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## **The Impact of Multimodal Prehabilitation on the Incidence of Postoperative Complications in Patients Undergoing Colorectal Cancer Resection: A Narrative Review**

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## **Abstract**

**Background** Colorectal cancer (CRC) resection imposes profound physiological stress, often leading to acute catabolism, immunosuppression, and a drastic decline in functional capacity. While Enhanced Recovery After Surgery (ERAS) protocols have revolutionized intra- and postoperative care, multimodal prehabilitation capitalizes on the preoperative window. By integrating physical therapy, targeted nutritional support, psychological interventions, and medical optimization, this approach aims to maximize the patient's physiological and psychological reserves prior to surgical trauma.

**Aim** To evaluate the efficacy of multimodal prehabilitation in mitigating postoperative complications in CRC patients and to assess the physiological foundations and methodological challenges present in current literature.

**Materials and methods:** This narrative review was conducted using articles sourced from PubMed by keywords: colorectal cancer, colorectal surgery, multimodal prehabilitation, postoperative complications, ERAS. We examined randomized clinical trials, observational studies, meta-analyses published between 2021-2026. Due to the narrative nature of this review, study selection was based on thematic relevance rather than strict methodological criteria.

**Results:** The majority of studies included in this review demonstrated that multimodal prehabilitation significantly reduces the incidence of postoperative complications in patients undergoing colorectal cancer (CRC) resection.

**Conclusions:** Multimodal prehabilitation proactively optimizes functional and immunological reserves, reducing the incidence of postoperative complications. However, considerable methodological heterogeneity persists across trials regarding intervention duration, adherence to FITT principles, and evaluation metrics. Future high-quality research must standardize protocols and assessment tools to facilitate the routine integration of prehabilitation into perioperative care.

**Key words:** multimodal prehabilitation, colorectal cancer, colorectal surgery, postoperative complications, ERAS.

## 1. Introduction

Colorectal cancer poses a tremendous challenge to modern healthcare. According to the latest GLOBOCAN 2022 report, it ranks third among all cancers in terms of global incidence, with a total of 1,926,425 new cases (global CRC incident cases), and second in terms of mortality.<sup>1</sup> Simulations of incidence and mortality trends highlight alarming projections for the coming decades. Assuming the global CRC incidence rate remains at the 2022 level, the number of new cases is projected to rise to 2.36 million in 2050, representing an increase of over 22% compared to the baseline year.<sup>2</sup>

Surgical resection is the primary form of radical treatment for colorectal cancer.<sup>3</sup> Unfortunately, extensive surgery within the abdominal cavity constitutes a tremendous burden on the body. It acts as a strong stress stimulus, triggering a response that leads to acute catabolism, increased metabolic demand, and immunosuppression.<sup>4</sup> According to current literature, such an operation may be associated with a sudden decline in the patient's physiological and functional capacity by as much as 20-40%. Furthermore, patients experience significant fatigue even 6 to 8 weeks postoperatively.<sup>5</sup>

Over the past few years, perioperative patient management has been revolutionized by the implementation of Enhanced Recovery After Surgery (ERAS) protocols. They have profoundly impacted treatment outcomes—decreasing the length of hospital stay (LOS), mitigating postoperative complications, and streamlining clinical procedures.<sup>6</sup> These protocols are predicated on strategies such as the avoidance of prolonged preoperative fasting, a preference for minimally invasive (laparoscopic) approaches over traditional methods, the optimization of perioperative anesthesia, and the implementation of early mobilization.<sup>2,7</sup> Nevertheless, as traditional ERAS pathways predominantly target the intra- and postoperative windows, extending these optimization efforts into the preoperative phase is increasingly recognized as a highly beneficial strategy.

Multimodal prehabilitation aims to actively engage the patient in their preoperative preparation. It capitalizes on the surgical waiting period to optimize the patient's condition. This approach encompasses multidisciplinary interventions that target modifiable risk factors to reduce the incidence of both overall and acute postoperative complications.

## **2. Multimodal prehabilitation**

It is a multidisciplinary approach to care introduced during the preoperative phase. Primary goal of this program is to enhance the patient's physiological and psychological reserves, enabling them to better withstand the burden of surgical intervention and the oncological disease. Consequently, this strategy optimally capitalizes on the period between diagnosis and surgery.<sup>8</sup>

Although a standardized protocol has not yet been established, the intervention is primarily based on three core pillars: exercise training, nutritional support, and psychological preparation. Some sources propose the inclusion of a fourth pillar, namely comprehensive medical optimization.

### **2.1. Physical therapy**

Effective exercise training should be implemented as a structured, individualized program. It typically encompasses endurance (aerobic) training, resistance (strength) training, and optionally, breathing exercises.

