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Review

Prehabilitation and functional recovery for colorectal cancer patients

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ABSTRACT

Cancer and its treatments are associated with functional decline that has impactful consequences on quality of life, and care continuum. Thus, optimizing perioperative functional capacity has been identified as a research and clinical priority in cancer care. The process of enhancing physical fitness before an operation to enable the patient to withstand the stress of surgery has been termed prehabilitation. Main elements are preoperative exercise, nutrition therapy, and anxiety-reduction techniques. Given the growing body of evidence on prehabilitation efficacy, this narrative review will summarize the rational underlying preoperative interventions, and propose a structured clinical pathway aimed at optimizing preoperative functional capacity.

Introduction

Surgery is a major stressor. The response of the body to injury consists in an ancestral systemic reaction aimed to maintain vital functions and restore homeostasis [1]. Stress response is normally adaptive and time-limited, and it is assumed to provide a survival advantage [2,3]. However, a prolonged activation of this pathway, even after the removal of the noxious stimulus, may contribute to worsen clinical and functional status. During the initial phase, activation of the hypothalamic-pituitary axes and the innate immune system promote fast availability of energetic substrates, minimize excessive inflammation, and preserve vascular tone. In contrast, the late phase is associated with uncontrolled catabolism and resistance to anabolic signals, increased oxidative potential that lead to tissue damage, development of weakness and/or myopathy, and increased susceptibility to infection.

Unlike trauma and critical illness, elective surgery is a ‘scheduled stress’. Thus, the idea of preventing or attenuating the stress response and its consequences has attracted medical science for a century [4]. Considerable progress has been made in recent years towards improving surgical care, and ERAS represents a unique milestone in that direction [5,6]. Only in the recent past, however, there has been appropriate attention to the clinical impact of reduced functional capacity on care continuum [7,8]. Indeed, the main determinants of functional capacity (physical, nutrition, and psychological status), identified as risk factors for poor surgical outcome, are potentially modifiable conditions [9]. This awareness has caused a conceptual shift away from attempting to restore functional capacity after surgery towards preventive strategies [10].

Prehabilitation is a multidisciplinary intervention that aims at using the preoperative period to prevent or attenuate the surgery-related functional decline and its consequences. Multimodal prehabilitation includes exercise training, nutritional therapy, and anxiety reduction strategies. Despite an incomplete and still evolving understanding, a mounting clinical evidence developed in last 5 years allows us for the development of a rational preoperative approach aiming at attenuating surgical-related functional decline. This narrative review will summarize the rational of preoperative interventions, explain how prehabilitation could impact upon current practice, outline our thoughts on preoperative pathway, review the evidence, and speculate upon how care will further evolve.

The prehabilitation approach

Colorectal cancer is associated with both unhealthy lifestyle attitude (low physical activity and poor food intake) and pathological organ response to specific interventions (exercise intolerance and metabolic dysfunction). Multimodal prehabilitation aims

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at assessing for these specific conditions and intervening in high-risk population. This approach is supported by emerging evidence of effectiveness in selected, deconditioned patients [11,12]. Fig. 1 shows our proposal for a rational preoperative approach in the context of multimodal prehabilitation. Limited surgical or perioperative society guidelines exist on how to optimally screen, assess, and intervene on surgical patients' physical status; thus, we suggest a practical pathway that attempts to meet the needs of majority of patients. The counseling and the consequent interventional strategies should be run by specialized healthcare providers, such dieticians, psychologists, exercise physiologists, physiotherapists and sport specialists. The treatment of special conditions goes beyond the purpose of this review, and the care pathway of each patient must be planned and personalized. For instance, in the nutrition session we propose a classical optimal carbohydrates/fat ratio whereas it is known that a higher fat intake would be beneficial in some weight-losing cancer patients with insulin resistance [13].

