

# Meta-analysis of rehabilitation strategies for patients with rectal cancer undergoing chemotherapy and radiotherapy: evaluation of efficacy and safety

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## ABSTRACT

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**Keywords:** Rectal neoplasms, chemotherapy adjuvant, radiotherapy adjuvant, rehabilitation, meta-analysis.

**Background:** To evaluate the effectiveness and safety of rehabilitation strategies for rectal cancer patients undergoing chemotherapy or radiotherapy via meta-analysis. **Materials and Methods:** We searched PubMed, Web of Science, Embase, and Cochrane Library for English-language studies from inception to April 2025. Eligible studies were screened, quality-assessed using Cochrane and CASP tools, and meta-analyzed with RevMan 5.4. **Results:** A total of eighteen studies were included, all of which were of acceptable quality. The meta-analysis showed that in most outcome measures, such as health-related physical fitness, body indices, and exercise questionnaire scores, there were no significant differences between the exercise group and the usual care group ( $P>0.05$ ). When compared to the usual care group, the exercise group had a higher  $VO_2$  at the anaerobic threshold (AT), with a pooled OR of 2.65 (95% CI: 0.71, 4.59). In the assessment of quality of life, the Short Form-36 (SF-36) showed that after exercise, there were significant improvements in role - physical function (OR=9.10, 95% CI: 3.24, 14.97) and social function (OR=7.04, 95% CI: 0.33, 13.75) compared to the levels before exercise. There were no significant differences in the incidence of adverse events between the two groups (OR=1.57, 95% CI: 0.54, 4.57). **Conclusion:** Rehabilitation strategies incorporating exercise for patients with rectal cancer undergoing chemotherapy enhance  $VO_2$  at AT and specific quality-of-life indicators, with safety comparable to usual care.

## INTRODUCTION

Rectal cancer poses a substantial worldwide public health issue, and treatment regimens differ depending on the tumor's stage. For locally advanced cases, the standard approach usually involves 5-6 weeks of neoadjuvant chemoradiotherapy (NACRT), after which total mesorectal excision is performed <sup>(1)</sup>. For high-risk patients after surgery, adjuvant chemotherapy or radiotherapy is advised to lower the risk of recurrence <sup>(2)</sup>. Regardless of tumor stage, chemoradiotherapy (either concurrent or sequential) induces overlapping and unique adverse effects: chemotherapy-related fatigue, diarrhea, and hand-foot syndrome, combined with radiotherapy-specific toxicities such as radiation proctitis (long-term incidence up to 60% <sup>(3)</sup>), pelvic fibrosis, and pelvic floor muscle dysfunction <sup>(4)</sup>. These impairments collectively reduce patients' quality of life (QoL), disrupt treatment adherence, and compromise tumor response and long-term prognosis <sup>(5)</sup>, making the development of safe, well-tolerated rehabilitation strategies an urgent clinical priority.

Exercise-based non-pharmacological interventions have shown efficacy in mitigating treatment-related impairments in breast and lung

cancer populations <sup>(6)</sup>, yet their role in rectal cancer—especially among patients undergoing concurrent chemoradiotherapy (CCRT) or adjuvant radiotherapy—remains understudied <sup>(7)</sup>. The few existing studies on rectal cancer rehabilitation primarily focus on chemotherapy-only cohorts; limited evidence addresses the specific needs of radiotherapy patients, such as managing radiation-induced pelvic floor dysfunction or mucosal injury <sup>(8)</sup>. While preliminary data suggest exercise may alleviate fatigue in NACRT patients <sup>(9)</sup>, the consistency of its efficacy across physical, psychological, and functional outcomes, as well as its safety in the context of radiotherapy-induced tissue sensitivity, requires systematic validation.

In recent years, studies on rehabilitation strategies for rectal cancer patients have increased, but most are limited to single intervention modalities (e.g., exercise or nutritional support) or single-dimensional assessments (e.g., focusing solely on physical fitness or adverse reactions). For example, Loughney *et al.* <sup>(10)</sup> showed that exercise improved sleep efficiency in chemotherapy patients but had no significant impact on daily step count or physical activity level (PAL). Arthuso *et al.* <sup>(11)</sup> noted that radiotherapy-induced fatigue and perceived

"treatment-related harm" were key barriers to sustained exercise adherence in post-NACRT cohorts, yet no study has integrated interventions targeting both chemotherapy and radiotherapy toxicities. A crucial further gap exists in assessing outcomes related to rectal cuff injuries (such as anastomotic cuff inflammation and leakage sequelae) - a prevalent complication that impacts the success of rehabilitation. Traditional imaging methods (like computed tomography [CT] and magnetic resonance imaging [MRI]) are extensively utilized to assess these injuries, yet they have significant drawbacks: CT lacks the soft - tissue resolution needed to detect mucosal healing, and although MRI is better for anatomical visualization, it has low sensitivity in identifying early inflammatory changes or functional impairments of the rectal cuff <sup>(12)</sup>. This imaging limitation hinders accurate evaluation of rehabilitation efficacy, as tissue-level recovery cannot be objectively quantified.

This study innovatively integrates multi-modal rehabilitation strategies (e.g., exercise combined with pelvic floor training for radiotherapy-induced dysfunction) and employs a meta-analysis to systematically evaluate outcomes across four dimensions: physical fitness (e.g., peak oxygen uptake, walking endurance), physical indices (BMI, lung function), quality of life [assessed via European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Short Form-36 Health Survey (SF-36)], and safety (adverse events). Through systematic literature searching, strict screening of high - quality studies (including cohorts undergoing CCRT or adjuvant radiotherapy), and interpreting the findings in light of the constraints of conventional imaging when assessing cuff injuries, we strive to establish an evidence - based chain of evidence. Specifically, we seek to identify common characteristics of effective interventions, clarify dose-response relationships, and fill gaps in radiotherapy-focused rehabilitation research and objective outcome measurement. This work intends to provide a scientific, comprehensive intervention pathway for the whole-course management of rectal cancer patients undergoing chemotherapy and radiotherapy, with dual goals of improving treatment tolerance and enhancing long-term QoL.

## MATERIALS AND METHODS

### Approach to literature search

Computerized searches were carried out in PubMed, Web of Science, Embase, and Cochrane Library, covering the time from the beginning of each database up to April 2025, and only studies published in English were included. Using PubMed as an illustration, the English-language search strategy was

as follows:

(Rectal Cancer[Title/Abstract]) AND (Chemotherapy[Title/Abstract]) OR (Radiotherapy [Title/Abstract])) AND (Prehabilitation[Title/Abstract]) AND (Exercise[Title/Abstract]) OR (Nutritional Support[Title/Abstract]) AND (Efficacy [Title/Abstract]) AND (Safety[Title/Abstract]).

