

CLINICAL RESEARCH PROTOCOL

**Trimodal prehabilitation for cystectomy patients to enhance post-operative care:
A randomized control trial**

Protocol Number:	2017CRIF-JMARTYN
Version Date:	Nov 11, 2017
Principal Investigator:	<p>Jason Martyn, PT MScPT Rockyview General Hospital Department of Allied Health 7007 14 St SW Calgary, AB T2V 1P9</p> <p><i>Phone: 403-943-3575 Fax: 403-943-3332</i> <i>E-mail: jason.martyn@ahs.ca</i></p>
Co-Investigators:	<p>Chelsia Gillis, RD MSc, PhD Student Community Health Sciences University of Calgary 2500 University Drive NW Calgary, AB T2N 1N4</p> <p>Dr. Eric Hyndman, MD PhD Rockyview General Hospital #6638 7007 14 St SW Calgary, AB T2V 1P9</p>
Funding Organization:	<p>Clinical Research Innovation Fund Physiotherapy Alberta, University of Alberta, Department of Physical Therapy</p>
Registered:	ClinicalTrials.gov Identifier:

Protocol Signature Sheet

Ethics # and Study Title:

Signature of Principal Investigator (Lead and Participating Site)

I agree to the terms of this protocol and all amendments. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Printed Name of Lead Site PI:	Printed Name of Participating Site PI:
Site:	Site:
Signature:	Signature:
Date:	Date:

Signatures of Co-Investigators

The undersigned co-investigator(s) acknowledge that he/she is aware of being listed as a co-investigator to the above named study, he/she has read the protocol and he/she agrees to participate in the above named study as outlined in the protocol, and according to the principles of Good Clinical Practice (GCP) and local regulations.

1. Name (print):

Signature:

Date:

2. Name (print):

Signature:

Date:

3. Name (print):

Signature:

Date:

Table of Contents

LIST OF ABBREVIATIONS.....	5
PROTOCOL SYNOPSIS.....	6
1 INTRODUCTION	8
1.1 Abstract.....	8
1.2 Background.....	8
2 STUDY RATIONALE.....	9
2.1 Risk / Benefit Analysis	10
3 STUDY OBJECTIVES.....	11
3.1 Research Question	11
3.2 Primary Objective	11
3.3 Secondary Objectives.....	12
4 STUDY DESIGN.....	12
4.1 Study Overview	12
4.2 Population	13
4.3 Inclusion Criteria	13
4.4 Exclusion Criteria	13
4.5 Total Number of Participants and Sample Size Justification.....	13
4.6 Recruitment & Informed Consent.....	13
5 RESEARCH METHODS AND PROCEDURES	14
5.1 Treatment Groups	14
5.2 Components of Trimodal Prehabilitation.....	15
5.3 Method of Assigning Subjects to Treatment Groups.....	17
5.4 Blinding.....	17
5.5 Supply of Protein Supplements.....	17
5.6 Measures of Treatment Compliance	17
5.7 Adverse Events Reporting	18
6 CLINICAL ASSESSMENT & OUTCOME MEASURES	18
6.1 Demographics	18
6.2 Medical History	18
6.3 Physical Examination.....	18
6.4 Vital Signs & Spirometry.....	18

6.5	Hematology & Blood Chemistry Profile.....	18
6.6	Nutrition.....	19
6.7	Functional Outcomes	19
6.8	Subjective Outcomes.....	19
6.9	Traditional/Clinical Outcomes.....	20
6.10	Interviews.....	20
7	EVALUATIONS BY VISIT	20
7.1	Visit 1 (Baseline / Surgical consent).....	20
7.2	Visit 2 (Pre-admission Clinic appointment).....	20
7.3	Visit 3 (Pre-operative, day of surgery).....	21
7.4	Visit 4 (Post-operative follow-up appointment at 4 weeks).....	21
7.5	Visit 5 (Post-operative follow-up appointment at 8 weeks).....	21
7.6	Visit 6 (Interviews)	21
8	DISCONTINUATION/WITHDRAWAL OF SUBJECTS.....	21
8.1	Early discontinuation and/or withdrawal of subjects from trimodal prehabilitation.....	21
9	STATISTICAL METHODS AND CONSIDERATIONS	22
9.1	Quantitative Analysis.....	22
9.2	Power & Sample Size	22
10	DATA COLLECTION, RETENTION AND MONITORING	23
10.1	Data Collection	23
10.2	Data Identifiers.....	23
10.3	Confidentiality and Privacy	24
10.4	Storage, Retention and Disposal	25
11	ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS	25
11.1	Health Research Ethics Board of Alberta: Cancer Committee	25
11.2	Standard Operating Procedures.....	25
11.3	Protocol Amendments.....	25
11.4	Informed Consent Form.....	25
11.5	Publications.....	26
	REFERENCES	27

