Supportive Care in Cancer (2023) 31:673
https://doi.org/10.1007/s00520-023-08140-4

RESEARCH

Home-based prehabilitation improves physical conditions measured by ergospirometry and 6MWT in colorectal cancer patients: a randomized controlled pilot study

Daniel Triguero-Cánovas[1] · Francisco López-Rodríguez-Arias[1] · Manuel Gómez-Martínez[2] · Luis Sánchez-Guillén[1] · Franc Peris-Castelló[2] · María José Alcaide-Quirós[1] · Pedro Morillas-Blasco[2] · Antonio Arroyo[1] · Jose Manuel Ramírez[3]

Received: 8 July 2023 / Accepted: 23 October 2023 / Published online: 6 November 2023

Abstract

Purpose/background Prehabilitation aims to improve physical condition in the preoperative period and, therefore, decrease the loss of cardiopulmonary capacity postoperatively, with the aim of reducing complications and promoting an early recovery. This study aims to evaluate the impact of home-based prehabilitation on the physical condition of patients treated surgically for colorectal cancer.

Methods A prospective and randomized clinical study was conducted on 60 patients during two periods from October 2018 to February 2019 and from September 2019 to September 2020, in a single university hospital. Patients were randomized into two study groups (30 per group): prehabilitation vs. standard care. Changes in physical condition, measured at diagnosis, the day before surgery, and at 6–8 weeks after surgery using the cardiopulmonary exercise testing (CPET) and the 6-minute walk test (6MWT) were evaluated.

Results Prehabilitation reduced postoperative complications (17.4% vs. 33.3%, $p = 0.22$) and hospital stay (5.74 vs. 6.67 days, $p = 0.30$). 6MWT showed a significant improvement in the prehabilitation group (+78.9 m). Six weeks after surgery, prehabilitation showed a significant improvement in the 6MWT (+68.9 m vs. −27.2 m, $p = 0.01$). Significant differences were also observed in the ergospirometry between the diagnosis and postoperative study (+0.79 METs vs. −0.84 METs, $p = 0.001$). A strong correlation was observed between CPET and 6MWT (0.767 ($p < 0.001$)).

Conclusion Home prehabilitation achieved lower overall postoperative complications than standard care and reached significant improvements in 6MWT and CET. A strong correlation was observed between CET and 6MWT, which allows validation of 6MWT as a valid and reliable measure of functional exercise capacity in colorectal patients when other, more specific and expensive tests are not available.

Trial registration Registered in ClinicalTrials.gov in August 2018 with registration number https://clinicaltrials.gov/study/NCT03618329?cond=Prehabilitation%20cancer&term=arroyo&distance=50&rank=1 (NCT03618329). Initial results published in Supportive Care in Cancer: Effect of home-based prehabilitation in an enhanced recovery after surgery program for patients undergoing colorectal cancer surgery during the COVID-19 pandemic. DOI: https://doi.org/10.1007/s00520-021-06343-1.

Keywords Colorectal cancer · Prehabilitation · Home-based · Ergospirometry/Cardiopulmonary exercise testing · 6-minute walk test

✉ Luis Sánchez-Guillén
drsanchezguillen@gmail.com

[1] Department of General Surgery, Colorectal Unit, Elche University Hospital, University Miguel Hernández of Elche, Alicante, Spain

[2] Department of Cardiology, Elche University Hospital, University Miguel Hernández of Elche, Alicante, Spain

[3] Department of General Surgery, Colorectal Unit, University Hospital Lozano Blesa, University of Zaragoza, Zaragoza, Spain

Abbreviations

CRC	colorectal cancer
CPET	cardiopulmonary exercise testing
PreH	prehabilitation group
SC	standard care group
ERAS	enhanced recovery after surgery
METs	metabolic equivalents of task
6MWT	6-minute walk test
HR	heart rate
VO2	oxygen consumption

VCO2	carbon dioxide production
VE	minute ventilation
RER	respiratory exchange rate
BMI	body mass index
ASA-PS	American Society of Anesthesiologists-Physical Status
C-D	Clavien-Dindo

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death worldwide [1]. Surgery is the standard treatment, and despite technological advances and patient management during and after the intervention, this is not exempt from risks, complications, and longer hospital stays, which increase with age and the fragility of patients [2–4]. In developed countries, the median age at diagnosis of colorectal cancer has increased to 70 years [5], so it is necessary to create individualized programs optimized for fragile patients with high surgical risk.

In addition to age, other factors, such as malnutrition, sarcopenia, or low cardiorespiratory fitness, are associated with worse perioperative outcomes and a delay in the onset of adjuvant chemotherapy, with globally worse oncological outcomes [6–11]. Adequate cardiorespiratory function and physical capacity of a patient with colorectal cancer should be considered in the perioperative period [12].