### Criteria for including and excluding literature

**Study design and inclusion criteria:** Published randomized controlled trials (RCTs) or single-arm intervention studies (both domestic and international). Study Population: Participants with a pathologically confirmed diagnosis of rectal cancer undergoing chemotherapy, radiotherapy, or both.. **Rehabilitation strategies:** In RCTs: The exercise group received exercise rehabilitation training, while the control group received standard rehabilitation care.

In single-arm intervention studies: Participants underwent exercise rehabilitation training. **Outcome measures:** Including health-related fitness outcomes, body indices, the Godin Leisure-Time Exercise Questionnaire, QoL (assessed via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Trial Outcome Index-physical/functional/colorectal (TOI-PFC), Short Form-36 Health Survey (SF-36), Muscle Function Scale-Short Form (MFSI-SF)), and incidence of adverse events (including adverse reactions and mortality).

### Chemotherapy and radiotherapy regimens:

**Chemotherapy:** Fluoropyrimidine - based protocols are widely adopted for neoadjuvant or adjuvant treatment of rectal cancer. Take 5 - fluorouracil (5 - FU) as an example: it has two main administration modes during radiotherapy. One is continuous intravenous infusion at a rate of 225 mg/m<sup>2</sup> per 24 hours, which is given either 5 to 7 days a week on radiotherapy days or throughout the entire radiotherapy course from start to finish. The other mode involves intravenous bolus injection of 5 - FU at 400 mg/m<sup>2</sup>, combined with a 20 mg/m<sup>2</sup> intravenous bolus of leucovorin calcium, administered on days 1 to 4 of the 1st and 5th weeks of radiotherapy. As an oral alternative to 5 - FU, capecitabine is usually prescribed at 825 mg/m<sup>2</sup>, taken twice daily for 5 days a week during radiotherapy. For certain cases requiring enhanced efficacy, oxaliplatin may be incorporated into the regimen. A typical example is the Folfox regimen: on day 1, 85 mg/m<sup>2</sup> of oxaliplatin is intravenously infused in 500 ml of glucose solution; from day 1 to day 5, 400 mg/m<sup>2</sup> of fluorouracil is intravenously dripped in 250 ml of glucose solution (or normal saline), along with 200 mg/m<sup>2</sup> of leucovorin calcium via intravenous drip. This entire cycle is repeated every 14 days.

**Radiotherapy:** Preoperative radiotherapy is a standard approach for locally advanced rectal cancer. In the scenario of long-course preoperative chemoradiotherapy, the irradiation field typically encompasses the primary tumor along with the draining areas of regional lymph nodes. The total radiation dose is generally between DT45 Gy and DT50.4 Gy, divided into 25 to 28 fractions and delivered over 5 to 5.5 weeks. If necessary, an additional local dose boost of 5.4 Gy (given in 3 fractions) can be added, or intensity - modulated radiotherapy (IMRT) can be used to achieve an equivalent radiation dose. For T4 tumors or those that are locally unresectable, initial chemoradiotherapy with 5 - FU or capecitabine is first administered, using the same irradiation range and dose as preoperative radiotherapy. If the tumor remains unresectable after this initial treatment, further chemoradiotherapy is required, and the local tumor dose is increased to 60 to 70 Gy. Postoperative radiotherapy is indicated based on the pathological stage of the tumor after surgery (e.g., T3N0 or T1 - 3N1 - 2). The radiation field in this case includes the tumor bed and the regional lymph node drainage areas, and the total dose is comparable to that of preoperative radiotherapy. Clinically, it is advised to initiate postoperative radiotherapy within 3 months after the surgical procedure.

#### **Exclusion criteria:**

- (1) Duplicate publications;
- (2) Literature lacking or having incomplete data regarding primary outcome measures;
- (3) Studies with outcome measures inconsistent with inclusion criteria;
- (4) Publications available only as abstracts, with full texts unavailable.
- (5) Lectures, abstracts, and review articles.

#### **Literature screening and data extraction**

Two researchers separately carried out literature screening, data extraction, and cross-checking in line with the inclusion and exclusion criteria. The initial screening was done by reading titles and abstracts to rule out ineligible or duplicate publications. The full texts of potentially pertinent studies were then further examined to decide on the final inclusion. The extracted data comprised: author, year of publication, study design, sample size, type of anticancer treatment (chemotherapy alone, radiotherapy alone, or chemoradiotherapy), intervention specifics, duration of rehabilitation training, and outcome measures. Any differences were settled by consulting a third researcher.

#### **Literature quality assessment**

Two researchers independently appraised the methodological quality of the included studies using internationally recognized, evidence-based tools

customized for various study types, thereby ensuring the reliability of the meta - analysis.

RCTs: They were evaluated by employing the Cochrane Risk of Bias Tool (RoB 2.0) <sup>(13)</sup>, which encompasses aspects like the generation of random sequences, allocation concealment, blinding methods, the completeness of outcome data, selective reporting, and other possible biases.

For single-arm intervention studies: They were assessed using the Critical Appraisal Skills Programme (CASP) checklist designed for non-randomized studies <sup>(14)</sup>. This checklist focuses on the representativeness of sample selection, the clarity in describing interventions, the objectivity of outcome measures, the completeness of follow-up, and the control of confounding factors.. Every study went through independent dual evaluation and cross-verification. Disagreements were settled via discussion or by consulting a third researcher. The results of the quality assessment were synthesized based on study types and anticancer treatment groups (chemotherapy vs. radiotherapy) to facilitate subsequent stratified meta-analyses.

#### **Statistical analysis**

Meta-analyses were carried out with RevMan 5.4 software. The  $I^2$  statistic was utilized to assess heterogeneity across studies. When  $P \geq 0.10$  and  $I^2 < 50\%$ , which signifies low heterogeneity, a fixed-effects model was adopted. If  $P < 0.10$  and  $I^2 \geq 50\%$ , indicating notable heterogeneity, a random-effects model was employed. In situations where  $P \geq 0.10$  yet  $I^2 \geq 50\%$ , the  $I^2$  statistic served as the main criterion for choosing the model. Sensitivity analysis was executed by excluding individual studies one by one and recalculating the pooled effect sizes.

## **RESULTS**

#### **Literature filtering and study enrollment**

Databases yielded a total of 153 records, and no extra records were obtained from other sources. Following the removal of 103 duplicate records, 12 irrelevant ones were excluded in the screening stage. Full - text evaluations were carried out on 38 articles, and in the end, 18 studies <sup>(15-32)</sup> were included for qualitative synthesis.

