Rev Col Med Fis Rehab 2024;34(Supl. 1):e454 - http://revistacmfr.org
http://doi.org/10.28957/rcmfr.454

Asociación Colombiana de Medicina Física y Rehabilitación

Revisión

Multimodal oncological prehabillitation

Prehabilitación oncológica multimodal

Diana Molinares[1]

[1]Assistant Professor. Director of Oncology Rehabilitation Medicine for SCCC. Program Director Physical Medicine and Rehabilitation Residency. Program Director Cancer Rehabilitation Medicine Fellowship. Department of Physical Medicine and Rehabilitation. University of Miami-Miller School of Medicine. Miami, Florida, United States of America.

Abstract

Physical function and quality of life are severely impacted by cancer and oncological treatments. In light of these findings over the last two decades, the focus of cancer rehabilitation research has shifted to preventive interventions. These interventions, known as prehabilitation, aim to improve patients' physical, mental, and nutritional status before oncological treatment. The term prehabilitation was first defined in 2013 by Silver *et al.* as "a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments. Since then, the impact of prehabilitation has been evaluated in multiple cancer types with beneficial results. This review aims to describe the benefits of rehabilitation in the cancer continuum and the effects on the different disease groups.
Keywords. Prehabilitation, rehabilitation, nutritional sciences, quality of life, disease prevention, cancer.

Resumen

La función física y la calidad de vida son aspectos que se ven gravemente afectados por el cáncer y los tratamientos oncológicos. Según los hallazgos de la presente revisión, en las últimas dos décadas la investigación en rehabilitación oncológica se ha centrado en intervenciones preventivas, las cuales son conocidas como prehabilitación y tienen como objetivo mejorar el estado físico, mental y nutricional de los pacientes antes del tratamiento oncológico.
El término prehabilitación fue definido por primera vez en 2013 por Silver *et al.* como "un proceso en el continuo de atención del cáncer que se produce entre el momento del diagnóstico de cáncer y el comienzo del tratamiento agudo, e incluye evaluaciones físicas y psicológicas que establecen un nivel funcional de referencia, identifican las deficiencias y proporcionan intervenciones que promueven la salud física y psicológica para reducir la incidencia o la gravedad de las deficiencias futuras". Desde entonces, se ha evaluado el impacto de la prehabilitación en múltiples tipos de cáncer con resultados beneficiosos.
La presente revisión tiene como objetivo describir los beneficios de la prehabilitación en el continuo del cáncer y los efectos sobre los diferentes grupos de enfermedades.
Palabras clave. Prehabilitación, rehabilitación, ciencias de la nutrición, calidad de vida, prevención de enfermedades, cáncer.

How to cite. Molinares D. Prehabilitation oncologica multimodal. Rev Col Med Fis Rehab. 2024;34(Supl. 1):e454. http://doi.org/10.28957/rcmfr.454.

Corresponding author. Diana Molinaes. E-mail: dmolinares@med.miami.edu
Received. 27.08.24. **Accepted.** 02.10.24. **Published.** 26.11.24.
ISSN impreso. 0121-0041. **ISSN electrónico.** 2256-5655.

http://doi.org/10.28957/rcmfr.454

Introduction

The concept of prehabilitation

Exercise has been identified as having an essential role in improving or maintaining the function of oncological patients[1,2]. Physical exercise has been integrated into enhanced recovery after surgery (ERAS) pathways. The preoperative component of the ERAS protocols focuses on optimizing the patient prior to surgical interventions, and exercise is one of the pillars of this approach (Figure-1). Nonetheless, a multimodal approach has been found to be comprehensive and effective in improving oncologic patients' function, facilitating recovery, and becoming the standard of care. In addition to exercise, improving nutritional intake, psychological well-being, and tobacco cessation are the other pillars of multimodal prehabilitation (Figure-2).

Figure 1. Timeline of rehabilitation interventions.
Source: own elaboration.

Exercise	Nutrition	Psychology	Tabacco cessation
Aerobic-high/medium intensity Resistance and strengthening Stretching Inspiratory muscle training	Oral nutritional Assessment and dietary counseling Parenteral Nutrition	Education Surgery Coping strategies Psychotherapy Enhanced support	Counseling Nicotine replacement Medication

Figure 2. Components of a multimodal prehabilitation program.
Source: own elaboration.