Prehabilitation aims to optimize the patient's health in terms of physical, nutritional, and cognitive status in the period between diagnosis and surgery, with the aim of reducing complications and promoting an early recovery of activity prior to the intervention [12], which is one of the main objectives to mitigate the loss of cardiorespiratory function in the early postoperative period [13–17]. For these patients, prehabilitation programs can be performed under supervision or without supervision on an outpatient basis, with an actual debate about in-hospital vs. home-based prehabilitation. Moreover, it is still unknown which tests are the most accurate, provide the best information on the patient's physical condition, help adapt the patient's prehabilitation, and anticipate perioperative complications [18]. The ideal test to predict the risk of postoperative complications should determine the aerobic capacity and functional reserve that would enable the patient to cope with the physical demands of surgery. Cardiopulmonary exercise testing (CPET) includes a wide spectrum of clinical applications. It can be used to evaluate patient physical fitness and has been considered as the gold standard for predicting surgical risk, but despite its usefulness, ergospirometry is not available in most hospitals [19]. Moreover, its value as a routine preoperative test for predicting postoperative complications after CRC surgery remains unknown.

The main objective of the study is to evaluate the impact of outpatient prehabilitation on the physical condition of patients treated surgically for colorectal cancer, measured with the 6MWT and CPET, and to establish a relationship between both tests.

Methods

This is a prospective, randomized, controlled, clinical study with two study groups, the prehabilitation group (PreH) and the standard care (SC) group.

Patients treated for colorectal cancer were consecutively selected from October 2018 to February 2019 and from September 2019 to September 2020. The COVID-19 pandemic forced the study to be conducted over 2 different time periods. Patients with metastatic disease or nutritional supplementation at diagnosis and/or neoadjuvant chemotherapy–radiotherapy were excluded. In addition, a minimum physical condition and/or autonomy allowing the patient to safely perform the program exercises was needed.

We designed a study with 60 patients, assuming a 20% loss.

All patients were evaluated in clinics where they were informed about the prehabilitation program, and the program was explained. Informed consent was obtained, and block randomization was performed using a previously obtained random sequence in two groups: the CS group and the PreH group. Patients in both groups underwent minimally invasive surgery performed by members of the colorectal surgery unit and followed Enhanced Recovery After Surgery (ERAS) standardized perioperative care protocols.

The main variables of the study were changes in physical condition, measured using metabolic equivalents of task (METs) and the 6-minute walk test (6MWT). These measurements were evaluated at diagnosis, the day before surgery (in the PreH group), and at 6–8 weeks after surgery in both groups. The CPET study was carried out in collaboration with the hospital cardiology department.

Symptom-limited CPET was performed on a symptom-limited treadmill (General Electric T2100®, Germany) with continuous breath-by-breath respiratory gas exchange analysis (Carefusion, Germany, software V 5.72). A ramped Bruce protocol or a modified ramped Bruce protocol was followed for treadmill testing. The CPET operating physician chose the protocol based on his clinical criteria. Electrocardiograms were continuously monitored, and dynamic changes were considered when ST segment depression >1 mm was observed. Arrhythmias were reported. The duration of the exercise was expressed in minutes.

Measurements included heart rate (HR), blood pressure, arterial blood oxygen saturation, oxygen consumption (VO2), carbon dioxide production (VCO2), and minute ventilation (VE). The quality of exercise effort was assessed by respiratory exchange rate [RER = (VCO2/VO2)]. RER > 1.05 was considered maximal effort.

Expiratory flow measurements were taken using a mass flow sensor calibrated with a mixture of gasses of known concentration before each test.

Peak O_2 consumption was defined as the average VO2 during the last minute of exercise and expressed as ml/kg of body weight per minute. The MET of physical capacity was obtained by dividing the peak VO2 by 3.5.

The clinical variables analyzed included age, sex, body mass index (BMI), major comorbidities, American Society of Anesthesiologists-Physical Status (ASA-PS) score, type of surgery, tumor stage, and use of anxiolytic and/or antidepressant medications. Hospital stay time and postoperative complications in the first 30 days were collected and divided into minor (classified as Clavien–Dindo (C-D) I-II), which included low-risk events such as surgical wound infection, and postoperative and major ileus pneumonia (Clavien–Dindo III-IV), including life-threatening events and cases requiring radiological, surgical, or endoscopic intervention, such as anastomotic leakage [20]. We considered anastomotic leakage that required radiological drainage (Grade B, C-D IIIa) to be minor and anastomotic leakage that required surgical reintervention (Grade C, C-D IIIb) to be major [21].

This study obtained approval from the ethics committee of our hospital with registration number NCT03618329.

Prehabilitation program

The prehabilitation program was trimodal, with recommendations for physical activity, nutritional supplementation, and relaxation exercises to be performed by patients during the preoperative period and during 6–8 weeks after surgery.

The exercise program was based on daily aerobic exercises and 3 weekly sessions of muscle endurance exercises. It was individualized according to the physical condition of the patient at the time of diagnosis as measured by ergospirometry and 6MWT (Fig. 1). Muscle endurance exercises were simple and functional, and they could be performed without additional materials. In the postoperative period, aerobic exercise was resumed from the moment of discharge, and muscle endurance exercises were delayed until 3–4 weeks.