Aiming at increasing the quality of perioperative care by accelerating recovery, prehabilitation should be integrated into best perioperative management and ERAS pathway, representing its clinical and scientific development. Thus, clinical elements of usual preoperative care (such as risk assessment, medication management, perioperative blood management, and smoking cessation) and ERAS pathway (such as minimally invasive surgical approach when feasible, multimodal analgesia, minimized blood loss and perioperative fluid administration, preoperative oral carbohydrate loading, early oral nutrition, respiratory physiotherapy, and early mobilization) are not further explained in this paper. In our 3-step approach, *all patients* should be screened before surgery, and further tests and intervention should involve high-risk population:

1. *Screening.* Its main purpose is to predict the probability of poor outcome, and whether specific interventions could modify this risk. *All patients* should be screened preoperatively.
2. *Assessment.* This is a detailed examination of functional variables by an expert clinician, dietitian, kinesiologist/physiotherapist, or nurse. It is a time and resource-consuming process, and should involve only high risk population identified with screening tools. Mandatory elements are comprehensive history, exercise and dietary habits, functional evaluation in form of signs/symptoms, and laboratory or clinical testing results. A detailed description of a physical, nutritional, and psychological assessment goes beyond the purpose of this review.
3. *Intervention.* Training and nutritional program need to be personalized and prescribed based on specific assessments, ensuring high quality clinical standard and patients' safety. Specific interventions such as physical therapy in patients with severely impaired cognition/motion, or nutritional therapy in severely compromise oral intake require special consideration.

Why exercise?

Poor physical fitness carries an impressive worldwide burden [14]. Interest in cancer rehabilitation has grown exponentially during last decades, addressing the urgent demand of improving