Malnutrition is a prevalent finding among cancer patients. Although the prevalence can vary depending on the cancer type, malnutrition is identified in 15-40% of the patients with a recent cancer diagnosis. These numbers can increase to 40-80% during cancer treatment[3]. Zang *et al.*[4] performed a meta-analysis to investigate the relationship between malnutrition and adverse outcomes in cancer patients. The authors identified that 12-80% of cancer patients are at risk of malnutrition, which is associated with increased postoperative complications, with an odds ratio of 2.27 (95% CI 1.81-2.84). Gastrointestinal, head and neck, lung, and hematological cancers have been found among the most common cancer types associated with malnutrition[5]. Most of these cancers require surgical intervention as part of the treatment. Improving perioperative nutrition is associated with decreased postoperative complications and length of stay, becoming a vital element of a prehabilitation program[2].

Mood disorders, particularly depression, are prevalent among cancer patients, with prevalence rates ranging from 5% to 60%. These disorders have a detrimental impact on recovery and prognosis[2,6,7]. Prehabilitation interventions often incorporate techniques to alleviate anxiety, such as breathing exercises, counseling, and coping strategies. Despite the variability in interventions and outcomes, there is strong evidence supporting the effectiveness of these approaches in improving patients' moods[8]. Authors like Grassen *et al.* also describe the positive effect of preoperative stress management training on patients' mood disturbance and depressive symptoms. However, research has not identified

Rev Col Med Fis Rehab 2024-34(Supl. 1):e454 - http://revistacmfr.org
http://doi.org/10.28957/rcmfr.454

psychological prehabilitation effectiveness as a unimodal approach[8]. Nonetheless, there is strong evidence that supports its inclusion as part of multimodal prehabilitation programs[8-10].

Traditionally, smoking tobacco cessation have been considered part of the multimodal approach. Active smoking has been associated with surgical complications, increasing the risk to up to 22%[11]. A meta-analysis performed to determine the benefits of smoking cessation demonstrated a relative risk reduction of up to 41%, with increases of 19% for each week, especially for wound healing and pulmonary complications. In addition to smoking cessation, other interventions included in multimodal prehabilitation, such as Inspiratory muscle training with increased resistance and cognitive therapy, both showed promising results[2].

Interventions and outcomes measures

Exercise

Exercise interventions in prehabilitation are often heterogenous[12]. From supervised to independent, exercise interventions can include aerobic and/or resistance exercise or a mix of modalities. Similarly, depending on the protocol, the intensity and frequency can vary. Although some studies highlight the benefits of high-intensity interval training, other protocols based the aerobic activity recommendations on the exercise guidelines for cancer survivors: moderate-intensity aerobic activity combined with resistance exercise three times a week[13-16]. The duration of the program also has been variable from protocol to protocol. However, most studies agree that a minimum of 6-8 weeks is needed to see a significant improvement.

A comprehensive meta-analysis conducted in 2021 evaluated the feasibility of exercise-based prehabilitation in 1371 cancer patients. The study revealed a completion rate of 89.7%[17]. However, depending on the nature of the oncological process, the patient's participation and completion of program rates may vary. Colorectal cancer, one of the most studied cancer sites in prehabilitation research, reports the highest level of acceptability, ranging between 90-100%[17]. On the other hand, a randomized control clinical trial on esophageal cancer patients reports lower compliance (68%). Nonetheless, this study demonstrated that prehabilitation in this cancer population is not only safe and feasible but also improves physical function, even in those patients receiving neoadjuvant chemotherapy[18].

Prehabilitation in lung cancer patients has been extensively studied. Cardiovascular reserve, assessed as part of preoperative evaluation, helps determine fitness levels and the need for prehabilitation[19]. Prehabilitation programs should be tailored to individual patients, considering factors like surgical timing, exercise history, and anticipated rehabilitation needs. While moderate-intensity exercise is commonly recommended, high-intensity interval training (HIIT) has shown promise in lung cancer patients. HIIT programs, typically lasting 7 to 4 weeks, incorporate aerobic activity, strengthening, and respiratory exercises. Patients exercise 2-4 times weekly at moderate to vigorous intensity for 10-90 minutes. HIIT may be particularly beneficial for patients with shorter preoperative time[20]. Additionally, studies suggest that respiratory muscle strengthening can reduce postoperative complications. However, the heterogeneity of existing research makes it challenging to draw definitive conclusions.

Aerobic exercise has traditionally been the cornerstone of physical activity prehabilitation interventions for cancer patients. However, recent research has expanded the scope of aerobic exercise interventions to address common cancer-related impairments. This focus has yielded promising results, demonstrating decreased symptoms and potentially improved preparation for oncological treatments, including surgery[21]. In 2019, the American College of Sports Medicine updated its guidelines for exercise in oncological patients. These guidelines recommend a comprehensive approach that includes both aerobic and resistance exercises based on a robust body of evidence. Strong evidence supports the benefits of aerobic exercise in addressing cancer-related fatigue, health-related quality of life, physical function, anxiety, and depression. Additionally, there is moderate evidence for the positive impact of aerobic exercise on sleep. In terms of resistance exercises, there is strong support for their effectiveness in managing lymphedema, cancer-related fatigue, health-related quality of life, and physical function[13].

