Using multimodal prehabilitation to improve outcomes for frail patients undergoing resection of colorectal cancer

BACKGROUND

Colorectal cancer is the third most common cancer in North America, and it is the second leading cause of cancer death in both men and women (1). The median age at diagnosis is 69 years (2) and the primary approach to treatment of colorectal cancer and the only curative approach is surgery (3). In 2013, 6300 persons were diagnosed with colorectal cancer in Quebec and 5229 underwent colorectal resection with a mean hospital stay of 11 days (4). Within the McGill hospitals, approximately 600 patients underwent colorectal resection in 2013 at the Montreal General Hospital and Jewish General Hospital with a mean length of stay of 9 days. These resections required 5400 bed-days, the large majority of which were needed for the postoperative recovery period. Clearly, rapid return to full functioning after colorectal cancer surgery has the potential to improve outcomes for patients e.g. allowing them to return home and resume normal activities earlier and begin other adjuvant treatments promptly. Furthermore accelerated early recovery after colorectal cancer surgery would also have health-economic benefits including more efficient use of available hospital beds for this type of surgery.

Recovering from the stress of surgery and colorectal cancer

Despite major advances in surgical technology, anaesthesia, analgesia, and perioperative care, complications after colorectal resection occur in 25-60% of patients. As such, colorectal surgery is an important target for quality improvement and is the general surgery procedure with the greatest proportion of adverse outcomes and longest length of hospital stay (5, 6). Even in patients without medical or surgical complications, major abdominal surgery is associated with a 40% reduction in functional capacity. As a result an extended period of recovery is required, and this is especially true for the elderly (7). Patients experience physical fatigue, disturbed sleep and a decreased ability to concentrate for up to 4 weeks after discharge (8), and their functional capacity is not fully recovered even 6-9 weeks after surgery (9, 10). Preoperative health status, functional capacity and muscle strength predict postoperative fatigue and complications (11, 12). Thus the elderly, persons with cancer and frail subjects with limited physiological reserve are the most susceptible to the negative effects of surgery (13, 14). Identifying ways to reduce the rate of post-operative complications, especially in high risk groups such as frail patients with cancer, would be of great practical benefit.

Why surgical prehabilitation?

Rehabilitation after surgery is now well-established for some surgical specialties and procedures. There have also been efforts to improve the surgical recovery by optimizing interventions during the intra-operative period (15). However relatively little emphasis has been placed on optimizing patient physical function in the pre-operative period, yet this offers many advantages as it is not affected by post-operative symptoms e.g. fatigue, or by concerns about disrupting the surgical incision site or dressings. For most elective procedures, including colorectal surgery, there is a waiting period prior to surgery, and this time on the waiting list when patients are motivated and available, is as an opportunity to intervene in a targeted fashion to try and improve post-operative recovery. Active engagement of the individual in the preparation process, may have benefits beyond the physical, and alleviate some of the

emotional distress surrounding the anticipation of surgery and the recovery process. *Prehabilitation* can be defined as a process designed to improve functional capacity in anticipation of an upcoming surgical stressor (16). The theoretical framework is based on the assumption that selected preoperative interventions can improve a patient's baseline physiological status, and thus help develop a buffer of functional capacity to mitigate the predictable detrimental effects of the upcoming surgery. In this way the patient will be better prepared for surgery and able to achieve an earlier return to normal functioning after surgery. Three systematic reviews (17-19) assessing the effect of preoperative exercise therapy on various clinical outcomes (pain, length of hospital stay, postoperative complication rate) in a variety of surgical procedures (6 orthopedic, 4 cardiac, 1 vascular and 1 abdominal) indicated that physical activity has a positive impact on postoperative length of hospital stay and complications. However, very little work has been done in abdominal surgery (1 study in the systematic reviews) and this study was not done in patients in whom all aspects of perioperative care were optimized.