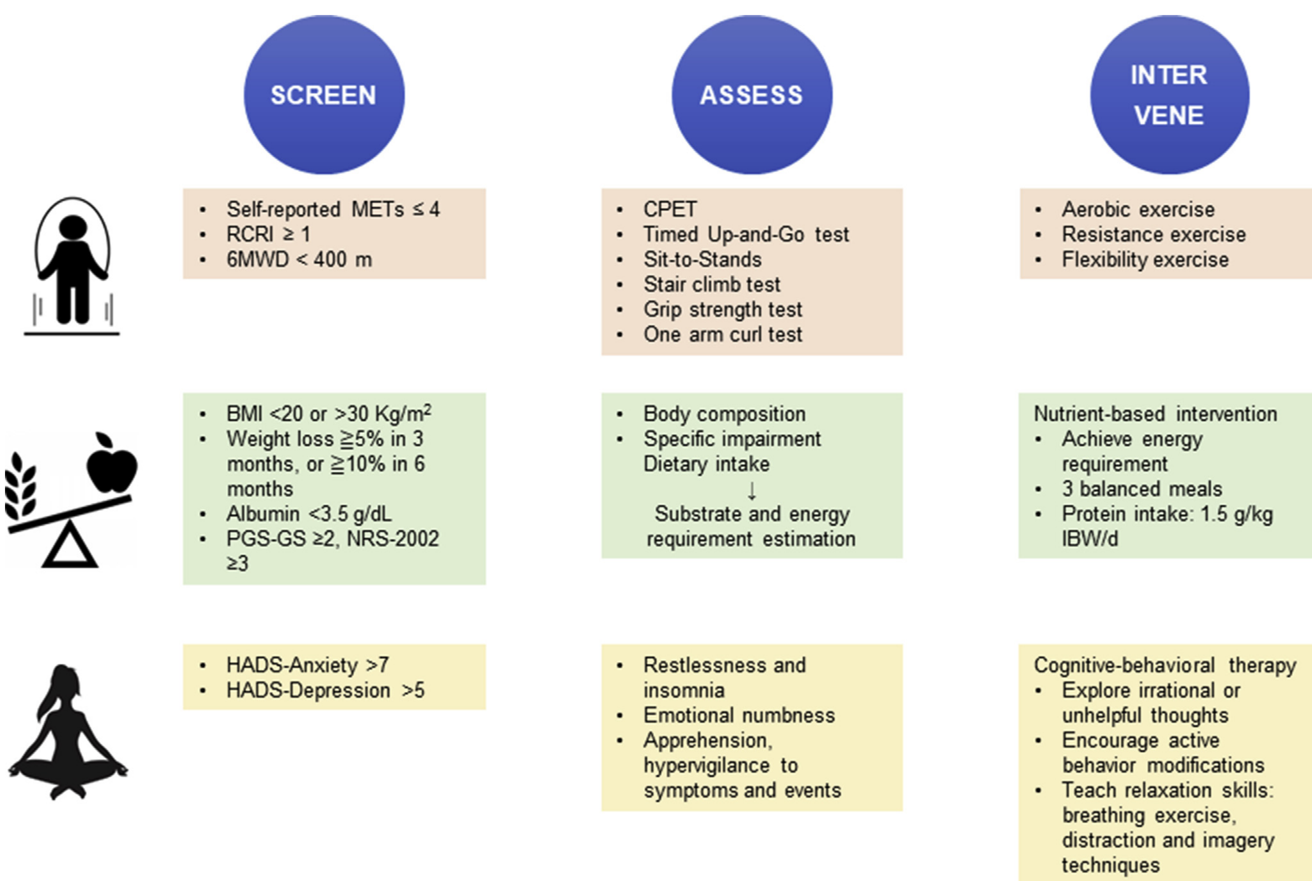

Fig. 1. Proposed clinical pathway for preoperative functional optimization of patients undergoing colorectal cancer surgery. 6MWD, 6-min walking distance; BMI, body mass index; CPET, Cardiopulmonary exercise testing; HADS, Hospital Anxiety and Depression Scale questionnaire; Anxiety and Depression sub-scale; IBW, ideal body weight; METs, metabolic equivalent; NRS-2002, Nutrition Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; RCRI, Revised Cardiac Risk Index.

quality of life in a growing population of survivors. The novel approach of prehabilitation focuses the ability of exercise to deliver a physiologic stress that causes an adaptive response in all organs and tissue, thus improving the ability to withstand the incoming stress of surgery [15].

Cardiorespiratory fitness is determined by the capacity to meet the increase in oxygen consumption during daily activities, exercise, and stress conditions. The ability to both deliver and utilize oxygen and substrates could be impaired by cancer and its treatments, such as surgery, chemotherapy, radiotherapy, and hormone therapy [16]. In this setting, the potential role of exercise to revert or treat this condition is now a proof of concept [17]. In contrast, the potential impact on immune-modulation is poorly understood and more controversial, since both anti- and pro-inflammatory mediators could be stimulated by different exercise interventions [18]. Although aerobic training is the single most studied intervention [19], both resistance and endurance exercise promote a synergistic effect on tissue protein synthesis and aerobic capacity, and should be included in a preoperative programme [20–22]. Older adults should perform 150 min of moderate-intensity physical activity a week or 75 min of vigorous-intensity activity, and strengthening activities involving major muscle groups should be performed on at least 2 days per week [23].

Screening

Self-reported functional capacity could be evaluated with patient's history, and expressed in metabolic equivalents (METs), where 1 MET is the resting oxygen consumption. Climbing a flight of stairs or walking up a hill are activities associated with METs >4, and they are considered a 'safe' threshold below which postoperative complications are more likely to occur [24]. Validated tools to assess perioperative risk of major cardiac complications are: Revised Cardiac Risk Index [25], ACS NSQIP MICA [26], and ACS NSQIP Surgical Risk Calculator [27]. A simple, objective, and inexpensive measure of functional capacity is the 6-min walk test, that measures the distance covered over 6 min at a brisk pace. Although it is an easy test, a high-quality, standardized protocol should be always followed [28]. A 6-min walking distance below 400 m is an indicator of impaired mobility, limited independence, and poor surgical outcome [29–31]. Recent findings show how this threshold could be used to identify the target population for prehabilitation intervention [11].

Assessment & intervention

Endurance and strength tests should be utilized to both assess physical status and prescribe exercise. Cardio Pulmonary Exercise Testing (CPET) is the gold standard to evaluate functional capacity and therapeutic response in numerous medical and surgical settings [32]. CPET metabolic cart measures gas exchange and ventilation parameters, allowing the evaluation of oxygen consumption during a ramped incremental exercise. CPET provides recognized clinical measure of surgical outcome in colorectal cancer, and it is a valuable tool to guide prehabilitation [33].

