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What is the role of physical exercise in the era of cancer prehabilitation? A systematic review

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ABSTRACT

Purpose: Exercise before surgery, as part of prehabilitation, aiming to enhance patients' functional and physiological capacity, has become widespread, necessitating an in-depth understanding.
Methods: A systematic search was conducted on Pubmed, Cochrane, and Scopus to examine the effect of exercise as prehabilitation, alone or in combination with other interventions, in patients with cancer. Interventional studies applying a single-arm, randomized controlled, or nonrandomized design were included.
Results: A total of 96 studies were included, and categorized according to cancer types, i.e., gynecological, breast, urological, gastrointestinal and lung cancer. For each cancer site, the effect of exercise, on physical fitness parameters and postoperative outcomes, including length of hospital stay and postoperative complications, was reported.
Conclusion: Exercise as prehabilitation may have an important role in improving physical fitness, postoperative outcomes, and accelerating recovery, especially in certain types of malignancies.

1. Introduction

With an estimated 24.6 million new cases and 12.9 million related deaths by 2030, cancer is one of the most common chronic diseases and the leading cause of death globally (IARC, 2023). Surgery represents one of the major pillars of cancer care, encompassing the preventive, diagnostic, curative, palliative, and reconstructive fields, and it was estimated that 80 % of patients would need surgery (Sullivan et al., 2015). Over the years, thanks to the introduction of successful screening programs and the advances in the diagnostic phase, a large number of patients with cancer are and will be diagnosed with an early stage of the disease. As a result, most patients are more likely to become eligible for curative cancer surgery aimed at locoregional control of the primary tumor (Sullivan et al., 2015). Nevertheless, surgery is often accompanied by postoperative complications (PoC), leading to an increased length of hospital stay (LoS), an elevated risk of intensive care unit admission, and an increase in perioperative mortality (Sullivan et al., 2015). Although postoperative outcomes depend on several factors, such as the type of surgical procedure, cancer stage, gender, and neoadjuvant treatments, growing evidence suggests that patients' physical functions are fundamental. For instance, preoperative pulmonary function and cardiorespiratory fitness have been found to be prognostic factors for PoC and overall survival in patients with lung cancer (Avancini et al., 2021). Additionally, a meta-analysis including studies on lung, bladder, liver, pancreatic, rectal, esophageal, and colorectal cancer found that a higher preoperative cardiorespiratory fitness was associated with the absence of postoperative and pulmonary complications (Steffens et al., 2021). Similarly, sarcopenia before surgery, i.e., the loss of skeletal muscle mass and strength, may negatively affect postoperative outcomes, such as complications and overall survival in colorectal, esophageal, pancreatic, and bladder cancers (van Vugt et al., 2015). Sarcopenia can culminate in a condition of frailty defined as

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"reduced reserve and resistance to stressors, resulting from cumulative declines across multiple organ systems, leading to the higher incidence of adverse outcomes" (Morley et al., 2013) is an independent risk factor of postoperative complications (Panayi et al., 2019), longer length of hospital stay and mortality (Lin et al., 2016). Therefore, it is clear that *"enhancing the functional and physiological capacity of individuals to enable them to withstand a stressful event (as surgery) and aid recovery after surgery"*, is fundamental (Batchelor et al., 2019).

Since the 2000s, the ERAS (Enhanced Recovery After Surgery) guidelines have been developed to optimize patients' preoperative multimodal management and substantially improve outcomes. To date, 23 guidelines have been available, many of which are referred to major cancer surgery (Society). Preoperative physical exercise is often included in the ERAS guidelines as a tool able to optimize patients' physical function to better cope with *"the homeostatic disturbance and stress response associated with surgery, which is characterized by catabolism and increased oxygen demand"* (Batchelor et al., 2019). In recent years, the research regarding physical exercise as prehabilitation in cancer is spread widely, with several published researches, and reviews. Nevertheless, the available reviews are focused on selective cancer sites (Avancini et al., 2021; Bundred et al., 2020; Falz et al., 2022; Toohey et al., 2023), anticancer specific treatment side effects (Loughney et al., 2016), specific exercise training and programs, e.g., high-intensity interval training (HIIT) or aerobic continuous training(Franssen et al., 2022); (Palma et al., 2021). To date a comprehensive review, collecting the most recent evidence for exercise prehabilitation among each cancer sites, is missing. In the current systematic review, we provide an overview of the interventional studies evaluating the impact of exercise prehabilitation among different cancer sites in order to identify the benefits and the current gaps in research.

2. Methods

A comprehensive PubMed, Scopus, and Cochrane search was conducted on May 29, 2023 and updated on March 1, 2024. The utilized keyword was related to exercise, e.g., preoperative exercise, preoperative physical activity, prehabilitation, and different cancer sites, e.g., breast, colorectal, lung, bladder, liver, esophageal, gastric, head and neck, ovarian, pancreatic, prostate, and skin. Detailed search strategy is presented in Appendix A. The review was performed and reported observing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021). The following inclusion criteria were applied: i) adults patients affected by cancer; ii) patients must be scheduled for surgery; iii) physical exercise could be delivered alone or in combination with other approaches; iv) studies must be interventional; v) study design could be single-arm, randomized controlled or nonrandomized. Abstracts not published in extenso, reviews, meta-analysis, interventions not including physical exercise, case reports, non-English full text, and animal studies were excluded.

2.1. Study selection, data extraction, risk of bias, and data syntesis

Two independent reviewers (L.T. and N.D.B.) verified the studies inclusion criteria. Initially, the screening were performed by evaluating title and abstract, and subsequently the evaluation of the selected references was undergo to full-text assessment by the same two authors. Discrepancies were resolved by a third author (A.B.). A series of data were extracted by each study, as reported in Appendix A. Risk of bias assessment was perfomed by two independent authors (A.B. and C.C.). Different tools were used according to the study design. The Cochrane risk-of-bias tool for randomized trials (RoB 2), and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS 2) were use to evaluated the risk of bias for randomized controlled studies and nonrandomized research, respectively. Risk of bias was categorized as "low", "moderate" and "high" (Seo et al., 2023; Sterne et al., 2019). Given the heterogeneity in the study design, intervention, and population, a qualitative syntesis in narrative form is provided, focusing on the different cancer sites. According to the Guidnce on th Conduct of Narrative Synthesis in Systematic Reviews (Popay et al., 2006), the data were examined using tables and narrative descriptions.

3. Results

Study selection flow-chart is presented in Appendix A. Briefly, among the 2831 results, a total of 2653 were selected for title/abstract screening. After, full-text revision, 96 studies, exploring explored the role of an exercise program, defined as *"planned, structured, and repetitive body movement to improve or maintain one or more components of physical fitness"* (Caspersen et al., 1985), as component of cancer prehabilitation, were included. Risk of bias assessment is reported in the Appendix A. Herein, we report the main findings, caregorized by cancer types.

3.1. Gynecologic cancers

Only two studies (Table 1) have been conducted on patients with gynecologic cancers (Diaz-Feijoo et al., 2022; Lee et al., 2020). A single-arm trial, including 19 patients with endometrial cancer, has evaluated the feasibility of a 2-week supervised preoperative exercise program composed of moderate/vigorous aerobic, resistance, and core stability activities performed five times per week. The protocol was shown to be feasible, without adverse events, and postintervention assessments revealed an increase in cardiorespiratory fitness (25.3 vs. 27.9 mL/kg/min, $p<0.001$), strength (lower limbs, 23.8 vs. 28.8 times, $p<0.001$; handgrip 26.4 vs. 28.3 kg, $p<0.001$), anxiety (6.8 vs. 3.3 points, $p<0.001$), depression (6.1 vs. 3.1 points, $p<0.001$) and some domains of quality of life (QoL), while body composition did not significantly change (Lee et al., 2020). ***Diaz-Feijoo B. et al.*** have proposed a multimodal prehabilitation intervention lasting a median of 2 weeks and including exercise, i.e.,HIIT, resistance exercises, and respiratory physiotherapy, nutritional counseling with protein and immunonutrients supplementation, plus psychological support, in addition to standard care based on ERAS protocol, fo patients affected by ovarian cancer, scheduled to undergo surgery. Compared to a historical cohort that had followed only the standard ERAS protocol, the interventional group exhibited a higher preoperative albumin level (0.180 vs. 0.235 g/L, $p=0.007$), a shorter LoS (7 vs. 5 days, $p=0.04$) and shorter time to starting chemotherapy (35 vs. 25 days, $p=0.03$), while no differences were observed for intensive care unit stay, intraoperative complications, and PoC (Diaz-Feijoo et al., 2022). Overall, the introduction of exercise as prehabilitation in gynecological cancer is still in its early stages. Additional investigations are required to explore and clarify the role of exercise in this subset of cancers.

3.2. Breast cancer

Exercise in breast cancer, during and after adjuvant setting, is widely studied, while few investigations are available for the prehabilitation context (Table 1) (Brahmbhatt et al., 2020; Heiman et al., 2022; Heiman et al., 2021; Knoerl et al., 2022; Ligibel et al., 2019). A feasibility study proposing a home-based aerobic and upper quadrant-specific resistance training, 3–5 days per week, in 22 patients reported good adherence to the intervention. An increase of 57.10 m in the "*Six minutes walking test*" (a surrogate of cardiorespiratory fitness) prior to surgery and its maintenance at 6 and 12 weeks after the surgical intervention was observed; no changes were detected for upper-limb strength, shoulder range of motion, and lymphedema, whereas fatigue and physical component of QoL overall worsened at post-surgery time points (Brahmbhatt et al., 2020).

Nevertheless, single-arm investigations are unable to distinguish between the effect of the treatment versus non-treatment; in this case, a randomized controlled design may be helpful to demonstrate the real contribution of exercise. Following this line, two randomized controlled

Table 1
Studies investigating exercise prehabilitation in gynecological, breast and urological cancers.