Preparing the patient for surgery

a. Enhanced Recovery After Surgery (ERAS) program

The ERAS program for colorectal resection (20), which includes a bundle of evidence-based perioperative elements (e.g. patient education, optimization of medical conditions, glycemic control, smoking and alcohol cessation, minimally invasive surgery, epidural analgesia, early nutrition and mobilization), is associated with significantly less postoperative morbidity and shorted length of hospital stay (21).

b. Physical activity

Physical activity remains the cornerstone of the prehabilitation program. The benefits of a physically active lifestyle are innumerable and have been demonstrated in many disabling conditions (hypertension, diabetes, coronary heart disease, arthritis). Increased physical activity and fitness, in the elderly population as well as in cancer patients, is associated with decreased all-cause mortality, morbidity, and disability (22-24). In surgical patients, low cardiorespiratory fitness, as defined by formal testing (e.g. aerobic threshold <10.9 ml/kg/min) or walking capacity (eg 6-minute walk test distance <390 m) is associated with higher risk of postoperative complications (25-27). Since physical fitness can be considered a modifiable risk-factor for postoperative complications, it would seem advantageous to use the preoperative period to improve fitness with a structured prehabilitation program.

c. Enhancing nutrition

Colon cancer patients may have a variety of non-specific gastrointestinal and abdominal symptoms leading to poor caloric intake. Moreover, the malignancy itself may exert a chronic systemic inflammation response that manifests as perturbations in glucose metabolism, insulin resistance, and blunted whole body protein anabolism and weight loss and cachexia (28). Over half of patients presenting for colorectal resection will have had significant preoperative weight loss, and up to 20% of patients will have lost more than 10% of their body weight (29, 30). Preoperative malnutrition is an independent predictor for mortality after colorectal cancer surgery, with an odds ratio of 1.33 (31). Additional evidence for nutritional optimization is based

on the fact that exercise and dietary protein interact synergistically to produce greater gains in fat-free mass, greater muscle protein synthesis and increased strength (32). Protein intake is the primary stimulus for muscle protein synthesis, and whey is rich in leucine, thus playing a key role in muscle protein synthesis by regulating the mTOR protein signaling pathway (33).

d. Modulating anxiety and depression

The preoperative period is a difficult time period for cancer patients. They express fear of the uncertainty and of death. Moreover, most patients undergoing operations for malignancy become increasingly anxious and depressed as the days progress during the waiting period. A relationship between stress and wound repair is not only statistically significant, but also clinically relevant (34). A systematic review of the impact of psychosocial status on postoperative outcomes showed that perceived stress and worry about the operation are both associated with prolonged recovery, postoperative complications, and impaired wound healing in elective surgery (35).

Our experience with surgical prehabilitation

Our multidisciplinary group at the MGH has conducted research on prehabilitation in colorectal cancer patients and using a perioperative ERAS program that started in 2010. The initial research work focused on the impact of 4-weeks of preoperative intense exercise on postoperative functional walking capacity, assessed using the validated 6min walk test (6MWT) as the primary outcome (36). This randomized controlled trial (RCT) (37) identified that intense exercise alone may not be the optimal intervention approach in this population leading us to consider additional elements namely nutritional enhancement and strategies to deal with anxiety and depression (38). Similarly, a pilot study using a nutritional intervention alone demonstrated only a positive although modest increase in functional capacity (39). Based on this early work, a pilot study (40) followed by a RCT (41) using a trimodal 4-week prehabilitation program (home-based moderate aerobic and resistance exercise, nutrition counselling and daily whey protein supplementation, and anti-anxiety relaxation strategies) confirmed a synergistic effect of exercise and nutrition that extended beyond the preoperative period. In this RCT, patients were randomized to either begin the trimodal intervention in the preoperative period (Prehab group) or after surgery (Rehab group), with 6MWT used as the primary outcome to estimate recovery. In the Prehab group, over 80% of patients were returned to baseline functional walking capacity 8 weeks after surgery; whereas only 60% of the Rehab group that started the program after surgery, and only 40% of a historical controls receiving neither prehabilitation, nor rehabilitation, had returned to baseline. Though we have found more rapid recovery of walking capacity with prehabilitation, we have not observed differences in clinical outcomes such as postoperative complications when studying unselected colorectal cancer patients. Thus we believe that a more focussed approach which targets prehabilitation to patients at greater risk of post-operative complications will be the most effective way to deploy this type of intervention. Specific subgroups of colorectal surgery patients, such as the elderly frail, may be more likely to benefit clinically from prehabilitation. Frailty is an emerging concept in clinical medicine and the Fried score for frailty, with 5 phenotypic criteria (weight loss, weakness, exhaustion, low physical activity, and slow walking speed), is commonly used to diagnose frailty (42). Evidence suggests that patients preoperatively identified as intermediately frail (Fried score 2-3) and frail (Fried score 4-5) are at increased risk for complications after surgery (14). As our multimodal prehabilitation program tackles important domains of frailty