LIST OF ABBREVIATIONS

6MWT	six minute walk test
10mWT	10-meter walk test
30s STS	30-second sit-to-stand
AE	adverse event
AHS	Alberta Health Services
ASA	American Society of Anesthesiologists
BMI	body-mass index
CRP	C-reactive protein
DAD	Discharge Abstract Database
EC	Ethics Committee
ERP	enhanced recovery protocol
ERAS	Enhanced Recovery After Surgery
FACT-BL	Functional Assessment of Cancer Therapy - Bladder
GCP	Good Clinical Practice
HEP	home exercise programme
HIA	Health Information Act
HREBA-CC	Health Research Ethics Board of Alberta – Cancer Committee
ICF	informed consent form
IRISS	Institutional Research Information Services Solution
IS	incentive spirometer
NSQIP	National Surgical Quality Improvement Program
PaCER	Patient and Community Engagement Research
PG-SGA	Patient Generated Subjective Global Assessment
PORC	Post-operative Radical Cystectomy
RC	radical cystectomy
RCT	randomized control trial
RGH	Rockyview General Hospital
RIOT	return to intended oncological treatment
TC	Total Cardiology

PROTOCOL SYNOPSIS

TITLE	Trimodal prehabilitation for cystectomy patients to enhance post-operative care: A randomized control trial
VERSION	1.0
STUDY DESIGN	Pragmatic RCT with assessor blinding
STUDY	52 weeks
STUDY CENTRES	Single Centre Trial (Rockyview General Hospital, Calgary, AB)
PRIMARY OBJECTIVE	To investigate the effects of a trimodal 8-week prehabilitation program on the return to function of patients undergoing RC as measured by six-minute walk test (6MWT) and walking speed, as well as on traditional clinical outcome measures including length of hospital stay, rates of morbidity, and return to oncological treatment.
SECONDARY OBJECTIVES	<p>To investigate the impact and patient acceptability of a trimodal 8-week prehabilitation program on patient satisfaction and quality of life, as determined through questionnaires, and patient interviews</p> <p>To investigate the effects of a trimodal 8-week program on traditional outcomes including length of hospital stay, rates of morbidity, and return to oncological treatment</p> <p>To establish appropriate criteria that effectively identifies and triages those patients who would benefit most from prehabilitation</p> <p>To evaluate which functional outcome measures represent a valid index of recovery and are sensitive to change.</p>
NUMBER OF PARTICIPANTS	50
DIAGNOSIS AND MAIN INCLUSION CRITERIA	<p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female ≥ 18 years of age at time of consent for surgery. 2. Documentation of bladder cancer diagnosis as evidenced by diagnostic imaging and biopsy. 3. May or may not receive adjuvant therapy. 4. Written informed consent obtained from subject <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Presence of a condition or abnormality that in the opinion of the

	<p>investigator would compromise the safety of the patient or adherence to the program. This includes:</p> <ol style="list-style-type: none"> a. American Society of Anesthesiologists (ASA) health class status 4-5; b. Co-morbid medical, physical, and/or mental conditions including dementia, disabling orthopedic and neuromuscular disease, psychosis; c. Severe cardiac abnormalities, end-stage organ disease, sepsis, or morbid obesity (BMI greater than 35); <ol style="list-style-type: none"> 2. Undergoing radical cystectomy for a reason other than bladder cancer. 3. Poor comprehension of English or French 4. Screened by Total Cardiology staff and determined to be inappropriate for prehabilitation at their facility.
INTERVENTION / CONTROL GROUP	<p>Control: Radical cystectomy. Enhanced Recovery Protocol will be followed. Home exercise program & nutritional information provided.</p> <p>Intervention: Trimodal prehabilitation received prior to radical cystectomy. Enhanced Recovery Protocol will be followed.</p>
DURATION OF PARTICIPATION	16 weeks
EVALUATIONS	5 evaluation visits and 8 individual interviews conducted by a PaCER trained researcher.
STATISTICS Primary Analysis Plan	An available case analysis without imputation of missing values will be conducted. All analyses will be performed using Stata 14.1 (2015, StataCorp). All continuous variables will be reported as mean, 95% confidence interval. Categorical variables will be presented as frequency (%) and compared using Pearson's χ^2 test. A mixed effects model will be used to analyze repeated measures, including our primary outcome the 6MWT. A P-value <0.05 will be considered statistically significant.
Rationale for Number of Subjects	Funding is limited to \$15,000. This allows for a study of ~25 prehabilitation participants and 25 participants undergoing standard-of-care treatment.