#### **Features and quality of included studies**

The fundamental attributes of the 18 included studies (such as sample size, intervention length, and chemotherapy/radiotherapy plans) are outlined in table 1. Patients with rectal cancer in studies <sup>(28)</sup> and <sup>(32)</sup> received chemotherapy intervention, while patients in the remaining studies all received combined intervention of chemotherapy plus

radiotherapy. The methodological quality was evaluated with the CASP checklist: most RCTs scored  $\geq 7$  points (out of 10), indicating high quality; most single - arm intervention studies were rated "Fairly good" in sample representativeness, intervention protocol description, and outcome measure

objectivity. Follow - up completeness was mainly "Average," and confounding bias control was rated "Average" to "Fairly good." Overall, the quality of included studies was acceptable for meta - analysis (table 2).

**Table 1.** Basic characteristics of included studies.

Serial number	First author year	Country	Research type	Inclusion number	Male	Age (years)	NACRT Protocol	Rehabilitation strategy	Training (weeks)	Outcome
[15]	Morielli 2018	Canada	RCT	32	21 (67%)	57 $\pm$ 12	NACRT	exercise	6	EORTC QLQ-C30
[16]	Morielli 2021	Canada	RCT	36	24 (67%)	57 $\pm$ 12	NACRT	exercise	6	VO2 at peak, 6MWT
[17]	Loughney 2021	UK	RCT	33	26 (79%)	60.5 $\pm$ 12	NACRT	exercise	9	EORTC QLQ-C30, VO2 at AT
[18]	Alejo 2019	Madrid	SGIS	12	3 (25%)	61 $\pm$ 7	NACRT	exercise	—	EORTC QLQ-C30, VO2 at peak, BMI
[19]	West 2019	UK	RCT	35	26 (74%)	67.5 $\pm$ 9.35	NACRT	exercise	—	VO2 at AT, VO2 at peak
[20]	Singh 2018	Australia	SGIS	10	7 (70%)	54.6 $\pm$ 14.1	NACRT	exercise	10	EORTC QLQ-C30, MFSI-SF
[21]	Moug 2019		RCT	48	31 (65%)	65.9 $\pm$ 10.5	NACRT	exercise	13	EORTC QLQ-C30, 6MWT, BMI, Complications
[22]	Morielli 2016	Canada	SGIS	18	12 (67%)	57.5 $\pm$ 10.4	NACRT	exercise		SF-36, VO2 at peak, 6MWT
[23]	Singh 2017		SGIS	12	5 (42%)	54.4 $\pm$ 12.9	NACRT	exercise	16	EORTC QLQ-C30, SF-36, MFSI-SF, Godin Leisure-Time Exercise Questionnaire
[24]	Heldens 2016	Netherlands	SGIS	9	8 (89%)	64.4 $\pm$ 10.9	NACRT	exercise	5	6MWT
[25]	West 2015	United Kingdom	SGIS	25	17(68%)	67.7 $\pm$ 9.2	NACRT	exercise	14	VO2 at AT, VO2 at peak, FEV1, FEV1/FVC, Haemoglobin, BMI, mortality
[26]	Lee 2018	Australia	RCT	8	5 (63%)	$\geq 18$	NACRT	exercise	—	Complications,
[27]	Lin 2014	China	RCT	45	26 (58%)	56.5 $\pm$ 10.3	NACRT	exercise	12	EORTC QLQ-C30, Godin Leisure-Time Exercise Questionnaire, 6MWT,
[28]	Adamsen 2009	Denmark	RCT	269	196 (73%)	average 47 (range 20-65)	Chemotherapy	exercise	6	EORTC QLQ-C30
[29]	Lee MK 2018	Korea	RCT	72	35 (48.6%)	56.3 $\pm$ 9.4	Radiotherapy, and/or chemotherapy	exercise	6	Godin Leisure-Time Exercise Questionnaire, 6MWT, BMI
[30]	Zimmer 2018	Germany	RCT	24	21 (88%)	50-81	NACRT	exercise	4	TOI-PFC, 6MWT
[31]	West 2014	United Kingdom	SGIS	12	10 (83%)	69 $\pm$ 10	NACRT	exercise	—	VO2 at peak, FEV1, FEV1/FVC, Haemoglobin, BMI
[32]	Kim 2019	Korea	RCT	71	35 (49%)	56.25 $\pm$ 9.45	Adjuvant chemotherapy	exercise	12	TOI-PFC, Godin Leisure-Time Exercise Questionnaire

SGIS: Single-group intervention study; NACRT: Neoadjuvant chemoradiation treatment; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; TOI-PFC: Trial Outcome Index-physical/functional/colorectal; SF-36: Short Form-36 Health Survey; MFSI-SF: Muscle Function Scale-Short Form; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; BMI: Body Mass Index.

Table 2. Results of literature quality assessment.

Serial number	First author year	Research type	Cochrane	CASP				
				Representativeness of the sample	Clarity of intervention description	Objectivity of outcome measures	Completeness of follow-up	Control of confounding bias
[15]	Morielli 2018	RCT	8	—	—	—	—	—
[16]	Morielli 2021	RCT	8	—	—	—	—	—
[17]	Loughney 2021	RCT	7	—	—	—	—	—
[18]	Alejo 2019	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Average
[19]	West 2019	RCT	9	—	—	—	—	—
[20]	Singh 2018	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Fairly good
[21]	Moug 2019	RCT	8	—	—	—	—	—
[22]	Morielli 2016	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Average
[23]	Singh 2017	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Average
[24]	Heldens 2016	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Fairly good
[25]	West 2015	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Average
[26]	Lee 2018	RCT	8	—	—	—	—	—
[27]	Lin 2014	RCT	8	—	—	—	—	—
[28]	Adamsen 2009	RCT	7	—	—	—	—	—
[29]	Lee MK 2018	RCT	7	—	—	—	—	—
[30]	Zimmer 2018	RCT	8	—	—	—	—	—
[31]	West 2014	SGIS	—	Fairly good	Fairly good	Fairly good	Average	Fairly good
[32]	Kim 2019	RCT	7	—	—	—	—	—

"Fairly good" indicates that the evaluation result for this dimension met reasonable standards. "Average" indicates certain limitations but does not fully negate the study's value. "—" indicates that relevant data were not provided or not included in the assessment. SGIS: Single-group intervention study; CASP: Critical Appraisal Skills Programme.

