Review Article

Nutrition and exercise prehabilitation in elderly patients undergoing cancer surgery

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Surgical resection is the primary and most effective treatment for cancer patients. While such a traumatic intervention often accompanies different degrees of postoperative risk largely depending on the patient's health status. Due to the high prevalence of malnutrition or low cardiorespiratory fitness in elderly cancer patients, prehabilitation is an optimal program to reduce postoperative complications and enhance recovery from surgical trauma. An increasing body of evidence suggests that improving nutrition and taking aerobic exercise or strength training prior to major surgery can help reduce postoperative morbidity, mortality, or length of stay. However, there are still controversies regarding the manner, intensity, or duration of preoperative nutrition and exercise training in elderly patients, as well as the impact on delaying cancer treatment. This article reviews the impact of prehabilitation on improving postoperative outcomes in the multi-modal or single-modal pathway, aiming to maximize its effectiveness and increase medical practitioners' attention on enhancing the physical condition of the elderly cancer patients preoperatively.

Key Words: prehabilitation, preoperative support, enhanced recovery, cancer treatment, nutrition

INTRODUCTION

Over the past two decades, it has been increasingly realized that surgical success depends on the operation itself and on whether the patient can recover to a healthy state as soon as possible. Enhanced recovery after surgery (ERAS), based on evidence-based medicine, involves a series of perioperative measures that have been passed down for more than a century, which can effectively reduce postoperative complications, shorten hospital stays, and reduce medical costs.[1] Although surgical processes are performed in accordance with these guidelines, some patients, especially elderly cancer patients (patients over 65 years of age according to WHO definition), exhibit difficulties in reaching the ERAS goal.[2] Generally, elderly patients exhibit poor nutritional status, reduced muscle mass, and suppressed cardiopulmonary functions, therefore, incidences of adverse events during the perioperative period are higher, which makes it more complicated and difficult to implement ERAS in elderly patients than in young and middle-aged patients.

Prehabilitation, a new concept in preoperative management, has been included in the application and promotion of ERAS in recent years. Its emphasis is on optimum utilization of community and outpatient medical resources, and, in combination with preoperative physical exercise, nutritional support, and psychological intervention, the body's functional reserves are optimized to cope with surgical stress, thereby reducing postoperative complications and enhancing recovery.[3] Prehabilitation was first applied in 1946 where it was used for training before recruitment in World War II. After two-month physical training, about 85% of recruits exhibited a significant improvement in their physical fitness.[4] Then, prehabilitation was gradually introduced in medical practice, such as in sports medicine, etc., to improve organ functions and enhance tolerance to treatment. With the introduction and application of ERAS, the concept of prehabilitation has been further expanded, and surgical prehabilitation has emerged as a result.[5] Implementation of prehabilitation in elderly surgical candidates is of great significance to improving clinical outcomes.[6,7] However, prehabilitation is still in its infancy, and the specific implementation method and intensity have not been established.[8] Besides, it has not been established whether prehabilitation in cancer patients results in postponement of cancer treatment, thereby increasing the risk of tumor metastasis and affecting long-term prognosis.

Prehabilitation involves three aspects: nutritional therapy, physical exercise, and psychological intervention,

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Manuscript received 07 May 2021. Initial review completed 18 May 2021. Revision accepted 14 June 2021.
doi: 10.6133/apjcn.202109_30(3).0001

however, studies have aimed at evaluating nutrition and exercise.[9] Therefore, we briefly elucidate on psychological interventions, with a focus on applications and prospects of nutrition and exercise prehabilitation in elderly cancer surgical patients.

PHYSICAL AND PSYCHOLOGICAL FEATURES OF GERIATRIC PATIENTS AND PREOPERATIVE EVALUATION

Physical and psychological status of geriatric patients is different from that of young and middle-aged patients. Elderly patients are highly associated with poor cardiopulmonary functions and psychological problems, including anxiety. Preoperative preparation is unique for this patient group.

Cardiac functions

Diastolic dysfunction among the elderly is very common and is the main pathophysiological factor for several cardiovascular diseases. As age increases, the heart exhibits obvious degenerative changes, which are mainly manifested by myocardial fiber reduction, deposition of “aging pigment” lipofuscin, and fatty infiltrations of the myocardium, all of which reduce myocardial compliance and contraction efficiency. The higher the severity of diastolic dysfunction, the higher the risk of heart failure, and it can even predict all-cause mortality.[10,11] In addition, reduction of elastic fibers in blood vessel walls and formation of atherosclerotic plaques lead to narrowing of the vascular lumen and insufficient organ perfusion. As a result, hypertension and myocardial ischemia are common in elderly patients, and the risk of thromboembolism is also higher. Therefore, given suppressed cardiac functions among geriatric patients, relative assessments should be performed before surgery. The commonly used tests for clinical assessments include electrocardiogram and echocardiography, which are used to check cardiac functions for geriatric patients undergoing surgery. Holter dynamic ECG monitoring, myocardial perfusion scan or coronary angiography can also be performed when needed.