The patients received dietary recommendations, highlighting the limitation of caloric intake to avoid weight gain and the reduction of toxic habits, such as smoking and alcohol. Hyperproteic nutritional supplementation, high in vitamin D and calcium-β-hydroxy-β-methylbutyrate (CaHMB)

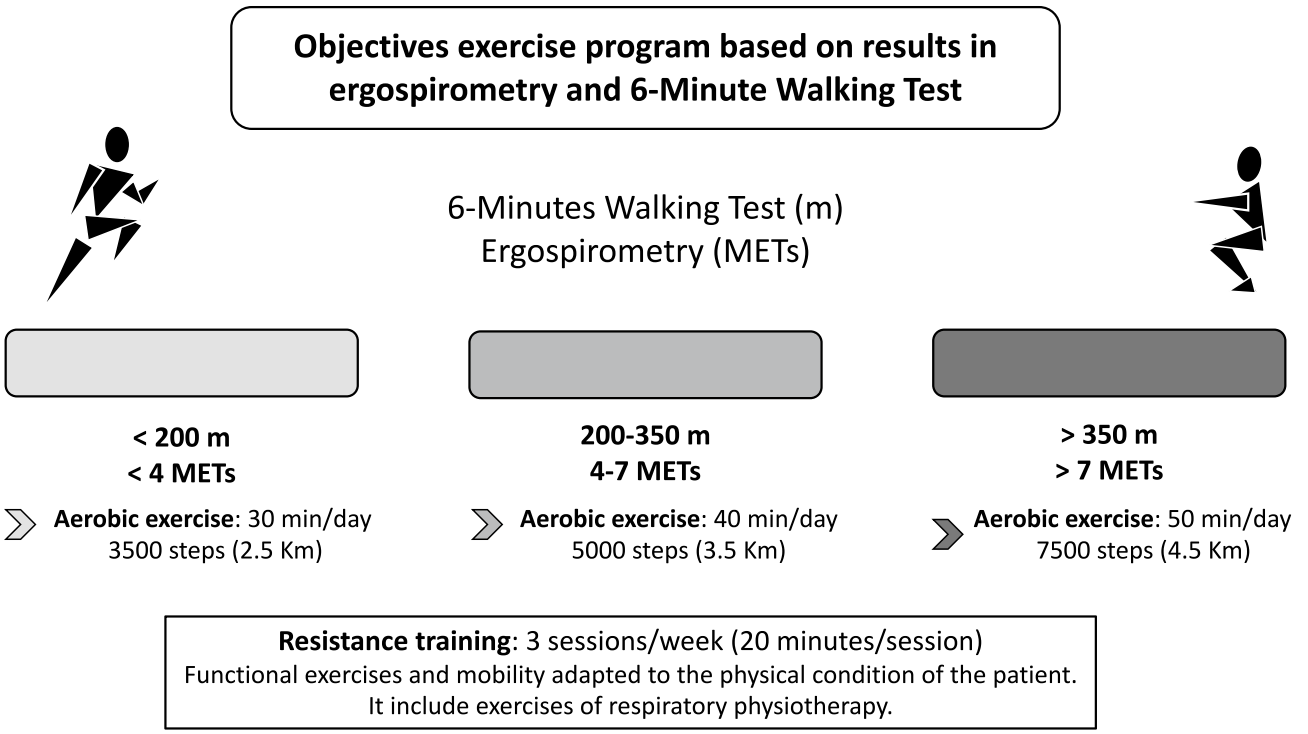

Fig. 1 Algorithm of the objectives of the prehabilitation program according to the results obtained by ergospirometry (CPET) and 6-minute walking test

(Ensure Plus Advance, Abbott), was also administered to ensure a minimum supply of 1.2 to 1.5 g of protein/kg/day. To reduce perioperative anxiety, at the time of diagnosis, all patients received recommendations for relaxation and breathing exercises at least twice a week.

Patients in the SC group who agreed to participate in the study did not receive any education or recommendation on patterns of physical activity, nutrition, or relaxation according to standard clinical practice (ERAS protocols).

Statistical analysis

Data analysis was performed using IBM SPSS Statistics software. Continuous variables are described as medians and standard deviations, and discrete variables are described as frequencies and percentages. The comparative analysis between the PreH group and SC group was performed using a *t* test or Mann–Whitney *U* test from independent samples for continuous variables and the chi-squared test or Fisher's exact test for discrete variables. Pearson's correlation coefficient was calculated between the results of the 6MWT and ergospirometry. *P* values <0.05 were considered significant.

Results

A total of 66 patients were evaluated to participate in the study. Six were excluded, 2 for their refusal to participate and 4 for not fulfilling the required characteristics (autonomy to carry out the home-based prehabilitation program). Finally, 60 patients were randomized, 30 in the PreH group and 30 in the SC group. There were 16 losses during follow-up, 11 as a result of the COVID-19 pandemic and 5 for heart disease detected by CPET that contraindicated surgery until the study of cardiorespiratory function was completed. Figure 2 shows the CONSORT diagram of the study.