### Health-related fitness outcomes

Meta-analysis results for health-related fitness are presented in figure 1. The key findings are as follows:

Volume of oxygen consumption ( $VO_2$ ) at anaerobic threshold (AT): Three studies<sup>(17,19,25)</sup> were included in the analysis, and the exercise group showed a significantly higher  $VO_2$  at AT compared to the usual care group (pooled odds ratio [OR]=2.65, 95% confidence interval [CI]: 0.71–4.59,  $Z=2.67$ ,  $P=0.008$ ), indicating a statistically significant beneficial effect of exercise.

Peak  $VO_2$  (group comparison): Three studies<sup>(16,19,25)</sup> suggested a tendency for higher peak  $VO_2$  in the exercise group, but the difference was not significant (pooled OR=2.33, 95% CI: -1.66–6.32,  $Z=1.27$ ,  $P=0.20$ ).

Peak  $VO_2$  (single-group pre-post): Three studies<sup>(18,22,31)</sup> found no significant change in peak  $VO_2$  before and after exercise (pooled OR=1.03, 95% CI: -3.26–5.31,  $Z=0.47$ ,  $P=0.64$ ).

6-minute walk test (6MWT, group comparison): Five studies<sup>(16,21,27,29,30)</sup> revealed no significant difference between the exercise group and the usual care group (pooled OR= -87.31, 95% CI: -334.55–159.94,  $Z=0.69$ ,  $P=0.49$ ).

6MWT (single-group pre-post): Two studies<sup>(22,24)</sup> found no significant change in 6MWT distance before and after exercise (pooled OR= -24.87, 95% CI: -78.95–29.20,  $Z=0.90$ ,  $P=0.37$ ).

### Body indices

Meta-analysis of body indices showed no statistically significant differences in all outcomes:

BMI (group comparison): Two studies<sup>(21,29)</sup> were included, with a pooled OR of -0.32 (95% CI: -1.58–0.94,  $Z=0.50$ ,  $P=0.62$ ).

BMI (single-group pre-post): Three studies<sup>(18,25,31)</sup> found no significant change, with a pooled OR of 0.07 (95% CI: -0.61–1.75,  $Z=0.08$ ,  $P=0.94$ ).

Forced expiratory volume in 1 second ( $FEV_1$ , single-group pre-post): Two studies<sup>(25,31)</sup> showed a pooled OR of 0.03 (95% CI: -0.31–0.37,  $Z=0.19$ ,  $P=0.85$ ), indicating no significant change.

$FEV_1$ /forced vital capacity (FVC, single-group pre-post): Two studies<sup>(25,31)</sup> revealed a pooled OR of -0.43 (95% CI: -4.65–3.79,  $Z=0.20$ ,  $P=0.84$ ), with no significant difference.

Hemoglobin (single-group pre-post): Two studies<sup>(25,31)</sup> found a pooled OR of 0.18 (95% CI: -0.44–0.79,  $Z=0.56$ ,  $P=0.58$ ), showing no significant change.

### Godin leisure-time exercise questionnaire scores

Meta-analysis results for exercise volume (assessed by the Godin Questionnaire) were no significant differences between the exercise group and the usual care group across all intensity levels:

Strenuous-intensity exercise: Three studies<sup>(23,29,32)</sup> yielded a pooled OR of 0.82 (95% CI: -0.09–1.72,  $Z=1.76$ ,  $P=0.08$ ).

Moderate-intensity exercise: Three studies<sup>(23,29,32)</sup> showed a pooled OR of 67.98 (95% CI: -93.79–229.75,  $Z=0.82$ ,  $P=0.41$ ).

Mild-intensity exercise: Two studies<sup>(23,29)</sup> found a pooled OR of -1.19 (95% CI: -3.41–1.04,  $Z=1.04$ ,  $P=0.30$ ).

Total exercise volume: Three studies<sup>(23,29,32)</sup> revealed a pooled OR of 147.89 (95% CI: -26.84–322.62,  $Z=1.66$ ,  $P=0.10$ ).

Total exercise volume (MET): Two studies<sup>(27,29)</sup> showed a pooled OR of 579.95 (95% CI: -887.11–2047.01,  $Z=0.77$ ,  $P=0.44$ ).

