Study of Long-Term Follow-up of Exercise Levels Following Participation in a Prehabilitation Program in Esophagogastric Cancer

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Background: Sedentary behavior is emerging as an important field of scientific enquiry for cancer survivorship. The posttreatment period is associated with prolonged recovery, deterioration in quality of life, disability, poor mental health, and reduced productivity. Exercise in cancer survivors has been linked with reduced fatigue, improved functional outcomes, and improved survival. **Purpose:** To evaluate the effect of a surgical cancer prehabilitation program on the long-term physical and psychological health in a cohort of patients undergoing surgery for esophagogastric cancer. **Methods:** The PREPARE program is a multimodal cancer prehabilitation program. All patients who underwent curative esophagogastric cancer surgery and completed the PREPARE program were included in the study. Weekly activity scores, self-efficacy, exercise testing, and hand grip strength were assessed. **Results:** A total of 39 patients met the eligibility criteria. At baseline, 31% of patients were active, 13% were moderately active, and 56% were insufficiently active. At follow-up, 44% of patients were active, 13% were moderately active, and 44% were insufficiently active. There was a significant increase in leisure score index ($P = .048$, $z = -1.981$), $\dot{V}O_{2max,}$ $mL.kg^{-1}.min^{-1}$ ($P \leq .01$), and hand grip strength ($P \leq .01$) from baseline to follow-up. There was no change in self-efficacy through baseline to follow-up. **Limitations:** Improvements in the postoperative period could be expected as part of recovery. The absence of a control group makes this difficult to establish. **Conclusion:** Starting prehabilitation at the time of diagnosis leads to sustained confidence and improved activity and exercise levels in the posttreatment period. **(Rehab Oncol 2020;38:110–115)** *Key words: cancer survivorship, exercise, esophagogastric cancer, prehabilitation, rehabilitation*

By 2030 it is estimated that there will be around 50 million people worldwide who have survived cancer.[1] While survival rates for nearly all types of cancers have improved,[2] there is a growing realization of the adverse effect cancer and its treatment consequences has on cancer survivors.[3]

The posttreatment period is associated with prolonged recovery in nearly all domains of quality of life.[4] There is not only a higher risk of medical morbidity such as cardiac disease, but reported poor long-term quality of life, disability,[5] anxiety and depression,[6] social problems,[7] and reduced work productivity.[4] It is for these reasons that cancer is not only perceived as an acute illness, but one with chronic ill-health ramifications.[8] This shifting paradigm has led to a growing number of research studies on the posttreatment management and rehabilitation of people with cancer.[9]

Rehabilitation Oncology

The authors declare no conflicts of interest.

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DOI: 10.1097/01.REO.0000000000000205

The primary intervention in a number of cancer rehabilitation studies involves physical activity (PA) and/or structured exercise. The rationale/hypothesis is that PA is associated with improved recovery,[10] better quality of life,[11] and more importantly, disease-free survival.[10]

There is an emerging body of research on the role of PA during and after cancer treatment, but the evidence is variable.[12] This is most likely due to a number of factors including type of exercise, timing of program commencement, and strategies used to improve uptake and adherence.

However, introducing behavioral change, at a time when people are physically compromised due to treatment side effects, may reduce the potential uptake (or adherence). Rehabilitation, in this context, is a reactive model of care. Prehabilitation, on the other hand, capitalizes on the teachable moment,[13] and enables principles of behavior change to be embedded before, or early on, in the treatment trajectory. The transtheoretical model (TTM) describes a change in mainly habitual behavior through a cyclical process, and the time of cancer diagnosis is the opportune moment to induce change. In this context, prehabilitation uses the period before and during treatment to move people through the stages of change of the TTM model to maintenance, the ideal stage of behavior, during rehabilitation. The rationale is that people who have been successfully through the TTM stages and have been adherent to the prehabilitation program will be more likely to commit to sustained healthy behaviors in the rehabilitation period.[14]

The evidence to support prehabilitation before cancer surgery is steadily increasing. Its application in colorectal cancer surgery has so far yielded positive findings, showing improvements in both functional capacity and recovery.[15-17] Furthermore, few reports have shown physical benefits in patients undergoing surgery for lung and prostate cancer.[18,19] The effect of prehabilitation on postoperative outcomes has been poorly understood so far; however, a number of large-scale studies are currently in progress aimed at providing this crucial evidence.[20-22]

Surgery for esophagogastric (OG) cancer is associated with a significant deterioration in physical function and prolonged recovery.[23] However, there is a strong rationale for improving functional capacity prior to OG surgery to facilitate earlier recovery and quicker restoration of quality of life.[24]

The aim of this study is to evaluate the effect of a cancer surgical prehabilitation program on long-term physical and psychological health in a cohort of patients undergoing surgery for OG cancer.