Table 1 presents the demographic characteristics of the patients: age, sex, BMI, ASA classification for anesthesia, comorbidities (diabetes, hypertension and smoking), type of surgery performed, tumor stage, postoperative

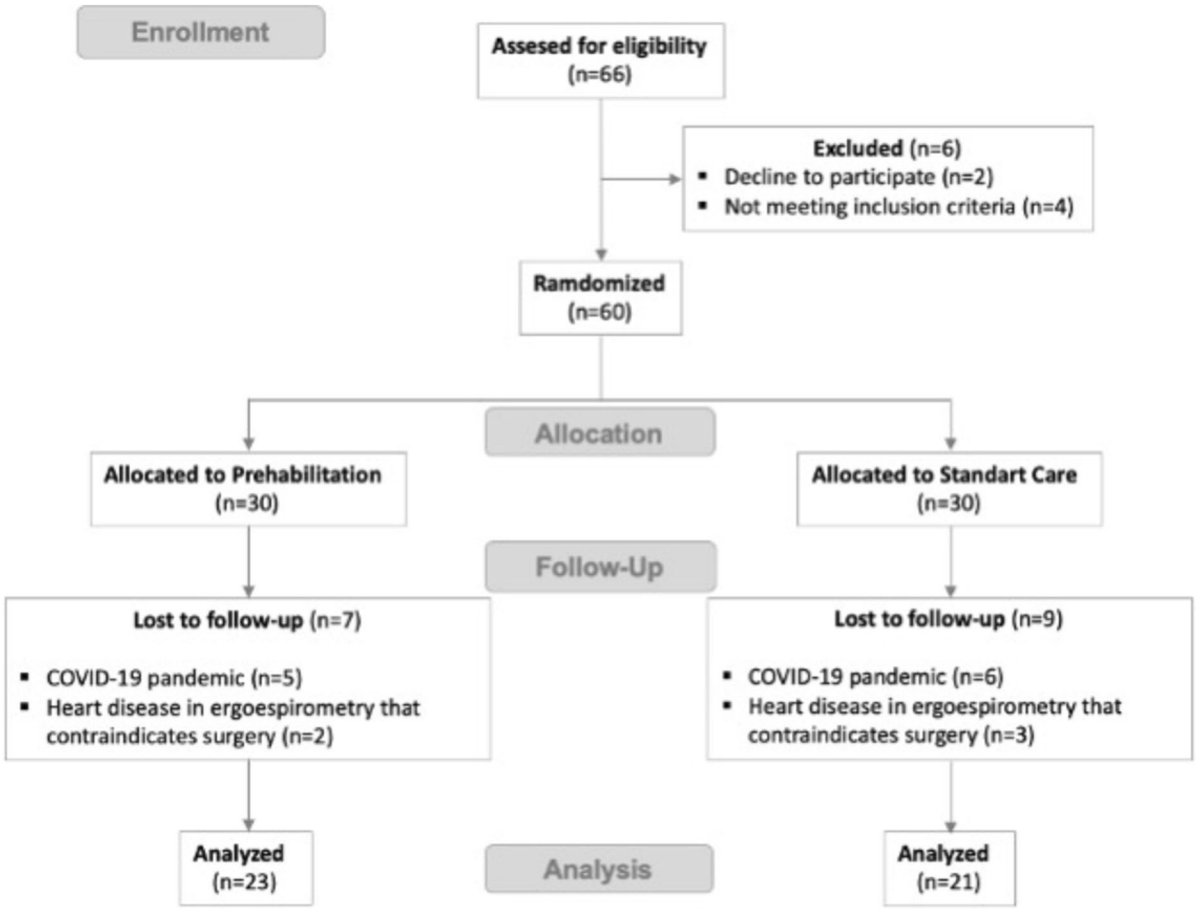

Fig. 2 CONSORT diagram for the trial

Table 1 Demographic characteristics, type of surgery performed, tumor stage, postoperative complications, and length of hospital stay of the study patients