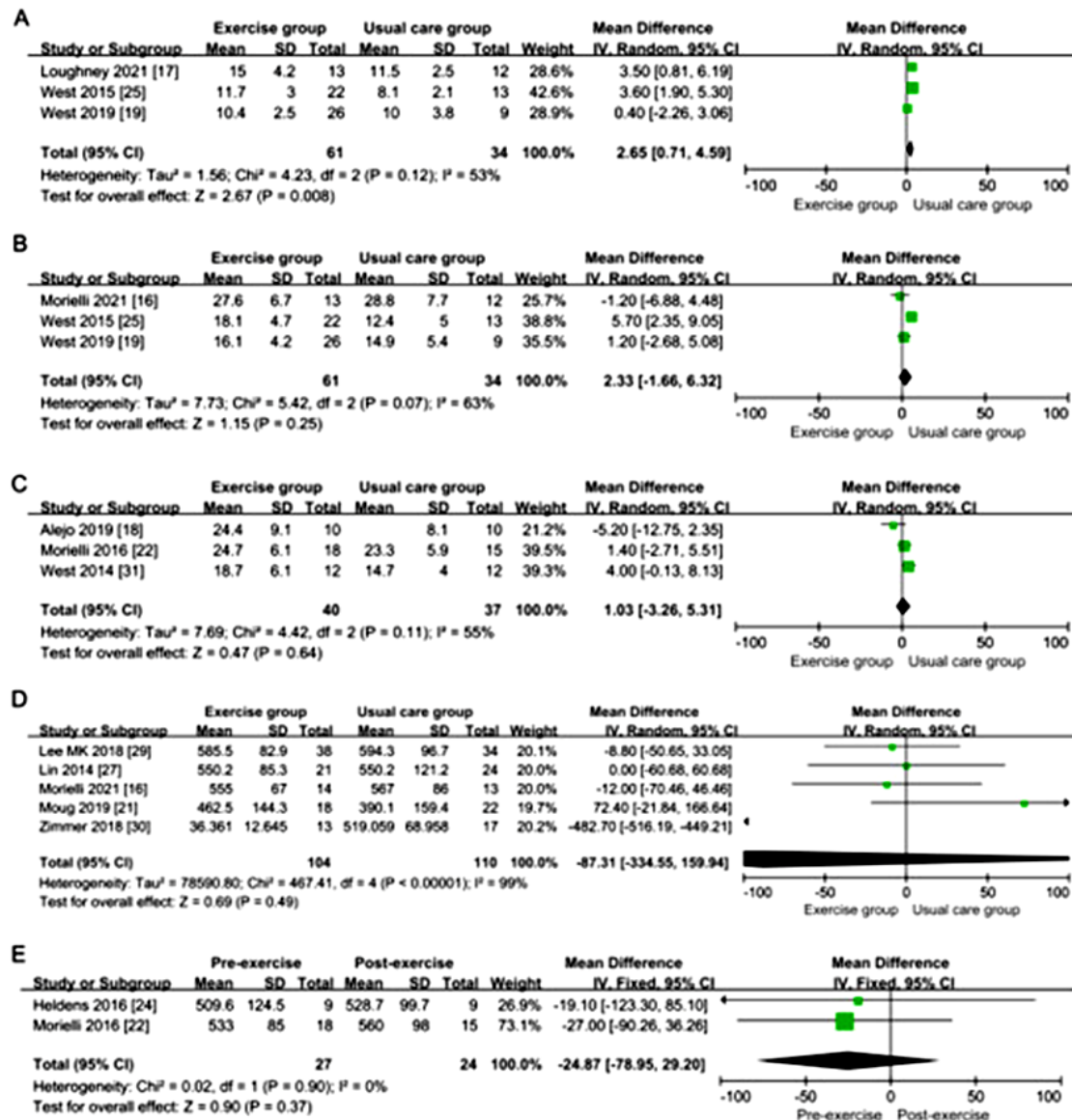


Figure 1. Forest map of the Meta-analysis of Health-Related Fitness Outcomes; (A) VO<sub>2</sub> at AT; (B) VO<sub>2</sub> at peak (group - comparison); (C) VO<sub>2</sub> at peak (single - group); (D) 6MWT (group - comparison); (E) 6MWT (single - group).

### Quality of life (QoL)

QoL was measured using four scales (EORTC QLQ-C30, TOI-PFC, SF-36, MFSI-SF), with the following key findings from meta-analysis:

Group comparison: No significant differences were observed between the exercise group and the usual care group in global health status, physical function, role function, emotional function, cognitive function, social function, or symptom scores (e.g., fatigue, nausea/vomiting, pain) (all  $P > 0.05$ ).

Single-group pre-post: No significant changes were detected in all QoL domains before and after exercise (all  $P > 0.05$ ). There was a non-significant trend of increased constipation (pooled OR=7.48, 95% CI: -3.16–16.31,  $P = 0.10$ ).

TOI-PFC: Between the exercise group and the usual care group, no significant differences were found in physical well-being, functional well-being,

social/family well-being, or emotional well-being (all  $P > 0.05$ ). A non-significant trend of improved social/family well-being was noted in the exercise group (pooled OR=1.32, 95% CI: -0.52–3.16,  $P = 0.16$ ).

SF-36: Meta-analysis results for SF-36 (single-group pre-post comparison) are shown in figures 2:

Physical functioning: Two studies (22, 23) found a pooled OR of 3.11 (95% CI: -0.58–6.80,  $Z = 1.65$ ,  $P = 0.10$ ), with no significant change.

Role-physical function: Two studies (22, 23) revealed a significant improvement post-exercise (pooled OR=9.10, 95% CI: 3.24–14.97,  $Z = 3.04$ ,  $P = 0.002$ ).

Bodily pain: Two studies (22, 23) showed a pooled OR of 5.27 (95% CI: -1.93–12.47,  $Z = 1.44$ ,  $P = 0.15$ ), with no significant change.

General health: Two studies (22, 23) found a pooled OR of 2.89 (95% CI: -3.03–8.81,  $Z = 0.96$ ,  $P = 0.34$ ), with no significant change.

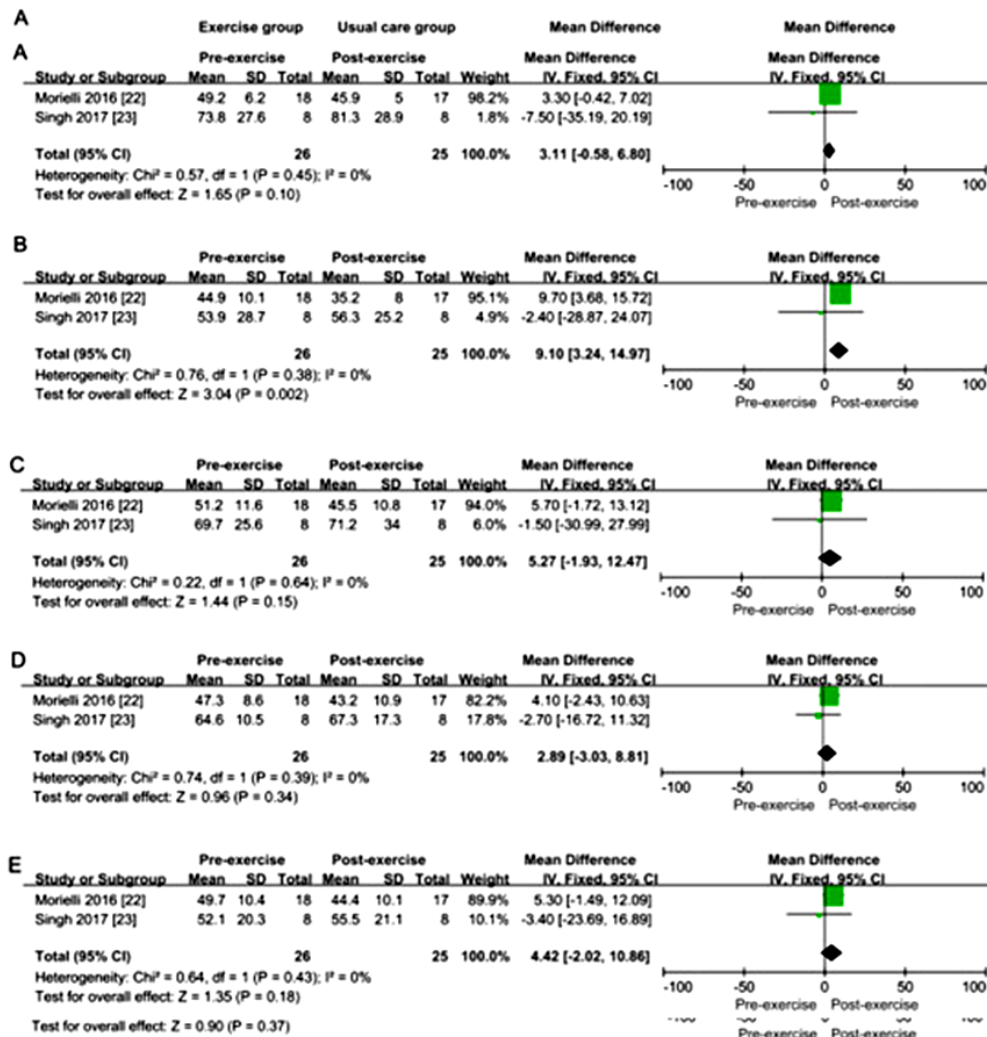


Figure 2. Forest plot of Short Form-36 Health Survey (SF-36) Meta-analysis; (A) Physical functioning; (B) Role physical; (C) Bodily pain; (D) General health; (E) Vitality.