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Gynecologic cancer				
Sang-Hwa L. et al. (2020)	Single arm 17 pts with endometrial cancer, stage I and III	NR	At least 5 sessions in 2 weeks of resistance training, 3 sets for 12 reps, core stability training, + moderate/vigorous walking program, 10,000 steps daily	↑ VO_{2max}, strength, QoL, depression and anxiety ↔ body composition and BMI.
Diaz-Feijoo B. et al. (2022)	RCT 34 pts with ovarian cancer, stage III-IV	Past neoadjuvant chemotherapy	2–4 weeks of supervised HIIT training, resistance training, and respiratory physiotherapy plus nutritional counseling with protein supplementation plus psychological preparation *vs.* standard of care	↓ IG vs. CG: LoS and time to starting adjuvant chemotherapy; ↔ IG vs. CG: PoC.
Breast cancer				
Ligibel J. et al. (2019)[1]	RCT 48 pts with breast cancer, stage I-III	None	4 weeks of supervised sessions twice a week, including 30–45 min. moderate aerobic training and 20 min strength training + unsupervised aerobic training to reach 180 min weekly *vs.* mind-body intervention	↑ IG vs CG: physical activity level, leptin, upregulation in cytokine-cytokine receptors interaction pathway, NF-kB signaling pathway, chemokine signaling pathway, natural killer cell-mediated cell cytotoxicity, Jak-STAT signaling pathway, antigen processing and presentation, T-cell receptor signaling pathway; ↔ IG vs. CG: BMI, Ki-67 expression, adiponectin, IGF-1, CRP, IL-6, insulin receptor, clave caspase-3, tumor immune biomarkers.
Knoerl R. et al. (2021)[1]	RCT 48 pts with breast cancer, stage I-III	None	4 weeks of supervised sessions twice a week, including 30–45 min. moderate aerobic training and 20 min strength training + unsupervised aerobic training to reach 180 min weekly *vs.* mind-body intervention	↑ CG vs. IG: cognitive functioning, 1-month after surgery; ↔ IG vs. CG: anxiety, depression, stress, physical function, role functioning, fatigue, pain, insomnia, 1-month after surgery.
Brahmbhatt P. et al. (2020)	Single arm 22 pts with breast cancer, stage I-III	None	4 weeks of home-based program, 3–5 days per week of 30–40 min. aerobic training at moderate-intensity and resistance training, 2–3 sets of 10–12 reps, 2–3 days per week	↔ 6MWT, waist circumference, body composition, BMI, strength, lymphedema circumference, QoL, fatigue, prior surgery, at 6- and 12-week after surgery.
Heiman J. et al. (2020)[2]	RCT 400 pts with breast cancer, stage I-III	None	2 weeks of 30 min. daily aerobic training at moderate intensity plus 4-week postoperative supervised 30 min. daily aerobic training at moderate intensity (after discharge) *vs.* standard care	↔ IG vs. CG: PoC, readmission rate, reoperation rate, physical and mental recovery.
Heiman J. et al. (2022)[2]	RCT 400 pts with breast cancer, stage I-III	None	2 weeks of 30 min. daily aerobic training at moderate intensity plus 4-week postoperative supervised 30 min. daily aerobic training at moderate intensity (after discharge) *vs.* standard care	↔ IG vs.CG: QoL at 4 weeks and 12 months after surgery.
Urogenital cancer				
Blackwell J.E. M. et al. (2020)	RCT 40 pts with mixed genitourinary cancers (prostate, bladder, kidney)	NR	4 weeks, 3–4 times per week, of supervised HIIT (1 min. exertions at high intensity; 2 min. recovery) *vs.* standard care	↑ IG vs. CG: anaerobic threshold, VO_{2peak}, systolic and diastolic blood pressure; ↔ IG vs.CG: body composition
Singh F. et al. (2016)	Single arm 10 pts with prostate cancer	NR	6 weeks, 2 times week of resistance training, 2–4 sets of 6–12 reps, and 20 min. of aerobic training at 60–80 % HRmax	↑ strength, 400 m walk, chair rise, 6 m fast walk from baseline to pre-surgery; 6 m usual walk, from baseline to post-surgery; ↓ strength, lean mass, from pre-surgery to post-surgery; lean mass from baseline to post-surgery; ↔ lean and fat mass from baseline to pre-surgery; strength, 400 m walk, chair rise, 6 m fast walk, from baseline to post-surgery.
Santa Mina D. et al. (2018)[3]	RCT 86 pts with prostate cancer, stage I-III	NR	4–8 weeks, 3–4 times per week, of home-based 25 min. aerobic at moderate intensity, resistance training, 8 sets of 8–12 reps, and pelvic floor exercises *vs.* pelvic floor exercises and educational guidebook	↑ IG vs. CG: sexual function at 4-week after surgery; anxiety prior surgery and at 26 weeks after surgery; BMI, waist circumference, strength at 26 weeks after surgery; body fat prior surgery, at 4 and 12 weeks after surgery; 6MWT at 4 weeks after surgery; ↔ IG vs. CG: QoL, physical activity level, symptoms, depression, prior surgery, at 4, 12 and 26 weeks after surgery.
Au D. et al. (2019)[3]	RCT 38 pts with prostate cancer, stage I-III	NR	4–8 weeks, 3–4 times per week, of home-based 25 min. aerobic at moderate intensity, resistance training, 8 sets of 8–12 reps, and pelvic floor exercises *vs.* pelvic floor exercises and educational guidebook	↑ IG vs. CG: physical activity level during postoperative day 1; ↔ IG vs. CG: physical activity level during post discharge week 1; No relationship between 6MWT, LoS and physical activity level.
Jensen B.T. et al. (2014)[4]	RCT 129 pts with bladder cancer, stage I-IV	NR	2 weeks of home-based resistance exercises and aerobic training, twice a day, plus 7 days post-	↑ IG vs. CG: personal activities of the daily living, distance walked during the first 7 days postoperatively;

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
			operative supervised respiratory, resistance and aerobic training, tice per day, *vs.* standard care	↔ IG vs. CG: LoS, PoC, readmission rate, mortality, nutritional intake. PADL and walking distance first 7 days postoperative
Jensen B.T. et al. (2014)[4]	RCT 129 pts with bladder cancer, stage I-IV	NR	2 weeks of home-based resistance exercises and aerobic training, twice a day, plus 7 days post-operative supervised respiratory, resistance and aerobic training, tice per day, *vs.* standard care	↑ IG vs. CG: QoL (dyspnea, constipation, abdominal flatulence and urinary problems) at 4-month post-surgery; ↑ CG vs. IG: QoL (insomnia) at 4-month post-surgery; ↔ IG vs. CG: QoL (global health score, functional scales, remaining symptoms scales, sexual interest and activity, body image, catheter and stoma problems) at 4-month post-surgery.
Jensen B.T. et al. (2016)[4]	RCT 107 pts with bladder cancer, stage I-IV	NR	2 weeks, twice a day, of home-based resistance exercises, 10–15 reps, and daily, 30 min. aerobic training *vs.* standard care	↑ IG vs. CG: muscle power.
Banerjee S. et al. (2017)	RCT 60 pts with bladder cancer	Past neoadjuvant chemotherapy	3–6 weeks, 2 times per week, of supervised HIIT (6 sets of 5 min. at high intensity and 2.5 min. at low intensity) *vs.* standard care	↔ IG vs. CG: $VO_{2peak,}$ PoC, LoS.
Jensen B.T. et al. (2019)	Single arm 32 pts with bladder cancer	Neoadjuvant chemotherapy	2 weeks of home-based resistance exercises, 6–10 reps, twice a day and daily aerobic training 30 min. per day plus nutritional counseling with protein supplementation	↑ strength, bone mass from baseline to pre-surgery; 6MWT, body weight, bone mass and BMI from baseline to 6 weeks post-surgery; ↔ body weight from baseline to pre surgery; strength from baseline to 6 weeks.
Minnella E.M. et al. (2019)	RCT 70 pts with bladder cancer, stage I-III	Neoadjuvant chemotherapy (IG: 51.4 %; CG: 48.6 %)	4 weeks, 3 times per week of home-based, moderate-intensity aerobic training, 25 min., and resistance training, 3 sets of 8–12 reps plus nutritional counseling with protein supplements plus psychological support *vs.* standard care	↓ CG vs. IG: 6MWT at 4 weeks after surgery ↔ IG vs. CG 6MWT prior surgery and 8 weeks after surgery; physical activity level, QoL prior surgery, at 4 and 8 weeks after surgery.
Kaye D.R. et al. (2020)	Single arm 54 pts with bladder cancer, II-IV	Neoadjuvant chemotherapy and/ or radiation (63.3 %)	4 weeks, 3 times per week of resistance training, 1–2 sets of 12–15 reps and 30 min. of aerobic training at 50 % HRmax	↑ 6MWT, VO_{2max}, gait speed, timed up-and-go from baseline to prior surgery; QoL baseline to prior surgery and 90 days after surgery; ↔ lean body mass from baseline to prior surgery.

Abbreviations: ↑, significant improvement; ↓, significant worsening; ↔, no significant change, IG, interventional group; CG, control group; pts, patients; RCT, randomized controlled trial; HIIT, high-intensity interval training; 6MWT, six minutes walking test, BMI, body mass index; VO2max, maximal oxygen consumption; VO2peak, peak oxygen consumption; QoL, quality of life; PoC, post-operative complications; LoS, length of hospital stay; NR, not reported; HRmax, maximal heart rate.

trials have tested the efficacy of exercise before surgery in breast cancer. *Ligibel et al.* have investigated the impact of a structured exercise intervention in newly diagnosed patients with early-stage breast cancer scheduled to undergo surgery but not for neoadjuvant treatments. A total of 49 patients were randomized to receive a mind-body intervention or an exercise program composed of two supervised exercise sessions per week, of moderate-intensity aerobic exercise and resistance training, plus an unsupervised aerobic program to reach a total of 180 minutes of physical activity per week. No differences for QoL, stress, anxiety, and depression were detected at post-intervention and 1-month post-surgery assessments. In contrast, a significant increase in cognitive function was observed in favor of the mind-body group (Knoerl et al., 2022). The translational analysis revealed no significant changes in adiponectin, IGF-1, C-reactive protein, interleukin-6 levels, tissue biomarkers (i.e., Ki-67, cleaved caspase 3, insulin receptor), and tumor immune markers such as $CD4^{+}$, $Cd56^{+}$, $FOXP3^{+}$, $CD8^{+}$, and $CD163^{+}$. On the contrary, the exercise group demonstrated a significant reduction in leptin (p=0.008) and upregulation of those pathways related to inflammation and immunity, including cytokine-cytokine receptor interactions, the NF-kB signaling pathway, chemokine signaling pathway, natural killer cell-mediated cell cytotoxicity, Jak–STAT signaling pathway, antigen processing and presentation, and T-cell receptor signaling pathway, suggesting that exercise may play a role in reducing carcinogenesis (Ligibel et al., 2019). Another trial tested the effect of 30 minutes of daily unsupervised aerobic physical activity performed two weeks before and four weeks after surgery in 370 patients with early-stage breast cancer who did not receive neoadjuvant treatments compared to standard of care. The intervention did not significantly improve QoL, physical and mental recovery at 4 weeks and 12 months post-surgery, and did not reduce PoC (Heiman et al., 2022; Heiman et al., 2021).

To date, the evidence regarding preoperative exercise in breast cancer is scarce, with conflicting results. More studies are needed to evaluate both the safety and efficacy of exercise in this context, as well as in patients receiving systemic neoadjuvant therapies.

3.3. *Urological cancers*

Urologic cancers include an umbrella of malignancies that affect the organs and structures of the urinary systems and male reproductive systems, often treated with surgery and thus highly eligible for prehabilitation. A randomized controlled trial (Table 1) including 40 patients with prostate, bladder, and kidney cancers scheduled for surgery has investigated the impact of 12 sessions within four weeks of HIIT. Although, compared to the controls, no differences in body composition parameters were observed, patients allocated to the intervention reported significant improvements in cardiorespiratory fitness (mean difference-MD 2.26 mL/kg/min; 95 % CI: 1.25–3.26), systolic (−8.2 mmHG; 95 CI:-16.09 to −0.29) and diastolic (-6.47 mmHG; 95 %CI:-12.56 to −0.38) blood pressure, muscle thickness (MD 0.22 mm; 95 %CI: 0.02–0.41) and muscle pennation angle (MD 2.49 degrees; 95 % CI: 0.42–4.55), suggesting an enhancement in the muscle quality (Blackwell et al., 2020).

Analyzing the single tumor site, two studies have been conducted on patients with prostate cancer (Au et al., 2019; Santa Mina et al., 2018; Singh et al., 2017). A single-arm research on ten men with localized prostate cancer found that presurgical aerobic and resistance exercise performed twice a week for six weeks increased muscle strength and physical performance from baseline to presurgery, whereas no changes were observed for body composition. Six weeks after surgery, patients reported a decrease in strength and lean mass, while the improvements in physical performance were maintained (Singh et al., 2017). Similar results were obtained by *Santa Mina et al.*, who compared the impact of a home-based combined aerobic and resistance activities performed 3–4 days per week plus daily pelvic floor exercises versus pelvic floor exercises alone in 86 men undergoing radical prostatectomy. The program resulted safe with only five non-serious events reported, and, compared to controls, participants allocated to intervention exhibited improvements in fat percentage percentage (−1.26 %; 95 % CI: −2.02 to −0.50, p=0.001) and anxiety (- 1.49 points; 95 % CI: −2.87 to −0.10, p=0.035) before surgery. Additionally, the interventional arm exhibited a better cardiorespiratory fitness and an improvement in fat mass at 4 weeks after surgery and a greater handgrip strength and anxiety level at 26 weeks post-surgery, whereas no significant changes were detected for erectile function, QoL, fatigue, PoC, and LoS (Santa Mina et al., 2018).