METHODS

Ethical Approval

This study has national Heath Research Authority ethical approval (IRAS ID 223668) and is registered with the joint research committee at Imperial College London/ Imperial Healthcare NHS Trust.

Patients

All patients, older than 18 years, who had undergone resection for primary OG cancer and completed the PREPARE program between January 2015 and January 2018 were invited to participate. Exclusion criteria included failure to complete the program in its entirety or disease recurrence (local or distant).

Study Protocol

The PREPARE program is a novel, multimodal, cancer prehabilitation program developed by Imperial College Healthcare NHS Trust for patients with OG cancer. The program provides coaching and tailored support in areas of physical fitness, respiratory exercises, eating well, psychological well-being, asking about medication, removing bad habits (smoking and alcohol), and enhanced recovery after treatment. It begins prior to the commencement of neoadjuvant chemo/radiotherapy (NAC) once a patient is deemed suitable for curative surgery and continues to the time of their surgery. A weekly, personalized exercise program is agreed with the patient. Adherence to the program is monitored weekly and the program is modified according to their clinical condition and progress.

Data are collected for functional capacity, self-efficacy, and grip strength, at 4 scheduled time points (Figure):

- PREPARE 1 (P1) = at diagnosis
- PREPARE 2 (P2) = completion of NAC or baseline for the non-NAC patients (3-6 weeks prior to surgery)
- PREPARE 3 (P3) = within 1 week prior to surgery
- PREPARE 4 (P4) = 6 to 8 weeks after surgery

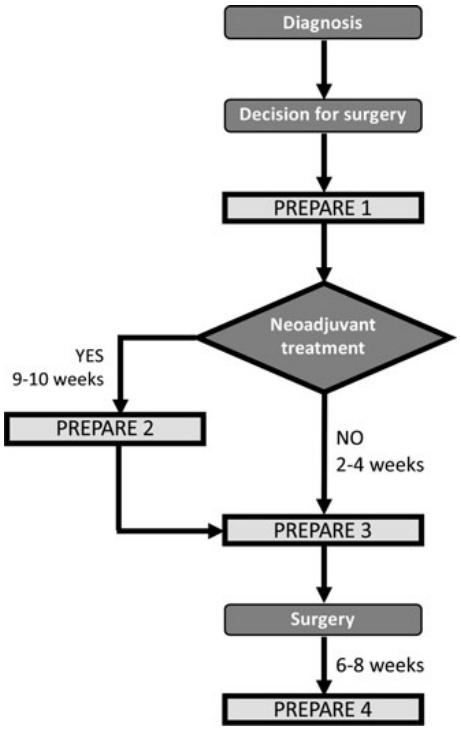

Fig. The PREPARE pathway.

The PREPARE 4 consultation builds on the learning acquired during prehabilitation. The importance of routine exercise is discussed, and the aim is to agree an ongoing PA program focused on recovery. This includes strategies to incorporate PA into their daily routine and how to progress PA for lasting benefit. The concept of PA is reiterated at all follow-up appointments by all members of the multiprofessional clinical team.

Study Measures

Weekly Leisure-Time Physical Activity. Patients were asked to complete the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ). This is a validated tool for the assessment of PA and has been used in a range of health care studies, including studies of cancer patients.[25,26]

Patients record how many times in a typical week they complete mild, moderate, and strenuous activities lasting at least 15 minutes. The frequencies given by the patient are multiplied by the metabolic equivalent value of each activity (3, 5, and 9, respectively, for each category) to account for the intensity of each activity. These results are added together to give the leisure score index (LSI), in standardized units, which reflects the weekly leisure-time physical activity (LTPA).

The LSI derived from the strenuous and moderate activities can be used to classify the result in relation to the health benefits of their weekly activity[27]:

- 24 or more: active (substantial benefits)
- 14 to 23: moderately active (some benefits)
- Less than 14: insufficiently active (less substantial or low benefits)

The "mild" activities are not included when using this classification. An LSI of 24 or higher meets the American College of Sports Medicine guidelines for recommended activity levels in healthy adult participants.[26]

Patients were asked to complete the GSLTPAQ to determine their LTPA scores at 2 time points: at baseline (prior to starting the PREPARE program, P1) and at the point of follow-up following completion of their cancer treatment.

Exercise testing. The Chester-Step Test was used to assess aerobic fitness by predicting maximal aerobic power under submaximal conditions. Using a protocol of escalating speed and step height, patients exercised until they achieved 70% of their heart rate reserve and/or a rate of perceived exertion of 12 to 14 and/or were limited by symptoms.[27] The attained protocol level and heart rate are used to calculate a validated prediction of $\dot{V}O_{2max}$ $mL.kg^{-1}.min^{-1}$.[27,28]

Exercise testing was performed at 3 time points: prior to prehabilitation (P1), 6 to 8 weeks after surgery (P4), and at follow-up.