Vitality: Two studies yielded a pooled OR of 4.42 (95% CI: 2.02–10.86, Z=1.35, P=0.18), showing no significant change.

Social functioning: Two studies (22, 23) indicated a significant improvement post-exercise (pooled OR=7.04, 95% CI: 0.33–13.75, Z=2.06, P=0.04).

Role-emotional function: Two studies found a pooled OR of -4.13 (95% CI: -11.55–3.30, Z=1.09, P=0.28), with no significant difference.

Mental health: Two studies (22, 23) showed a pooled OR of -1.18 (95% CI: -7.05–4.70, Z=0.39, P=0.69), with no significant change.

Physical health component: Two studies (22, 23) revealed a pooled OR of 4.09 (95% CI: -7.09–15.27, Z=0.72, P=0.47), with no significant difference.

Mental health component: Two studies (22, 23) found a pooled OR of -1.30 (95% CI: -6.93–4.32, Z=0.45, P=0.65), with no significant difference.

**MFSI-SF:** Before and after exercise, no significant changes were detected in the scores of the general scale, physical scale, emotional scale, mental scale, vigor scale, or total scale (all P>0.05).

### Safety outcomes (adverse events)

Adverse events were defined as complications (e.g., fatigue exacerbation, musculoskeletal discomfort) or mortality during follow-up. Among the included studies, Singh 2018 (20) and Heldens 2016 (24) reported no adverse events in the exercise group; Moug 2019 (21), Lee 2018 (26), and West 2015 (25) reported mild adverse events. Meta-analysis showed no significant difference in adverse event incidence between the exercise group and the usual care group (pooled OR=1.57, 95% CI: 0.54–4.57, Z=0.83, P=0.41).

## DISCUSSION

This meta-analysis systematically assessed how effective and safe exercise interventions are for rectal cancer patients undergoing chemotherapy. It drew on 18 studies (including RCTs and single - group intervention studies) and carried out a thorough evaluation across four aspects: physical fitness, physical indices, quality of life, and safety. In health-

related physical fitness outcomes, the exercise group demonstrated significantly superior anaerobic threshold oxygen uptake ( $VO_{2atAT}$ ) compared to the routine care group, suggesting exercise may enhance submaximal exercise capacity by improving cardiopulmonary endurance—this aligns with previous meta-analyses in breast cancer patients, where moderate-intensity aerobic exercise was shown to enhance mitochondrial function and oxygen utilization efficiency<sup>(33)</sup>. However, peak oxygen uptake ( $VO_{2atpeak}$ ) and 6-minute walk distance (6MWT) showed no significant changes, a finding that contradicts Triguero-Cánovas *et al.*'s<sup>(34)</sup> single-center RCT (which reported a 50% improvement in 6MWT); this discrepancy may stem from differences in exercise modality (only one included study used mixed aerobic + resistance training) and intervention duration (most single-aerobic interventions lasted 4 weeks), highlighting these factors as potential influencers of walking endurance.

For physical indices, no significant differences were observed in body mass index (BMI), pulmonary function [Forced Expiratory Volume in One Second (FEV1), FEV1/Forced Vital Capacity (FVC)], or hemoglobin levels, indicating short-term exercise (average 12 weeks) is insufficient to alter body composition or mitigate chemotherapy-related anemia/respiratory dysfunction. This is linked to chemotherapy-induced inflammatory responses [(e.g., elevated Interleukin-6 (IL-6)] that counteract exercise's beneficial effects on fat metabolism<sup>(35)</sup>, suggesting combined nutritional support or respiratory rehabilitation may be necessary. In quality-of-life assessments, exercise significantly improved physical role function (SF-36) and social function (single-group analyses)—the former likely due to enhanced muscle strength reducing limb function decline, and the latter consistent with the "behavioral activation" mechanism in psychosocial theory<sup>(36)</sup>. However, most domains of the EORTC QLQ-C30 and TOI-PFC (e.g., fatigue, emotional function) showed no significant differences; this may relate to insufficient intervention intensity (only two studies used high-intensity interval training [HIIT], which is more effective for regulating central fatigue<sup>(37)</sup>) and patient expectancy effects impacting subjective assessments. Regarding safety, no significant differences in adverse event rates or mortality were found between groups, consistent with Shah-Abadi *et al.*'s<sup>(38)</sup> report of zero adverse events, though three single-group studies noted mild complications (73% rate), emphasizing the need for exercise supervision and individualized protocols.

The findings of this study exhibit both similarities and differences with recent meta-analyses. For example, Singh *et al.*<sup>(39)</sup> reported exercise significantly improved fatigue in colorectal cancer patients, but their inclusion of post-surgical patients (vs. this study's focus on chemotherapy phase)

suggests treatment stage heterogeneity explains divergent results. A breast cancer study<sup>(40)</sup> also found exercise improved quality of life in social/physical functioning, potentially linked to effects on sex-specific symptoms (e.g., menopausal syndrome), underscoring the need for cancer-type stratified analyses. Potential mechanisms underlying exercise's effects include: ① regulating the inflammatory microenvironment via exercise-induced Interleukin-10 (IL-10) elevation to mitigate systemic inflammation<sup>(41)</sup>; ② improving gut microbiota (e.g., increasing *Lactobacillus* abundance) to alleviate chemotherapy-related diarrhea<sup>(42)</sup>; ③ enhancing treatment tolerance by promoting skeletal muscle mitochondrial biogenesis and reducing 5-FU-induced myotoxicity<sup>(43)</sup>. However, non-significant changes in diarrhea and muscle strength here may reflect small sample sizes or short intervention durations.

While this study provides evidence-based insights, it has limitations requiring cautious interpretation. Included studies exhibited high heterogeneity in exercise protocols (modes: aerobic, resistance, yoga; intensity: 30–70% $VO_{2max}$ ) and design differences between single-group studies and RCTs, though subgroup analysis showed aerobic exercise alone significantly improved  $VO_{2atAT}$ <sup>(44)</sup>. With a median follow-up of 9 weeks, long-term data on tumor recurrence and overall survival (OS) are lacking—while a single-arm study<sup>(18)</sup> noted short-term survival benefits of 6-week exercise in advanced Gastrointestinal cancer patients, this was not validated here. Additionally, only 15% of included studies involved locally advanced patients, and no stratified analysis between NACRT and adjuvant chemotherapy groups limits generalizability to specific populations.