Regarding bladder cancer, single-arm studies have demonstrated the safety and feasibility of a 4-week exercise prehabilitation program (Kaye et al., 2020) and of a 2-week resistance and aerobic training as part of a multidisciplinary intervention comprising nutritional counseling with oral supplementation (Jensen et al., 2019). However, results from randomized controlled studies did not find any advantages in postoperative outcomes, including PoC and LoS. *Banerjee et al.*, in 60 patients scheduled for radical cystectomy, tested a HIIT versus usual care. Although no effects on PoC and LoS have been observed, a trend toward statistical significance for the cardiorespiratory fitness was detected in favor of the exercise group (MD 1.33 mL/kg/min; 95 % CI: −0.004–2.70, p=0.057) (Banerjee et al., 2018). Similarly, another investigation on 129 patients with bladder cancer exploring two weeks of preoperative, home-based, twice-a-day aerobic and resistance exercise followed by a seven days rehabilitation program including respiratory, strength, and aerobic exercises, walking, and mobilization still reported no benefits on PoC and LoS compared to standard of care (Jensen et al., 2015). Nevertheless, such study found a significant increase in muscle power at the end of the preoperative intervention (absolute difference=0.3 W/kg; 95 %CI: 0.08–0.5; p<0.006) (Jensen et al., 2016), and enhancements in some QoL domains, such as dyspnea, constipation, and abdominal flatulence, at 4-month follow-up (Jensen et al., 2014). Just one trial, exploring the impact of a multimodal exercise, diet, and relaxation techniques intervention as prehabilitation in bladder cancer, is available (Minnella et al., 2021). This investigation did not find improvements in PoC, cardiorespiratory fitness, or QoL before surgery, but a significant preservation in the functional status was recorded at four weeks after surgery, suggesting that multimodal prehabilitation may help to accelerate recovery (Minnella et al., 2021).

Although exercise prehabilitation has been demonstrated to be safe and feasible in urological cancers, the efficacy remains elusive. Future studies should confirm the impact of prehabilitation in prostate and bladder cancers and investigate this intervention in those cancers, such as kidneys and testicular, to date, underexplored.

3.4. Gastrointestinal cancers

Gastrointestinal cancers enclose a wide range of malignancies located in the digestive tract, such as the esophagus, stomach, liver, pancreas, intestine, colon, and rectum. Currently, abundant literature has been published about the effect of preoperative exercise on this population (Table 2).

Focusing on gastroesophageal cancers, almost all the investigations agreed about the positive impact of preoperative exercise on the physical outcomes, such as cardiorespiratory fitness (Akiyama et al., 2021; Argudo et al., 2021; Christensen et al., 2019; Halliday et al., 2021; Minnella et al., 2018; Piraux et al., 2020), and inspiratory muscle strength (Argudo et al., 2021; Valkenet et al., 2016), QoL (Allen et al., 2022; Argudo et al., 2021; Piraux et al., 2020), and patient-reported outcomes (Allen et al., 2022; Piraux et al., 2020), whereas little consensus has been found for muscle strength (Akiyama et al., 2021; Allen et al., 2022). In this sense, a randomized controlled trial has compared the impact of HIIT and strength exercises performed twice weekly in 50 patients with gastroesophageal cancer undergoing neoadjuvant treatments. After a mean of 17.5 exercise sessions, patients allocated to the intervention experienced a significant increase in cardiorespiratory fitness (+1.39 $mL/min^{-1}/kg$, 95 %CI: 0.03–2.74), strength of the lower (+26.9 kg, 95 %CI: 17.6–36.3) and upper (+8.9 kg, 95%CI: 5.4–12.4) limbs, and in some QoL domains (Christensen et al., 2019). Regarding clinical outcomes, on one side, some authors did not find improvements in terms of PoC (Akiyama et al., 2021; Allen et al., 2022; Christensen et al., 2019; Minnella et al., 2018), whereas the majority reported a beneficial effect (Akiyama et al., 2021; Cho et al., 2014; Halliday et al., 2021; Inoue et al., 2013; Mazzola et al., 2017; Yamana et al., 2015). On the contrary, conflicting results emerged for LoS (Allen et al., 2022; Inoue et al., 2013; Mazzola et al., 2017; Minnella et al., 2018) and postoperative mortality (Akiyama et al., 2021; Allen et al., 2022), even if some positive impacts have been observed (Cho et al., 2014; Halliday et al., 2021; Mazzola et al., 2017). For instance, a prospective study has tested a 16-week program, including home-based aerobic and strength training at moderate/vigours intensity, nutritional and psychological support, in 83 patients affected by esophageal cancer undergoing neoadjuvant chemotherapy and has compared it with a historical cohort of patients with similar characteristics (Halliday et al., 2021). The propensity score-matched analysis revealed a lower incidence of overall pulmonary complications (32 % vs. 68 %, p=0.001) and postoperative pneumonia (26 % vs. 66 %, p=0.001), and a shorter LoS (10 days vs. 13 days, p=0.018) in the intervention group than the controls. Participation in the prehabilitation intervention was the only independent predictor of postoperative pneumonia (OR=0.23, 95 %CI: 0.09–0.55, p=0.001) (Halliday et al., 2021).

Five investigations have been conducted on patients affected by cancers of the hepato-biliary pancreatic tract (Ausania et al., 2019; Dunne et al., 2016; Kitahata et al., 2018; Nakajima et al., 2019; Ngo-Huang et al., 2019). Whereas no significant enhancements have been reported for muscle strength (Nakajima et al., 2019; Ngo-Huang et al., 2019), body composition (Nakajima et al., 2019), and QoL (Dunne et al., 2016; Ngo-Huang et al., 2019), an increase in cardiorespiratory fitness (Dunne et al., 2016; Nakajima et al., 2019; Ngo-Huang et al., 2019) has been detected. Nevertheless, such improvement appears insufficient to translate it into an advantage in postoperative outcomes, including complications (Ausania et al., 2019; Dunne et al., 2016; Kitahata et al., 2018), and mortality (Dunne et al., 2016; Nakajima et al., 2019), even if contrasting findings have been observed for LoS (Ausania et al., 2019; Kitahata et al., 2018; Nakajima et al., 2019). In this regard, *Nakajima et al.* proposed a 4-week program of home-based training, including aerobic and strength training three times per week, and amino acid supplementation, for 76 patients with hepato-pancreato-biliary cancers. Compared to a historical cohort, the intervention group exhibited improvements in cardiorespiratory fitness, and LoS (23 days vs. 30 days, p=0.045), while no significant changes in muscle strength and mass, PoC, and mortality have been observed (Nakajima et al., 2019).

Exercise prior to surgery, alone or in combination with other interventions, in patients affected by colorectal cancer has been studied in 27 investigations. Overall, almost all the research did not find significant improvements in PoC (Bousquet-Dion et al., 2018; Carli et al., 2020; Dronkers et al., 2010; Fulop et al., 2021; Gillis et al., 2014; Huang et al., 2016; Janssen et al., 2019; Karlsson et al., 2019; Li et al., 2013; Onerup et al., 2022; van Rooijen et al., 2019; Wang et al., 2023), mortality (Fulop et al., 2021; Huang et al., 2016; van Rooijen et al., 2019; Wang et al., 2023), LoS (Berkel et al., 2022; Bousquet-Dion et al., 2018; Carli et al., 2020; Dronkers et al., 2010; Fulop et al., 2021; Gillis et al., 2014; Huang et al., 2016; Karlsson et al., 2019; Li et al., 2013; Onerup et al., 2022; van Rooijen et al., 2019), muscle strength (Karlsson et al., 2019; Morielli et al., 2021; Singh et al., 2017; Wang et al., 2023) and mass (Moug et al., 2020; Singh et al., 2017), QoL (Carli et al., 2020; Dronkers

Table 2
Studies investigating exercise prehabilitation in gastrointestinal cancers.

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Valkenet K. et al. (2016)	Single arm115 pts with mixed gastrointestinal cancers (pancreas, liver, colon, esophagus, and stomach)	NR	30 days, 2 times per week of supervised aerobic training, 20–30 min. per session at 60–85% HRmax + resistance training, 5 exercises, 3 sets of 20–25 or 13–20 reps + 20 min daily inspiratory muscle training + 5 times per week 30 min of moderate physical activity	↑ maximal inspiratory muscle strength and endurance; ↔ VO_{2max}, strength.
Mazzola M. et al. (2017)	Prospective vs. historical cohort 75 pts with mixed gastrointestinal cancers (stomach, esophagus, and pancreas)	Neoadjuvant treatment (IG: 27 %; CG: 14 %)	Moderate intensity walking for 30 min., 3 times per week + 3 sessions per day of 10 inspiration/expiration cycles (breathing exercises) plus oral supplementation plus smoking interruption *vs.* standard care	↑ IG vs. CG in 30 days and 3 months mortality; overall and severe PoC; ↔ IG vs. CG in LoS; readmission in hospital; post-discharge institutionalization.
Inoue J. et al. (2013)	Two arms retrospective 100 pts with esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 59 %; CG: 68.3 %)	5 days per week of 40–60 min. daily supervised training consisting of: inspiratory muscle training, 3 exercises performed in 3 sets of 10 reps + resistance training + 15 min. of aerobic training plus respiratory training during the outpatient period plus postoperative respiratory rehabilitation until discharge from the hospital *vs.* standard care	↑IG vs. CG in incidence and grade of PoC; ↔ EX vs. CG in durations of intubation, LoS, operation-related factors.
Yamana I. et al. (2015)	RCT 60 pts with esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 43.3 %; CG: 50 %) and/or radiation (IG: 10 %; CG: 16.7 %)	More than 7 days of daily 60 min supervised training consisting of: respiratory muscle and thoracic stretching, deep and coughing training + strength training + 20 min. of aerobic training *vs.* standard care	↑IG vs. CG in PoC, pneumonia score, ↔ IG vs. CG in rate of anastomic leakage, chylothorax, recurrent nerve palsy. Standard of care was a predictor of postoperative complications.
Akiyama Y. et al. (2020)	Retrospective 48 pts with esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 73.9 %; CG: 44 %)	4 weeks of home-based inspiratory muscle training, 4–5 sets of 10 deep inspirations daily, + 20 min. of walking and 20 sets of 10 squats per day + 7 days of supervised aerobic training, 10–30 min at 60–70 % HRmax and 20 sets of 10–15 reps performed twice a week + postoperative rehabilitation *vs.* 4 weeks of home-based inspiratory muscle training, 4–5 sets of 10 deep inspirations per day, + 20 min. of walking and 20 sets of 10 squats per day + postoperative rehabilitation	↑ IG vs. CG in 6MWT before surgery and postoperatively; ↑ IG vs. CG in respiratory complications; pneumonia; total protein at 6 months; total bilirubin and blood urea nitrogen immediately after surgery; ↔ IG vs. CG in overall PoC, mortality, strength before surgery and postoperatively; ↔ IG vs. CG in white blood cell, C-reactive protein, albumin, aspartate transaminase, blood urea nitrogen, creatinine, weight loss, immediately after surgery, after 3 and 6 months.
Halliday L.J. et al. (2020)	Single arm 67 pts with esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 100 %)	16 weeks of home-based, personalized aerobic and strength training to reach 150 min of moderate/vigorous intensity (i.e., 13–15 RPE)	↑ VO_{2max} between the end of neoadjuvant chemotherapy and before surgery; ↔ VO_{2max} between baseline and the end of neoadjuvant chemotherapy; Adherence to the intervention was associated with an increase in VO_{2max}. The level of physical activity and the increase in VO_{2max} over the intervention program were associated with a lower risk of pneumonia.
Halliday L.J. et al. (2020)	Two arms nonrandomized 122 pts with esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 88 %; CG: 87 %)	16 weeks of home-based, personalized aerobic and strength training to reach 150 min of moderate/vigorous intensity (i.e., 13–15 RPE) plus nutritional support plus psychological support *vs.* standard of care	↑IG vs. CG in incidence of 60-day pulmonary complications, postoperative pneumonia, LoS, severe PoC, and drain removal in the unmatched analysis, nasogastric tube removal in the matched analysis. ↔ IG vs. CG in PoC, 30-day readmission, mobilization, oral intake, fluid balance, pain control, day 0 extubation.
Christensen J. F. et al. (2018)	RCT 50 pts with gastro-esophageal cancers, I-III stage	Neoadjuvant treatment (IG: 95 %; CG:90 %)	75 min. of supervised twice a week HIIT consisting of 4×4 min with 3 min. low intensity active recovery between high intensity bout + 4 exercises of resistance training, 3 sets of 8–12 reps *vs.* standard care	↑IG vs. CG: physical well-being; ↑ IG: VO_{2peak}, strength; ↔IG vs. CG: treatment failure, complications of neoadjuvant treatment, PoC, social, emotional, and functional well-being, and QoL subscale; ↔ IG: body composition.
Minnella E.M. et al. (2018)	RCT 68 pts with gastro-esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 70 %; CG: 60 %)	Home-based program of 30 min. of moderate-intensity aerobic training 3 days a week + 30 min. of resistance training, 3 sets of 8–12 reps at moderate-intensity plus nutritional support *vs.* standard care	↑IG vs. CG in 6MWT before surgery and postoperatively; ↔IG vs. CG in incidence and severity of PoC; LoS; emergency department visits; readmission rate.
Piraux E. et al. (2020)	Single arm 23 pts with gastro-	Neoadjuvant chemotherapy (13 %)	2–4 weeks, home-based program, 3 times per week, 30 min. of aerobic training at	↑ in QoL, anxiety from baseline to presurgery; 6MWT and functional well-

