2015;33:1–16.

[31] Barberan-Garcia A, Ubré M, Roca J, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery. Ann Surg 2018;267:50–6.