The physical intervention of multimodal prehabilitation is exercise training. Although it seems to be a simple concept, it needed to be properly defined and recognized as a "planned, structured, repetitive, and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" [34]. For instance, giving advice of walking is not prescribing exercise. Delivering a behavioral intervention is a complex process that relies on patients' volitional effort, and the researcher/clinician should promote and facilitate both the personal commitment and the quality of the intervention. In our experience, main elements are the close monitoring of the adherence to prescription, the encouragement of the compliance to the program, the continuous feed-back to patients' effort, and the introduction of supervised training session.

When designing a training program, it is recommended to follow the international recognized guidelines [35]. There are three main categories of exercise (aerobic, resistance and flexibility training), that complement each other, and lead to a comprehensive functional outcome improvement. Aerobic training, involving large muscle groups that use oxygen-supplied energy, is the cornerstone intervention for increasing aerobic capacity [19]. Stationary and recumbent-type bikes, stair climbing machines and treadmills are the most common used equipment. The duration depends upon the intensity of the activity, but each bout should last 10 min' at least. Exercise intensity and module, in form of either moderate intensity continuous or high intensity interval training, should be based on CPET-derived variables, ensuring an individualized protocol for each participant [8,33]. In resistance training, muscles work against an applied force or weigh aiming at improving strength. Eccentric resistance exercise at high intensity is most beneficial [36], although not always feasible in unfit patients. Stretching and strengthening exercise, warm-up and cooldown activities should always be performed in a training session.

Why nutrition?

Malnutrition, affecting two in three patient, is one of the most impactful and undertreated oncologic condition [37,38]. It is associated with higher risk of surgical complication, longer hospital length of stay, low tolerance to adjuvant therapy, higher rate of mortality, and increased health-care costs [39–43]. Both tumor and surgery cause a systemic inflammation response that can alter insulin and anabolic resistance, energy expenditure rate, patterns of hormonal secretion, and lipolysis/proteolysis pathway. Clinical sequelae include anorexia, poor appetite, weight loss, and muscle mass wasting, and could lead to condition such as cachexia or sarcopenia. Furthermore, medical treatments and tumor-mass effect could alter food intake and/or absorption because of dysphagia (for oral ulcers, difficult chewing, or xerostomia), taste alteration, nausea, vomiting, constipation or diarrhea, abdominal discomfort, and motility disorders. Older age, impaired physical function, and gastrointestinal tract cancer are additional nutritional risk factors [44]. The clear and consistent relationship between nutrition, cancer and surgery is the rational for proactive preoperative intervention. However, despite the strong evidence, the support from surgeons, and the evident cost-effectiveness, only 1 in 5 patients receive any preoperative dietary intervention, and only 1 in 5 hospitals have screening processes [45–47]. In the last decades, significant progress has been made in the field of metabolism, and a cultural shift evolves from nutrition as a baseline support to a therapeutic intervention; thus, we strongly believe in the need of implementing this knowledge into an evidence-based nutrition approach in major surgery.

Screening

From a practical point of view, the use of parameters such as BMI, involuntary weight loss or BMI-adjusted weight loss [48], and plasma albumin levels remains unquestioned in nutritional screening; however, Patient-Generated Subjective Global Assessment (PG-SGA) and Nutritional Risk Screening 2002 (NRS-2002) are the most appropriate tool to identify the presence of undernutrition or the risk of developing undernutrition, and to start nutritional therapy [49]. Second line tools are Mini Nutritional Assessment (MNA), MNA short form [50], Nutritional Risk Index (NRI) [51].