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Table 2 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
	esophageal cancers, I-III stage	Neoadjuvant chemoradiotherapy (54.2 %)	65–74 % HRR + moderate-intensity (i.e., 4–6 RPE) resistance training, 1–4 sets of 8–12 reps + 5 times per week of 15 min of inspiratory muscle training	being from 4 to 12 weeks after surgery; emotional well-being and anxiety from baseline to 4 weeks after surgery; anxiety and emotional well-being from baseline to 12 weeks after surgery; ↓ in 6MWT, QoL from presurgery to 4 weeks after intervention; ↔ in 6MWT from baseline to presurgery; ↔ baseline vs. 12 weeks postop: 6MWT, QoL, depression.
Allen S.K. at al. (2021)	RCT 54 pts with gastro-esophageal cancers, I-IV stage	Neoadjuvant chemotherapy (IG: 100 %; CG: 96 %) or chemoradiotherapy (IG: 0 %; CG: 1 %)	15 weeks, 60 min. 2 times per week of supervised training consisting of: 25 min. aerobic training at 40–60 % HRR, or 11–20 RPE, + resistance training, 6 exercises, 2 sets of 12 reps + 60 min. of home-based resistance and core stability training plus nutritional support plus psychological support *vs.* standard care	↑IG vs. CG in strength at 6 weeks after surgery, QoL at middle chemotherapy, at 2–6 weeks, and 6 months after surgery, anxiety and depression before surgery, at 6 weeks and 6 months after surgery, rate of patients who completed full dose of chemotherapy; ↓ IG vs. CG rate of patients requiring a reduction in dose or deferral of the next chemotherapy cycle; ↔IG vs. CG: anaerobic threshold, VO_{2peak}, skeletal muscle indexed, LoS, PoC, readmission, mortality at 30 and 90 days and 3 years.
Argudo N. et al. (2021)	Single arm 33 pts with gastro-esophageal cancers, III-IV stage	Neoadjuvant chemoradiotherapy (52 %) or perioperative chemotherapy (48 %)	5 weeks, 5 times per week, of 40 min. HIIT (1 min. 80 % W_{peak}, 2 min. 40 % W_{peak}) + inspiratory/espiratory muscle training, 5 sets of 10 reps plus nutritional support	↑ VO_{2max}, 6MWT, maximal inspiratory and expiratory pressure, QoL domains as, role and social function, fatigue, and appetite loss; ↔ strength and other QoL domains;
Cho H. et al. (2014)	RCT 72 pts with gastric cancers, I-III stage	NR	4 weeks of aerobic training performed 3–7 days per week + resistance training 1–2 days per week *vs.* standard care	↑IG: BMI, abdominal circumferences, volume of visceral fat; ↑ IG vs. CG: LoS, total all grades intra-abdominal and wound infection PoC; ↔ IG: volume of subcutaneous fat; ↔ IG vs. CG: intraoperative outcome, respiratory, extra and intra-abdominal PoC, anastomotic leakage, pancreatic fistula, bleeding.
Dunne D.F.J. at al. (2016)	RCT 38 pts with liver cancers, I-IV stage	Adjuvant or neoadjuvant treatment (IG: 55 %; CG: 41 %)	4 weeks, 12 sessions of supervised interval training alternating moderate (60 % VO_{2peak}) and vigorous (90 % VO_{2peak}) *vs.* standard care	↑IG vs. CG: VO_2 at the anaerobic threshold; ↔ IG vs. CG: VO_{2peak}, QoL, PoC, LoS.
Kitahata Y. et al. (2018)	Prospective vs. historical cohort 576 pts with hepatobiliary-pancreatic-tract cancers	NR	1 week prior to surgery of supervised, twice a day, 70 min. aerobic training at 60 % VO_2 max + resistance training + respiration instruction plus 7 weeks postoperative rehabilitation including walking squats and stepping up and down stairs and aerobic training *vs.* standard care	↑IG vs. CG: pulmonary PoC, LoS; ↔IG vs. CG: postoperative mortality, severe complications, pancreatic fistula, delayed gastric emptying, bile leakage, abdominal abscess, and bleeding and wound infection.
Nakajima H. et al. (2018)	Prospective vs. historical cohort 152 pts with hepatobiliary-pancreatic-tract cancers, I-IV stage	No	4 weeks, 3 times per week of home-based, moderate (3–4 RPE) aerobic training at least 30 min.+ 5 resistance training exercises, 2 sets of 10 reps plus nutritional supplementation *vs.* no prehabilitation	↑ IG: prognostic nutritional index, 6MWT, total fat mass, muscle/fat ratio; ↓ IG: BMI; ↓ CG: BMI; serum albumin; ↔ IG: strength, total muscle mass, 10-m usual walking speed;
Ausania F. et al. (2019)	RCT 40 pts with pancreatic cancers	No	12 days (median)of 5 supervised sessions of 20 min. HIIT + 20 min. muscle tonic exercises + unsupervised home-based functional and breathing exercises *vs.* standard care	↑IG vs. CG: delayed gastric emptying; ↔IG vs. CG: PoC, pancreatic leak rate, LoS, and hospital readmission.
Ngo-Huang A. et al. (2019)	Single arm 50 pts with pancreatic cancers	Neoadjuvant chemotherapy and/or chemoradiation	16 weeks home-based training at moderate intensity (12–13 RPE), including: 20 min. walking, 3 days per week, 30 min. resistance training, 3 sets of 8–12 reps, 2 days per week plus nutritional counseling	↑IG: 6MWT, 5 times sit-to-stand test, 3-meter walk test; ↔IG: strength, QoL.
Dronkers J.J. et al. (2009)	RCT 42 pts with colon cancers, II-IV stage	NR	2–4 weeks, 60 min of supervised resistance training, 1 set of 8–15 reps at 60–80 % 1RM, 15 min. inspiratory muscle training at 10–60 % of maximal inspiratory pressure and 20–30 min. moderate aerobic training at 55–75 % HR max *vs.* home-based exercise advise	↑ IG vs. CG: maximal inspiratory pressure, respiratory muscle analyzer energy, physical activity level, RMA energy between baseline and presurgery; ↔IG vs. CG: time up and go, strength, maximal inspiratory pressure, physical work capacity, QoL, fatigue, PoC, and LoS.

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Table 2 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Carli F. et al. (2010)	RCT 133 pts with colorectal cancers	Neoadjuvant chemotherapy and/or radiotherapy	4 weeks home-based, daily 20–30 min. of aerobic training starting at 50 % HRmax + strength training, 3 exercises, 8–12 reps, twice a week (IG) *vs.* home-based, daily 30 min. walking + 5 min. daily breathing exercises (CG)	↑IG: in VO_{2peak}, depression prior to surgery, and anxiety at 10-week follow-up; ↑ CG: in anxiety at 10-week follow-up; ↓IG: in 6MWT prior to surgery and at 10 weeks after surgery; ↓CG: in VO_{2peak}; ↔CG: in 6MWT prior to surgery and at 10 weeks after surgery, depression prior to surgery at 10 weeks follow-up, anxiety prior to surgery;
Li C. et al. (2012)	Prospective vs. historical cohort 87 pts with colorectal cancers, I-III stage	NR	Mean 33 days, 3 times per week of home-based, 30 min. moderate aerobic training + resistance training to volitional fatigue plus nutritional counseling with protein supplementation plus psychological support *vs.* standard care	↑IG: anxiety and depression prior to surgery; ↑ IG vs. CG: 6MWT at 4 and 8 weeks after surgery; ↔ IG vs. CG: PoC, LoS, QoL.
Gillis C. et al. (2014)	RCT 89 pts with colorectal cancers, I-III stage	Neoadjuvant therapy (IG prehab: 26 %; IG rehab: 21 %) Adjuvant within 8 weeks (IG prehab: 37 %; IG rehab: 33 %)	4 weeks prior to surgery, 3 times per week of home-based aerobic training, 20 min. at 40 %HRres + 20 min. resistance training, 8 exercises, 8 sets of 12 reps, plus nutritional counseling with protein supplementation plus psychological support*vs.*8 weeks after surgery of 3 times per week of home-based aerobic training, 20 min. at 40 %HRres + 20 min. resistance training, 8 exercises, 8 sets of 12 reps plus nutritional counseling with protein supplementation plus psychological support	↑IG prehab vs. IG rehab: 6MWT prior to surgery and at 8 weeks after surgery; ↔IG prehab vs. IG rehab: 6MWT at 4 weeks after surgery, QoL, anxiety and depression at 4-and 8 weeks after surgery, PoC, LoS, readmission rate.
Huang G.H. et al. (2015)	Retrospective 26 pts with colorectal cancers	Neoadjuvant chemotherapy and/or radiotherapy (IG: 42 %)	Median 74 days, 3–5 times per week, of aerobic interval and strength training at 60–80 of HRmax, lasting 20–45 min. per session	↑VO_{2peak}, anaerobic threshold; ↑ VO_{2peak}, anaerobic threshold in responders; ↓ VO_{2peak}, anaerobic threshold in non-responders; ↔ responders vs. non-responders: PoC, mortality, and LoS; Responders are more likely to increase VO_{2peak}, anaerobic threshold and less likely to experience complications.
Chen B.P. et al. (2016)	RCT 116 pts with colorectal cancers, I-IV stage	NR	4 weeks of home-based aerobic training, 20 min. at 50 % HRmax + resistance training, 8–12 reps plus nutritional counseling with protein supplementation *vs.* 4 weeks program after surgery of home-based aerobic training, 20 min. at 50 % HRmax + resistance training, 8–12 reps plus nutritional counseling with protein supplementation	↑IG prehab vs. CG rehab: moderate/vigorous physical activity level, 6MWT prior to surgery.
Bousquet-Dion G. et al. (2018)	RCT 80 pts with colorectal cancers, I-III stage	Neoadjuvant therapy (IG prehab: 14 %; IG rehab: 15 %) Adjuvant within 8 weeks (IG prehab: 5 %; IG rehab: 8 %)	4 weeks prior to surgery, 3–4 times per week of 30 min. aerobic training at 60–70 % HRmax + resistance training, 8 exercises, 2 sets of 8–15 reps + one a week of supervised exercise session including 55 min. moderate-intensity aerobic and resistance training + 3 days of early mobilization after surgery *plus* nutritional counseling with protein supplementation *plus* psychological support *vs.* + 3 days of early mobilization after surgery + 8 weeks, 3–4 times per week of 30 min. aerobic training at 60–70 % HRmax + resistance training, 8 exercises, 2 sets of 8–15 reps *plus* nutritional counseling with protein supplementation *plus* psychological support	↑IG prehab vs. IG rehab: moderate-intensity physical activity prior to surgery and at 8 weeks after surgery; ↔IG prehab vs. IG rehab: 6MWT prior to surgery, at 4 and 8 weeks after surgery, postoperative complications, LoS, readmission rate.
Bruns E.R.J. et al. (2018)	Single arm 14 pts with colorectal cancers, I-III stage	NR	18–32 days of home-based, 7-min resistance training, 6 exercises, to perform daily *plus* nutritional counseling	↑ fried score, 4-meter gait speed, short physical performance battery, overall QoL; ↓ handgrip strength; ↔ clinical frailty scale.
Gillis C. et al. (2018)	RCT 139 pts with colorectal cancers	NR	4 weeks prior surgery of 50 min. home-based aerobic and resistance training trice a week + similar supervised training once a week plus nutritional counseling with protein supplementation plus psychological support + 8 weeks	↑IG prehab vs. CG rehab: lean body mass and fat mass at 4 and 8 weeks post surgery; ↔IG prehab vs. CG rehab: lean body mass and fat mass prior to surgery.