	Study cohort ($n = 44$)	Prehabilitation ($n = 23$)	Standard care ($n = 21$)
Age median (years)	67,68 (SD = 7,99)	68,09 (SD = 7,67)	67,24 (SD = 8,51)
Sex ratio (F:M)	15:29	7:16	8:13
Body mass index median (kg/m^2)	28,14 (SD = 8,26)	28,06 (SD = 10,21)	26,3 (SD = 5,02)
ASA			
1	5 (11,4%)	4 (17,4%)	1 (4,8%)
2	31 (70,4%)	16 (69,2%)	15 (71,4%)
3	8 (18,2%)	3 (13%)	5 (23,8%)
Comorbidity			
Diabetes	7 (15,9%)	4 (17,4%)	3 (14,3%)
Smoker	7 (15,9%)	4 (17,4%)	3 (14,3%)
Hypertension (HTA)	19 (43,2%)	12 (52,2%)	7 (33,3%)
Type of surgery			
Right hemicolectomy	16 (36,4%)	8 (34,8%)	8 (38,1%)
Left hemicolectomy	8 (18,2%)	4 (17,4%)	4 (19%)
Sigmoidectomy	14 (31,8%)	9 (39,1%)	5 (23,8%)
Low anterior resection	6 (13,6%)	2 (8,7%)	4 (19%)
TNM staging system			
T0-T1-Tis	15 (34%)	11 (47,8%)	4 (19%)
T2-T3	23 (52,3%)	11 (47,8%)	12 (57,1%)
T4	6 (13,6%)	1 (4,3%)	5 (23,8%)
N0	32 (72,7%)	19 (82,6%)	13 (61,9%)
N1	12 (27,3%)	4 (17,4%)	8 (38,1%)
Complications			
Global complications			
Anastomosis leak	4 (9,1%)	2 (8,7%)	2 (9,5%)
Surgical site infections	3 (6,8%)	0 (0%)	3 (14,3%)
Ileus	4 (9,1%)	1 (4,3%)	3 (14,3%)
Length of stay (days)		5,74 (SD = 3,54)	6,67 (SD = 3,49)

complications, and length of hospital stay. No statistically significant differences were found between the two study groups.

In the comparative analysis between the two groups, overall postoperative complications were lower in the PreH group than in the SC group (17.4% vs. 33.3%; $p = 0.22$). The overall percentage of anastomotic leakage was 9.1% (2 patients in each group). Two patients in the PreH group had major leakage requiring surgical treatment, and two patients in the SC group had minor leaks; both cases were treated with radiological drainage. Postoperative ileus was more frequent in the SC group (14.3% vs. 4.3%; $p = 0.22$). Infectious complications were only present in the SC group, with 3 surgical wound infections and 1 case of pneumonia.

The length of hospital stay was lower in the PreH group (5.74 vs. 6.67 days; $p = 0.30$).

The relationship between anastomotic leakage and comorbidities was analyzed, and 5.4% of leaks were observed in nonsmoking patients compared to 28.6% in smokers ($p = 0.05$).

Previously to the prehabilitation intervention, the mean distance covered in the 6MWT was 344.9 m (SD = 138.6) in the SC group and 300.6 m (SD = 85.6) in the PreH group, with no statistically significant difference ($p = 0.216$). After the preoperative period of prehabilitation, an average improvement of 78.9 m was observed in the PreH group. Six weeks (45 days) after the surgery, the SC group had a mean distance traveled of 313.9 meters (SD=154.2), and the PreH group had a mean distance of 372.1 m (SD = 115.7). These results are shown in Fig. 3.

Comparing the distance traveled at the time of diagnosis and weeks after the surgery, we observed a slight worsening in the SC group, with a decrease of 27.2 m (SD = 59.5), and a significant improvement in the PreH group, with an increase of 68.9 m (SD = 129.8); these results were statistically significant ($p = 0.01$).

Cardiorespiratory function measured by ergospirometry at diagnosis showed a mean of 10.5 METs (SD = 3.43) in the SC group and 10.36 METs (SD = 2.99) in the PreH group ($p = 0.85$). The improvement observed after the prehabilitation

period in the PreH group was 0.99 METs. At 6 weeks after surgery, the SC group had a mean of 9.65 METs (SD = 3.53), while the PreH group had a mean of 11.15 METs (SD = 3.27). These results are shown in Fig. 4.

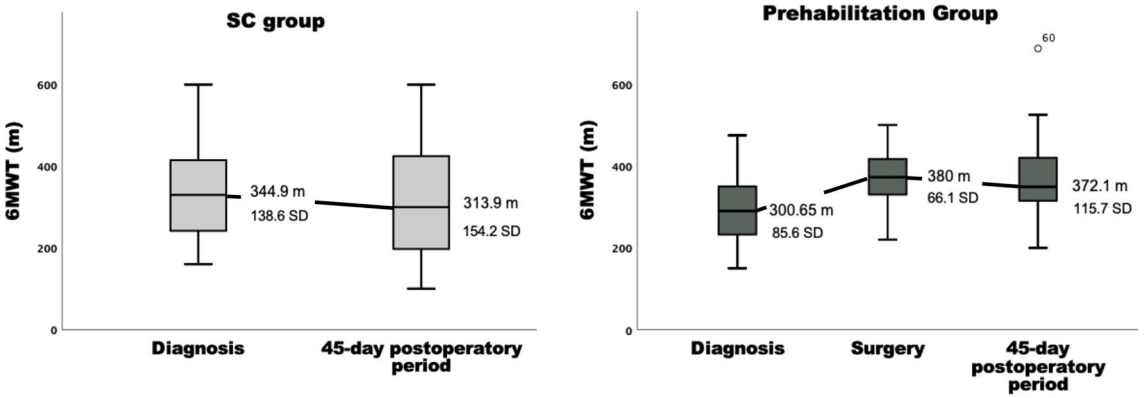

Fig. 3 Box diagram showing the mean and SD of the 6MWT at diagnosis, at surgery and on postoperative day 45 in both groups