Research studies utilized previously validated measurements of physical function. The Six-Minute-Walk-distance (6MWD) test is the most common measure used to determine the effects of prehabilitation. This test evaluates cardiorespiratory fitness in a safe and well-tolerated manner. It is a validated, standardized method in which results are adjusted based on an equation that includes gender, weight, and height. Based on this equation, it is possible to predict the percentage predicted value for an adult individual[22]. There is more than one equation that can be used as a reference, and even though some of them include the age of the person, some authors have found that age has a minimal effect[23]. Several meta-analyses evaluated the effect of prehabilitation on the physical function of patients assessed with the 6MWD test. In all the metanalysis, which included different oncological pathologies, patients who underwent multimodal prehabilitation had improvements in the 6MWD test[17,24-26].

Peak oxygen consumption (VO_2 peak) is more accurate than the 6MWD test to measure cardiopulmonary fitness[27]. However, it is a more expensive and less available test. VO_2 peak has been particularly tested in patients with lung cancer undergoing prehabilitation with HIIT, with evidence of improvement[28]. Regarding the relationship between VO_2 and survival in lung cancer patients, Lindenmann *et al.*[29] conducted a retrospective analysis that included 342 patients. In this study, the author found that patients with lower pre-operative VO_2 peaks were associated with lower overall and non-tumor-related survival. This study highlights the importance of improving VO_2 peak prior to surgical interventions, especially in lung cancer patients. At this time, HIIT seems to be a viable tool to improve cardiovascular fitness as part of a multimodal rehabilitation program.

The effects of exercise prerehabilitation programs have been evaluated in different ways. In addition to the 6MWD test and the VO_2 peak tests, including the anaerobic threshold for cardiopulmonary exercise testing, Time Up & Go, grip strength, incremental shuttle walk test, and skeletal muscle mass tests, have been investigated as physical performance predictors with promising results. Nonetheless, further investigation is needed[30,31].

Nutrition

Nutrition optimization is a fundamental pillar of cancer prehabilitation programs. Up to eighty percent of cancer patients have been found to have some degree of malnutrition[32]. these nutritional challenges arise from a complex interplay of factors, with inflammatory mediators playing a particularly significant role[32]. Additionally, side effects from oncological treatment, such as nausea, vomiting, anorexia, and changes in taste, can contribute to poor nutritional intake. While this issue affects patients with various cancer types, those with head and neck and gastrointestinal cancers are at the highest risk of malnutrition[33-36]. In head and neck (H&N) cancer patients, malnutrition is a risk factor for mortality[37,38]. Dysphagia, either from cancer or some of the treatments, like surgery and radiation, has a significant effect on the patient's ability to eat, which often results in malnutrition and the need for a tube-feeding[33].

Similarly, patients with gastrointestinal cancers are particularly susceptible to preoperative malnutrition, with rates as high as 80%[39]. Dysphagia, obstruction, malabsorption, and nausea are some of the contributors to poor oral intake. Given the direct impact on swallowing, esophageal cancer patients frequently experience dysphagia and weight loss, placing them at a heightened risk of malnutrition[40,41]. Up to 60% of this patient population is malnourished at the time of surgery[42]. Furthermore, colorectal cancer is associated with moderate to severe malnutrition in about 35% due to its effect on bowel function, especially obstruction[43]. In hepatopancreatic-biliary cancers, weight loss is common and present in 80% of the patients at the time of diagnosis[44,45].

Malnutrition is an independent risk factor for postoperative complications and is considered a cornerstone of cancer prehabilitation programs. Appropriate evaluation and initiation of nutritional therapy reduce surgical complications and accelerate recovery[46]. There is no consensus on what screening tool should be used for the stratification of patients. The tool selection often depends on the type of cancer, patient age, familiarity, and clinical flow

Rev Col Med Fis Rehab 2024-34(Supl. 1):e454 - http://revistacmfr.org
http://doi.org/10.28957/rcmfr.454

of the medical provider. A review in 2021 studied the effectiveness of several tools in predicting postoperative outcomes[47]. This review found that serum albumin and prealbumin are both effective. Furthermore, assessments such as the Subjective Global Assessment, Prognostic Nutritional Index, Nutrition Risk Score, and Nutrition Risk Screening 2002 are also valuable and applicable tools to determine the nutritional level of colorectal cancer patients[47]. Similarly, these nutritional screening tools were found effective in patients with head and neck cancer and are believed to apply to other disease groups[48]. Subjective Global Assessment is considered the goal standard as it encompasses functional capacity, gastrointestinal symptoms, metabolic stress, weight, and dietary intake, along with physical examination that includes subcutaneous, muscle mass, and edema, which can be time-consuming[49]. Although these tools are validated for screening purposes, none has been studied or found useful in measuring the impact of nutritional prehabilitation interventions.