1 INTRODUCTION

1.1 Abstract

A trimodal preoperative intervention known as prehabilitation (involving exercise, nutrition and psychological care) has been found to successfully improve functional recovery, an important patient-centered outcome, in colorectal surgery patients following the Enhanced Recovery After Surgery (ERAS) pathway. It is unknown whether the same program will be effective in patients undergoing surgery for bladder cancer (cystectomy). It is an opportune time to study prehabilitation at the Rockyview General Hospital given the recent roll-out of the Enhanced Recovery Protocol (ERP) for cystectomy patients and ongoing implementation of an integrated prehabilitation program.

Objective: To evaluate the appropriateness of a standardized prehabilitation program for implementation into an ERP for cystectomy patients and determine whether prehabilitation facilitates earlier recovery of functional capacity, as measured by six-minute walk test (6MWT)

Hypothesis: Prehabilitation will ultimately improve recovery of functional capacity, clinical and patient-centered outcomes in patients undergoing radical cystectomy for bladder cancer.

Design: A pragmatic randomized control trial of radical cystectomy patients following ERP and an 8-week trimodal prehabilitation program consisting of exercise therapy combined with nutritional counselling, protein supplementation, and psychological care will be compared to a cohort of patients following ERP care alone.

Main Outcome Measures: Return to preoperative functional walking capacity, as assessed using the validated six-minute walk test at the 8th postoperative week. All measures will be recorded at baseline, the day of surgery, and four and eight weeks after surgery. Traditional clinical outcome measures (e.g., length of hospital stay) will also be evaluated. Finally, patient interviews will be conducted to evaluate the appropriateness of prehabilitation.

Conclusion: The proposal will provide insight into the feasibility and effectiveness of trimodal prehabilitation for radical cystectomy patients and ultimately lead to improved clinical outcomes and reduced morbidity.

1.2 Background

In 2017 an estimated 8,900 Canadians will be diagnosed with bladder cancer¹. The mainstay of surgical treatment for muscle-invasive bladder cancer is radical cystectomy (RC) with lymph node dissection. Large prospective cohort studies suggest that at least 64% of patients undergoing RC experience at least one complication within 3 months^{2,3}. In an attempt to reduce

these complications and shorten length of hospital stay postoperatively, Rockyview General Hospital (RGH) is implementing a new enhanced recovery protocol (ERP) that will employ multidisciplinary, evidence-based clinical interventions, drawing upon the Enhanced Recovery After Surgery (ERAS) protocols⁴ for its development. ERAS protocols have been shown to reduce length of hospital stay and morbidity post-colorectal surgery, and provide an evidence-based, multidisciplinary approach to surgical care. It is unclear whether available evidence suggests ERPs facilitate earlier recovery of strength and function, and previous efforts to improve recovery have traditionally focused on the postoperative period, during which cancer patients may be fatigued, concerned about disturbing the healing process, or anxious as they await additional treatments for their underlying condition.⁵ Given this, the preoperative period may in fact be a more salient time to intervene. Optimizing an individual's functional capacity can begin during the waiting period before surgery as it capitalizes on the better physical health compared with the acute postoperative period^{6,7}. Moreover, interventions prior to surgery can potentially improve complication rates perioperatively. This process of enhancing an individual's functional capacity to withstand the stress of surgery is called prehabilitation⁸.

Randomized controlled trials (RCTs) have demonstrated that a comprehensive trimodal prehabilitation program, a program consisting of exercise therapy, nutritional counseling with protein supplementation, and psychological care before surgery, improved the functional exercise status of colorectal surgery patients⁹. In fact, twice as many prehabilitated patients¹⁰ had returned to their pre-surgery walking capacity by the eighth postoperative week compared to traditional care⁵. A case study of a frail, elderly cystectomy patient reveals similar improvements¹¹ and a recently published RCT concludes that a dedicated 2-week exercise program for patients undergoing RC can improve muscle power and allow for earlier return to preoperative function¹². These results suggest that establishing a prehabilitation program for patients undergoing RC may also provide benefits. Indeed, RC patients may attain a greater benefit from prehabilitation since the rate of complications post-cystectomy is more than double that reported for colectomy¹³.