#### **2.1.1. Endurance (aerobic) training**

Endurance training is most commonly implemented as supervised high-intensity interval training (HIIT). For this purpose, a cycle ergometer, treadmill, or rowing machine is typically utilized. During the session, the patient should perform interval exercises, reaching 85–100% of their maximum heart rate or 90% of peak power output, alternated with periods of active recovery.

The training sessions should be supervised and conducted three times a week, and supplemented with unsupervised, low- to moderate-intensity physical activity four times a week, lasting approximately 30-60 minutes per day.

#### **2.1.2. Resistance (streanght) training**

The primary objective of resistance training is to stimulate muscle protein synthesis and prevent atrophy. The exercises should engage the upper and lower body, as well as the core. Resistance

training should be performed using a load precisely determined based on a one-repetition maximum (1RM) test. As prehabilitation progresses, the load is progressively increased, starting at 65% of the 1RM in the first week and reaching up to 80% of the 1RM. Such training should be performed 2 to 3 times a week under the supervision of a specialist.

### 2.1.3. Breathing exercises

Although breathing exercises are not incorporated into all protocols, they seem to have an impact on the postoperative recovery phase. These include deep breathing techniques, effective coughing, and strengthening of the inspiratory muscles.

This preparation aims to minimize pulmonary complications following abdominal surgeries.<sup>9,10</sup>

## 2.2. Nutritional support

Cancer, exercise training, and surgical intervention increase the body's requirement for structural and energy substrates. Nutritional intervention aims to mitigate malnutrition and maximize the anabolic effects of exercise.

Current guidelines primarily focus on an adequate dietary protein intake, which should be approximately 1.2–1.5 g per kilogram of body weight. Proper nutrient timing is also crucial: consuming 20–30 g of whey protein within 30–60 minutes post-resistance training and immediately before sleep is recommended.<sup>3</sup> This strategy enhances both nocturnal and post-exercise muscle protein synthesis.

Furthermore, the diets of colorectal cancer patients are often enriched with immunomodulatory and anti-inflammatory substances, such as arginine, glutamine, omega-3 polyunsaturated fatty acids. Arginine is crucial for upregulating the immune response, glutamine serves as an essential substrate for maintaining the intestinal mucosal barrier and driving lymphocyte proliferation. Omega-3 fatty acids results in decreased production of pro-inflammatory cytokines.<sup>11</sup>

Multivitamin supplements are also introduced into the diet, placing special emphasis on vitamin D3 due to its impact on protein synthesis, skeletal muscle hypertrophy, and the regulation of mitochondrial oxidative phosphorylation.<sup>12,13</sup>

### **2.3. Psychological support**

Psychological support is a crucial element of preparing the patient for surgery and facilitating postoperative recovery. A cancer diagnosis inevitably triggers psychological distress. Among colorectal cancer patients, clinical depression is diagnosed in 57% of cases, whereas 47% are found to suffer from anxiety.<sup>2</sup>

Using validated questionnaires, such as the Hospital Anxiety and Depression Scale (HADS), GAD-7, and PHQ-9, trained staff perform a screening assessment of the patient's mental state.<sup>2,5</sup> The support, usually administered by a psychologist, is designed to provide the patient with tailored coping mechanisms. The protocol incorporates relaxation techniques, mindfulness practices, and guided imagery combined with breathing exercises. Such measures not only mitigate psychological stress but also elevate motivation and establish realistic expectations for the convalescence phase.

### **2.4. Preoperative Optimization**

It focuses on correcting risk factors and behaviors that may be detrimental to the patient. Great importance is attached to the elimination of addictions, with a particular focus on smoking cessation and reduction of alcohol consumption.<sup>9,14-17</sup>

Further crucial elements involve diagnosing and treating uncorrected anemia, because low hemoglobin significantly increases the risk of complications. According to current literature, correction should be initiated when hemoglobin concentrations fall below 8.0 mmol/L in men and 7.5 mmol/L in women.<sup>9</sup>

During the initial assessment, comprehensive laboratory tests are performed to evaluate glycated hemoglobin (HbA1c), lipid profile, vitamin and mineral status, white blood cell count, as well as liver and kidney function parameters. These measures aim to diagnose and control comorbid conditions, ensuring they are stabilized to the greatest extent possible prior to surgery.