Although the importance of adequate nutrition in the perioperative period is well recognized, there is no consensus on the prehabilitation interventions or outcome measures. General recommendations include increasing protein intake to meet 1-1.5g/kg of ideal weight[18,33,36]. However, this is not consistent across prehabilitation studies. The source of protein also can vary from food to protein supplement[50]. Some unimodal nutritional prehabilitation programs have been shown to improve some surgical outcomes. However, they have failed to show improvement in nutritional biomarkers[34,51]. Nutritional interventions also range from providing nutritional advice to delivering every single meal. Tweed *et al.*[52] conducted a study to evaluate the feasibility and efficiency of a prehabilitation program where all meals were delivered to subjects for four weeks with the goal of meeting the protein requirements. Minimal information has been published regarding nutrition in head and neck patients. A review study in 2022 evaluated the effect of enriched formula over routine standard formula. The nutritional goal of these studies was to mitigate weight loss. Although patients had good tolerance to both formulas, the studies did not find that the intervention was effective in reducing weight loss, physical function, length of stay, or post-surgical complications.

Despite the lack of direct, measurable effects of nutrition in the literature, there is enough evidence to support nutritional interventions as part of multimodal prehabilitation programs in cancer patients. However, further research should focus on identifying the most accurate reproducible tool to evaluate the effectiveness of nutritional interventions. Additionally, standard protocols should be established depending on the cancer type, patient characteristics, and severity of malnutrition.

Psychological well-being

The prehabilitation process starts during a challenging period of the cancer continuum, soon after diagnosis. At this time, patients are working on understanding their new medical condition, and the amount of information, appointments, and fears could be very overwhelming, and the addition of an exercise and nutrition program could add another level of challenges[53]. Psychological support can play a crucial role in addressing psychosocial factors such as anxiety, pain, and catastrophizing. By providing emotional support and coping strategies, psychological interventions can enhance patient motivation to participate in other components of the multimodal prehabilitation program and improve overall compliance[54]. A multicenter, international, randomized clinical trial that included 251 patients evaluated the effect of multimodal prehabilitation in the recovery of patients undergoing elective nonmetastatic colorectal cancer. The authors demonstrated that Psychological 1-1 sessions focusing on anxiety management, relaxation techniques, breathing exercises, exercise, nutrition, and smoking cessation were statically significantly effective in a faster and better postoperative recovery[55].

Similar to exercise and nutrition, there are no standards for evaluating prehabilitation psychological interventions. Three studies that evaluated the effectiveness of multimodal prehabilitation in lung cancer utilized two distinct validated tools to determine the baseline of patients' psychological well-being, which includes Hospital Anxiety and Depression Score and the Short Form (SF) 36 questionnaire[56-58]. Regarding psychological interventions, similar to other cancer populations, there is a considerable variation of techniques to

provide psychological/well-being support during prehabilitation programs[19].

Mood disorders, such as depression, have been linked to prolonged hospitalization[59]. Psychological interventions have proven to be effective in reducing mood disturbances and stress. In a study of 159 patients with prostate cancer undergoing surgical resection, those who received psychological support versus standard care had fewer mood disorders and improved postoperative parameter[60].

Smoking

Smoking cessation is a vital component of the traditional multimodal prehabilitation program. There is compelling evidence that quitting smoking benefits patients with cardiothoracic tumors, particularly those with lung cancer. Additionally, strong support exists for smoking cessation programs in patients with brain and gastrointestinal cancers who are scheduled for surgery, as smoking is associated with an increased risk of surgical complications[61,62]. Interventions for smoking tobacco cessation may include counseling, medications, medications, etc.

Conclusion

The growing number of cancer survivors is a testament to advancements in oncological treatment and surgical techniques, allowing for longer life expectancies. Additionally, with further development of minimally invasive surgical techniques, patients who in the past would not be considered surgical candidates are now candidates for curative surgical interventions. Despite the advancements in oncological treatment, the morbidity and physical and functional impact associated with them continue to challenge patients' mobility and functional independence. Medical and physical optimization prior to the start of treatment, especially before surgical interventions, can improve physical activity markers and post-surgical outcomes and accelerate recovery.