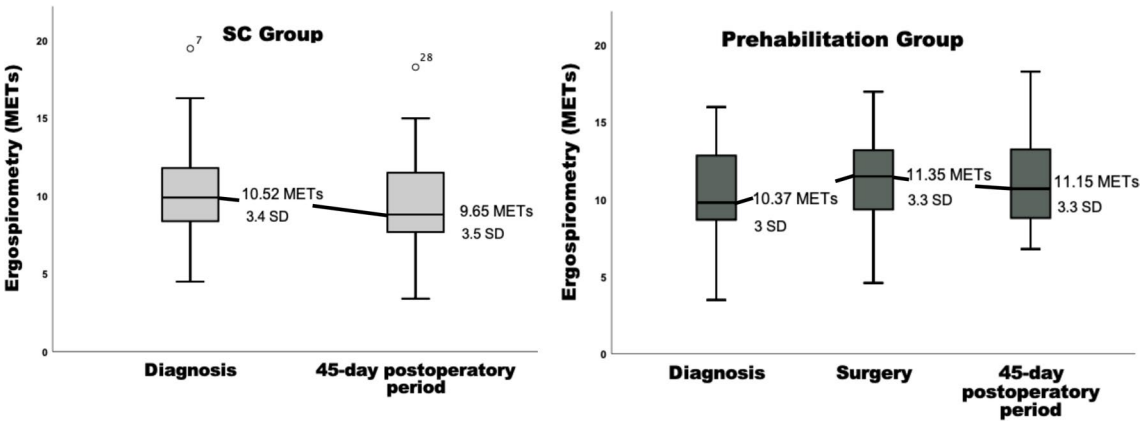

Fig. 4 Box diagram showing the mean and SD in ergospirometry at diagnosis and day 45 postoperatively

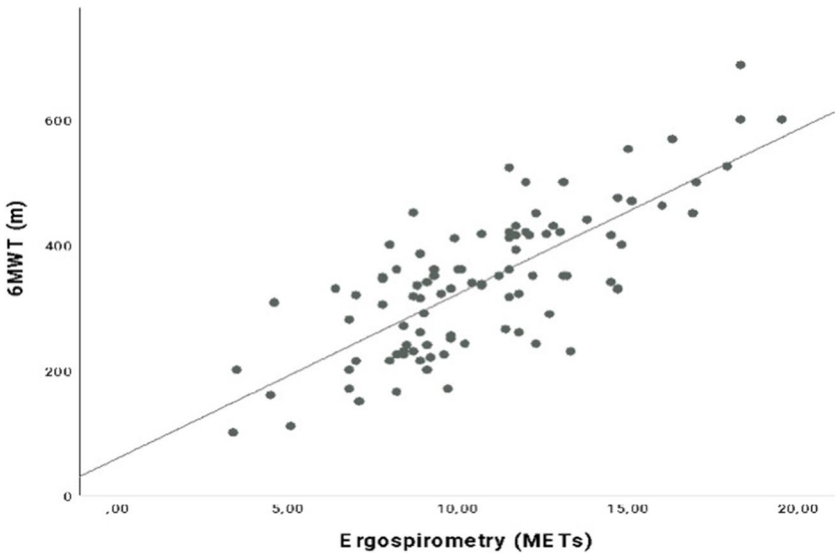

Fig. 5 Scatterplot representing the relationship between ergospirometry and the 6-minute walking test results

The difference observed between the diagnosis and the postoperative study was −0.84 METs in the SC group (SD = 0.99) and 0.79 METs in the PreH group (SD = 1.9), with statistically significant differences ($p = 0.001$).

Pearson's correlation between the CPET measurements in METs and the 6MWT in meters presented a strong correlation of 0.767 ($p < 0.001$). Figure 5 shows the relationship between the two measurements.

Discussion

The present study indicates the importance of preoperative prehabilitation, reporting a decrease in perioperative complications and hospital stay, as well as a good correlation between 6MWT and CPET, allowing an assessment of the patient's physical condition.

In our study, we did not observe differences in terms of major complications such as anastomosis leakage; however, patients treated with prehabilitation presented with minor complications such as surgical wound infection, ileus, and pneumonia. The hospital stay was one day shorter in the group treated by the prehabilitation protocol. The integration of physical exercise in prehabilitation programs helps to reduce pulmonary complications and overall comorbidity in patients undergoing major abdominal surgery [22, 23]. In addition, physical exercise programs associated with prosthetic supplementation in colorectal cancer surgery, compared to protein supplementation alone, reduce the length of hospital stay by 2 days [24, 25]. Therefore, prehabilitation improves the perioperative physical condition and potentially reduces the risk of complications in the postoperative period [26].