2 STUDY RATIONALE

Recent research⁶⁻¹³ demonstrates that many side effects associated with surgical stress can be attenuated utilizing well designed interventions. In view of the impact of cancer on physical, nutritional and psychological status, it is necessary to optimize body reserves preoperatively to prepare the patient for the stress of surgery. This study will provide guidance to clinicians for optimizing RC patients preoperatively and will contribute to our understanding of which outcome measures represent a valid index of recovery and are sensitive to changes. Additionally, RGH has recently implemented an ERP for patients undergoing RC which includes the option for an 8-week prehabilitation program hosted in the community through Total Cardiology (TC). Total Cardiology is a private cardiology practice in Calgary with a dedicated multi-disciplinary

team of health care practitioners including cardiologists, kinesiologists, and registered dietitians. Their scope-of-practice includes guided exercise programs specifically for patients undergoing cardiac rehabilitation and they are well versed with exercise stress testing. Given this opportunity, it is an optimal time to study the effects of such a program, the results for which can be directly applied to the improvement and refinement of the current prehabilitation program.

The results of this pilot randomized study will form the basis for potential multi-site studies and will assist with obtaining additional funding. In addition, the organizational and logistical details established here in, provide a framework for which future surgical prehabilitation programs can be based, with an aim of optimizing the preoperative period and minimizing morbidity.

2.1 Risk / Benefit Analysis

2.1.1 Risk Assessment

Risks associated with an exercise program include minor aches and pains, potential for mechanical injuries, such as strains & sprains, and cardiovascular problems, such as heart arrhythmias, heart attack, or sudden cardiac arrest¹⁴. Participants undergo a medical evaluation by the Total Cardiology team to ensure participants are sufficiently healthy and medically stable to participate in a program. By tailoring the exercise programs to the individual needs of each participant, risks for mechanical injuries and exercise-associated complications are sought to be minimized. Participants are encouraged to take rests and keep physical activity within a moderate range to ensure safe participation in the program.

Typical risks associated with the use of oral nutrition supplements are rare, but include constipation, diarrhea, nausea and vomiting. Participants will undergo evaluation by a Registered Dietitian and will be monitored for adverse effects throughout the program. Pre-existing medical conditions such as diabetes may impact the ability to use nutritional supplements. These conditions will be reviewed by the Registered Dietitian and an appropriate personalized nutrition care plan will be developed in conjunction with the participant.

With respect to interviews, sharing personal experiences of surgery might make some patients uncomfortable. Participants will be advised to share only what they are comfortable with sharing. Participants will be informed that if at any time they experience feelings of anxiousness, sadness, or discomfort, they have the right to take a break during the interview, postpone the interview, or withdraw their consent to participate.

2.1.2 Benefit Assessment

Generally speaking, the benefits associated with exercise and good nutritional intake, far outweigh the risks. Exercise has been linked to improving the status of many physical and mental conditions including cardiovascular disease, mental health, obesity, diabetes, and chronic pain and has been shown to improve cardiovascular function by optimizing the ventilation/perfusion

of the lungs and improving the cardiac output of the heart¹⁵. As the purpose of this study is to observe how side effects associated with surgical stress may be attenuated, the benefits of these interventions will become clearer. Given the large number of positive effects of exercise and good nutrition, it is hoped these initiatives will facilitate the recovery process and reduce impact to a person's functional status, thereby improving quality of life.

In view of the impact of cancer on physical, nutritional and psychological status, it is necessary to optimize body reserves preoperatively to prepare the patient for the stress of surgery. This study could provide some direction to guide clinicians in optimizing the perioperative period in patients undergoing bladder surgery as well as contributing to our understanding of which outcome measures represent a valid index of recovery and are sensitive to changes.

Finally, by conducting individual interviews, participants will have a direct impact on how prehabilitation is carried out in the future. They will have the opportunity to shape the program and ensure it is in accordance with their capabilities and beliefs. It should also be mentioned that this study has the potential to affect organizational change within Alberta Health Services by providing the groundwork research for which future health care management decisions can be made in an evidence-based manner.

This said, it is not immediately clear that prehabilitation will lead to the proposed functional benefits and our team is acutely aware of additional costs associated with such a program (i.e. facility & protein supplement costs). Benefits for participants are best contrasted with a control group following the standard of care and a basic home exercise program and can allow for better decision making from an organizational level.