Self-efficacy. Self-efficacy is one's belief in their ability to succeed in specific situations or accomplish a task.[29] The Lorig 6-item scale quantifies self-efficacy using 6 questions, each with a 10-point Likert scale. The overall self-efficacy score is the mean score from the 6 questions. The score has good internal consistency[29] and is recommended for use in cancer survivors.[30]

Self-efficacy was assessed at 3 time points: P1, P4, and at follow-up.

Hand Grip Strength. Hand grip strength (HGS) was assessed using a dynamometer (Takei Scientific Instruments Co Ltd, Nigata, Japan). This is measured as kilograms. This was assessed at P1, P4, and at follow-up.

Statistical Analysis

Nonparametric tests were used throughout. Results were compared using Friedman and Wilcoxon signed rank tests. Post hoc analysis using a Wilcoxon signed rank test with Bonferroni correction was undertaken where appropriate. A significance level of $P < .05$ was used throughout. Statistical analysis was performed using SPSS version 24 (IBM, New York).

RESULTS

Of the 91 patients who participated in the program, 62 patients met the eligibility criteria and were invited to participate in the study. Of these, 39 patients consented to participate in this study (Table 1).

Median follow-up time from surgery was 13 months.[5-21]

Leisure-Time Physical Activity

A total of 39 patients completed the GSLTPAQ at baseline and at follow-up.

At baseline, 12 (31%) patients were classified as active, 5 (13%) were moderately active, and 22 (56%) were insufficiently active. Of the 22 patients who scored less than 14, 19 (86%) patients were completely sedentary with an LSI of 0.

At follow-up, 17 (45%) patients were classified as active, 5 (13%) were moderately active, and 16 (42%) were insufficiently active. Of the 17 insufficiently active individuals, 12 (71%) were completely sedentary. Thus, the number of patients who scored an LSI of 0 reduced from 86% to 71% at follow-up ($P = .003$, interquartile range [IQR] 0-10).

TABLE 1
Demographics

Eligible patients, n	62
Patients who completed the study, n	39
Gender, male/female (%)	30/9 (77%/23%)
Age, median (range), y	64 (55-73)
Procedure	
Esophagectomy, n (%)	26 (67%)
Total gastrectomy, n (%)	9 (23%)
Extended total gastrectomy, n (%)	2 (5%)
Subtotal gastrectomy, n (%)	2 (5%)

There was a significant increase in the LSI from baseline to follow-up; the median LSI at baseline was 3 and at follow-up this had increased to 15 ($P = .048$, $z = -1.981$).

Exercise Testing

Thirty-four patients undertook follow-up exercise testing. There was a significant increase in $\dot{V}O_{2max}$ mL.kg^{-1}.min^{-1} from baseline to follow-up ($P = .000$, $\chi^2 = 24.734$). On post hoc analysis, there was no change between $\dot{V}O_2$ at P1 and P4 ($P = .581$, $z = -0.552$), which was followed by a significant increase in patients' $\dot{V}O_{2max}$ mL.kg^{-1}.min^{-1} from P4 to follow-up ($P = .000$, $z = -3.946$) (Table 2).

Self-efficacy

There was no change in self-efficacy across P1 to follow-up ($P = .484$, $\chi^2 = 1.450$). Medians and IQRs are given in Table 2.

Hand Grip Strength

HGS was recorded from P1 through to follow-up. There was a significant reduction in HGS from P1 to P4 ($P = .004$, $z = -2.887$). This was followed by a significant increase in HGS from P4 to follow-up, with the mean score returning close to baseline ($P = .004$, $z = -2.868$). Medians and IQRs are shown in Table 2.

DISCUSSION

We have found evidence of sustained improvement in PA following participation in a structured prehabilitation program, with a corresponding increase in physical fitness from the early postoperative period to a median follow-up of 13 months after surgery. Very few studies have addressed the effects of prehabilitation beyond the time of surgery, so our findings offer an important insight into some of the potential long-term benefits of prehabilitation.

Considering both the LSI and the PA classification findings together, we have found evidence of both increased overall PA to a level with known health benefits following prehabilitation. At baseline, we found large variability in PA levels, with under a third meeting the recommended guidelines for undertaking a healthy amount of exercise per week.

The median recorded LSI is notably low. PA levels increased at follow-up, with an increase in the median LSI from 3 to 15. We observed both an increase in the proportion of patients who were classified as active alongside a fall in the proportion of patients in the lowest PA category.$\dot{V}O_{2max}$ mL.kg^{-1}.min^{-1} at follow-up was also significantly higher than at baseline or at 6 to 8 weeks after surgery, in keeping with higher levels of PA in our cohort.