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Table 2 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
			postsurgery of 50 min. home-based aerobic and resistance training trice a week plus nutritional counseling with protein supplementation plus psychological support *vs.* 8 weeks postsurgery of 50 min. home-based aerobic and resistance training trice a week plus nutritional counseling with protein supplementation plus psychological support	
Janssen T.L. et al. (2019)	Prospective vs. historical cohort 678 pts with colorectal cancers	NR	Mean 39 days of home-based personalized exercise depending on patient's capabilities including aerobic, resistance and respiratory muscle training *plus* nutritional counseling	↑IG vs. CG: LoS; ↓ IG vs. CG: serious PoC (grade III-IV); ↔ IG vs. CG: incidence of delirium, PoC, unplanned intensive care admission, readmission.
Karlsson E. et al. (2019)	RCT 23 pts with colorectal cancers, I-IV stage	Neoadjuvant radiation (IG:10 %; CG: 18.2 %)	2–3 weeks of 6 supervised training including inspiratory muscle training, 30 breaths at 50 % of maximal capacity twice a day + high-intensity functional strength exercises at 7–8 RPE + aerobic training at 7–8 RPE plus the other days, unsupervised home-based exercises, following aerobic recommendation, 2–3 times per week of functional strength exercises and inspiratory muscle training twice a day vs. standard care	↑ IG vs. CG: maximal inspiratory pressure (presurgery); ↔ IG vs. CG: walking distance, strength, gait speed (preoperative and postoperative), PoC, LoS, patient-reported recovery.
Northgraves M. J. et al. (2019)	RCT 22 pts with colorectal cancers	Neoadjuvant chemoradiotherapy (IG: 40 %; CG: 27.3 %)	3 times per week of 60 min. aerobic training, 25 min. at 40–60 % HRres + 2 resistance circuit training including 4 exercises, 3–4 sets each *vs.* standard care	↑ time up and go, stair climb test, 6MWT, strength, five times sit to stand (no statistical significance test was performed).
van Rooijen S. J. et al. (2019)	Two arms nonrandomized 50 pts with colorectal cancers, I-IV stage	No	4 weeks, 3 times per week, of supervised HIIT (3 blocks at 85–100 % VO_{2peak}, 3 blocks at 20 % VO_{2peak}) + resistance training, 5 exercises, 2 sets of 10 reps, at 65 %-75 % 1RM)*plus* protein supplementation *plus* psychological support vs. nutritional counseling	↑IG vs. CG: 6MWT prior to surgery and 30 days after surgery; ↔IG vs. CG: PoC, LoS, readmission rate, mortality.
Carli F. et al. (2020)	RCT 120 pts with colorectal cancers, I-IV stage	Neoadjuvant chemotherapy (IG prehab: 12.7 %; CG rehab: 11.1 %)	4 weeks, prior surgery of supervised 30 min. moderated aerobic training and 25 min. strength training, once a week + home-based daily walking at moderated intensity and resistance training trice a week plus nutritional counseling with protein supplementation plus psychological support *vs.* 4 weeks program, after surgery, of supervised 30 min. moderated aerobic training and 25 min. strength training, once a week + home-based daily walking at moderated intensity and resistance training trice a week plus nutritional counseling with protein supplementation plus psychological support	↔IG prehab vs. CG rehab: overall and severe PoC, LoS, emergency department visits, readmission rate; ↔IG prehab vs. CG rehab: 6MWT, QoL, anxiety, depression, energy expenditure, prior to surgery, and 4 weeks after surgery.
Fulop A. et al. (2020)	RCT 184 pts with colorectal cancers, I-IV stage	Adjuvant chemotherapy (IG:10 %; CG:22 %)	3–6 weeks of home-based, daily 30 min. moderate aerobic training + 10–15 min. of deep breathing/coughing exercises + incentive spirometer exercises, 4–5 times per day + nutritional counseling with protein supplementation + psychological support + standard ERAS peri-operative protocol *vs.* standard ERAS peri-operative protocol + nutritional counseling	↑IG vs. CG: 6MWT, anxiety and QoL prior tosurgery; ↔IG vs. CG: depression, incentive spirometry, FVC prior to surgery and at 4 and 8 weeks after surgery, 6MWT at 4 and 8 weeks after surgery, PoC, LoS, and mortality.
de Klerk M. et al. (2021)	Two arms retrospective cohort study 359 pts with colorectal cancers, I-IV stage	Neoadjuvant radiotherapy (IG: 3 %; CG: 8 %) or chemoradiation (IG: 7 %; CG:6 %)	At least 4 weeks of supervised high-intensity aerobic training, 3 times per week, + home-based low intensity aerobic training, four times per week plus nutritional counseling with protein supplementation *vs.* standard care	↑IG vs. CG: overall PoC, number patients with 2 or more complications, LoS, unplanned readmission; ↔ EX vs. CG: surgical complications, prolonged LoS, reintervention, mortality; Prehabilitation was significantly associated with less PoC.
Suen M. et al. (2021)	Single arm 22 pts with colorectal cancers	NR	2–4 weeks, of 60 min. supervised aerobic training at 60–75 % HRres + resistance training + home-based aerobic training trice a week plus nutritional materials	↑ 6MWT, strength prior surgery; ↓ 6MWT, strength, distress, fatigue, anxiety, QoL after surgery; ↔ body composition; other functional assessment.

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Table 2 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Berkel A.E.M. et al. (2022)	RCT 74 pts with colorectal cancers, I-III stage	Neoadjuvant chemoradiotherapy	3 weeks, 3 times per week of supervised 30 min. HIIT + 20 min. of resistance training, 8 reps at 70–82 % 1RM + home-based 30 min. moderate-intensity aerobic training twice a week *vs.* nutritional and smoking cessation counseling	↑ IG: aerobic threshold, $VO_{2peak;}$ ↑IG vs. CG: overall complication rate; ↔IG vs. CG: type of complication, readmission rate, ICU admission, LoS, quadriceps strength; Prehabilitation was associated with a decrease of PoC.
Onerup A. et al. (2022)	RCT 761 pts with colorectal cancers, I-IV stage	Neoadjuvant radiotherapy, neoadjuvant chemoradiotherapy, neoadjuvant chemo-or immunotherapy	14 days of home-based, daily 30 min. moderate aerobic training + inspiratory muscle training, 2 sets of 30 breaths at 30 % maximal inspiratory pressure, twice a day, + 4 weeks program, after surgery, of daily 30 min. moderate aerobic training *vs.* standard care and information	↔IG vs. CG: self-assessed physical recovery at 4 weeks after surgery,30–90 days and type of PoC, LoS, readmission rate.
Wang W. et al. (2023)	Two arms retrospective 525 pts with colorectal cancers	NR	7 days prior to surgery of supervised 20 min. aerobic training at 60–75 % HRres + 25' resistance training + breaths exercises, performed thrice per day, plus nutritional counseling with protein supplementation plus psychological support +perioperative care vs. perioperative care	↑ IG vs. CG: 6MWT, anxiety, LoS, time to first ambulation, time to first flatus; ↑ IG vs. CG: QoL mental function 1 month after surgery; ↔ IG vs. CG: strength, weight, fat, depression, PoC, mortality, time to first defecation, readmission; ↔ IG vs. CG: QoL physical function 1-, 3- and 6- months after surgery; QoL mental function 3- and 6- months after surgery.
West M.A. et al. (2014)	Two arms nonrandomized 35 pts with rectal cancers, II-IV stage	Neoadjuvant chemoradiotherapy (IG: 100 %, CG: 100 %)	6 weeks, 3 times per week of supervised HIIT (4–6 intervals of 3 min. of moderate intensity, 2 min. severe intensity) *vs.* standard care	↑ IG vs. CG: tumor response to neoadjuvant chemoradiotherapy, VO_{2peak}, anaerobic threshold and number of steps; ↔ IG vs. CG: BMI, FEV1, FVC, hemoglobin level.
Morielli A.R. et al. (2015)	Single arm 18 pts with rectal cancers	Neoadjuvant chemoradiotherapy (IG: 100 %)	During neoadjuvant treatment, 6 weeks of supervised moderate aerobic training at 40–60 % VO_2res, performed trice a week + after neoadjuvant treatment, 6–8 weeks of supervised or unsupervised or combination of 150 min. per week of moderate-intensity aerobic exercise	↑ QoL (physical, role and social functioning, general health, vitality) and cancer-specific QoL (physical, social and emotional well-being, diarrhea, fatigue) from post-neoadjuvant treatment to presurgery; ↑ role-emotional and social well-being from baseline to pre-surgey; ↓ QoL (physical, role and social functioning, general health, vitality) and cancer-specific QoL (physical, social and emotional well-being, diarrhea, fatigue) from baseline to post-neoadjuvant treatment; ↔ depression, anxiety stress, self-esteem, sleep quality from baseline to post-neoadjuvant treatment, and from post-neoadjuvant treatment to presurgery.
Loughney L. et al. (2017)	RCT 35 pts with rectal cancers	Neoadjuvant chemoradiation	6 weeks of HIIT (4–6 intervals of 3 min. of moderate intensity, 2 min. severe intensity) *vs.* standard care	↑ IG vs. CG sleep efficiency, sleep duration, and lying down time; ↔ EX vs. CG step count, metabolic equivalent, active energy expenditure, physical activity duration, total energy expenditure.
Singh F. et al. (2017)	Single arm 12 pts with rectal cancers	Neoadjuvant chemoradiation	16 weeks of 60 min. supervised resistance training, 6 exercises, 2–4 sets of 6–12 reps and 20 min aerobic training at 60–80 % HRmax performed twice a week + home-based 15 min aerobic training twice a week	↑ 400-meter walk from baseline to presurgery; ↓ strength and endurance, lean mass, fat mass, from presurgery to postsurgery; ↓ lean mass from baseline to postsurgery; ↔ strength and endurance, lean mass, fat mass, QoL, fatigue, from baseline to presurgery; ↔400-meter walk QoL, fatigue, from presurgery to postsurgery; ↔400-meter walk, strength and endurance, fat mass, QoL, fatigue, from baseline to post-surgery.
Moug S.J. et al. (2019)	RCT 48 pts with rectal cancers	Neoadjuvant chemoradiotherapy (IG: 100 %: CG: 100 %)	13/17-week of an unsupervised walking program based on steps count vs. usual care	↔ IG vs. CG: steps per day, BMI, waist circumference, 6MWT, QoL, fatigue.