Pulmonary functions

Postoperative pulmonary complications among the elderly are important causes of mortality and prolonged hospitalization. In geriatric patients with significant declines in muscle mass and strength, the risk of postoperative pulmonary infection is significantly increased due to respiratory muscle atrophy, decreased lung compliance, decreased pulmonary cilia function, weak cough reflex, and difficulties in clearing respiratory secretions.[12] In addition, obstructive pulmonary disease is an unfavorable factor that causes insufficient tissue oxygen supply and delayed wound healing.

It is essential to evaluate pulmonary functions in elderly patients. In clinical settings, the commonly used assessments include: i. Stationary pulmonary function tests, including vital capacity (VC), forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF) and maximal ventilatory volume (MVV), which are associated with postoperative pulmonary complications. Exercise has been shown to effectively improve the above indicators.[13] ii. Dynamic cardiopulmonary function tests, including, a) The 6-minute walking distance (6 MWD) test, which is the maximum distance that a patient can walk within 6 minutes. The greater the distance, the better the patient’s tolerance for surgery and the lower the incidence of postoperative pulmonary infections.[14] b) Cardiopulmonary exercise test (CPET), which objectively assesses cardiopulmonary reserve and exercise endurance. This test can detect dynamic changes of the body’s oxygen consumption (VO_2) and CO_2 output (VCO_2) under different exercise loads in real time. Moreover, this method evaluates the heart-lung-skeletal muscle group, and is a necessary test for determining a patient's exercise capacity to individualize the aerobic training program.[15]

Malnutrition

Malnutrition, which is common among patients undergoing gastrointestinal surgery, is an independent risk factor for postoperative complications. Timely screening of geriatric patients for nutritional risk before surgery and appropriate nutritional therapy has been shown to reduce complications and accelerate postoperative recovery.[16] Nutritional metabolism among the elderly has the following characteristics: i. The baseline metabolic rate is lower than that of young and middle-aged people; ii. Protein catabolism is relatively enhanced, while anabolism is suppressed, leading to negative nitrogen balance; iii. Suppressed glucose metabolism rate and tolerance; and iv. Inhibited lipid catabolism, higher risks of hyperlipidemia and atherosclerosis. Due to tumor- or treatment-associated chronic inflammation and disturbances in endocrine, metabolic, and central nervous systems, cancer patients are more likely to experience different degrees of malnutrition, sarcopenia, cachexia, and myosteatosis.[17-19] Therefore, preoperative nutritional assessment or intervention for elderly cancer patients is important.

Based on the characteristics of geriatric patients, nutritional risk screening and assessment before surgery should be performed. Commonly used tools include: i. Mini Nutritional Assessment (MNA), which involves two phases, nutritional screening and assessment. It is simple, fast, and easy to operate. The MNA method is used for nutritional assessment of geriatric patients in community settings; ii. Nutritional Risk Screening 2002 (NRS-2002), which is used for nutritional risk screening among hospitalized patients; iii. Malnutrition Universal Screening Tool (MUST), which is simple, fast, and is suitable for nutritional status assessment in community as well as in inpatient settings; iv. The Patient-Generated Subjective Global Assessment (PG-SGA) tool, which has become a standard nutritional assessment tool in oncology, but it does not include risk screening, when compared to MUST and NRS-2002. Due to the fact that it does not include body composition measurement or biochemical testing, its clinical applications are limited; v. Nutritional risk index (NRI), which is often used for nutritional assessment of patients undergoing major abdominal and thoracic surgeries; vi. Global Leadership Initiative on Malnutrition (GLIM), which is a malnutrition assessment tool for adult inpatients that was released in 2018 and aims at unifying malnutrition assessment standards and vii. Perioperative Nutrition Screen (PONS), which is a modified version of MUST. It evaluates nutritional risk based on patient's BMI, recent changes in weight, dietary intake and preoperative albumin levels.

Psychological features

Compared to adults of other age groups, geriatric patients, especially cancer patients administered with neoadjuvant therapy or those who require a stoma, are more likely to experience psychological problems as a result of surgical-induced stress. The occurrence is associated with education levels, family support, and preoperative education. Delirium, anxiety, depression, and fear are common psychological problems experienced by geriatric patients. The above mentioned psychological problems can have a negative impact on postoperative functional recovery and increase pain associated complications after abdominal surgery.[20,21] Although preoperative psychological intervention is intricate, improving patients' awareness of their medical conditions and encouraging them to be co-operative with treatment is beneficial for early functional recovery and long-term outcomes.