As well as an increase in $\dot{V}O_{2max}$ mL.kg^{-1}.min^{-1} at follow-up, we found it was maintained from the time of diagnosis through to 6 to 8 weeks after surgery. This is an important finding, as these patients have undergone a lengthy operation with a high postoperative morbidity and long recovery, which often results in long-term disability.[31-33] In addition, many patients also received NAC between these assessments. Previous studies have shown that prehabilitation can prevent functional deterioration associated with NAC and improve physical fitness prior to surgery.[34] Our findings suggest that this approach helped maintain fitness levels in the early postoperative recovery. This is in keeping with the concept that prehabilitation provides a "physiological buffer" to protect against the stress of surgery.[35,36]

The proportion of patients classified as "active" in our study increased from 31% at baseline to 45% at follow-up. A study of breast cancer survivors found similar results, albeit over a shorter follow-up; 32% were classified as "active" at baseline using the GSLTPAQ classification, with 45% classified as "active" 3 months after an exercise program.[37]

Other studies of breast and prostate cancer patients report baseline LSI scores of 17 to 23, which increased to 25 to 32 after an exercise intervention. In contrast, control groups who did not receive an exercise program had LSI scores of 15 to 28.[38,39]

These scores are much higher than we have seen in our patient population. This may reflect several factors including the demographic, the disease burden of OG cancer, and associated baseline deconditioning. People with OG cancer are typically frail, malnourished with poor physical reserve.[40,41] Additionally, while the GSLTPAQ is widely used in cancer research to assess PA, there is substantial heterogeneity in how the results are reported.[26] These studies also include mild activities within their LSI score, which we did not due to the lack of evidence to support health improvement from this type of activity.[42]

TABLE 2
Median and Interquartile Ranges

	P1/Baseline (Median, IQR)	P4 (Median, IQR)	Follow-up (Median, IQR)
Leisure-time physical activity	3 (0-25)	Not measured	15 (0-35)
Weekly METs	0.4 (0-3.6)	Not measured	2.1 (0-5)
$\dot{V}O_{2max}$, mL.kg^{-1}.min^{-1}	16.3 (13.9-19.7)	16.8 (12.2-19.3)	21 (18.9-25.2)
Self-efficacy	8.1 (6.1-9.1)	8.6 (7.3-9.5)	8.5 (6-9.4)
Grip strength	32 (26.7-36.3)	29.4 (22-34.1)	31.3 (27-36.6)

Abbreviations: IQR, interquartile range; MET, metabolic equivalent; P1, prepare 1; P2, prepare 2; $\dot{V}O_{2max}$, volume of oxygen consumption.

It is acknowledged that a significant life-changing event, such as the diagnosis of cancer, offers a "teachable moment" and an opportunity for behavior change as highlighted in the TTM (stages of change).[43] This, however, may be short-lived in the absence of a program of support.[44,45] The findings from our study demonstrate evidence of sustained, and increased, PA levels. This highlights the importance of providing personalized programs, at the outset, in order to increase the likelihood for long-term and sustained change.

Majority of patients with OG cancer receive neoadjuvant treatment prior to surgery. OG cancer therefore has the benefit of a prolonged "lead in" time before surgery, which allows sufficient time for behavior change to embed and habits to be formed. PREPARE 4 merely facilitates the transition from prehabilitation to rehabilitation by providing an opportunity to reevaluate physical function and, building on the skills acquired prior to surgery, develop a revised PA plan moving forward.

This study has observed both sustained increases in PA and preserved self-efficacy with a median follow-up of 13 months after surgery. OG cancer surgery has a demanding and prolonged recovery, which is recognized to cause a significant deterioration in quality of life that may persist for up to 3 years after surgery.[46-48] Therefore, our findings of increased PA, increased physiological fitness, and preserved self-efficacy over this period are noteworthy.

LIMITATIONS

This study does, however, have important limitations. This is an observational, longitudinal study of outcomes after prehabilitation, with no control group for comparison. As patients had a diagnosis of cancer at baseline, some of the improvements in PA may reflect an absence of disease. Additionally, it is not possible to exclude the fact that behavior change may have occurred organically following the diagnosis of cancer, and irrespective of prehabilitation. Finally, only 62% of the eligible patients agreed to participate in this study. The health of those who declined to participate is not known, as health records were only accessed if consent was provided. This could result in either an over- or underestimate of PA levels in our population.

CONCLUSION

There is currently little long-term follow-up data on the benefits of prehabilitation. This study has provided new evidence into the long-term effect of a multimodal prehabilitation intervention on sustained behavior changes in individuals with a primary OG cancer diagnosis.

These findings warrant further investigation to establish whether structured prehabilitation can have benefits beyond the immediate perioperative period. Only then will the true potential of prehabilitation be realized.

ACKNOWLEDGMENTS

The authors wish to acknowledge Kerri Cooper for her assistance with data collection and overall support with the project.

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