Clinically, these results imply giving priority to 150 minutes per week of moderate-intensity aerobic exercise (such as brisk walking) for patients experiencing physical deterioration during chemotherapy. This can boost submaximal capacity and physical role function. Patients with poor baseline fitness [Eastern Cooperative Oncology Group (ECOG)  $\geq 2$ ] should initiate low-intensity exercise (10-minute daily walking) with gradual progression and pre-exercise cardiovascular assessment (e.g., electrocardiogram). Future research should explore multimodal interventions (exercise + nutrition/psychological therapy) to comprehensively improve outcomes.

## CONCLUSION

This meta-analysis shows exercise interventions significantly improve specific physical fitness indicators ( $VO_{2atAT}$ , physical role function) and are safe for rectal cancer patients undergoing chemotherapy, but have limited effects on overall

quality of life and basic physical indices. Clinically, aerobic exercise (with dose optimization and individualization) should be integrated into multidisciplinary rehabilitation. Future large-sample, long-term studies and mechanistic research are needed to clarify exercise's oncological effects, providing precise evidence for rectal cancer whole-course management.

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**Ethical consideration:** This study is a meta-analysis based on previously published studies, and all included research has obtained ethical approval from the respective institutional review boards (IRBs) or ethics committees of the original study institutions. No additional human or animal subjects were involved in this meta-analysis, so no separate ethical approval was required.

## REFERENCES

- Nakanishi T, Matsuda T, Yamashita K, Hasegawa H, Sawada R, Harada H, et al. (2024) Alb-dNLR score as a novel prognostic marker for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy. *Anticancer Res*, **44**(1): 229-237.
- Ashrafi A, Yu J, Kim AT, Ye JC, David EA, Wightman SC, et al. (2023) Adjuvant chemotherapy, not radiotherapy, prolongs survival for node-negative non-small cell lung cancer with positive surgical margins. *JTCVS Open*, **14**: 472-482.
- Esswein K, Ninkovic M, Kröpfl V, Gasser E, Profanter C, et al. (2025) Radiofrequency ablation: Solution for a long-time therapeutic dilemma of chronic radiation proctitis? *Endosc Int Open*, **a26051079**.
- Cui YY, Wen LY, Chen XY, Bai XH, et al. (2023) Pelvic floor dysfunction and its influencing factors during radiotherapy in cervical cancer survivors: A cross-sectional study. *Eur J Oncol Nurs*, **64**: 102307.
- Guo Y, Guo Z, Zhang J, Qian G, Ji W, Song L, Guo Z, Han Z, et al. (2025) Short- and long-term outcomes of neoadjuvant chemotherapy compared with neoadjuvant chemoradiotherapy for locally advanced rectal cancer: an updated meta-analysis. *BMC Gastroenterol*, **25**(1): 87.
- Bliggenstorfer JT, Hashmi A, Bingmer K, Chang C, Liu JC, Ginesi M, et al. (2023) Sarcopenia in patients with rectal adenocarcinoma: An opportunity for preoperative rehabilitation. *Am Surg*, **89**(12): 5631-5637.
- Kagawa Y, Smith JJ, Fokas E, Watanabe J, Cercek A, Greten FR, et al. (2024) Future direction of total neoadjuvant therapy for locally advanced rectal cancer. *Nat Rev Gastroenterol Hepatol*, **21**(6): 444-455.
- Bosch NM, Kalkdijk-Dijkstra AJ, Broens PMA, van Westreenen HL, Pierie JPEN, Klarenbeek BR, van der Heijden JAG, et al. (2024) FORCE trial group. Implementation of Pelvic Floor Rehabilitation after rectal cancer surgery: A qualitative study guided by the Consolidated Framework for Implementation Research (CFIR). *PLoS One*, **19**(6): e0301518.
- Schmitz KH, Brown JC, Irwin ML, Robien K, Scott JM, Berger NA, et al. (2025) ENICTO consortium. exercise and nutrition to improve cancer treatment-related outcomes (ENICTO). *J Natl Cancer Inst*, **117**(1): 9-19.
- Loughney L, West MA, Dimitrov BD, Kemp GJ, Grocott MP, Jack S, et al. (2017) 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)*, **6**: 3.
- Arthuso FZ, Morielli AR, Usmani N, Joseph K, Nijjar T, Tankel K, et al. (2023) Effects of exercise on motivational outcomes in rectal cancer patients during and after neoadjuvant chemoradiation: A phase II randomized controlled trial. *Semin Oncol Nurs*, **39**(4): 151419.
- Arndt K, Vigna C, Kaul S, Fabrizio A, Cataldo T, Smith M, Messaris E, et al. (2023) Magnetic resonance imaging accuracy in staging early and locally advanced rectal cancer. *Surg Oncol*, **50**: 101987.
- Lin W, Li C, Clement EA, Brown CJ, Raval MJ, Karimuddin AA, et al. (2024) Surgical outcomes in total neoadjuvant therapy for rectal cancer versus standard long-course chemoradiation: A systematic review and meta-analysis of randomized controlled trials. *Ann Surg*, **279**(4): 620-630.
- Spencer RK, Elhage KG, Jin JQ, Davis MS, Hakimi M, Bhutani T, Liao W, et al. (2023) Apremilast in palmoplantar psoriasis and palmoplantar pustulosis: A systematic review and meta-analysis. *Dermatol Ther (Heidelb)*, **13**(2): 437-451.
- Morielli AR, Usmani N, Boulé NG, Severin D, Tankel K, Nijjar T, et al. (2018) Exercise during and after neoadjuvant rectal cancer treatment (the EXERT trial): study protocol for a randomized controlled trial. *Trials*, **19**(1): 35.
- Morielli AR, Usmani N, Boulé NG, Severin D, Tankel K, Joseph K, et al. (2021) Feasibility, safety, and preliminary efficacy of exercise during and after neoadjuvant rectal cancer treatment: A phase II randomized controlled trial. *Clin Colorectal Cancer*, **20**(3): 216-226.
- Loughney L, West MA, Moyses H, Bates A, Kemp GJ, Hawkins L, et al. (2021) Fit4Surgery group. The effects of neoadjuvant chemoradiotherapy and an in-hospital exercise training program on physical fitness and quality of life in locally advanced rectal cancer patients: a randomized controlled trial (The EMPOWER Trial). *Perioper Med (Lond)*, **10**(1): 23.
- Alejo LB, Pagola-Aldazabal I, Fiuza-Luces C, Huerga D, de Torres MV, Verdugo AS, et al. (2019) Exercise prehabilitation program for patients under neoadjuvant treatment for rectal cancer: A pilot study. *J Cancer Res Ther*, **15**(1): 20-25.
- West MA, Astin R, Moyses HE, Cave J, White D, Levett DZH, et al. (2019) Exercise prehabilitation may lead to augmented tumor regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol*, **58**(5): 588-595.
- Singh F, Galvão DA, Newton RU, Spry NA, Baker MK, Taaffe DR, et al. (2018) Feasibility and preliminary efficacy of a 10-week resistance and aerobic exercise intervention during neoadjuvant chemoradiation treatment in rectal cancer patients. *Integr Cancer Ther*, **17**(3): 952-959.
- Moug SJ, Mutrie N, Barry SJE, Mackay G, Steele RJC, Boachie C, et al. (2019) Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from the REX trial. *Colorectal Dis*,