As our results show, with an improvement of 79 m in the 6MWT and 1 MET measured by ergospirometry, prehabilitation improves physical condition in the preoperative period and decreases the loss of functional capacity in the early postoperative period (−27 m and −0.84 METS in the SC group vs. +69 m and +0.8 METs in the PreH group) in relation to baseline physical capacity at diagnosis, and the results in the 6MWT were comparable to those reported by Li et al. [16]. This improvement in the physical condition associated with prehabilitation protocols allows the patient to recover their normal daily activity quickly and be prepared for possible future treatments. Therefore, it could have important clinical and prognostic significance since it would decrease the time until the start of possible adjuvant chemotherapy, also improving the associated oncological results [6, 27].

To the best of our knowledge, this is the first project to study functional capacity in patients treated for colorectal cancer by analyzing spirometric values and 6MWT, correlating the two results, in an unsupervised home-based prehabilitation program.

The 6MWT is a common and low-cost test. One of the main strengths of this study is that it discovered a good correlation with ergospirometry ($r = 0.767$ ($p < 0.001$)), which will allow us to perform an initial screening of the physical capacity of the patient and define objectives depending on the initial condition of the patient. The scatterplot shows that some patients with poor results in the 6MWT have good physical condition according to CPET, which indicates that this test may underestimate the results in those patients who do not reach a maximum effort; this "target group" of patients would benefit from the spirometric risk study to assess their physical condition.

Studies have been published on exercise programs with hospital supervision [14, 17, 18, 28], home supervision [15], and without supervision [29–31], showing better adherence in supervised patients but without differences in terms of improvement in physical condition, hospital stay, or complications. Our prehabilitation program is performed on an outpatient basis from a triptych delivered to the patient during the diagnostic consultation, a follow-up sheet given on the preoperative day and exercises performed during the preoperative and postoperative periods, achieving good results in meeting objectives.

The exercise programs proposed within the prehabilitation protocols differ both in the types of exercises performed: aerobic [15–17], anaerobic, both [14, 18, 29, 30], and/or respiratory exercises and in the duration of the exercises, and the same protocol was used for all patients regardless of basal physical ability. Programs with individual objectives, such as ours, facilitate adherence compared to less defined and more complex programs.

As limitations of our work, we must highlight the small sample size resulting from being a pilot study. However, the randomization process allowed us to highlight the results.

Conclusions

Home-based prehabilitation significantly attenuates the loss of functional capacity in patients with colorectal cancer. The 6MWT is a basic but efficient test to study the physical capacity of patients and assess perioperative changes, with a good correlation with ergospirometry, which may be reserved only for selected patients.

Author contribution All authors contributed to the manuscript. Daniel Triguero-Cánovas, Francisco López-Rodríguez-Arias, Luis Sánchez-Guillén, María José Alcaide-Quirós, Antonio Arroyo. Jose Manuel Ramírez wrote the main manuscript text. Manuel Gómez-Martínez Franc Peris-Castelló, Pedro Morillas-Blasco, and participated in the clinical research.

Data Availability The data that support the findings of this study are available on request from the corresponding author, L. S-G. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declarations

This study obtained approval from the ethics committee of Elche University Hospital and registered in ClinicalTrials.gov in August 2018 with registration number NCT03618329. Initial results published in Supportive Care in Cancer: Effect of home-based prehabilitation in an enhanced recovery after surgery program for patients undergoing colorectal cancer surgery during the COVID-19 pandemic. DOI: https://doi.org/10.1007/s00520-021-06343-1.
The authors have no conflicts of interest to declare. All co-authors have seen and agreed with the contents of the manuscript, and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Conflict of interest No conflicts of interest of financial nature.