(physical, nutritional and psychological), we believe that targeting the intervention to patients with higher Fried scores may be a resource-effective way to provide prehabilitation and ultimately improve postoperative outcomes. In a subset of 50 patients having colorectal surgery at the Montreal General Hospital, we found that 25% were intermediately frail or frail with an average age of 72 years, ASA 3 and 6MWT of 316 m. Interestingly, patients with 6MWT< 400 m at baseline had increased the 6 minute walking distance by an average of 45 m after 4 weeks of prehabilitation (minimal important difference is 20 m) (43). This finding suggests that the physiological reserve of frail patients can indeed be increased even within a short period of prehabilitation leading to greatest benefits in terms of reducing or preventing post-operative complications and accelerating their recovery.

HYPOTHESIS

1) Prehabilitation using a 4-week multimodal protocol in frail (Fried score >2) patients will reduce postoperative complications after surgery for colorectal cancer compared to use of post-operative rehabilitation.

2) The addition of a prehabilitation is more effective than post-operative rehabilitation alone in improving markers of early post-operative recovery and health-related quality of life in patients with this population.

OBJECTIVES

We will use this multicenter trial at the MGH and JGH to explore whether prehabilitation can improve outcomes in frail elderly patients undergoing colorectal surgery. Further analysis will also be made to see if this intervention is cost effective.

PATIENTS AND METHODS

The study is based on our previously published RCT and is designed as a single-blind parallel-arm superiority RCT (Prehabilitation vs Rehabilitation). This design allows us to assess the impact of adding either 4- week prehabilitation intervention or 4-week rehabilitation intervention on surgical complications and length of hospital stay, as well as the overall impact on functional capacity and quality of life at 30-days post hospital discharge. In addition this design has been chosen to avoid the risk of bias and poor recruitment if we were to offer only a non-intervention control group. The 4-week period interval between diagnosis and surgery is within the time recommended by the Canadian Oncological Society (44). Perioperative care will be based on the ERAS colorectal guidelines (20), fully functional at the MGH since 2010 (45) and initiated at the JGH this year. The trajectory of the study is presented in Figure 1. Patients scheduled for colorectal surgery will be recruited at the surgical clinics by the clinical coordinator and will be screened for frailty (Fried score) after having been identified by the surgeons as candidates for surgery. Patients are ineligible if the Fried score <2, they do not speak English or French, if they have premorbid conditions that contraindicate exercise, including dementia, Parkinson disease or previous stroke with paresis, and taking carbidopa/levodopa, donepezil hydrochloride, or long standing antidepressants. All eligible patients will perform baseline measurements (Table 1) administered by a person not aware of group allocation and study hypothesis, and thereafter they will be randomly assigned on a 1:1 ratio by computer generated random numbers either to prehabilitation (Prehab) group or to rehabilitation (Rehab) group. The Prehab group will undergo a physical and nutritional assessment and receive instructions on the home-based

multimodal program by a kinesiologist and a nutritionist respectively. The program will then start and continue for 4 weeks before surgery (see prescription in Figure 2). During this time the patients will also receive one supervised exercise session per week for 4 weeks at the hospital lab. The Rehab group, instead, will undergo the assessment by the kinesiologist and the nutritionist two day before surgery and will start the multimodal program at home after hospital discharge and continue for 4 weeks, with one supervised exercise session per week at the hospital lab (Figure 1). Measurements (Table 1) will be taken before randomization (Baseline), two days before surgery (Preop), at hospital discharge (Discharge) and 4 weeks after hospital discharge (4 weeks postop). To facilitate adherence to the multimodal program, all patients will receive a standard instructional booklet with a diary where the patients will be asked to document all activities (exercise, diet, symptoms, pain) related to the program. The protocol has already been approved by the MGH ethics board, will be submitted to the JGH ethics board and is registered on ClinicalTrials.gov.