- 21(5): 548-562.
22. Morielli AR, Usmani N, Boulé NG, Tankel K, Severin D, Nijjar T, et al. (2016) 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*, **43**(3): 352-62.
  23. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Galvão DA, et al. (2017) Feasibility and efficacy of presurgical exercise in survivors of rectal cancer scheduled to receive curative resection. *Clin Colorectal Cancer*, **16**(4): 358-365.
  24. Heldens AF, Bongers BC, de Vos-Geelen J, van Meeteren NL, Lenssen AF, et al. (2016) 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*, **42**(9): 1322-30.
  25. West M (2015) The effects of neoadjuvant chemoradiotherapy and a structured exercise training program on physical fitness and in vivo mitochondrial function in advanced rectal cancer patients [D]. *University of Liverpool*.
  26. Lee CHA, Murnane A, Heriot AG, Ismail H, Riedel B, et al. (2018) Randomized pilot study of enhanced structured preoperative exercise program for patients with rectal cancer requiring neoadjuvant therapy before major resection. *Journal of the American College of Surgeons*, **227**(4): S73-S74.
  27. Lin KY, Shun SC, Lai YH, Liang JT, Tsauo JY, et al. (2014) Comparison of the effects of a supervised exercise program and usual care in patients with colorectal cancer undergoing chemotherapy. *Cancer Nurs*, **37**(2): E21-9.
  28. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, et al. (2009) Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomized controlled trial. *BMJ*, **339**: b3410.
  29. Lee MK, Kim NK, Jeon JY, et al. (2018) Effect of the 6-week home-based exercise program on physical activity level and physical fitness in colorectal cancer survivors: A randomized controlled pilot study. *PLoS One*, **13**(4): e0196220.
  30. Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, et al. (2018) Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Support Care Cancer*, **26**(2): 615-624.
  31. West MA, Loughney L, Lythgoe D, Barben CP, Adams VL, Bimson WE, et al. (2014) 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*, **9**(12): e111526.
  32. Kim JY, Lee MK, Lee DH, Kang DW, Min JH, Lee JW, et al. (2019) Effects of a 12-week home-based exercise program on quality of life, psychological health, and the level of physical activity in colorectal cancer survivors: a randomized controlled trial. *Support Care Cancer*, **27**(8): 2933-2940.
  33. Chiang CH, Chang YC, Haw Y, Tan JY, Chiang CH, Hsia YP, Chiang CH, et al. (2024) The effect of exercise on cardiotoxicity in women with breast cancer receiving anthracycline-based chemotherapy: A systematic review and meta-analysis. *Oncology*, **102**(6): 510-514.
  34. Triguero-Cánovas D, López-Rodríguez-Arias F, Gómez-Martínez M, Sánchez-Guillén L, Peris-Castelló F, Alcaide-Quirós MJ, et al. (2023) Home-based prehabilitation improves physical conditions measured by ergospirometry and 6MWT in colorectal cancer patients: a randomized controlled pilot study. *Support Care Cancer*, **31**(12): 673.
  35. Behranvand N, Nasri F, Zolfaghari Emameh R, Khani P, Hosseini A, Garssen J, Falak R, et al. (2022) Chemotherapy: a double-edged sword in cancer treatment. *Cancer Immunol Immunother*, **71**(3): 507-526.
  36. Romano KA, Heron KE, Sandoval CM, MacIntyre RI, Howard LM, Scott M, Mason TB, et al. (2023) Weight bias internalization and psychosocial, physical, and behavioral health: A meta-analysis of cross-sectional and prospective associations. *Behav Ther*, **54**(3): 539-556.
  37. Bjørke ACH, Buffart LM, Raastad T, Demmelmaier I, Stenling A, Nordin K, Berntsen S, et al. (2022) Exploring moderators of the effect of high vs. low-to-moderate intensity exercise on cardiorespiratory fitness during breast cancer treatment - analyses of a subsample from the phys-can RCT. *Front Sports Act Living*, **4**: 902124.
  38. Shah-Abadi ME, Pak H, Kazemini A, Najari D, Tafti SMA, Keramati MR, Keshvari A, Fazeli MS, Behboudi B, et al. (2024) Effect of kegel pelvic floor muscle exercise on improving urinary disorder in rectum cancer patients after rectal surgery: a randomized clinical trial. *Int J Colorectal Dis*, **39**(1): 169.
  39. Singh B, Hayes SC, Spence RR, Steele ML, Millet GY, Gergele L, et al. (2020) Exercise and colorectal cancer: a systematic review and meta-analysis of exercise safety, feasibility and effectiveness. *Int J Behav Nutr Phys Act*, **17**(1): 122.
  40. Sikandari MH, Siddiqui A, Ahmad M, Shaikh S, Khuwaja S, Ahmad F, et al. (2024) Effect of exercise on fatigue and depression in breast cancer women undergoing chemotherapy: a systematic review and meta-analysis. *Support Care Cancer*, **32**(8): 515.
  41. Pahlavani HA (2023) Exercise therapy to prevent and treat Alzheimer's disease. *Front Aging Neurosci*, **15**: 1243869.
  42. Zhang Y, Wang C, Lang H, Yu H, Zhou M, Rao X, et al. (2024) The contrasting effects of two distinct exercise training modalities on exhaustive exercise-induced muscle damage in mice may be associated with alterations in the gut microbiota. *Int J Mol Sci*, **25**(14): 7837.
  43. Reisman EG, Hawley JA, Hoffman NJ, et al. (2024) Exercise-regulated mitochondrial and nuclear signaling networks in skeletal muscle. *Sports Med*, **54**(5): 1097-1119.
  44. Sadri F (2025) PROTACs in Colorectal Cancer: A New Era in Targeted Protein Degradation Therapy. *Adv Clin Pharmacol Ther*, **2**(1): 1-16.