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Furthermore, a medication review should be conducted, involving a critical assessment of the patient's current pharmacotherapy. The objective is to avoid polypharmacy and to verify

medications in terms of their impact on the planned surgical procedure and potential adverse effects.<sup>3,15,19</sup>

### **3. Molecular and physiological basis of multimodal synergy**

Major surgical intervention triggers a profound catabolic response within the patient's body. To effectively mitigate postoperative muscle wasting, the simultaneous implementation of physical conditioning, adequate macro- and micronutrient provision, and psychological support is imperative.<sup>20</sup>

Preoperative exercise training induces the expression of PGC-1 $\alpha$  (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). This pivotal protein stimulates mitochondrial biogenesis and oxidative metabolism, thereby optimizing tissue oxygen utilization and significantly reducing the risk of complications associated with postoperative hypoxia. This physiological adaptation substantially bolsters the patient's metabolic reserve, shielding them from severe energy depletion in response to surgical trauma. Furthermore, physical exertion stimulates the systemic release of exer kines—signaling molecules renowned for their potent anti-inflammatory properties and capacity to promote tissue regeneration.

Resistance training activates the mTOR kinase pathway, which governs the growth and hypertrophy of muscle fibers. However, this process requires an optimal anabolic environment, achieved through the targeted provision of high-quality protein, particularly whey protein. This supplies the essential amino acids required for tissue remodeling—most notably leucine, a direct and potent stimulator of the mTOR pathway.<sup>21</sup>

Furthermore, the implementation of immunonutrition—fortified with arginine, glutamine, and omega-3 polyunsaturated fatty acids—exerts a direct modulatory effect on the immune response at the molecular level. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) incorporate into the phospholipid bilayer of leukocyte cell membranes, competitively replacing arachidonic acid. Consequently, this substitution attenuates the synthesis of highly pro-inflammatory eicosanoids (such as prostaglandins and leukotrienes) and inhibits the activation of the nuclear factor kappa B (NF- $\kappa$ B) transcription factor. Ultimately, this mitigates the systemic inflammatory response (SIR) and protects the intestinal mucosal barrier against oxidative stress-induced damage.

Conversely, the profound anxiety associated with an oncological diagnosis drives the chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in an excessive release of glucocorticoids, most notably cortisol. This hormone exerts potent immunosuppressive and catabolic effects. Appropriately targeted psychological interventions effectively attenuate systemic stress hormone levels, thereby restoring the patient's optimal anti-tumor immune defense and mitigating the risk of postoperative infectious complications and delayed wound healing.

Importantly, psychological support is instrumental in fostering the patient's motivation to strictly comply with exercise and dietary protocols. Therefore, it constitutes the bedrock of a successful prehabilitation program.

#### **4. Research results**

Large-scale systematic reviews and meta-analyses indicate that multimodal prehabilitation constitutes an effective strategy for mitigating postoperative complications in patients undergoing colorectal cancer resection.

A randomized clinical trial by Molenaar et al.<sup>14</sup>, which compared the implementation of a multimodal program against standard care, demonstrated that the intervention significantly reduced the rate of severe postoperative complications (defined, inter alia, as a Comprehensive Complication Index [CCI] score > 20). The incidence of such complications decreased from 29.7% in the control group to a mere 17.1% in prehabilitated patients (OR = 0.47; 95% CI: 0.26–0.87;  $p = 0.02$ ). However, it should be noted that the observed *post hoc* power was only 64%. Furthermore, the study reported a significant reduction in systemic medical complications (e.g., respiratory events) among the prehabilitation cohort, dropping from 27.3% to 15.4% compared to standard care (OR = 0.48; 95% CI: 0.26–0.89;  $p = 0.02$ ).

Conversely, a meta-analysis by Widanage et al.<sup>22</sup> observed a substantial decrease in overall postoperative complications (OR = 0.60; 95% CI: 0.42–0.86;  $p = 0.02$ ). However, regarding severe complications (Clavien-Dindo grade  $\geq$  III), the analysis did not reveal statistically significant differences (OR = 0.65; 95% CI: 0.13–3.29;  $p = 0.37$ ).

In contrast, an analysis by Heil et al.<sup>16</sup> indicated that high-risk patients undergoing optimization exhibited a 55% lower overall complication severity score (95% CI: -71% to -32%) relative to the standard care cohort.

It appears that the reduction in postoperative infection rates is largely attributable to adequately implemented nutritional support. A systematic review and meta-analysis by Steffens et al.<sup>10</sup> provided moderate-certainty evidence that preoperative nutritional intervention significantly decreases the incidence of infectious complications by 35% (relative risk [RR] = 0.65) compared to standard management. Moreover, recent systematic review by Yang et al.<sup>23</sup> highlights high-quality evidence supporting the efficacy of preoperative immunonutrition in reducing systemic postoperative infections, including a significant decrease in surgical site infections (SSI).

As demonstrated in the systematic review and network meta-analysis by Li et al.<sup>24</sup> exclusively the multimodal approach leads to a statistically significant reduction in the incidence of postoperative complications (OR = 0.47; 95% CrI: 0.26–0.85) and a measurable decrease in the length of hospital stay (MD = -1.17 days; 95% CrI: -1.77 to -0.57). Furthermore, this strategy proved highly efficacious in mitigating preoperative anxiety levels (SMD = -0.69; 95% CrI: -1.34 to -0.04).