3 STUDY OBJECTIVES

3.1 Research Question

Does an 8-week trimodal prehabilitation program consisting of exercise therapy combined with nutritional counseling, protein supplementation, and psychological care of patients undergoing radical cystectomy improve postoperative functional and quality of life (QOL) outcomes compared to patients who follow ERP care alone?

3.2 Primary Objective

- To investigate the effects of a trimodal 8-week prehabilitation program on the return to function of patients undergoing RC as evaluated by functional outcome measures including the six-minute walk test (6MWT) and walking speed (10m walk test).

3.3 Secondary Objectives

- To investigate the impact and patient acceptability of a trimodal 8-week prehabilitation program on patient satisfaction and quality of life, as determined through questionnaires and patient interviews.
- To investigate the effects of a trimodal 8-week program on traditional outcomes including length of hospital stay, rates of morbidity, and return to oncological treatment
- To establish appropriate criteria that effectively identifies and triages those patients who would benefit most from prehabilitation, so that efficient health care service can be made accessible to those who need it most.
- To evaluate which functional outcome measures represent a valid index of recovery and are sensitive to change.

4 STUDY DESIGN

4.1 Study Overview

This is a single center, single-blind, pragmatic randomized-control trial. There will be a total of 50 (fifty) participants in the study. Each participant will be randomly enrolled into a prehabilitation or no-prehabilitation group at time of consent for RC and those in the intervention group will undergo 8 weeks of prehabilitation through the Total Cardiology program, hosted through the Repsol Centre. Each participant, independent of study group assignment, will receive the standard treatment as outlined in the Enhanced Recovery Protocol (ERP) for Radical Cystectomies (see Appendix 1). Those enrolled in the prehabilitation group will attend 2 supervised exercise-based sessions per week and will complete a home-exercise program three times per week (total 5 exercise sessions per week). In addition, they will receive 5 protein supplement drinks per week to consume after exercise, and will attend classes on nutrition and stress/anxiety reduction techniques. Measurements will be taken at baseline, 6 weeks (as a part of their regularly scheduled pre-admission clinic appointment), 8 weeks (just prior to surgery), 4 weeks post-op, and 8 weeks post-op.

Those patients enrolled in the no-prehabilitation group will receive a general, unsupervised, home-exercise program, information regarding good nutrition. They will be followed at their regularly scheduled appointments. Again, measurements will be taken at the same time intervals as the prehabilitation group.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment groups will be established:

- Standard ERP + Trimodal Prehabilitation
- Standard ERP

Total duration of subject participation will be approximately sixteen weeks. Total duration of the study is expected to be approximately 1.5 years.

4.2 Population

Subjects with a diagnosis of bladder cancer, scheduled for elective bladder surgery, who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.3 Inclusion Criteria

1. Male or female \geq 18 years of age at time of consent for surgery.
2. Documentation of bladder cancer diagnosis as evidenced by diagnostic imaging and biopsy.
3. May or may not receive adjuvant therapy.
4. Written informed consent obtained from subject.

4.4 Exclusion Criteria

1. Presence of a condition or abnormality that in the opinion of the investigator would compromise the safety of the patient or the quality of the data. This includes:
 - a. ASA health class status 4-5;
 - b. Co-morbid medical, physical, and/or mental conditions including dementia, disabling orthopedic and neuromuscular disease, psychosis;
 - c. Severe cardiac abnormalities, end-stage organ disease, sepsis, or morbid obesity (BMI greater than 35);
2. Undergoing radical cystectomy for a reason other than bladder cancer.
3. Poor comprehension of English or French.
4. Screened* by Total Cardiology staff and determined to be not appropriate for prehabilitation at their facility.

* TC will conduct an exercise stress test on candidates with a moderate or high Framingham Index.

4.5 Total Number of Participants and Sample Size Justification

A total of 50 participants who meet the inclusion criteria and are willing to participate in the study will be enrolled, with 25 participants randomly allocated to each study treatment group. As this is a pilot study, we have funding for at most 25 participants to undergo prehabilitation.

4.6 Recruitment & Informed Consent

At RGH, patients diagnosed with bladder cancer and consent to surgery are operated on by Dr. Eric Hyndman, Dr. Martin Duffy, Dr. Geoffrey Gotto, Dr. Richard Baverstock, Dr. Richard Barr, and Dr. Kevin Carlson. A total of approximately 80 radical cystectomies are completed annually.