Assessment & intervention

Cancer-associated malnutrition may result from A) reduced dietary intake or unmatched energy expenditure, and/or deficiency of B) protein or C) other macronutrients. The nutrient-based intervention of multimodal prehabilitation addresses all these points from the assessment phase to the intervention:

A) *Meet energy requirement.* Energy requirement is the amount of macro- and micronutrients needed to meet daily expenditure, maintain energy store, and promote physiologic metabolic processes. Energy requirement in patients with cancer is extremely variable [52], and one in four patient with gastro-intestinal cancer shows a hypermetabolic state [53]. Thus, formula such as Harris and Benedict equations is not accurate, and resting energy expenditure should be determined with indirect calorimetry and adjusted for the additional exercise and physical activity prescribed. Hypermetabolism, considered as an early marker of cancer cachexia, is a central nutritional target, since it is associated with negative energy balance, weight loss, systemic inflammation, and alteration of performance status [54]. Insidiously, it occurs in patients with a good physical status [54], then its early detection is extremely important. Waiting for validated targeted therapy [55], we strongly suggest utilizing indirect calorimetry to personalize preoperative caloric intake.

B) *High protein diet.* In view of altered muscle protein metabolism, protein intake adequacy is key component of prehabilitation. Protein synthesis could be increased with amino acids supplementation in patient with cancer [56,57], and high protein intake could improve the whole-body net protein balance during acute stress [58,59]. Based on this rationale and following current international guidelines [60,61], dietary therapy in prehabilitation aims to achieve a daily protein intake of 1.5 g/kg of ideal body weight. Good quality proteins from poultry, fish, dairy, eggs, and plant represent the first-line source, whereas supplementations should be prescribed only if needed. Whey protein or essential amino acids such as leucine are strong anabolic triggers, and should be preferred over other supplemental protein source [62,63]. In presence of moderate-advanced chronic kidney disease (and no ongoing dialysis), protein intake should not be > 1.0 g/kg/d [64]. Although hypothesized to exert a positive effect on tumor grow and host metabolism, specific regimens such as caloric restriction, ketogenic diet or pharmacological intervention still lack of clinical evidence, and are not currently included in prehabilitation [65–67].

C) *Balanced meal.* The third element of nutritional intervention aims at guaranteeing an adequate intake and proportion of all macronutrients. A balanced meal is defined by with a 2:1:2 ratio between starches, meat (or alternative protein sources) and vegetables. Patients should be taught basic dietary suggestions, e.g. limiting the intake of high-fat foods, preferring whole-grain products, limiting sugar-rich foods with poor nutritional value, limiting alcohol intake, or eating meals at regular hours with proper interval [68]. All patients should receive nutritional education, and should be able to estimate the size a serving.

Why anxiety coping strategies?

Psychological distress drives an impressive burden in oncologic care, and cancer patients often experience anxiety, depression, low self-esteem and fears of recurrence and death [69]. International studies reported rates of emotional distress in cancer patients ranging from 35% to 45% [70]. The reason for detecting and intervening on psychosocial disorders is not only limited to the relief of a mood distress and the consequent improvement in quality of life [71]. Preoperative anxiety and depression have negative impact on wound healing, infection rate, length of hospital stay, and adherence to medical treatment [72–75]. Based on this evidence, a growing interest on psychological issues in cancer care has developed. Unfortunately, primary concern focuses on cancer survivors after treatment. Once again, our clinical model proposes a cultural shift aiming at preventing rather than cure the functional impairment associated with cancer and its treatments, including psychological distress. Recent findings suggest that anxiety, rather than depression, should be the target of clinical efforts aimed at improving its recognition and treatment [76].

The psychological component of multimodal prehabilitation is a nonpharmacological, cognitive-behavioral intervention. The aim is reducing anxiety symptoms and cancer-related distress by promoting an active-behavioral and active-cognitive coping within the relative short time allowed before surgery. During a single psychosocial visit, patients are encouraged to disclose personal beliefs and understanding about cancer and surgery, to reframe thoughts and experience to more positive interpretations, to reduce maladaptive lifestyle modifications. Furthermore, relaxation and imagery techniques are taught to the patients, such as passive breathing exercise accompanied by either passive or active muscle relaxation, simple meditation skills, and guided imagery. Patients are encouraged to participate in their favorite daily activities, and to do not avoid social contact. Psychotherapy, anxiolytic medications, and hypnosis are specific approaches that go beyond the purpose of prehabilitation, and are therefore not included.