Nevertheless, it is imperative to acknowledge that not all studies corroborate the impact of multimodal prehabilitation on postoperative complication rates. Trials conducted by Srinivasan et al.<sup>25</sup>, Pesce et al.<sup>5</sup> and Bojesen et al.<sup>15</sup> found no statistically significant differences in morbidity between the prehabilitation and control groups.

## **5. Discussion**

The primary objective of this review was to evaluate the impact of multimodal prehabilitation on the incidence of postoperative complications in patients undergoing elective resection for colorectal cancer. The analysis of current literature suggests that preoperative optimization can help mitigate the rate of systemic adverse events.

Given the multifactorial nature of health deficits in oncological patients, optimal clinical efficacy is achieved through the implementation of programs that integrate structured physical conditioning, targeted nutritional interventions, psychological support, and medical

optimization. The superiority of this multimodal approach over unimodal interventions stems from a profound synergistic effect at both the cellular and physiological levels, where each foundational pillar modulates mutually complementary metabolic pathways.<sup>11</sup>

Despite the solid physiological foundations of the multimodal synergy concept, significant discrepancies regarding the efficacy of prehabilitation persist in the literature. The heterogeneity of research findings stems from several fundamental methodological barriers.

There is substantial heterogeneity in the applied intervention protocols. This pertains to both the duration of prehabilitation—which typically lasts 4 weeks, but in some cases it can be as short as 5 days<sup>25</sup>—and the lack of rigorous standardization of physical conditioning, including the failure to adhere to the FITT principles (frequency, intensity, time, type). An additional issue is the high variability in methods used to assess patients' baseline nutritional status, coupled with the widespread marginalization of the psychological pillar.

Another challenge is the so-called ceiling effect. The vast majority of contemporary studies are conducted in specialized centers with well-established ERAS protocols, and procedures are predominantly performed using minimally invasive (laparoscopic) techniques. These modern standards inherently and radically reduce the risk of complications in control groups. Given such a low baseline incidence of adverse events, many studies are statistically underpowered to demonstrate an additional, clinically significant benefit derived directly from prehabilitation itself.

A further challenge lies in the vast diversity of methods used to assess and report postoperative complications. The variance in applied classification systems (e.g., relying exclusively on the Clavien-Dindo scale as opposed to utilizing the Comprehensive Complication Index [CCI] to measure cumulative morbidity) precludes researchers from consistently aggregating data and formulating unequivocal conclusions in meta-analyses.

Finally, a major barrier is the specific nature of designing prehabilitation trials, particularly the impossibility of implementing classical blinding (for both the patients and the personnel supervising the intervention). This inherent lack of objectification makes these trials highly susceptible to systematic bias, which may ultimately lead to the distortion of final efficacy outcomes.

However, the overall impact on total complication rates remains a subject of ongoing research and the overall certainty of evidence is currently considered low to moderate.

## **6. Conclusions**

Preoperative optimization, aimed at maximizing the patient's physiological and psychological reserves, constitutes an effective strategy for preparing the organism to withstand the profound physiological stress associated with surgical intervention and the underlying oncological disease. Analysis of the current literature demonstrates that this approach contributes to a substantial reduction in the incidence of postoperative complications. Nevertheless, to successfully overcome existing methodological barriers and enable the objective assessment of outcomes, the development of universal clinical guidelines for prehabilitation programs is imperative. Future research endeavors must be predicated on standardized interventional protocols, including strictly defined exercise parameters based on the FITT principles (frequency, intensity, time, type). Consequently, further rigorously designed, adequately powered clinical trials are essential to draw definitive, evidence-based conclusions.

## **Author Contribution**

Conceptualization, Katarzyna Sordyl; methodology, Katarzyna Sordyl, Oliwia Bolek, Piotr Szczepański, Oliwia Grzelak; validation, Katarzyna Sordyl, Maria Fengier, Oliwia Grzelak; formal analysis, Katarzyna Sordyl, Weronika Kuśmierczyk, Jakub Trzaskowski; investigation, Katarzyna Sordyl, Justyna Kącikowska, Krzysztof Rogulski; resources, Magdalena Majkowska, Justyna Kącikowska, Weronika Kuśmierczyk; writing—original draft preparation, Katarzyna Sordyl; writing—review and editing, Katarzyna Sordyl, Oliwia Bolek, Maria Fengier; visualization, Krzysztof Rogulski, Jakub Trzaskowski; supervision, Piotr Szczepański, Magdalena Majkowska. All authors have read and agreed to the published version of the manuscript.

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