Outcome measures

The measurements will be completed as shown in Table 1. The primary outcome will be the Comprehensive Complications Index (CCI) based on the postoperative complications recorded up to 30 days after surgery and graded by severity using the Clavien-Dindo classification (46). Classification grades will then be converted into the CCI, which integrates all complications with their respective severities on a continuous scale ranging from 0 (no burden from complications) to 100 (death). Previous studies supported the validity of the CCI as a measure of postoperative morbidity and suggested that, in comparison to traditional morbidity measures (e.g. rate overall complications, rate of severe complications), it provides a more comprehensive and sensitive endpoint for studies evaluating strategies to reduce postoperative complications (47, 48). Thus we have chosen the CCI as primary outcome as it represents the most definitive and clinically relevant measure of global impact for this intervention. Secondary outcomes will include: hospital length of stay, 30-day readmission rates, functional walking capacity, anxiety and depression and health- related quality of life at 30-days post-discharge.

Statistics and sample size

Sample size requirement for this trial was estimated for an α level of 0.05 and 90% power to detect a 10 point difference in the CCI scale between groups. This difference of 10 points is considered clinically relevant as it reflects 1-grade difference in the Clavien-Dindo classification. In a previous work (49) at the MGH and JGH the mean CCI was 10.45 (SD 15.8). Based on these estimates, a sample of 60 participants per group is considered sufficient for our analysis and accounts for a possible increase in data variance. Assuming that 396 patients (66% of the total 600) diagnosed with colorectal cancer are operated each year in both hospitals, approximately 99 of these patients (25%) will be classified as intermediately frail or frail. Based on previous trial experience, approximately 80% of these patients will be eligible and agree to participate. Therefore, we estimate that 120 participants can be feasibly enrolled in one and half years. Linear regression will be used to estimate the extent to which prehabilitation decreases CCI scores in comparison to rehabilitation. The impact of prehabilitation on secondary outcome measures will be analyzed using cox-regression and logistic regression. Both crude and adjusted coefficients will be reported. The analysis will be performed according to an intention-to-treat principle, with participants being analyzed in the groups to which they were allocated. To minimize potential bias arising from missing data from incomplete assessments or losses to

follow-up, multiple imputations will be carried out.

RELEVANCE AND FUTURE OUTLOOK

The proposed study represents an opportunity to intervene, treat or prevent impairments in a specific at-risk population: namely the intermediate frail and frail patients undergoing surgical resection of colorectal cancer. Combining targeted physical, nutritional and psychological interventions with medical optimization in a multimodal approach is likely to offer the best overall care. The results will also provide vital new evidence about whether a 4–week prehabilitation intervention is sufficient to impact postoperative outcomes. Importantly we have focused on those patients who have the most potential benefit from the prehabilitation program. Increasing functional reserve in frail patients has the greatest chance of positively impacting on complications and length of hospital stay. We believe the results of this study will be generalizable to other types of cancer, and will emphasize the notion of how important is to take advantage of this window of opportunity for each cancer patient population in order to improve patient outcomes and reduce direct and indirect health care costs.