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Table 2 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Moug S.J. et al. (2020)	RCT 44 pts with rectal cancers	Neoadjuvant chemoradiotherapy (IG: 100 %: CG: 100 %)	13/17-week of an unsupervised walking program based on steps count vs. usual care	↔ IG vs. CG: muscle mass.
Morielli A. et al. (2021)	RCT 36 pts with rectal cancers, I-IV stage	Neoadjuvant chemoradiotherapy (IG: 100 %: CG: 100 %)	5–6 weeks of supervised HIIT (5–8 blocks of 2 min. at 85 % VO_{2peak} and 2 min. at 40 % VO_{2peak}) plus 150 min. moderate/ vigorous intensity unsupervised training after the supervised period *vs.* usual care	↑ IG vs. CG: pathological response; ↔ IG vs. CG: VO_{2peak}, 6MWT, strength, flexibility, treatment toxicities, dosage, and neoadjuvant treatment completion;

Abbreviations: ↑, significant improvement; ↓, significant worsening; ↔, no significant change, IG, interventional group; CG, control group; pts, patients; RCT, randomized controlled trial; HIIT, high-intensity interval training; 6MWT, six minutes walking test, BMI, body mass index; VO2max, maximal oxygen consumption; VO2peak, peak oxygen consumption; QoL, quality of life; PoC, post-operative complications; LoS, length of hospital stay; NR, not reported; FEV1, forced expiratory volume in 1 second; FVC, force vital capacity; HRmax, maximal heart rate.

et al., 2010; Li et al., 2013; Moug et al., 2019; Singh et al., 2017; Wang et al., 2023), and fatigue (Dronkers et al., 2010; Moug et al., 2019; Singh et al., 2017); only few investigators found positive effects on these endpoints (Berkel et al., 2022; de Klerk et al., 2021; Janssen et al., 2019). Whereas limited and debated findings have been reported for other outcomes, such as anxiety (Carli et al., 2020; Carli et al., 2010; Fulop et al., 2021; Gillis et al., 2014; Li et al., 2013; Morielli et al., 2016), depression (Carli et al., 2020; Carli et al., 2010; Gillis et al., 2014; Li et al., 2013), sleep (Loughney et al., 2017), and respiratory parameters (Dronkers et al., 2010; Karlsson et al., 2019; West et al., 2014), consensus about the positive impact of presurgical exercise on cardiorespiratory fitness (Berkel et al., 2022; Carli et al., 2010; Chen et al., 2017; Fulop et al., 2021; Gillis et al., 2014; Huang et al., 2016; Li et al., 2013; Northgraves et al., 2020; Singh et al., 2017; Suen et al., 2022; van Rooijen et al., 2019; Wang et al., 2023; West et al., 2014) seems to be reached. Nevertheless, considerable variability in terms of exercise type, duration, intensity, and length of the program as well as in terms of multimodal prehabilitation, emerged across the studies. Programs lasted from a few days to 15–18 weeks, and exercise was often offered as part of a multimodal prehabilitation intervention, including different other approaches, such as nutritional and psychological ones. These heterogeneities make it hard to define the actual contribution of exercise in this setting and could partially explain the inconsistency in the results. However, intriguingly, two studies showed a positive impact of exercise on the neoadjuvant treatment response (Morielli et al., 2021; West et al., 2015). For example, *Morielli et al.* found that patients with rectal cancer who participated in a HIIT program performed during the neoadjuvant chemoradiotherapy reported a significantly higher rate of complete or near complete pathologic response compared to the usual care group, also after adjusting for baseline clinical stage imbalances (56%, 95%CI: 31–79% vs. 18%, 95%CI:4–43%; p=0.02) (Morielli et al., 2021). A similar effect on tumor regression was found by *West et al.*, who proposed an exercise program composed of HIIT, thus suggesting that exercise may interact with cancer treatments to improve their efficacy (West et al., 2015). Globally, exercise before surgery, on one side, may help optimize physical condition and improve postoperative outcomes in patients with gastroesophageal cancers; on the other, in colorectal cancer, its efficacy seems to be reduced, even if the preliminary evidence of positive interaction with anticancer treatments represent a stimulus to deepen this aspect.

3.5. *Lung cancer*

Preoperative exercise in resectable lung cancer is largely examined (Table 3). Generally, exercise interventions before lung cancer surgery last from 7 days to 4 weeks, including predominantly aerobic, strength, and respiratory exercises, and its duration and intensity are highly variable across the studies. In almost all the investigations, patients scheduled for resection did not undergo neoadjuvant treatments, thus explaining the short window dedicated to exercise. Concerning the effect on physical parameters, exercise can increase cardiorespiratory fitness (Bhatia and Kayser, 2019; Bobbio et al., 2008; Coats et al., 2013; Huang et al., 2017; Jones et al., 2007; Lai et al., 2017; Morano et al., 2013; Rispoli et al., 2020; Stefanelli et al., 2013) and muscle strength (Coats et al., 2013; Sebio García et al., 2017) as well as decrease the loss of function that inevitably occurs after surgical intervention (Stefanelli et al., 2013). For instance, a randomized controlled trial on 40 patients with stage I-II non-small cell lung cancer (NSCLC) found that 3-week preoperative training consisting of respiratory exercise and HIIT program produces a significant improvement in favor of intervention for cardiorespiratory fitness at the end of the prehabilitative program (17.8 ± 2.1 vs. 14.5 ± 1.2 mL/kg/min; p<.0.0001) and 60 days after surgery (17.8 ± 2.1 vs. 14.5 ± 1.2 mL/kg/min; p<.0.0001) (Stefanelli et al., 2013). Instead, the impact of exercise prehabilitation on pulmonary function is still debated, with some authors reporting no clear benefits (Bobbio et al., 2008; Coats et al., 2013; Jones et al., 2007; Lai et al., 2017; Lai et al., 2017; Morano et al., 2013; Perrotta et al., 2019; Rispoli et al., 2020) while others find a positive effect (Marhic et al., 2019; Pehlivan et al., 2011; Rispoli et al., 2020; Saito et al., 2017).

Most trials detected an improvement in PoC (Boujibar et al., 2018; Huang et al., 2018; Lai et al., 2017; Lai et al., 2017; Morano et al., 2013; Pehlivan et al., 2011; Rispoli et al., 2020; Saito et al., 2017) and LoS (Benzo et al., 2011; Fang et al., 2013; Gao et al., 2015; Lai et al., 2017a, 2017b; Morano et al., 2013; Pehlivan et al., 2011; Rispoli et al., 2020; Zhou et al., 2017), even if not all the investigations are concordant (Chesterfield-Thomas and Goldsmith, 2016; Licker et al., 2017; Sebio García et al., 2017; Sekine et al., 2005). *Lai et al.* tested a 7-day program including thoracic expansion, and incentive spirometry exercises performed thrice per day, abdominal breathing exercises twice daily, and aerobic training, 30 minutes per day in 101 patients with NSCLC stage I-IV scheduled for lobectomy. The postoperative assessment revealed that patients allocated to the intervention had a shorter LoS (6.1 ± 3.0 vs. 8.7 ± 4.6 days, p = 0.001) and a lower incidence of PoC (9.8% vs. 28.0%; p = 0.019) than the usual care group. Moreover, prehabilitation was found to be an independent prognostic factor of the PoC risk (Lai et al., 2017).

Exercise as prehabilitation in lung cancer failed to detect benefits in terms of postoperative mortality (Chesterfield-Thomas and Goldsmith, 2016; Fang et al., 2013; Licker et al., 2017), QoL, fatigue, and psychological status (Coats et al., 2013; Huang et al., 2017; Lai et al., 2017a, 2017b; Peddle et al., 2009; Sebio García et al., 2017). On the other hand, prehabilitation has been demonstrated to be effective in making operable patients who were initially functionally inoperable. In this sense, *Goldsmith et al.* offered exercise prehabilitation to 206 patients affected by NSCLC with borderline or poor pulmonary function, of which almost half were considered ineligible to undergo radical treatments. The program lasted 2–4 weeks, and patients were instructed to perform respiratory muscle training and breathing exercises three times per day and aerobic training twice a week at moderate/vigorous intensity. Following prehabilitation, the percentage of patients considered

Table 3
Studies investigating exercise prehabilitation in lung cancer.