Patients will be screened by the medical team for health conditions that would prohibit participation in the program and those that are selected for prehabilitation will undergo further exercise testing at the Total Cardiology program to ensure participants are medically suitable for the intervention. The following are the steps taken for recruitment:

1. Patients who consent to elective bladder surgery that meet the inclusion/exclusion criteria will be identified and initial contact will be made by the physician assistant (RC case manager) at a scheduled appointment. The physician assistant will introduce the study to the patients.
2. If the patient decides they would like more information about the study and is willing to be contacted by the research study coordinator, the physician assistant will inform the study coordinator (JM).
3. The study coordinator (JM) will then contact the patient to explain all details of the study. If the patient is interested in participating, the coordinator will schedule a time to complete the informed consent (Appendix 5) and preoperative/baseline assessments at RGH. At this time, the patient will also be given the written informed consent to further read on their own time.
4. When the patient arrives for their scheduled appointment at RGH, they will be given all study details from the coordinator. Any further questions on their behalf will be addressed and they will be asked to sign the informed consent. Only participants who have capacity to provide fully informed consent themselves will be asked to sign a consent form.
5. Once informed consent is obtained, the patient will undergo their preoperative/baseline assessments as outlined later in this document.
6. Patient will be randomized into one of the two study groups and the study protocol will begin. Further physical and nutritional assessments will be conducted by a Physiotherapist and Registered Dietitian respectively.

5 RESEARCH METHODS AND PROCEDURES

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject.

5.1 Treatment Groups

Currently, RGH utilizes a newly developed, multidisciplinary Enhanced Recovery Protocol for all patients undergoing a radical cystectomy. At this time, all patients undergoing a radical cystectomy are following the ERP. For the purpose of this study, two treatment groups will be established:

5.1.1 RGH Enhanced Recovery Protocol; No Prehabilitation

Patients in this group will follow the standard ERP developed at RGH. See Appendix 1 for details of the ERP. This group will receive general instructions on post-operative exercises, expectations, and discharge planning by a physiotherapist at their pre-admission clinic appointment. Post-operatively, the patient will follow a standardized pathway as outlined in Appendix 1.

5.1.2 RGH Enhanced Recovery Protocol and Prehabilitation

Patients in this group will additionally follow a trimodal prehabilitation program consisting of a guided exercise program, nutritional supplementation, and stress reduction/anxiety reduction strategies.

5.2 Components of Trimodal Prehabilitation

5.2.1 Exercise Program

The exercise component will consist of approximately two 60 min sessions of supervised resistance and aerobic exercises. The sessions will be under the supervision of a kinesiologist and will take place in collaboration with the Total Cardiology group out of the Repsol Sport Centre. Each participant's program will be individualized based upon the baseline fitness test and will include:

- 5 min warm-up,
- 25 min of aerobic exercise (starting at 30-40% of heart rate reserve (HRR) and progressing to 50-60% HRR as tolerated by participant),
- 25 min of resistance training (6 exercises targeting major muscle groups performed at moderate intensity), and
- 5-10 min cool-down and stretching period.
- Clear explanations & demonstrations of program by the kinesiologist

In addition, patients will be asked to carry out a 60min aerobic-based exercise program at home (i.e. walking), unsupervised, 3 days/week, and complete incentive spirometry breathing exercises 3 times/day for 10 breaths. Incentive spirometry has been shown to have beneficial effects on post-operative outcomes¹⁹ and will be included for this reason. Participants will record these additional activities in a journal that is provided to them at the start of their program.

Training intensity progression will be advised by the kinesiologist when the participant can complete aerobic exercise with mild exertion and/or when the participant can complete 15 repetitions of a given resistance exercise.

The kinesiologist will follow all participants to assess program adherence (including unsupervised sessions documented in patient's journal) and to address any barriers that may prevent ongoing participation.

The control group will receive the regular radical cystectomy information and will be asked to complete a 60min aerobic-based home exercise program, unsupervised, 5 days/week, along with incentive spirometry breathing exercises 3 times/day for 10 breaths. This group will also record their activities in a journal and a member of the research team will check in by telephone weekly to assess adherence and address any barriers or questions the patient may have.

5.2.2 Nutritional Supplementation

The nutritional status of patients affected by bladder cancer is directly influenced by the presence of cancer which has an impact on all aspects of intermediary (protein, carbohydrate, lipid, trace element, and vitamin) metabolism, and by other factors such as age, adjuvant cancer therapy and stage of the disease^{16,17}. In addition, a patient who is undernourished before surgery has greater risk of morbidity and mortality¹⁸. The primary goal of nutrition therapy during the perioperative period is to optimize nutrient stores preoperatively and provide adequate nutrition to compensate for the catabolic response of surgery post-operatively. This includes preventing the loss of lean body mass, something that is increasingly recognized as a therapeutic target for cancer care.