Why exercise + nutrition + relaxation? When 1 + 1 + 1 = 4

The short answer is that a multi-driven functional impairment needs to be addressed by a multimodal therapeutic strategy. Improving exercise tolerance in oncology patients is a unique challenge that goes beyond cardiopulmonary physiology, as cancer is a systemic disease affecting nervous, immune, endocrine, and cognitive systems. Thus, although there are no clinical studies comparing unimodal vs. multimodal approach, there is a strong rational for combining exercise training, nutritional therapy and anxiety reduction interventions.

The key target of conditioning interventions is the muscle system. Since it represents both a store and a source of key macronutrients, skeletal muscle has a critical role in whole body homeostasis [77]. Thus, maintenance of skeletal muscle not only allows locomotion and preserves functional independence, but also confers protection from adverse effects of metabolic dysfunction. Patients with colorectal cancer show:

- increased muscle protein breakdown;
- normal muscle protein synthesis in a fasted-state; *but,*
- impaired muscle protein synthesis in response to amino acid infusion alone, or exercise alone [78,79].

This is the result of an inflammation state associated with cancer, that produces a systemic metabolic alteration. Furthermore, surgery induces an acute on chronic inflammatory response that further accelerate this response, leading to an uncontrolled catabolism and resistance to anabolic signals [80–82]. Collectively, this desensitization to both nutrient- and physical-driven anabolic stimuli regulating muscle metabolism likely promotes an impactful functional impairment. On this basis, the well-known synergism between exercise and hyperproteic diet appears to be essential in the attempt to address the complex pathophysiology of the functional decline in colorectal cancer patients, and to overcome the state of anabolic resistance [83]. The impact of psychological distress on adherence to intervention and mood attitude speaks to the synergic effect of anxiety-reducing intervention and physical and nutritional therapy.

State of evidence

Although prehabilitation is not a new concept, trials on structured preoperative intervention aiming at improving perioperative functional capacity emerged only in the last decade. Table 1 and Table 2 summarize main characteristics of studies on surgical prehabilitation [84–92]. These trials included patients with colorectal cancer scheduled for surgery, and involved at least one of the multimodal components, exercise, nutrition, and/or anxiety-reduction techniques.

Over the last years, there has been a shift from a home-based to supervised training sessions; from unimodal to multimodal approach; and from a daily moderate activity to a 3 times per week moderate-high intensity exercise. Probably because of all the above changes, adherence to the intervention rises, and measure outcomes becomes clinically significant. Although the impressive difference among studies, in term of study design and outcome, this evidence constitutes the proof of concept of the efficacy of prehabilitation in optimizing functional capacity.

Although prehabilitation is an effective intervention, a recent study we conducted showed that 41% of participant did not improve their physical fitness [93]. Non-response to exercise is a common finding in medical research, and could be explained by several mechanisms, such as age, gender, disease stage, comorbidity, type of exercise and dietary intervention, genetic, epigenetic and metabolic traits [94,95]. Further research is required to identify these patients, and personalize an effective intervention.

Future directions and opportunities for research

- *Short-term surgical outcome.* Despite some recent evidence and a strong rational [12,96], a definitive association between prehabilitation and 'traditional' short-term postsurgical outcome (e.g. 30-day mortality, postoperative major complication, intensive care admission, reoperation, readmission, or length of stay) has yet to be shown.
- *Target frail and elderly with co-morbidities.* Although cancer incidence is higher in elderly, the proportion of patients with a cancer diagnosis undergoing surgery declines with age [97]. One of the main reason for this exclusion is low physical fitness, independently associated with worst surgical outcome [98]. Enhancing functional capacity before surgery could address this issue increasing the numbers of candidates eligible for curative-intent resection.
- *Early adjuvant chemo-radiotherapy.* Postoperative functional impairment is associated with delayed chemotherapy, and patients who received chemotherapy ≥8 weeks postoperatively have worse local and distant recurrence rates and worse overall survival [99]. The role of prehabilitation in shortening the waiting time for adjuvant therapy should be investigated.
- *Long term health-related factors.* It is widely recommended that cancer survivors should engage in regular physical activity and adopt a proper diet [100]. Even if it known that longstanding exercise intervention may promotes life-style change, the role of prehabilitation has not been addressed yet.
- *Long term cancer outcome.* After completion of the main treatment, exercise positively influences disease progression and tumor recurrence [101]. Whether prehabilitation could impact on cancer outcome is not known.
- *Improved oxygen consumption and in vivo proliferation capacity of cancer cells.* High rate non-oxidative breakdown of glucose is the key energetic pathway linked to cancer cell proliferation [102].