IMPLEMENTATION OF PREHABILITATION

Maintaining or quickly restoring sufficient oxygen supply to promote adequate cell metabolism is the foundation for maintaining organ function, particularly after major surgery. Patients with better cardiopulmonary functions can better meet surgical-associated increase in tissue demand for oxygen. Long-term endurance training has been shown to help patients with chronic heart failure improve cardiac functions, reduce the risk of death, improve life quality, and at the same time, improve muscle strength.[22-24] Various studies have evaluated the effect of exercise before admission on organ function recovery after surgery. Carli et al were the first to compare the effects of preoperative high-intensity physical training (stationary cycling) with low-intensity walking and breathing training on outcomes of colorectal surgery.[25] Although the average functional walking capacity of the two groups of patients was similar before and after surgery, 1/3 of the patients in the high-intensity training group exhibited worse walking abilities even before surgery, and their compliance was only 16%. Further analysis showed that advanced age (>75 years) and anxiety were negatively correlated with postoperative recovery. Subsequent studies supported this conclusion, that is, without considering factors such as tolerance, psychological acceptance, and nutritional status, intervention with exercise alone may not be enough.[26-28] However, before making a multimodal intervention plan, the impact and necessity of each intervention should be verified to maximize the effect of prehabilitation (Table 1).

Physical training

During prehabilitation, physical training is divided into two categories: aerobic exercise and strength training.

Aerobic exercise

Aerobic exercise refers to the exercise performed under sufficient oxygen supply. Common exercises include walking, speed walking, jogging, race walking, skating, long-distance swimming, cycling, Tai Chi, and fitness dance among others. It is characterized by medium intensity, long duration, and recruitment of multiple muscle groups, and is also known as endurance training. Aerobic exercise capacity represents cardiopulmonary function reserves, which in turn, is negatively correlated with postoperative mortality.[29] Currently, the most used assessment tool for aerobic capacity is CPET, in which maximum oxygen uptake (VO_2max), peak oxygen uptake (VO_2peak), and anaerobic threshold (the turning point from aerobic energy supply to anaerobic energy supply during exercise) are important indicators of cardiopulmonary function and aerobic exercise capacity.[30] Due to its simplicity and high tolerance, many studies incorporated aerobic training into physical exercise, however, there is no consensus on the type and intensity.[3,25,31-33] The individualized aerobic exercise program and supervised training have been shown to increase aerobic exercise capacity, thereby, increasing cardiopulmonary reserve and reducing postoperative complications.

Strength training

As the body ages, neuromuscular junction functions decline, hormone levels decrease, while skeletal muscle mass, strength and function undergo degenerative changes. Systemic metabolic changes in cancer patients have been shown to decrease and imbalance physiological reserves of multiple organ systems.[34-36] When geriatric cancer patients develop sarcopenia, cachexia, or decline in physical fitness and progress to a debilitating state, it is difficult for them to make a full recovery of physical functions due to the stress of injury.[37,38] The American College of Surgeons emphasized on the importance of sarcopenia and preoperative frailty assessment in geriatric cancer patients undergoing surgery for the following reasons: i. Sarcopenia is accompanied by a decline in muscle mass and function. After surgery, patients tend to get out of bed later and less frequently, affecting postoperative recovery; ii. Sarcopenia is closely associated with malnutrition, which is correlated with an increase in postoperative complications and prolonged hospital stay; iii. Sarcopenia increases the risk of infection as well as the risk and duration of assisted ventilation, leading to increased medical costs and readmission rates.[39]

Strength training, also known as resistance training, utilizes dumbbells or resistance bands to enhance muscle mass and strength, or utilizes one's own body weight, such as pushups and squats. It is usually combined with aerobic exercises such as speed walking and jogging to improve the effect of prehabilitation.

Physical training program

Intensity

Compared to moderate-intensity exercise, people who perform high-intensity exercises (≥ 60% aerobic exercise capacity) are better at regulating blood glucose levels, although there is no significant reduction in blood pressure or serum lipid levels.[40,41] With recent refinements of exercise interventions, high-intensity

Table 1. Clinical studies of different prehabilitation intervention modes

Author	Country	Study design	Patients	Cases	Prehabilitation intervention	Duration	Results
Barberan-Garcia[28,29]	Spain	RCT	high-risk patients for elective major abdominal surgery	125	high-intensity endurance training	4 weeks	increase aerobic capacity and enhance postoperative clinical outcomes, reduce 30-day hospital readmissions
Gillis[3]	Canada	RCT	undergoing colorectal cancer resection	77	a home-based intervention of moderate aerobic and resistance exercises and nutritional counseling with protein supplementation	4 weeks	achieve meaningful changes in postoperative functional exercise capacity
Carli[25]	Canada	RCT	undergoing colorectal cancer resection	112	strengthening regimen (bike/strengthening)	52 days	no differences in mean functional walking capacity
Carli[44]	Canada	RCT	undergoing colorectal cancer resection	110	exercise, nutritional, and psychological interventions	4 weeks	no differences in the 30-day comprehensive complications index
Brunet[33]	Canada + UK	non-randomized controlled pilot trial	with operable advanced stage rectal cancer	107	interval aerobic training (three times per week for 30 to 40 min)	6 weeks	fatigue and pain levels decreased and physical health perceptions increased, albeit not significantly
Dronkers[48]	Netherlands	RCT	elderly patients for elective abdominal oncological surgery	42	a short-term intensive therapeutic exercise	2-4 weeks	intensive exercise was feasible and improved the respiratory function, no differences in complications and length of stay