At the time of consent, patients will be instructed by a registered dietitian/member of research team to complete a self-administered online 24-hr recall for one weekday and one weekend day. The Automated Self-Administered 24-hour (ASA24®) dietary assessment tool, a free web-based tool that enables multiple, automatically coded, self-administered 24-hour recalls, was created by the National Cancer Institute (NCI).

At baseline, each patient will receive an appointment with a registered dietitian who will conduct a nutrition assessment using the Patient-Generated Subjective Global Assessment (PG-SGA). The PG-SGA is a validated nutrition risk assessment tool that stratifies patients as malnourished, at risk of malnutrition, or well nourished^{17,18}.

During their nutrition appointment, each patient will be provided with nutrition tips based on their food record analysis. Patients will also be supplied with a whey protein supplement (Ensure Enlive, Abbot), which provides 20g/day, to optimize post-exercise muscle protein synthesis. Patients will be instructed to take the supplement once per day within one hour of completing their exercise program to enhance compliance.

A registered dietitian will be available to patients on the supervised exercise days at Total Cardiology. The dietitian will follow patient progress and offer dietary suggestions as necessary to meet patient needs.

The patients will also be asked to complete a journal (Appendix 4) detailing the quantity of nutritional supplement consumed each day.

5.2.3 Anxiety Reduction Strategies

Patients undergoing bladder surgery for cancer may be anxious and/or depressed. The control group will receive general instructions in the preoperative clinic about the perioperative care and will receive an education booklet regarding the surgery, while those in the prehabilitation group will, in addition, attend an anxiety-reduction class at the Total Cardiology program. This class will educate participants on general anxiety reduction strategies that can be implemented in hope to relieve some of these issues.

5.3 Method of Assigning Subjects to Treatment Groups

Up to 50 eligible patients will be randomly assigned to the two groups in a 1:1 ratio using a computer-generated randomization process whereby brown sealed envelopes will be prepared and opened after the patient's consent has been signed.

5.4 Blinding

Due to the nature of the study, we are unable to conceal to the research staff or participants from the different aspects of trimodal prehabilitation. However, all research data will be coded with anonymous unique identifiers so statistical analysis is performed blinded and without bias. The assessor-blinded data will not be broken on completion of the clinical study.

5.5 Supply of Protein Supplements

Participants will receive forty (40) 8oz bottles of Ensure Enlive (Abbott) Nutrition Shake (variety of flavors) to be consumed 5 days per week after exercise sessions.

5.5.1 Dosage Regimen & Administration

Patients will receive ~20 grams of whey protein via the Ensure Enlive supplement (Abbot), five days/week, and will consume the nutritional supplement within an hour of their prehabilitation exercise component. Two days will be supervised at the Total Cardiology program and three days will be unsupervised and require patients to be responsible for keeping the product at their place of residence.

5.6 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the date and time they participate in the exercise component of their prehabilitation program (Appendix 4). This will include a section on type of exercise completed, if the protein supplement was consumed following exercise, and for any further reflections by the patient. They will be asked to bring their patient diary to each study

visit. Staff at Total Cardiology will record attendance to the guided exercise program and anxiety reduction class.

5.7 Adverse Events Reporting

AE reporting and documentation will be carried out as outlined in the HREBA-CC SOP 404.002GR (Guidance for Submitting a Reportable Event)

6 CLINICAL ASSESSMENT & OUTCOME MEASURES

6.1 Demographics

Demographic information consisting of age, gender, occupation, and educational level will be recorded at the first visit. These factors can play a role in surgery experience and recovery.

6.2 Medical History

Aside from the initial medical examination to ensure safe participation in the prehabilitation program, a full medical history will not be recorded. Instead, the Charlson Comorbidity Index will be used to classify the overall health of the participant. Each participant will be scored on the index.

6.3 Physical Examination

Physical examinations are completed as a regular part of their pre-surgical care. During the participant's visit to the preadmission clinic (PAC), 2 weeks prior to surgery, they will undergo medical screening by an Internist and Anaesthesiologist as standard practice. Qualified staff (physician assistant, nurse, and physiotherapist) may complete an abbreviated physical exam at all other visits as part of standard practice. New abnormal physical exam findings will be documented and the participant will be referred to a physician for further examination.