References

1. International Agency for Research on Cancer. Estimated age-standardized incidence and mortality rates (World) in 2018, worldwide, both sexes, all ages. gco.iarc.fr (accessed 21 December 2018).
2. Surveillance, Epidemiology, and End Results Program, National Cancer Institute. Cancer stat facts: colorectal cancer. https://seer.cancer.gov/statfacts/html/colorect.html. 2015. Accessed March 4, 2015.
3. Hewitt J, Long S, Carter B, Bach S, McCarthy K, Clegg A (2018) The prevalence of frailty and its association with clinical outcomes in general surgery: a systematic review and meta-analysis. Age Ageing 47(6):793–800. https://doi.org/10.1093/ageing/afy110
4. Fagard K, Leonard S, Deschodt M et al (2016) The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: a systematic review. J Geriatr Oncol 7(6):479–491. https://doi.org/10.1016/j.jgo.2016.06.001
5. Siegel R, DeSantis C, Virgo K et al (2012) Cancer treatment and survivorship statistics, 2012 [published correction appears in CA Cancer J Clin. 2012 Sep-Oct;62(5):348]. CA Cancer J Clin 62(4):220–241. https://doi.org/10.3322/caac.21149
6. Kim IY, Kim BR, Kim YW (2015) Factors Affecting Use and Delay (≥8 Weeks) of Adjuvant chemotherapy after colorectal cancer surgery and the impact of chemotherapy-use and delay on oncologic outcomes. PLoS One 10(9):e0138720. Published 2015 Sep 18. https://doi.org/10.1371/journal.pone.0138720
7. Malietzis Malietzis G, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT (2015) The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. Eur J Surg Oncol 41(2):186–196. https://doi.org/10.1016/j.ejso.2014.10.056
8. Feliciano EMC, Kroenke CH, Meyerhardt JA et al (2017) Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. JAMA Oncol 3(12):e172319. https://doi.org/10.1001/jamaoncol.2017.2319
9. Peel JB, Sui X, Matthews CE et al (2009) Cardiorespiratory fitness and digestive cancer mortality: findings from the aerobics center longitudinal study. Cancer Epidemiol Biomark Prev 18(4):1111–1117. https://doi.org/10.1158/1055-9965.EPI-08-0846
10. Schmid D, Leitzmann MF (2015) Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol 26(2):272–278. https://doi.org/10.1093/annonc/mdu250
11. West West MA, Lythgoe D, Barben CP et al (2014) Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth 112(4):665–671. https://doi.org/10.1093/bja/aet408
12. López Rodríguez-Arias F, Sánchez-Guillén L, Armañanzas Ruiz LI et al (2020) A narrative review about prehabilitation in surgery: current situation and future perspectives. Revisión narrativa de la prehabilitación en cirugía: situación actual y perspectivas futuras. Cir Esp (Engl Ed) 98(4):178–186. https://doi.org/10.1016/j.ciresp.2019.11.005
13. Gillis C, Loiselle SE, Fiore JF Jr et al (2016) Prehabilitation with whey protein supplementation on perioperative functional exercise capacity in patients undergoing colorectal resection for cancer: a pilot double-blinded randomized placebo-controlled trial. J Acad Nutr Diet 116(5):802–812. https://doi.org/10.1016/j.jand.2015.06.007
14. Bousquet-Dion G, Awasthi R, Loiselle SÈ et al (2018) Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. Acta Oncol 57(6):849–859. https://doi.org/10.1080/0284186X.2017.1423180
15. Dunne DF, Jack S, Jones RP et al (2016) Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg 103(5):504–512. https://doi.org/10.1002/bjs.10096
16. Li C, Carli F, Lee L et al (2013) Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc 27(4):1072–1082. https://doi.org/10.1007/s00464-012-2560-5
17. West MA, Loughney L, Lythgoe D et al (2015) Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth 114(2):244–251. https://doi.org/10.1093/bja/aeu318
18. Dronkers JJ, Lamberts H, Reutelingsperger IM et al (2010) Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clin Rehabil 24(7):614–622. https://doi.org/10.1177/0269215509358941
19. Weisman IM, Zeballos RJ (2001) Clinical exercise testing. Clin Chest Med 22(4):679–701
20. Clavien PA, Barkun J, de Oliveira ML et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250(2):187–196. https://doi.org/10.1097/SLA.0b013e3181b13ca2
21. Kulu Y, Ulrich A, Bruckner T et al (2013) Validation of the international study group of rectal cancer definition and severity grading of anastomotic leakage. Surgery 153(6):753–761. https://doi.org/10.1016/j.surg.2013.02.007
22. Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL (2020) A Systematic review and meta-analysis of physical exercise prehabilitation in major abdominal surgery (PROSPERO 2017 CRD42017080366). J Gastrointest Surg 24(6):1375–1385. https://doi.org/10.1007/s11605-019-04287-w
23. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE (2019) Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg 43(7):1661–1668. https://doi.org/10.1007/s00268-019-04950-y
24. Gillis C, Buhler K, Bresee L et al (2018) Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review

and meta-analysis. Gastroenterology 155(2):391–410.e4. https://doi.org/10.1053/j.gastro.2018.05.012
25. Lambert JE, Hayes LD, Keegan TJ, Subar DA, Gaffney CJ (2021) The Impact of Prehabilitation on Patient outcomes in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery: a PRISMA-accordant meta-analysis. Ann Surg 274(1):70–77. https://doi.org/10.1097/SLA.0000000000004527
26. Pang NQ, Tan YX, Samuel M et al (2022) Multimodal prehabilitation in older adults before major abdominal surgery: a systematic review and meta-analysis. Langenbeck's Arch Surg 407(6):2193–2204. https://doi.org/10.1007/s00423-022-02479-8
27. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 305(22):2335–2342. https://doi.org/10.1001/jama.2011.749
28. Barberan-Garcia A, Ubré M, Roca J et al (2018) Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 267(1):50–56. https://doi.org/10.1097/SLA.0000000000002293
29. Gillis C, Li C, Lee L et al (2014) Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 121(5):937–947. https://doi.org/10.1097/ALN.0000000000000393
30. Carli F, Charlebois P, Stein B et al (2010) Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg 97(8):1187–1197. https://doi.org/10.1002/bjs.7102
31. Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M (2015) Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. Scand J Urol 49(2):133–141. https://doi.org/10.3109/21681805.2014.967810