interval training can lower blood pressure and improve endothelial function, insulin resistance and mitochondrial biosynthesis.[42] Moreover, it exerts a significant effect on the improvement of cardiopulmonary functions.[43] Compared to traditional aerobic and resistance training, high-intensity interval training has less items, and is more suitable for improving cardiorespiratory reserves in a limited timeframe before surgery. In frail patients subjected to moderate-intensity training, even with nutritional and psychological interventions combined, there was little effect on incidences of postoperative complications within 30 days.[44] Guidelines from the United States Department of Health and Human Services as well as the American Cancer Society recommend that geriatric patients should have at least 150 min of moderate-intensity or 75 min of high-intensity physical activity, evenly distributed throughout every week, in order to have substantial health benefits. Moreover, these guidelines emphasize on individualized adjustments in training programs.[45,46] Therefore, most current studies use moderate-intensity training (50-70% of maximum heart rate, MHR) combined with appropriate amounts of high-intensity training (70-80% MHR) for interventions, and have achieved good results in improving clinical outcomes.[28,47]

Duration and frequency

There is no formal consensus on the duration of prehabilitation. It has been reported that a short period of 2-4 weeks of preoperative exercise does not improve postoperative complications and length of hospital stay in patients undergoing elective abdominal surgery.[48] Le et al advocate for a 6-8 week training course, and believe that compliance to preoperative exercise for more than 3 months is poor, while exercising for 2-4 weeks is insufficient.[27] There are differing opinions regarding the duration of exercise.[49] Although semi-elective surgery limits the time for prehabilitation training, training over 3 weeks in length can moderately improve cardiopulmonary functions and muscle strength reserve. In neoadjuvant therapy patients, there is usually a recovery period of 4-8 weeks (or even longer) before surgery, which provides a time window for prehabilitation.

Currently, there is no standard preoperative exercise intervention for geriatric cancer patients. Individualized training programs should be prepared by specialists based on patient's cardiopulmonary functions. Training programs should comply with the “FITT” principle: frequency (how often), intensity (how hard), time (long), and type (what kind of exercise).[9] The recommendation for prehabilitation in the general population is to start 4-8 weeks before surgery for at least 3 times a week (recommended every other day), 40-60 minutes each time, and perform moderate and high-intensity aerobic exercises, such as speed walking, jogging, cycling, swimming, and gymnastics among others reaching 60%-80% of MHR. As part of a comprehensive physical fitness program, resistance training for major muscle groups such as abdomen and lower extremities should also be performed. Seniors are encouraged to practice flexibility and balance trainings under supervision. During the prehabilitation period, patients must be regularly evaluated to verify compliance, adaptability, and effect of training. Moreover, exercise intensity and time should be gradually increased as tolerated, and the patient should be instructed to keep an exercise diary, etc..

Nutritional support

Although preoperative prehabilitation is an ideal intervention to improve health conditions of patients, there are many challenges in practice, including the short time interval between diagnosis and surgery, as well as the development of key and effective interventions based on patient compliance. Therefore, a good nutritional status is required to maximize the effect of exercise within a limited timeframe. If patients are malnourished, their responses to exercise training decreases and they cannot be cooperative enough to complete high-intensity training.[50] Earlier studies reported that geriatric patients subjected to endurance training alone had a 40% increase in muscle tone, while endurance training combined with nutritional support increased muscle tone by 130%.[51] Multimodal interventions, consisting of exercise and nutrition, are more effective than unimodal interventions, especially for high-risk patients undergoing major abdominal surgeries. Multimodal interventions can reduce incidences of complications (including cardiovascular events, infections and postoperative intestinal paralysis) by half. Postoperative ICU admission time is also shortened (1d Vs. 4d), and the demand for intraoperative vasopressors is reduced (15% vs. 30%).[29]