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Divisi D. et al. (2012)	Single arm 27 pts with lung cancer, stage I	NR	4 weeks, 6 times per week of 50 min. respiratory physiotherapy and 40 min. aerobic training	All patients, initially functionally ineligible, became eligible and underwent surgery; ↑ FEV1, FVC, DLCO, VO2max, 6MWT.
Pehlivan E. et al. (2019)	Single arm 23 pts with lung cancer	NR	15 days, home-based chest physiotherapy, daily walk at 80% HRmax HR, twice a day of inspiratory muscle training (30% MIP) and pulmonary rehabilitation	65% initially functionally ineligible of patients became eligible underwent surgery; ↑ FEV1, FVC, MIP, dyspnea, 6MWT, $VO2_{peak;}$ ↔MEP.
Liu Z. et al. (2019)	RCT 73 pts with lung cancer, stage I-III	Neoadjuvant therapy	2 weeks of home based, aerobic training, 3 times per week, 30 min min. per session at moderate intensity, and resistance training, 2 times per week, 3 sets of 10–12 reps plus nutritional counseling with protein supplementation and psychological support vs. standard care	↑ IG vs. CG: 6MWD, FVC ↔ IG vs. CG: FEV_1 and other pulmonary parameters, WHODAS 2.0, anxiety and depression, QoR-9, 30-day PoC, mortality, LoS and chest tube duration.
Harada H. et al. (2013)	Prospective vs. historical cohort 50 pts with lung cancer, stage I-III	No	2–5 weeks of supervised respiratory exercises and aerobic training plus nutritional support with aminoacidic supplementation (IG) vs. supervised conventional physical training once a week (CG)	↑ PoC in IG with poor preoperative conditions compared with similar in CG; ↑ PoC in IG with preoperative risk score >3 compared with similar in CG; ↑ IG vs. CG: FEV1, VC.
Sommer M.S. et al. (2016)	RCT (4 arms) 40 pts with lung cancer, stage I-III	Adjuvant chemotherapy	2 weeks of preoperative and 12 weeks of postoperative aerobic and strength activity initiated 2 weeks after surgery *vs.* 2 weeks of preoperative and 12 weeks of postoperative aerobic and strength activity initiated 6 weeks after surgery vs. 12 weeks of postoperative aerobic and strength activity initiated 6 wks after surgery *vs.*12 wks of postoperative aerobic and strength activity initiated 2 wks after surgery	Preoperative interventions not feasible Postoperative interventions safe and feasible ↑ 6MWT, strength (exercise adherence ≥ 70%) ↑ strength (exercise adherence ≥ 70%) ↔ $VO2_{peak}$, pulmonary parameters
Benzo R. et al. (2011)	RCT 9 pts with lung cancer	NR	4-week of exercise prehabilitation using guidelines *vs.* standard of care	Poor recruitment; The study was prematurely stopped due to the low likelihood of meaningful accrual; ↔ PoC, LoS, severe atelectasis, prolonged chest tube, prolonged mechanical ventilation.
	RCT 19 pts with lung cancer	NR	1 week, 10 sessions, twice a day, 20 min. aerobic training, resistance exercises, 2 sets of 10–12 reps, every other day, 10 min. breathing exercises and 15–20 min. daily inspiratory muscle training *vs.* standard care	↑ IG vs. CG: LOS, incidence and need of prolonged chest tube; ↔ shuttle walk test, intensive care unit hours, PoC, ventilation hours, respiratory failure, pneumonia and severe atelectasis.
Coats V. et al. (2013)	Single arm 13 pts with lung cancer, stage I-IV	Chemotherapy or palliative chemotherapy or palliative radiotherapy/ chemotherapy	4 weeks, 3–5 times per week of home-based aerobic training, 30 min. at 60–80% of the peak workload and resistance, exercises 1–2 set of 10–15 reps	↑ strength, 6MWT, perceived physical fitness, depression;↔ VO_{2peak}, QoL, anxiety.
Stefanelli F. et al. (2013)	RCT 40 pts with lung cancer, stage I-II	NR	3 weeks, 15 sessions, 3 hours sessions of respiratory exercises followed by high intensity training up to 30 min. at 70% peak work rate *vs.* standard care	↑ IG vs. CG: VO_{2peak} at pre-surgery and 60 days after surgery; ↓ FEV1, DLCO, VO_{2peak} at 60 days after surgery in IG and CG.
Chesterfield-Thomas G. et al. (2016)	2 arms no-RCT 42 pts with lung cancer	NR	7.1±6.5 days, 3 times per day of respiratory muscle training and breathing exercises, aerobic training and walking twice weekly, training in activities daily living, health education and pharmacology agents (if necessary) *vs.* patients underwent straight to surgery	↑ IG vs. CG: Thoracoscore, dyspnoea, PoC, postoperative mortality, performance status; ↔ IG vs. CG: LOS.
Lai Y. et al. (2016)	RCT 60 pts with lung cancer, stage I-IV	NR	1 week, of supervised, abdominal breathing exercises, 15–20 min. twice a day, 20 min expiration exercises, 3 times per day and 30 min. daily aerobic training *vs.* standard care	↑IG vs. CG: 6MWT, peak expiratory flow, PoC, ↔ IG vs. CG: FEV1, FVC, DLCO, QoL.
Morano M.T. et al. (2013)	RCT 24 pts with lung cancer, stage I-III	NR	4 weeks, 5 times per week of aerobic training 10–30 min. at 80% peak workload), and daily inspiratory muscle training, 10–20 min. at 20%-60% MIP *vs.* chest physical therapy	↑ IG vs. CG: FVC, 6MWT, MIP, MEP, LoS, bronchospasm, bronchopleural fistula, PoC, days with chest tubes; ↔ IG vs. CG: FEV1, intensive care unit stay, mechanical ventilation >48 h, pneumonia, atelectasis.
Jones L.W. et al. (2007)	Single arm 20 pts with lung cancer	NR	4 weeks of supervised aerobic training first week: 5 sessions, 20–30 min. at 60–65% VO2peak; second and third week, 4 sessions, 25–30 min at 60–65% VO2peak + 1 session, 20–25 min. at ventilatory threshold; fourth week, 3 sessions at 60–65% VO2peak, 1 threshold workout for 20–30 min. and 1 interval workout, 30 seconds at VO2peak followed by 60 seconds of active recovery (10–15 intervals)	↑ VO_{2peak}, 6MWT. ↑ VO_{2peak}, 6MWT in patients with ≥80% adherence vs. <80% adherence ↔ FVC, DLCO, FEV1.

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Table 3 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
Lai Y. et al. (2017)	RCT 101 pts with lung cancer, stage I-IV	NR	7 days of supervised, thoracic expansion exercises 3 times per day, 20 breaths per session, 15–30 min abdominal breathing exercises, twice daily, and aerobic training 30 min per day *vs.* standard care	↑ IG vs. CG: peak expiratory flow, 6MWT, PoC, LoS, hospital and drug expenses; ↔ QoL, fatigue, dyspnea; Preoperative regimen and number of risk factor are independent risk factors for PoC.
Lai Y. et al. (2019)	RCT 68 pts with lung cancer	NR	1 week of supervised, breathing exercise 3 times per day, 20 breaths per session, and aerobic training 30 min. per day vs. standard care	↑ IG vs. CG: 6MWT, emotional function, LoS, total, material and drug costs, PoC ↔ IG vs. CG: FEV_1, FVC, DLCO, peak expiratory flow, fatigue, dyspnea, QoL.
Gravier F.E. et al. (2019)	Single arm 50 pts with lung cancer, stage I-IV	Neoadjuvant chemotherapy	6 weeks, 3–5 times per week of 90 min supervised training including: 15–45 min. aerobic training, resistance exercises, 3 sets of 12 reps at 60–70% 1RM, and 15 min daily inspiratory muscle training at 30% MIP	↑ VO_{2peak} ↔ VE/VCO2 slope Patients performed ≥15 sessions improve VE/VCO2 and VO_{2peak} compared to performed <15 sessions. No difference considering different cancer stage.
Gravier F.E. et al. (2022)	RCT 36 pts with lung cancer, stage I-IV	No	3 weeks, 5 times per week of 90 min. supervised aerobic training, 15–45 min., resistance exercises, 3 sets of 12 reps at 60–70% 1RM, and 15 min. daily inspiratory muscle training at 30% MIP (IG) *vs.* 5 weeks, 3 times per week, of 90 min. supervised aerobic training, 15–45 min., resistance exercises, 3 sets of 12 reps at 60–70% 1RM, and 15 min. daily inspiratory muscle training at 30% MIP (CG)	↔ IG vs. CG: VO_{2peak} BMI, strength, QoL.
Saito H. et al. (2017)	2 arms retrospective 116 pts with lung cancer, stage I-III	No	2–4 weeks, 5 times per week of supervised breathing exercises, aerobic training plus postoperative breathing, chest, shoulder girdle, aerobic training until discharge *vs.* standard care	↑ IG vs. CG: FEV1, VC, PoC;↑ IG vs. CG: FEV1,1-month after surgery; ↔ IG vs. CG: VC, 1 and 6 months after surgery, FEV1, 6 months after surgery; Age, ppoFEV1 and pulmonary rehabilitation were independent risk factors for PoC.
Pehlivan E. et al. (2011)	RCT 60 pts with lung cancer, stage I-III	No	1 week, 3 times per day of walking and chest physiotherapy *vs.* standard care	↑ IG vs. CG: PoC, LOS; ↔ IG vs. CG: FEV1, DLCO, FVC and other pulmonary parameters.
Zhou K. et al. (2017)	2 arms retrospective 197 pts with lung cancer, stage I-IV	No	7 days of supervised aerobic exercises 30 min. daily, inspiratory muscle training (abdominal breathing, twice a day for 15–20 min. and inspiration exercises three times per day for 20 min.) *vs.* standard care	↑ IG vs. CG: PoC, LoS, postoperative expenses; ↓ IG vs. CG: preoperative expenses; ↔ IG vs. CG: in-hospital expenses.
Huang J. et al. (2017)	RCT (3 arms) 90 pts with lung cancer, stage I-III	NR	1 week of supervised inspiratory muscle training (abdominal breathing training, 2/3 times daily for 15–20 min. + thoracic breathing training (four times daily for 20 min.), aerobic training twice daily for 20 min (IG1). *vs.* inspiratory muscle training (IG2) *vs.* standard care (CG)	↑ IG1 vs. CG: PoC, LoS, 6MWT; ↑ IG1 vs. IG2, CG: PEF; ↔QoL (improvement only in global QoL), FEV1, FVC, DLCO.
Fang Y. et al. (2013)	RCT 61 pts with lung cancer,	NR	2 weeks, 5 times per week, of 40 min. aerobic exercises at 60–80% VO_{2max} and breathing exercises vs. standard care	↑ IG vs. CG: FVC, DLCO, VO_{2max}, oxygen therapy time, mechanical ventilation time, LOS; ↔cardiopulmonary complications, arrhythmia, pulmonary infection, atelectasis, postoperative failure, 30-days mortality.
Boujibar F. et al. (2018)	2 arms retrospective 34 pts with lung cancer, stage I-III	No	17 sessions, 3/5 sessions per week of 45 min. endurance training at ventilatory threshold, resistance exercises, 3 sets of 12 reps at 70% 1RM, and inspiratory muscle training at 30% MIP *vs.* standard care	↑ IG vs. CG: PoC; ↔ IG vs. CG: LoS.
Gao K. et al. (2014)	RCT 142 pts with lung cancer, stage I-IV	NR	3–7 days, twice daily abdominal breathing, 20–30 breaths each time, 20 min. breathing training device, twice daily 15–20 min. aerobic exercises and 15–20 min. on stair climbing *vs.* standard care	↑ IG vs. CG: PoC, LoS; ↔ IG vs. CG: hospital costs.
Perrotta F. et al. (2019)	Single arm 25 pts with lung cancer, stage I-III	NR	3 weeks of supervised 3-hour session, 5 times per week, respiratory exercises, high intensity training at 70% peak workload up to 30 min.	↑ VO_2peak, V_E/VCO_2; ↔ FEV1, DLCO and other pulmonary parameters.
Licker M. et al. (2016)	RCT 151 pts with lung cancer, stage I-III	Neoadjuvant chemotherapy	26 days, 2/3 times per week of supervised HIIT (two 10-min series of 15 seconds sprint at 80–100% peak work rate and 15 seconds pauses), resistance exercises *vs.* standard care	↑ IG vs. CG: VO2peak, 6MWT, respiratory complications, LoS in PACU; ↔ IG vs. CG: LoS, 30-day mortality, rate of admission to the intensive care unit.
Karenovics W. et al. (2016)	RCT 151 pts with lung cancer, stage I-III	Neoadjuvant chemotherapy	26 days, 2/3 times per week of supervised HIIT (two 10-min series of 15 seconds sprint at 80–100% peak work rate and 15 seconds pauses), resistance exercises *vs.* standard care	↔ IG vs. CG: mortality, VO_{2peak}, FVC, FEV1, DLCO at 1-year after surgery.
Bathia C. et al. (2019)	RCT 151 pts with lung cancer, stage I-III	NR	26 days, 2/3 times per week of supervised HIIT (two 10-min series of 15 seconds sprint at	↑ IG vs. CG: VO2peak, 6MWT.