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APPENDIX

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Figures & Tables

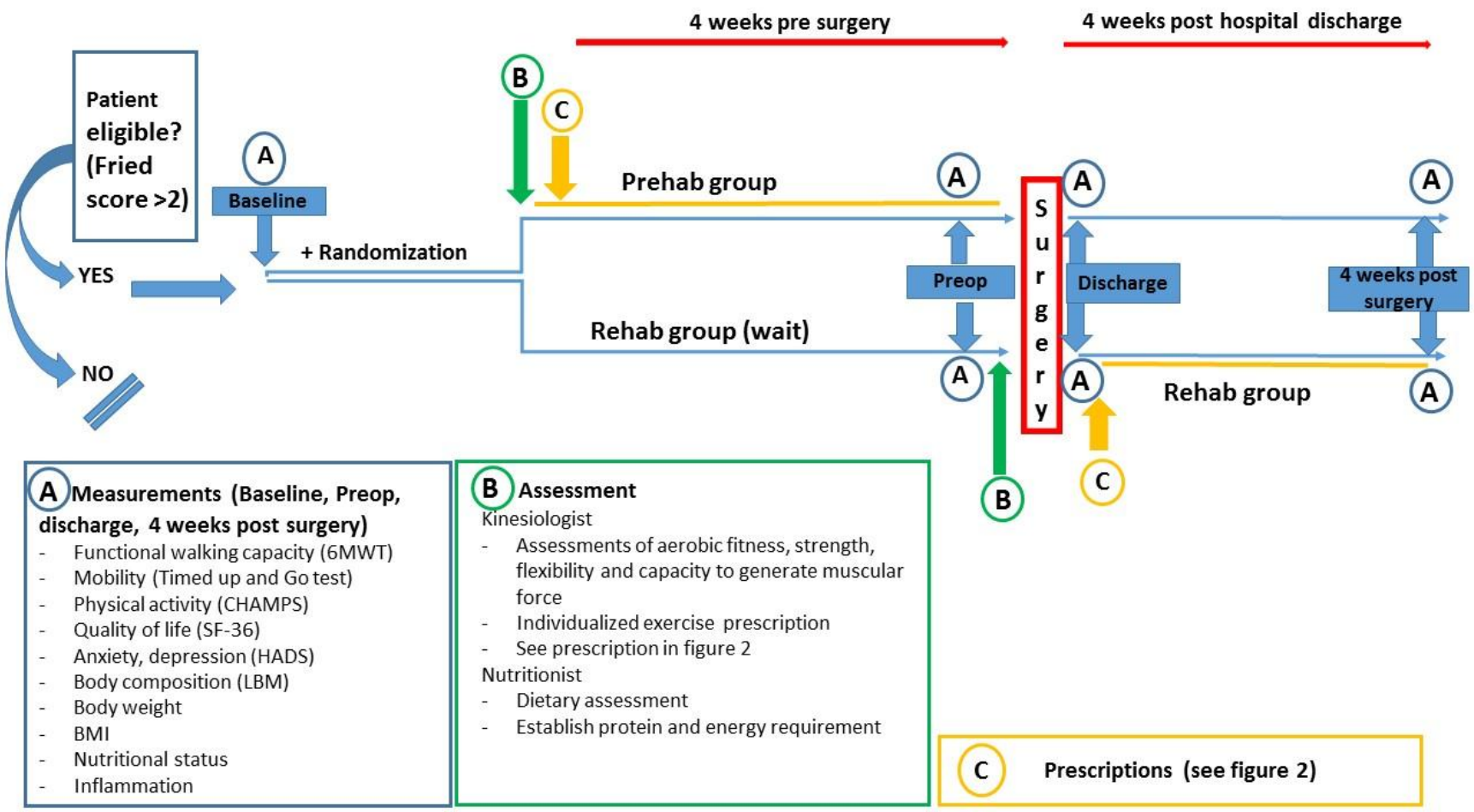

Figure 1 Trajectory of the study

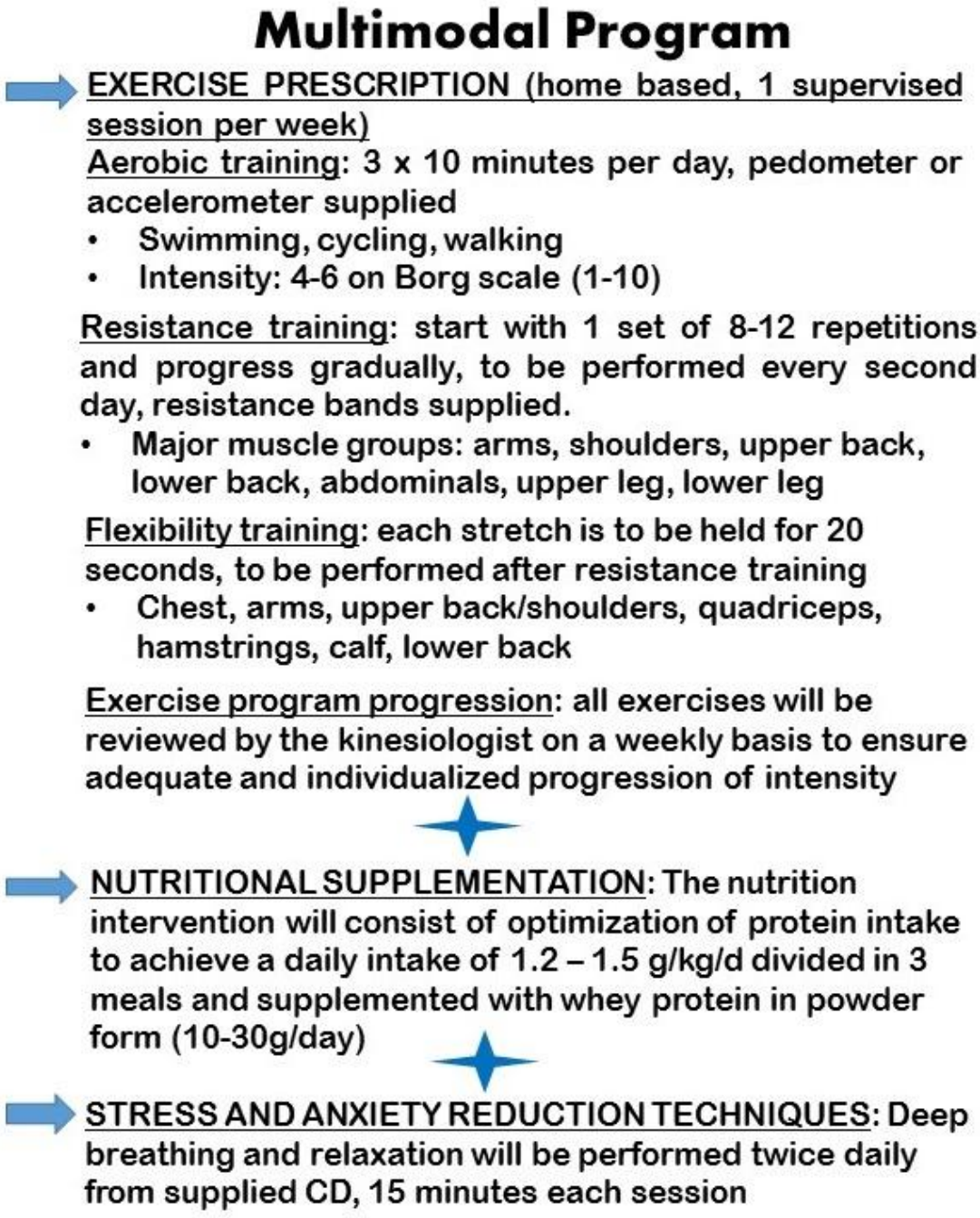

Figure 2 Prescriptions of the multimodal program

Table 1 Measurements and timing

Construct	Measure	Baseline	Preop	Discharge	4 weeks post op
Primary (Confirmatory)					
Postoperative complications	Comprehensive Complication Index (CCI)				X
Secondary (Exploratory)					
Time to readiness for discharge	Time to achieve discharge criteria			X	
Length of hospital stay	Time from surgery until actual hospital discharge			X	
Readmission rate	Readmission rate				X
Functional walking capacity	6MWT	X	X	X	X
Mobility	Time up and go	X	X		X
HRQL	SF-36	X	X		X
Physical activity	CHAMPS, steps	X	X		X
Anxiety & Depression	HADS	X	X		X
Adherence to the program	% Compliance to prescriptions		X		X
Confounding					
Demographics	Age, sex, language, education, work	X			
Body weight	Body weight	X			
BMI	BMI	X			
Nutritional status	PG-SGA	X			
Health Status	ASA, morbidity, medications	X			
Dementia	Mini-cog test	X			
Frailty	Fried Score	X			
Surgical incision	Open, laparoscopic	X			
Tumor stage	Tumor stage				X
Inflammation	Albumin, CRP,IL-1B, IL-6, creatine kinase	X			
Diabetic stage	Hb A1C	X			
Neoadjuvant therapy Adjuvant therapy		X			X
Complications					
Myocardial infarction					X
Stroke					X
Wound infection					X
Chest infection					X
Ileus					X
Bleeding					X
Dehiscence					X
Pulmonary embolism					X
Anastomotic leakage					X
Delirium					X

CCI= Comprehensive Complications Index; 6MWT= 6 minute walk test. HRLQ= Health related quality of life; SF-36 = Short Form 36; CHAMPS= Community Health Activity Model Program; HADS=Hospital Anxiety Depression Scale; BMI = Body Mass Index; PG-SGA = Patient Generated- Subjective Global Assessment; ASA= American Society of Anesthesiologists; CRP= C-reactive Protein; Hb A1C = glycosylate hemoglobin.