Preoperative nutritional intervention

A high-quality review evaluated the impact of different preoperative nutritional interventions on clinical outcomes for patients undergoing gastrointestinal surgeries.[52] Applications of immune-enhancing nutritional supplements before surgery have significant benefits. For severely malnourished patients, parenteral nutrition should be provided before surgery to reduce postoperative complications. Long-term randomized controlled trials (RCT) and meta-analysis have also shown that malnourished patients undergoing gastrointestinal surgeries who received individualized preoperative nutritional interventions (oral nutritional supplementation, enteral nutrition, or parenteral nutrition based on the patient’s nutritional status) had a 20% decrease in postoperative complications.[53] The major effect of preoperative nutritional supplementation in most patients is to increase protein reserves, which may be more important than the increase in caloric reserves. The ESPEN expert group recommends that daily protein intakes for the geriatric population under normal circumstances should be 1.0-1.2 g/kg, which should be increased to 1.2-1.5 g/kg when they have chronic or acute illnesses.[54,55] Patients should also be able to obtain enough energy from a variety of nutrients to maintain a good nutritional status in order to inhibit the body’s catabolism, increase exercise tolerance, and cope with the traumatic stress caused by major surgery.

Nutritional interventions in combination with psychological interventions

Management of geriatric cancer patients poses major challenges. Due to the decline in various physical functions or comorbidities, multiple interventions are required when managing this particular population. Therefore, the hypothesis that this high-risk population can benefit from multimodal prehabilitation involving nutritional, exercise, and psychological intervention is reasonable, and has been confirmed by multiple studies.[56-58] Structured and individualized prehabilitation programs can significantly improve postoperative outcomes in geriatric cancer patients, which is a hot topic in current clinical research.

THE IMPACT OF PREHABILITATION ON CANCER TREATMENT

In cancer surgery, the value of prehabilitation on postoperative outcomes has not been fully established. Patients scheduled for neoadjuvant therapy can proceed with prehabilitation at the same time because chemotherapy reduces physical fitness, when measured by maximum oxygen uptake.[59] However, for patients who do not need neoadjuvant therapy, will radical tumor resection be delayed due to implementation of prehabilitation? From a pathophysiologic perspective, under hypoxia, tumor cells induce the production of hypoxia-inducible factor (HIF-1) transcription factor, upregulate vascular endothelial growth factor (VEGF), and promote angiogenesis. Appropriate amounts of aerobic exercise can improve the hypoxic state in tumors, reducing the production of HIF-1, thereby, hindering tumor invasion and recurrence.[60] In addition, the lack of nutrients is closely associated with progression and metastasis of various tumors. Supplementation of nutrients can also inhibit tumors.[61,62]

From a clinical perspective, it has been estimated that the prevalence of malnutrition in cancer patients, whether in early or late stage, is between 28% and 57%.[63] Preoperative nutritional intervention can significantly reduce morbidity and mortality risks from malnutrition-related complications. The consensus from the North American Surgical Nutrition Summit recommends that, to potentially reduce the incidence and severity of complications, postoperative nutritional treatment for all high-risk patients should be shifted to active preoperative nutritional interventions.[64] When nursing cancer patients undergoing surgery, comprehensive dietary consultation, active nutritional risk screening, early nutritional intervention and development of physical exercise programs have gradually been recognized as important components of high-quality care. In addition, preoperative anxiety and other unhealthy mental states are also common among elderly patients. The accompanying stress responses can cause damage to the immune system, resulting in delayed wound healing, slowed functional recovery, and even cancer progression.[65] Other extended prehabilitation activities, such as smoking cessation before surgery and blood glucose adjustment, contribute to early postoperative recovery and can avoid delays in follow-up tumor treatment due to complications.

Timothy, a thoracic surgeon, implemented prehabilitation for all “medium risk” and “high risk” lung cancer patients for 4-8 weeks.[66] He believes that patients may have time to be prepared before surgery. Generally, cancer patients need to undergo biopsies and scans for staging and evaluation before determining the surgical plan. This preoperative waiting period provides an excellent opportunity for patients to physically and emotionally battle with cancer.

CONCLUSIONS

The ultimate goal of prehabilitation is to improve the nutritional status of patients, enhance cardiorespiratory reserves, increase surgical tolerance, minimize postoperative complications, and accelerate recovery after surgery. Implementation of prehabilitation activities, including exercise, nutrition, and psychological intervention can effectively improve clinical outcomes (Figure 1). However, the strategies through which prehabilitation can be effectively implemented in clinical practice have not been established. Studies should aim at determining which patients can benefit from prehabilitation, how patients can be evaluated, how long prehabilitation should take, and what should be included in the program. Clinical studies are needed to achieve optimum outcomes.

ACKNOWLEDGEMENTS

The first author Dr. Yanni Zhang shows her great respect for Prof. Guohao Wu and Dr. Shanjun Tan, thanking them for giving her the opportunity to further study. In addition, the author wants to express her deepest love to her parents, Mr. Yasheng Zhang and Mrs. Ju Shi, for their cultivation and encouragement.