Table 1
Characteristic of studies on prehablitation in colorectal cancer. PNR, prospective non-randomized trial; RCT, randomized controlled study.

Study	Design	Sample Size, n Prehab (Control)	Intervention			Duration, wk	Exercise		Compliance, %
			Exercise	Nutrition	Anxiety		Frequency, d/wk	Supervision	
Kim DJ, 2009 [83]	RCT	14 (7)	✓ moderate→high	✗	✗	4	7	No	74
Carli F, 2010 [84]	RCT	58 (54)	✓ moderate→high	✗	✗	6	7	No	16
Li C, 2013 [85]	PNR	42 (45)	✓ moderate	✓	✓	4	3	No	45
Gillis C, 2014 [86]	RCT	38 (39)	✓ moderate	✓	✓	4	3	No	78
West MA, 2015 [87]	PNR	22 (13)	✓ high interval	✗	✗	6	3	Yes	96
Gillis C, 2015 [88]	RCT	22 (21)	✗	✓	✗	4	-	-	94
Heldens A, 2016 [89]	PNR	9 (0)	✓ moderate	✗	✗	5.5	2	Yes	96
Loughney L, 2017 [90]	PNR	23 (10)	✓ high interval	✗	✗	6	3	Yes	-
Bousquet-Dion, 2018 [91]	RCT	37 (26)	✓ moderate	4	✓	4	3-4	1 d/w	98

Table 2
Outcome Measure. 6MWD, 6-min walking distance; VO_2 AT/peak, oxygen consumption at the anaerobic threshold/at peak exercise; VO_2max, maximal oxygen consumption.

Study	Functional Measure	Functional PreOp Change	Functional PostOp Change	Complication
Kim DJ, 2009 [83]	$\dot{V}O_2$max	0.5 (4.2) mL/kg/min	✗	✗
Carli F, 2010 [84]	6MWD	- 10.6 (7.3) m	-34.4 (9.9) m	No difference
Li C, 2013 [85]	6MWD	42 (41) m	37 (70) m	No difference
Gillis C, 2014 [86]	6MWD	25.2 (50.2) m	23.4 (54.8) m	No difference
West MA, 2015 [87]	① $\dot{V}O_2$AT ② $\dot{V}O_2$peak	① 2.12 [1.3-2.9] ② 2.65 [1.2-4.1] mL/kg/min	✗	✗
Gillis C, 2015 [88]	6MWD	20.8 (42.6) m	18.6 (65.1)	No difference
Heldens A, 2016 [89]	6MWD	9%	↓	✗
Loughney L, 2017 [90]	Daily Steps	22%	✗	✗
Bousquet-Dion, 2018 [91]	6MWD	21 (47) m	20 (54) m	No difference

Thus, it is widely accepted that cancer metabolism relies primarily on glucose delivery, and occurs in low-oxygen environment. However, a recent theory postulated that tumors are glycolytic because are hypoxic *in vivo* [103]. To the same extent, branched-chain amino acids support cancer energetic and biosynthetic demands [104,105]. Clinical consequences of one-month preoperative conditioning program (aimed at improving whole oxygen uptake capacity and increasing protein intake) on tumor microenvironments, energy metabolism, and proliferation capacity needs to be elucidated [106].

Conflict of interest statement

Authors declare no conflicts of interest.

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Both authors contributed to conception and design of the present work; and draft, reviewed, and approved the last version of the paper.

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