Multimodal prehabilitation programs have been shown to impact postoperative outcomes positively. The combination of exercise, nutrition, psychological interventions, and smoking cessation are the four cornerstones of most prehabilitation programs. However, tailored interventions that address specific cancer-related impairments, such as respiratory muscle strengthening in lung cancer patients, should be included. Lastly, although studies utilize validated tools, standardized, prehabilitation-specific interventions, and evaluation tools should be further investigated.

Contribution of the authors

No additional authors.

Ethical considerations

This review article did not have direct contact with human subjects. No IRB approval was needed.

Due to the ethical implications of withholding prehabilitation, a direct comparison between those receiving it and those not is challenging. However, a control group could be established if patients decline participation.

Conflicts of interest

None declared by the authors.

Funding

The author reports no financial disclosures or conflict of interest. This work was conducted independently, without any external funding.

Acknowledgments

None declared by the authors.

References

1. Del Bianco N, Borsati A, Toniolo L, Ciurnielli C, Belluomini L, Insolda J, *et al.* What is the role of physical exercise in the era of cancer prehabilitation? A systematic review. Crit Rev Oncol Hematol. 2024;198:104350. Disponible en: https://doi.org/10.1016/j.critrevonc.2024.104350.

2. Guerra-Londono CE, Cata JP, Nowak K, Gottumukkala V. Prehabilitation in Adults Undergoing Cancer Surgery: A Comprehensive Review on Rationale, Methodology, and Measures of Effectiveness. Curr. Oncol. 2024;31(4):2185-200. https://doi.org/10.3390/curroncol31040162.

3. Ravasco P. Nutrition in Cancer Patients. J Clin Med. 2019;8(8):1211. Disponible en: https://doi.org/10.3390/jcm8081211.

4. Zang Y, Xu W, Qiu Y, Gong D, Fan Y. Association between Risk of Malnutrition Defined by the Nutritional Risk Screening 2002 and Postoperative Complications and Overall Survival in Patients with Cancer: A Meta-Analysis. Nutr Cancer. 2023;75(8):1600-9. Disponible en: https://doi.org/10.1080/01635581.2023.2227402.

5. Bossi P, Delrio P, Mascheroni A, Zanetti M. The Spectrum of Malnutrition/Cachexia/Sarcopenia in Oncology According to Different Cancer Types and Settings: A Narrative Review. Nutrients. 2021;13(6):1980. Disponible en: https://doi.org/10.3390/nu13061980.

6. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, *et al.* Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12(2):160-74. Disponible en: https://doi.org/10.1016/S1470-2045(11)70002-X.

7. Caruso R, Nanni MG, Riba M, Sabato S, Mitchell AJ, Croce E, *et al.* Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. Acta Oncol. 2017;56(2):146-55. Disponible en: https://doi.org/10.1080/0284186X.2016.1266090.

8. Tsimopoulou I, Pasquali S, Howard R, Desai A, Gourevitch D, Tolosa I, *et al.* Psychological Prehabilitation Before Cancer Surgery: A Systematic Review. Ann Surg Oncol. 2015;22(13):4117-23. Disponible en: https://doi.org/10.1245/s10434-015-4550-z.

9. Crevenna R. Prehabilitation in the cancer care continuum. Support Care Cancer. 2022;30(2):1019-20. Disponible en: https://doi.org/10.1007/s00520-021-06649-0.

10. Silver JK, Flores LE. Integrating Prehabilitation into the Cancer Survivorship Framework. Eur Urol Focus. 2024;10(1):23-5. Disponible en: https://doi.org/10.1016/j.euf.2023.11.006.

11. Fernandez AC, Bohnert KM, Bicket MC, Weng W, Singh K, Englesbe M. Adverse Surgical Outcomes Linked to Co-occurring Smoking and Risky Alcohol Use Among General Surgery Patients. Ann Surg. 2023;278(2):201-7. Disponible en: https://doi.org/10.1097/SLA.0000000000005735.

12. Yang L, Alice A, Friedenreich CM. Physical activity for cancer prehabilitation: A scoping review. Crit Rev Oncol Hematol. 2024;196:104319. Disponible en: https://doi.org/10.1016/j.critrevonc.2024.104319.

13. 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(11):2375-90. Disponible en: https://doi.org/10.1249/MSS.0000000000002116.

14. Banerjee S, Manley K, Shaw B, Lewis L, Cucato G, Mills R, *et al.* Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. Support Care Cancer. 2018;26(5):1515-23. Disponible en: https://doi.org/10.1007/s00520-017-3991-2.

15. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, *et al.* Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk

for postoperative complications: results of a randomized clinical trial. Ann Surg. 2022;75(2):e299-e306. Disponible en: https://doi.org/10.1097/SLA.0000000000004702.

16. Minnella EM, Ferreira V, Awasthi R, Charlebois P, Stein B, Liberman AS, *et al*. Effect of two different preoperative exercise training regimens before colorectal surgery on functional capacity: a randomised controlled trial. Eur J Anaesthesiol. 2020;37(11):969-78. Disponible en: https://doi.org/10.1097/EJA.0000000000001215.

17. Michael CM, Lehrer EJ, Schmitz KH, Zaorsky NG. Prehabilitation exercise therapy for cancer: A systematic review and meta-analysis. Cancer Med. 2021;10(13):4195-205. Disponible en: https://doi.org/10.1002/cam4.4021.

18. Minnella EM, Awasthi R, Loiselle SE, Agnihotram RV, Ferri LE, Carli F. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. JAMA Surg. 2018;153(12):1081-9. Disponible en: https://doi.org/10.1001/jamasurg.2018.1645.

19. Wade-Mcbane K, King A, Urch C, Jeyasingh-Jacob J, Milne A, Boutillier CL. Prehabilitation in the lung cancer pathway: a scoping review. BMC Cancer. 2023;23(1):747. Disponible en: https://doi.org/10.1186/s12885-023-11254-x.

20. Avancini A, Cavallo A, Trestini I, Tregnago D, Belluomini L, Crisafulli E, *et al*. Exercise prehabilitation in lung cancer: Getting stronger to recover faster. Eur J Surg Oncol. 2021;47(8):1847-55. Disponible en: https://doi.org/10.1016/j.ejso.2021.03.231.

21. Wagoner CW, Capozzi LC, Culos-Reed SN. Tailoring the Evidence for Exercise Oncology within Breast Cancer Care. Curr Oncol. 2022;29(7):4827-41. Disponible en: https://doi.org/10.3390/curroncol29070383.

22. Enright PL, Sherrill DL. Reference Equations for the Six-Minute Walk in Healthy Adults. Am J Respir Crit Care Med. 1997;158(5 Pt 1):1384-7. Disponible en: https://doi.org/10.1164/ajrccm.158.5.9710086.

23. Halliday SJ, Wang L, Yu C, Vickers BP, Newman JH, Fremont RD, *et al*. Six-Minute Walk Distance in Healthy Young Adults. Respir Med. 2020;165:105933. Disponible en: https://doi.org/10.1016/j.rmed.2020.105933.

24. Daniels SL, Lee MJ, George J, Kerr K, Moug S, Wilson TR, *et al*. Prehabilitation in elective abdominal cancer surgery in older patients: systematic review and meta-analysis. BJS Open. 2020;4(6):1022-41. Disponible en: https://doi.org/10.1002/bjs5.50347.

25. Waterland JL, McCourt O, Edbrooke L, Granger CL, Ismail H, Riedel B, *et al*. Efcacy of prehabilitation including exercise on postoperative outcomes following abdominal cancer surgery: a systematic review and meta-analysis. Front Surg. 2021;8:628848. Disponible en: https://doi.org/10.3389/fsurg.2021.628848.

26. Rosero ID, Ramírez-Vélez R, Lucia A, Martínez-Velilla N, Santos-Lozano A, Valenzuela PL, *et al*. Systematic review and meta-analysis of randomized, controlled trials on preoperative physical exercise interventions in patients with non-small-cell lung cancer. Cancers (Basel). 2019;11(7):944. Disponible en: https://doi.org/10.3390/cancers11070944.

27. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, *et al*. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth. 2018;120(3):484-500. Disponible en: https://doi.org/10.1016/j.bja.2017.10.020.

28. Palma S, Hasenoehrl T, Jordakieva G, Ramazanova D, Crevenna R. High-intensity interval training in the prehabilitation of cancer patients-a systematic review and meta-analysis. Support Care Cancer. 2021;29(4):1781-94. Disponible en: https://doi.org/10.1007/s00520-020-05834-x.

29. Lindenmann J, Fink-Neuboeck N, Fediuk M, Maier A, Kovacs G, Balic M, *et al*. Preoperative Peak Oxygen Consumption: A Predictor of Survival in Resected Lung Cancer. Cancers (Basel). 2020;12(4):836. Disponible en: https://doi.org/10.3390/cancers12040836.