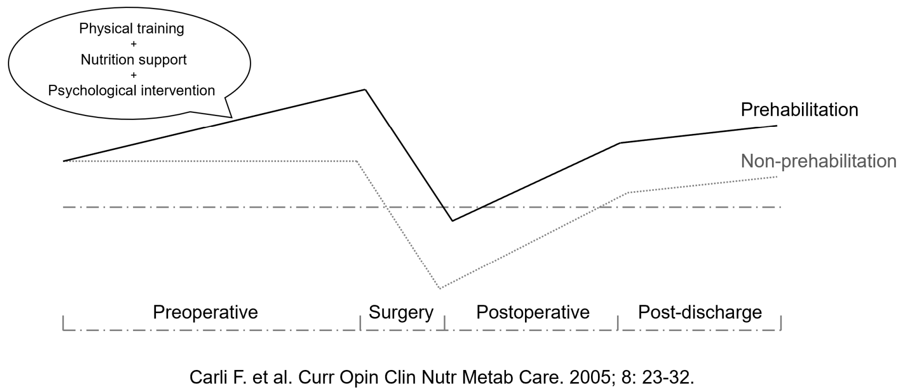

Figure 1. Impact of prerehabilitation on optimizing physical and psychological reserve and accelerating postoperative recovery. Modified from ref 67.

AUTHOR DISCLOSURES

The authors declare that they have no competing interests. This study was sponsored by the National Natural Science Foundation of China (81900484), Project funded by China Postdoctoral Science Foundation (2019M661370, 2020T130111), Shanghai Sailing Program (18YF1404700), Municipal Natural Science Foundation of Shanghai of China (19ZR1409100), and Construction Program of Key but Weak Disciplines of Shanghai Health Commission-Clinical Nutrition (2019ZB0105).

REFERENCES

1. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg. 2017; 152:292-8. doi: 10.1001/jamasurg.2016.4952.
2. Baré M, Mora L, Pera M, Collera P, Redondo M, Escobar A, Anula R, Quintana JM, CARESS-CCR Study Group. Type and consequences of short-term complications in colon cancer surgery, focusing on the oldest old. Clin Colorectal Cancer. 2020;19:e18-e25. doi: 10.1016/j.clcc.2019.11.003.
3. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121:937-47. doi: 10.1097/ALN.0000000000000393.
4. PREHABILITATION, rehabilitation, and revocation in the Army. Br Med J. 1946;1:192-7.
5. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019; 51:2375-90. doi: 10.1249/MSS.0000000000002116.
6. Grootswagers P, de Regt M, Domić J, Dronkers J, Visser M, Witteman B, Hopman M, Mensink M. A 4-week exercise and protein program improves muscle mass and physical functioning in older adults - A pilot study. Exp Gerontol. 2020;141:111094. doi: 10.1016/j.exger.2020.111094.
7. Hanna K, Ditillo M, Joseph B. The role of frailty and prehabilitation in surgery. Curr Opin Crit Care. 2019;25: 717-22. doi: 10.1097/MCC.0000000000000669.
8. Kow AW. Prehabilitation and its role in geriatric surgery. Ann Acad Med Singap. 2019;48:386-92.
9. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next. Anaesthesia. 2019;74(Suppl 1):20-6. doi: 10.1111/anae.14505.
10. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol. 2014;63:407-16. doi: 10.1016/j.jacc.2013.10.063.
11. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194-202. doi: 10.1001/jama.289.2.194.
12. Skloot GS. The effects of aging on lung structure and function. Clin Geriatr Med. 2017;33:447-57. doi: 10.1016/j.cger.2017.06.001.
13. Khosravi M, Tayebi SM, Safari H. Single and concurrent effects of endurance and resistance training on pulmonary function. Iran J Basic Med Sci. 2013;16:628-34.
14. Hattori K, Matsuda T, Takagi Y, Nagaya M, Inoue T, Nishida Y et al. Preoperative six-minute walk distance is associated with pneumonia after lung resection. Interact Cardiovasc Thorac Surg. 2018;26:277-83. doi: 10.1093/icvts/ivx310.
15. Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary exercise testing: what is its value. J Am Coll Cardiol. 2017;70:1618-36. doi: 10.1016/j.jacc.2017.08.012.
16. Lobo DN, Gianotti L, Adiamah A, Barazzoni R, Deutz N, Dhatariya K et al. Perioperative nutrition: Recommendations from the ESPEN expert group. Clin Nutr. 2020;39:3211-27. doi: 10.1016/j.clnu.2020.03.038.
17. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon K. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4: 17105. doi: 10.1038/nrdp.2017.105.
18. Otten L, Stobäus N, Franz K, Genton L, Müller-Werdan U, Wirth R, Norman K. Impact of sarcopenia on 1-year mortality in older patients with cancer. Age Ageing. 2019;48: 413-8. doi: 10.1093/ageing/afy212.
19. Aleixo G, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2020;145:102839. doi: 10.1016/j.critrevonc.2019.102839.
20. Laurino Neto RM, Herbella F. Effects of psychological problems on surgical outcomes. Rev Assoc Med Bras (1992). 2019;65:586-8. doi: 10.1590/1806-9282.65.5.586.
21. Gravani S, Matiatou M, Nikolaidis PT, Menenakos E, Zografos CG, Zografos G, Albanopoulos K. Anxiety and depression affect early postoperative pain dimensions after bariatric surgery. J Clin Med. 2020;10. doi: 10.3390/jcm10010053.
22. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation. 1999;99:1173-82. doi: 10.1161/01.cir.99.9.1173.
23. Pierson LM, Herbert WG, Norton HJ, Kiebzak GM, Griffith P, Fedor JM, Ramp WK, Cook JW. Effects of combined aerobic and resistance training versus aerobic training alone in cardiac rehabilitation. J Cardiopulm Rehabil. 2001;21: 101-10. doi: 10.1097/00008483-200103000-00007.
24. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, Hendrican K, Yusuf S. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). Am Heart J. 2002;144:23-30. doi: 10.1067/mhj.2002.123310.
25. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, Scott S, Mayo NE. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg. 2010;97: 1187-97. doi: 10.1002/bjs.7102.
26. Levett DZ, Edwards M, Grocott M, Mythen M. Preparing the patient for surgery to improve outcomes. Best Pract Res Clin Anaesthesiol. 2016;30:145-57. doi: 10.1016/j.bpa.2016.04.002.
27. Le Roy B, Slim K. Is prehabilitation limited to preoperative exercise. Surgery. 2017;162:192. doi: 10.1016/j.surg.2016.10.039.
28. Barberan-Garcia A, Ubre M, Pascual-Argente N, Risco R, Faner J, Balust J, Lacy AM, Puig-Junoy J, Roca J, Martinez-Palli G. Post-discharge impact and cost-consequence analysis of prehabilitation in high-risk patients undergoing major abdominal surgery: secondary results from a randomised controlled trial. Br J Anaesth. 2019;123:450-6. doi: 10.1016/j.bja.2019.05.032.
29. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, Momblán D, Balust J, Blanco I, Martínez-Pallí G. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg. 2018;267:50-6. doi: 10.1097/SLA.0000000000002293.