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Table 3 (*continued*)

Author (year)	Study design, sample size, cancer site and stage	Anticancer treatment	Intervention	Main results
			80–100% peak work rate and 15 seconds pauses), resistance exercises *vs.* standard care	
Garcia R.S. et al. (2016)	RCT 22 pts with lung cancer,	No	16 sessions, 3–5 times per week of interval endurance training, 1 min. at 80% or peak work rate and 4 min. at 50% of peak work rate (30 min total), resistance training, 3 sets of 15 reps, breathing exercises, 30 reps at 80% of the maximal vital capacity *vs.* standard care	↑ IG vs. CG: strength, QoL (physical summary components), exercise tolerance; ↑ IG vs. CG: strength, QoL (physical summary components), exercise tolerance, 3-month after surgery; ↔ IG vs. CG: LoS, PoC, 6MWT; ↔ IG vs. CG: exercise tolerance, strength, QoL immediately after surgery.
Bradley A. et al. (2013)	2 arms 363 pts with lung cancer	NR	4 sessions, twice weekly of supervised aerobic, resistance training and inspiratory muscle training plus rejoined rehabilitation program between 4 and 6 weeks after surgery for up to 3 months *vs.* standard care	↑ IG vs. CG: 6MWt, FEV1, LoS; ↔ IG vs. CG: PoC, readmission rate, intensive care unit, hospital and 30-day mortality.
Tenconi S. et al. (2021)	RCT 140 pts with lung cancer, stage I-II	No	14 prehabilitation sessions, including: 6 supervised sessions, 2–3 times per week, 2 hours of aerobic training, resistance training and respiratory muscle training + 8 home-based sessions, 3–4 times per week, 1 hour of respiratory muscle training and 30 min walking at 60–80% HRmax HR plus 8 weeks, 39 rehabilitation sessions including: 15 supervised sessions, 2 times per week, of aerobic, resistance, exercises and respiratory muscle training + 24 home-based sessions3–4 times per week, 1 hour of respiratory muscle training and 30 min walking at 60–80% HRmax HR *vs.* standard care	↑ IG vs. CG: 6MWT ↔ IG vs. CG: FEV_1, FVC, DLCO, LoS, QoL, HADS, pain, PoC.
Finley D.J. et al. (2021)	Single arm 18 pts with lung cancer, stage I-III	NR	3 weeks, 5 times per week, of home-based 30 min. aerobic training	↔ 6MWT.
Ferreira V. et al. (2020)	RCT 124 pts with lung cancer, stage I-IV	Neoadjuvant therapy	4 weeks, 3 times per week of home-based 30 min. aerobic training, resistance exercises, 2 sets of 8–12 reps plus nutritional counseling with protein supplementation plus psychological support + continue program 8 weeks after surgery *vs.* exercise program starting 8 weeks after surgery	↑ IG vs. CG: QoL, mental and physical summary at 4 weeks after surgery; physical summary at 8 weeks after surgery ↔ IG vs. CG: 6MWT at 4 and 8 weeks after surgery; LoS, 30 days emergency visits, readmission rate, mortality, PoC.
Ferreira V. et al. (2021)	RCT 34 pts with lung cancer, stage I-III	No	4 weeks, 1 time per week of supervised 30 min. aerobic training and 30 min. resistance exercises, 1–2 sets of 8–15 reps plus nutritional counseling with protein supplementation plus psychological support + home-based, daily 30 min. of moderate aerobic and resistance training every second day *vs.* standard care	↔ IG vs. CG: 6MWT, QoL, fatigue, anxiety, depression, physical activity level, body composition.
Goldsmith I. et a. (2022)	Single arm 216 pts with lung cancer, stage I-IV	NR	2–4 weeks, of respiratory muscle training and breathing exercises three times per day and aerobic training twice a week at moderate/ vigorous intensity	↑ dyspnea, 6MWT, rate of pts eligible for surgery and radical anticancer treatments.

Abbreviations: ↑, significant improvement; ↓, significant worsening; ↔, no significant change, IG, interventional group; CG, control group; pts, patients; RCT, randomized controlled trial; HIIT, high-intensity interval training; 6MWT, six minutes walking test, BMI, body mass index; VO2max, maximal oxygen consumption; VO2peak, peak oxygen consumption; QoL, quality of life; PoC, post-operative complications; LoS, length of hospital stay; NR, not reported; VE/CO2, ventilatory equivalent for CO2; VC, vital capacity; 6MWT, six minutes walking test; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; FVC, force vital capacity;

suitable for any radical treatment (48.2% vs. 93.1%; $p<0.05$) and ready to proceed with surgery (41.2% vs. 75.8%; $p<0.001$) drastically increased compared to baseline (Goldsmith et al., 2021).

Altogether, exercise prehabilitation in lung cancer appears to be the most studied context in which the evidence of improved postoperative outcomes is stronger.

4. Future directions and new opportunities

Overall, this overview of the literature on the effect of exercise, alone or in combination with other interventions, offers several starting points for reflection to address future research in this setting (Fig. 1).

The included studies show that exercise can increase cardiorespiratory fitness before surgery and accelerate recovery compared to rehabilitative programs across different cancer types. Nevertheless, whereas the beneficial role of exercise prehabilitation on postoperative outcomes has been demonstrated for some malignancies, the impact remains unclear for others. This elusiveness may be due to the relatively low amount of research and the limitation in the methodological quality of the trials, often not adequately powered to detect differences in clinical outcomes. Indeed, it is immediately evident that some cancer types, such as lung and gastrointestinal, are deeply analyzed in terms of the number of published studies, while others are poor or even never investigated, e.g., head and neck, kidneys, melanoma, breast, and gynecologic. Future investigations should overcome these information gaps.

Another interesting issue regards exercise prehabilitation in combination with systemic neoadjuvant treatments. Although neoadjuvant therapies aim to reduce tumor burden to increase the chance of undergoing surgical resection, they are often accompanied by different toxicities that may impact cardiorespiratory and musculoskeletal fitness. Paradoxically, these impairments may limit patients' surgical eligibility and expose patients to a high risk of developing PoC. As demonstrated in

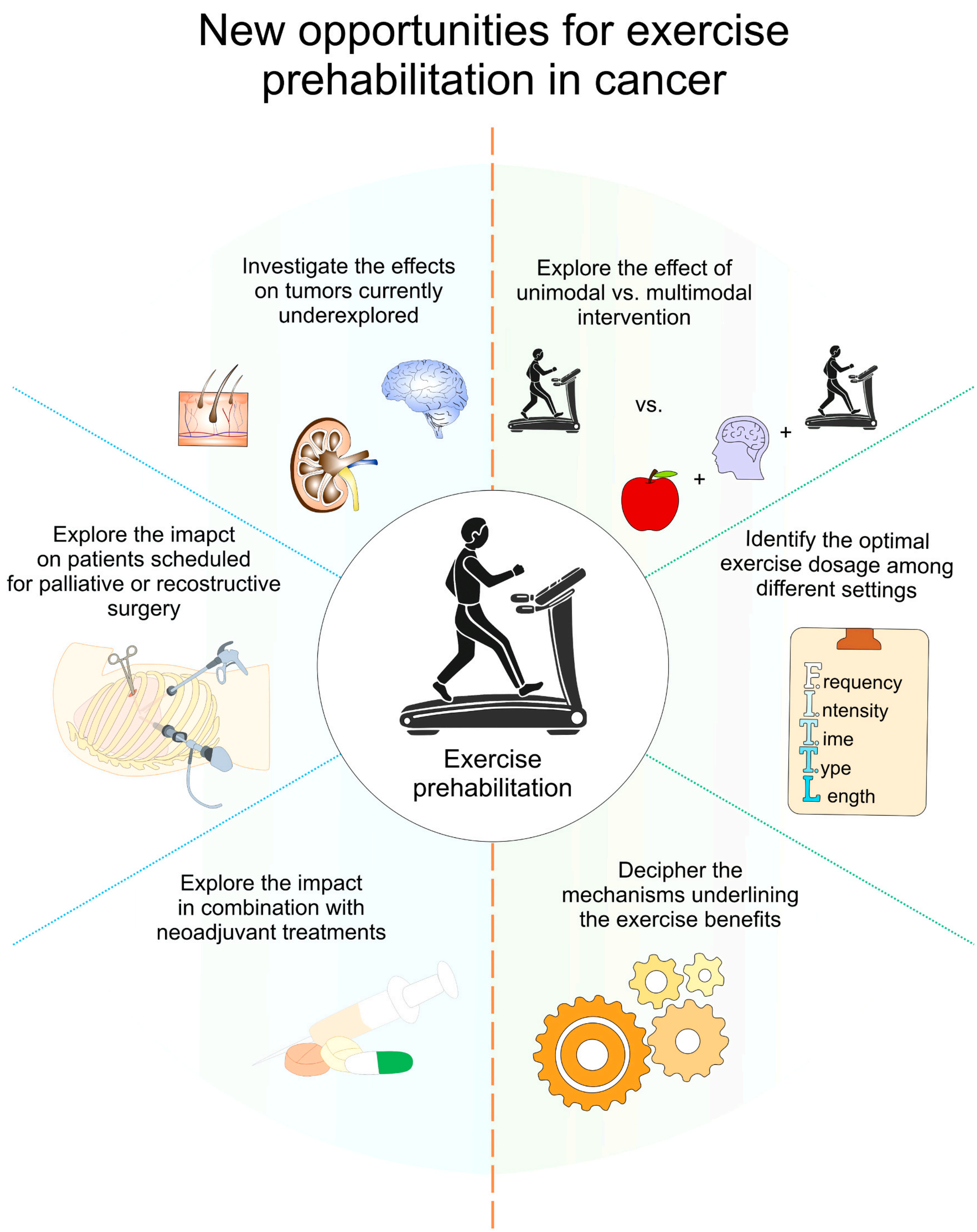

Fig. 1. Opportunities for future research in exercise prehabilitation in the oncological setting.

several investigations, exercise may reduce the loss of function in this phase and mitigate treatment-related adverse events to maximize the chance of undergoing surgery with the best physical condition possible. Moreover, exercise could synergize with neoadjuvant treatments, influencing their distribution, pharmacodynamics, and metabolism, thus increasing the pathological response. However, to date, only two investigations on rectal cancer have preliminarily explored this aspect, leaving the impact of exercise on treatment little known. The combination of exercise and neoadjuvant therapies, from this point of view, may offer an intriguing field for future studies, on one side, to enlarge the investigation to those malignancies yet not explored under neoadjuvant regiments (e.g., lung cancer) and on the other, to deciphering the potential effect and the underlying mechanisms sustaining exercise on tumor response.

Currently, most investigations include patients undergoing surgery with curative intent. Nevertheless, even palliative and reconstructive surgeries may expose patients to PoC risk and prolonged LoS, especially if considered that, for instance, palliative surgery is most proposed for patients with advanced cancer, who are frailer than other patients. Even in this case, exercise could help to physically prepare patients to face stressful events such as these kinds of surgery.

The final considerations regard the prescription of exercise during the prehabilitation phase. Across studies, unimodal or multimodal interventions have been tested. Nevertheless, a better understanding of the different impacts of the two modalities is needed in order to identify if exercise may be effective also alone and in which malignancies, or only in combination with other approaches. Additionally, up to now, the indications about exercise in the prehabilitation guidelines are general, without specific information regarding the optimal dosage. In the future, studies should address this lack in order to define the best type, frequency, duration, and intensity of exercise, as well as the length of the program, in consideration of the different possible settings. Indeed, it is possible to speculate that patients with colorectal cancer and those with lung malignancies would require different exercise dosages to obtain benefits from exercise as well as that the prescription of exercise may be adapted based on the neoadjuvant treatment regime.

Last but not least, although a recent review has reported the potential mechanisms underlying prehabilitation and surgical complications (Sibley et al., 2023)., exploring the mechanisms by which exercise prehabilitation may produce benefits, is another partially uncovered area that may help reinforce the importance of exercise and better personalize the prescription for each patient's need.

Overall, the introduction of exercise in the prehabilitation context appears effective in improving outcomes, especially in some malignancies. Given the rapidly evolving landscape, further research is necessary to investigate underexplored areas and define the optimal exercise dosage, considering each cancer setting.

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Nicole Del Bianco, Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Data curation. **Anita Borsati**, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Linda Toniolo**, Writing – review & editing, Visualization. **Christian Ciurnielli**, Writing – review & editing, Visualization. **Lorenzo Belluomini**, Writing – review & editing, Visualization. **Jessica Insolda**, Writing – review & editing, Visualization. **Marco Sposito**, Writing – review & editing, Visualization. **Michele Milella**, Writing – review & editing, Visualization. **Federico Schena**, Writing – review & editing, Visualization. **Sara Pilotto**, Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Data curation. **Alice Avancini**, Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Data curation, Supervision, Project administration.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104350.

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