30. Allen SK, Brown V, White D, King D, Hunt J, Wainwright J, *et al*. Multimodal Prehabilitation During Neoadjuvant Therapy Prior to Esophagogastric Cancer Resection: Effect on Cardiopulmonary Exercise test performance, muscle mass and quility of life-A pilot randomized clinical trial. Ann Surg Oncol. 2022;29(3):1839-50. Disponible en: https://doi.org/10.1245/s10434-021-11002-0.

31. Argillander TE, Heil TC, Melis RJF, van Duijvendijk P, Klaase JM, van Munster BC. Preoperative physical performance as predictor of postoperative outcomes in patients aged 65 and older scheduled for major abdominal cancer surgery: A systematic review. Eur J Surg Oncol. 2022;48(3):570-81. Disponible en: https://doi.org/10.1016/j.ejso.2021.09.019.

32. Bausys A, Mazeikaite M, Bickaite K, Bausys B, Bausys R, Strupas K. The role of prehabilitation in modern esophagogastric cancer surgery: a comprehensive review. Cancers (Basel). 2022;14(9):2096. Disponible en: https://doi.org/10.3390/cancers14092096.

33. Cantwell LA, Fahy E, Walters ER, Patterson JM. Nutritional prehabilitation in head and neck cancer: a systematic review. Support Care Cancer. 2022;30(11):8831-43. Disponible en: https://doi.org/10.1007/s00520-022-07239-4.

34. Wall J, Paul M, Phillips BE. Nutritional interventions in prehabilitation for cancer surgery. Curr Opin Clin Nutr Metab Care. 2023;26(6):497-507. Disponible en: https://doi.org/10.1097/MCO.0000000000000974.

35. Christopher CN, Kang DW, Wilson RL, Gonzalo-Encabo P, Ficarra S, Heislein D, *et al*. Exercise and Nutrition Interventions for Prehabilitation in Hepato-Pancreato-Biliary Cancers: A Narrative Review. Nutrients. 2023;15(24):5044. Disponible en: https://doi.org/10.3390/nu15245044.

36. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, *et al*. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology. 2018;155(2):391-410.e4. Disponible en: https://doi.org/10.1053/j.gastro.2018.05.012.

37. Langius JA, Zandbergen MC, Eerenstein SE, van Tulder MW, Leemans CR, Kramer MH, *et al*. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo) radiotherapy: a systematic review. Clin Nutr. 2013;32(5):671-8. Disponible en: https://doi.org/10.1016/j.clnu.2013.06.012.

38. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr. 2012;31(3):345-50. Disponible en: https://doi.org/10.1016/j.clnu.2011.11.001.

39. Deftereos I, Djordjevic A, Carter VM, McNamara J, Yeung JM, Kiss N. Malnutrition screening tools in gastrointestinal cancer: A systematic review of concurrent validity. Surg Oncol. 2021;38:101627. Disponible en: https://doi.org/10.1016/j.suronc.2021.101627.

40. Rubenstein JH, Shaheen NJ. Epidemiology, diagnosis, and management of esophageal adenocarcinoma. Gastroenterology. 2015;149(2):302-17.e1. Disponible en: https://doi.org/10.1053/j.gastro.2015.04.053.

41. Reim D, Friess H. Feeding challenges in patients with esophageal and gastroesophageal cancers. Gastrointest Tumors. 2016;2(4):166-77. Disponible en: https://doi.org/10.1159/000442907.

42. Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? Ann Surg Oncol. 2012;19(7):2128-34. Disponible en: https://doi.org/10.1245/s10434-012-2225-6.

43. Lohsiriwat V. The influence of preoperative nutritional status on the outcomes of an enhanced recovery after surgery (ERAS) programme for colorectal cancer surgery. Tech Coloproctol. 2014;18(11):1075-80. Disponible en: https://doi.org/10.1007/s10151-014-1210-4.

44. Olson SH, Xu Y, Herzog K, Saldia A, DeFilippis EM, Li P, *et al*. Weight Loss, Diabetes, Fatigue, and Depression Preceding Pancreatic Cancer. Pancreas. 2016;45(7):103-13. Disponible en: https://doi.org/10.1097/MPA.0000000000000590.

45. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. Br J Surg. 2014;101(2):109-13. Disponible en: https://doi.org/10.1002/bjs.9342.

46. Lobo DN, Gianotti L, Adiamah A, Barazzoni R, Deutz NEP, Dhatariya K, *et al*. Perioperative nutrition: Recommendations from the ESPEN expert group. Clin Nutr. 2020;39(11):3211-27. Disponible en: https://doi.org/10.1016/j.clnu.2020.03.038.

47. Gupta A, Gupta E, Hilsden R, Hawel JD, Elnahas AI, Schlachta CM, *et al*. Preoperative malnutrition in patients with colorectal cancer. Can J Surg. 2021;64/6):E621-9. Disponible en: https://doi.org/10.1503/cjs.016820.