30. Mezzani A. Cardiopulmonary exercise testing: basics of methodology and measurements. Ann Am Thorac Soc. 2017; 14:S3-3S11. doi: 10.1513/AnnalsATS.201612-997FR.
31. Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M. Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. Scand J Urol. 2015;49:133-41. doi: 10. 3109/21681805.2014.967810.
32. Jones LW, Eves ND, Kraus WE, Potti A, Crawford J, Blumenthal JA, Peterson BL, Douglas PS. The lung cancer exercise training study: a randomized trial of aerobic training, resistance training, or both in postsurgical lung cancer patients: rationale and design. BMC Cancer. 2010;10: 155. doi: 10.1186/1471-2407-10-155.
33. Brunet J, Burke S, Grocott MP, West MA, Jack S. The effects of exercise on pain, fatigue, insomnia, and health perceptions in patients with operable advanced stage rectal cancer prior to surgery: a pilot trial. BMC Cancer. 2017; 17:153. doi: 10.1186/s12885-017-3130-y.
34. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:601. doi: 10.1093/ageing/afz046.
35. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020; 21:300-7.e2. doi: 10.1016/j. jamda.2019.12.012
36. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin. 2017;67:362-77. doi: 10.3322/caac.21406.
37. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodríguez-Mañas L, Fried LP et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. J Nutr Health Aging. 2019;23:771-87. doi: 10.1007/s12603-019-1273-z.
38. Pisano C, Polisano D, Balistreri CR, Altieri C, Nardi P, Bertoldo F et al. Role of cachexia and fragility in the patient candidate for cardiac surgery. Nutrients. 2021;13:517. doi: 10.3390/nu13020517
39. Chan SP, Ip KY, Irwin MG. Peri-operative optimisation of elderly and frail patients: a narrative review. Anaesthesia. 2019;74(Suppl 1):80-9. doi: 10.1111/anae.14512.
40. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JAMA. 1999;282: 1433-9. doi: 10.1001/jama.282.15.1433.
41. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. Am J Cardiol. 2006;97:141-7. doi: 10.1016/j. amjcard.2005.07.130.
42. Boutcher YN, Boutcher SH. Exercise intensity and hypertension: what's new. J Hum Hypertens. 2017;31:157-64. doi: 10.1038/jhh.2016.62.
43. Liou K, Ho S, Fildes J, Ooi SY. High intensity interval versus moderate intensity continuous training in patients with coronary artery disease: a meta-analysis of physiological and clinical parameters. Heart Lung Circ. 2016;25:166-74. doi: 10.1016/j.hlc.2015.06.828
44. Carli F, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M et al. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. JAMA Surg. 2020; 155:233-42. doi: 10.1001/jamasurg.2019. 5474.
45. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The Physical Activity Guidelines for Americans. JAMA. 2018;320:2020-8. doi: 10.1001/jama.2018.14854.
46. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2012;62:30-67. doi: 10.3322/caac.20140.
47. Lau C, Chamberlain RS. Prehabilitation programs improve exercise capacity before and after surgery in gastrointestinal cancer surgery patients: a meta-analysis. J Gastrointest Surg. 2020;24:2829-37. doi: 10.1007/s11605-019-04436-1.
48. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, van Meeteren NL. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clin Rehabil. 2010;24: 614-22. doi: 10.1177/0269215509358941.
49. Mainini C, Rebelo PF, Bardelli R, Kopliku B, Tenconi S, Costi S, Tedeschi C, Fugazzaro S. Perioperative physical exercise interventions for patients undergoing lung cancer surgery: What is the evidence. SAGE Open Med. 2016; 4:2050312116673855. doi: 10.1177/2050312116673 855.
50. Carli F, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. Acta Oncol. 2017;56:128-33. doi: 10.1080/0284186X.2016.1266081.
51. Symons TB, Sheffield-Moore M, Mamerow MM, Wolfe RR, Paddon-Jones D. The anabolic response to resistance exercise and a protein-rich meal is not diminished by age. J Nutr Health Aging. 2011;15:376-81. doi: 10.1007/s12603-010-0319-z.
52. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev. 2012;11:CD008879. doi: 10.1002/14651858.CD008879.pub2.
53. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN J Parenter Enteral Nutr. 2011;35:473-87. doi: 10.1177/ 0148607110385698.
54. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33:929-36. doi: 10.1016/j.clnu.2014.04.007.
55. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H et al. ESPEN practical guideline: Clinical Nutrition in cancer. Clin Nutr. 2021;40:2898-913. doi: 10.1016/j.clnu.2021.02.005.
56. Bongers BC, Dejong C, den Dulk M. Enhanced recovery after surgery programmes in older patients undergoing hepatopancreatobiliary surgery: what benefits might prehabilitation have. Eur J Surg Oncol. 2021;47:551-9. doi: 10.1016/j.ejso.2020.03.211.
57. van Noort H, Heinen M, van Asseldonk M, Ettema R, Vermeulen H, Huisman-de Waal G, On the behalf of the Basic Care Revisited (BCR) Research group. Using intervention mapping to develop an outpatient nursing nutritional intervention to improve nutritional status in undernourished patients planned for surgery. BMC Health Serv Res. 2020;20:152. doi: 10.1186/s12913-020-4964-6.
58. Gillis C, Fenton TR, Sajobi TT, Minnella EM, Awasthi R, Loiselle SÈ, Liberman AS, Stein B, Charlebois P, Carli F.

Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials. Clin Nutr. 2019;38:1053-60. doi: 10.1016/j.clnu.2018.06.982.
59. West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth. 2015;114:244-51. doi: 10.1093/bja/aeu318.
60. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as adjunct therapy in cancer. Semin Radiat Oncol. 2019;29:16-24. doi: 10.1016/j.semradonc.2018.10.001.
61. Bobrowska-Korczak B, Gątarek P, Skrajnowska D, Bielecki W, Wyrebiak R, Kovalczuk T, Wrzesień R, Kałużna-Czaplińska J. Effect of zinc supplementation on the serum metabolites profile at the early stage of breast cancer in rats. Nutrients. 2020;12. doi: 10.3390/nu12113457.
62. Gröber U, Holzhauer P, Kisters K, Holick MF, Adamietz IA. Micronutrients in oncological intervention. Nutrients. 2016; 8:163. doi: 10.3390/nu8030163.
63. von Haehling S, Anker SD. Cachexia as major underestimated unmet medical need: facts and numbers. Int J Cardiol. 2012;161:121-3. doi: 10.1016/j.ijcard.2012.09. 213.
64. McClave SA, Kozar R, Martindale RG, Heyland DK, Braga M, Carli F et al. Summary points and consensus recommendations from the North American Surgical Nutrition Summit. JPEN J Parenter Enteral Nutr. 2013;37: 99S-105S. doi: 10.1177/0148607113495892.
65. Webster Marketon JI, Glaser R. Stress hormones and immune function. Cell Immunol. 2008;252:16-26. doi: 10.1016/j.cellimm.2007.09.006.
66. Batchelor T, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;55:91-115. doi: 10.1093/ejcts/ ezy301.
67. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care. 2005;8:23-32. doi: 10.1097/00075197-200501000-00005.