48. Kristensen MB, Isenring E, Brown B. Nutrition and swallowing therapy strategies for patients with head and neck cancer. Nutrition. 2020;69:110548. Disponible en: https://doi.org/10.1016/j.nut.2019.06.028.

49. Håkonsen SJ, Pedersen PU, Bath-Hextall F, Kirkpatrick P. Diagnostic test accuracy of nutritional tools used to identify undernutrition in patients with colorectal cancer: a systematic review. JBI Database System Rev Implement Rep. 2015;13(4):141-87. Disponible en: https://doi.org/10.11124/jbisrir-2015-1673.

50. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr. 2099;28(4):378-86. Disponible en: https://doi.org/10.1016/j.clnu.2009.04.002.

51. Kaibori M, Ishizaki M, Matsui K, Nakatake R, Yoshiuchi S, Kimura Y, *et al*. Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. Am J Surg. 2013;206(2):202-9. Disponible en: https://doi.org/10.1016/j.amjsurg.2012.07.035.

52. Tweed TTT, Sier MAT, Van Bodegraven AA, Van Nie NC, Sipers WMWH, Boerma EG, *et al*. Feasibility and Efficiency of the BEFORE (Better Exercise and Food, Better Recovery) Prehabilitation Program. Nutrients. 2021;13(10):3493. Disponible en: https://doi.org/10.3390/nu13103493.

53. Giles C, Cummins S. Prehabilitation before cancer treatment. BMJ. 2019;366:l5120. Disponible en: https://doi.org/10.1136/bmj.l5120.

54. Shen C, Gu L, Li N, Wang R, Yang X, Chu Z. Attitudes and perceptions of cancer patients and healthcare providers towards prehabilitation: A thematic synthesis. Br J Health Psychol. 2024;29(2):395-429. Disponible en: https://doi.org/10.1111/bjhp.12705.

55. Molenaar CJL, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi R, *et al*. Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery: The PREHAB Randomized Clinical Trial. JAMA Surg. 2023;158(6):572-81. Disponible en: https://doi.org/10.1001/jamasurg.2023.0198.

56. Yao L, Chen H, Xue B. Application and practice of trimodal prehabilitation model in preoperative management of patients with lung cancer undergoing videoassisted thoracoscopic surgery. Front Surg. 2023;9:1047977. Disponible en: https://doi.org/10.3389/fsurg.2022.1047977.

57. Schmid S, Minnella EM, Pilon Y, Rokah M, Rayes R, Najmeh S, *et al*. Neoadjuvant prehabilitation therapy for locally advanced non-smallcell lung cancer: optimizing outcomes throughout the trajectory of care. Clin Lung Cancer. 2022;23(7):593-9. Disponible en: https://doi.org/10.1016/j.cllc.2022.05.004.

58. Sebio García R, Yáñez-Brage MI, Giménez Moolhuyzen E, Salorio Riobo M, Lista Paz A, Borro Mate JM. Preoperative exercise training prevents functional decline after lung resection surgery: a randomized, singleblind controlled trial. Clin Rehabil. 2017;31(8):1057-67. Disponible en: https://doi.org/10.1177/0269215516684179.

59. Silver JK, Baima J. Cancer Prehabilitation: An Opportunity to Decrease Treatment-Related Morbidity, Increase Cancer Treatment Options, and Improve Physical and Psychological Health Outcomes. Am J Phys Med Rehabil. 2013;92(8):715-27. Disponible en: https://doi.org/10.1097/PHM.0b013e31829b4afe.

60. Cohen L, Parker PA, Vence L, Savary C, Kentor D, Pettaway C, *et al.* Presurgical stress management improves postoperative immune function in men with prostate cancer undergoing radical prostatectomy. Psychosom Med. 2011;73(3):218-25. Disponible en: https://doi.org/10.1097/PSY.0b013e31820a1c26.

61. Lau D, Ziewacz JE, Siddiqi HK, Pelly A, Sullivan SE, El-Sayed AM. Cigarette smoking: A risk factor for postoperative morbidity and 1-year mortality following craniotomy for tumor resection. J Neurosurg. 2012;116(6):1204-14. Disponible en: https://doi.org/10.3171/2012.3.JNS111783.

62. Gajdos C, Hawn MT, Campagna EJ, Henderson WG, Singh JA, Houston T. Adverse effects of smoking on postoperative outcomes in cancer patients. Ann Surg Oncol. 2012;19(5):1430-8. Disponible en: https://doi.org/10.1245/s10434-011-2128-y.