Prior to the commencement of their prehabilitation program, participants undergo a medical screening exam at the Total Cardiology facility to ensure patients are medically stable.

6.4 Vital Signs & Spirometry

Blood pressure, pulse, oximetry, and incentive spirometry will be performed after resting for 5 minutes. These will be obtained on all pre-surgical visits.

6.5 Hematology & Blood Chemistry Profile

Blood work is collected during their pre-admission clinic (PAC) appointment, as a regular part of pre-surgical care. Information used in the study will include the complete blood count, glycated hemoglobin HbA1C, erythrocyte sedimentation rate, albumin, and serum C-reactive protein.

6.6 Nutrition

The Patient-Generated Subjective Global Assessment will be measured at baseline/first appointment by a Registered Dietitian.

6.7 Functional Outcomes

A number of functional outcome measures will be utilized to help determine which measures represent a valid index of recovery and are sensitive to change in our post-surgical candidates.

a. 6-minute walk test (6MWT)

The 6MWT is an exercise test used to assess aerobic capacity and to a secondary extent, functional mobility. It is a standardized test that has been validated for a variety of populations and can be useful in monitoring a person's capacity to ambulate²⁰. Briefly, the 6MWT requires the participant to ambulate for 6 continuous minutes on a 30m track with a goal of ambulating as far as they can manage in the 6 minutes. The total distance ambulated is then recorded.

b. 10m walk test (10mWT)

In contrast to the 6MWT, the 10mWT takes place by having the participant ambulate a total of 10 meters at their preferred walking speed. The time it takes to ambulate the 10m is then measured and recorded. Walking speed standards have been well established in literature and are predictive of poor health outcomes.^{21,22}

c. 30s sit-to-stand test (30s STS)

The 30s STS test is well validated for a number of conditions and age groups and correlates with lower extremity strength and function. The test requires the participant to complete as many sit-to-stand movements as possible in 30 seconds. The number of stands is then recorded.

d. Hand-grip dynamometer

A hand-grip dynamometer allows for the measurement of various types of grip strength. Grip strength has been shown to be a predictor for upper extremity strength and function, and even as a predictor for ability to carry out activities of daily living²³. For this reason, hand-grip dynamometry allows for a simple objective measure of upper extremity function.

6.8 Subjective Outcomes

a. FACT-BL Questionnaire: is a reliable and valid questionnaire that comprehensively assesses quality of life concerns pertinent to bladder cancer patients.

b. EQ-5D Questionnaire: A short, generic quality of life questionnaire.

- c. Godin Leisure Time Exercise Questionnaire: A short questionnaire on self-reported physical activity.

6.9 Traditional/Clinical Outcomes

Clinical outcomes to be used in this study will include length of hospital stay, 30d readmission rate, return to intended oncological treatment (RIOT), and postoperative complications classified according to Clavien-Dindo classification. Data is collected prospectively.

6.10 Interviews

An amendment will be provided upon the completion of the RCT which includes details of the interview recruitment process and proposed interview questions.

7 EVALUATIONS BY VISIT

7.1 Visit 1 (Baseline / Surgical consent)

1. Review the study with the subject and obtain written informed consent (Appendix 5).
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record Charlson Comorbidity Index.
5. Record chemotherapy history and schedule for ongoing treatments.
6. Record vital signs.
7. Collect functional outcome measures (as listed above).
8. Perform and record incentive spirometry.
9. Randomize subject into treatment or control group.
10. If subject is selected for treatment group, schedule subject for commencement of trimodal prehabilitation with the Total Cardiology program. If selected for control group, subject will be given a home-exercise program and nutrition information as described above.
11. Explain how to complete the study journal (exercise & nutrition compliance).
12. Explain how to complete the online 24-hr food recall.
13. Complete baseline subjective questionnaires (as listed above).

7.2 Visit 2 (Pre-admission Clinic appointment)

1. Record any adverse events and review subject diary for adverse events/compliance.
2. Reinforce home based program and review of postoperative pathway.
3. Perform and record incentive spirometry.

4. Blood work (haematology and blood chemistry profile) completed as a part of their pre-admission screening with internal medicine. No additional blood tests will be requested for study purposes.

*Note: If after review by the medical team the patient is determined to be a poor candidate for surgery, participant will be withdrawn from the study at this point.

7.3 Visit 3 (Pre-operative, day of surgery)

1. Record any adverse events and review subject diary for adverse events/compliance.
2. Perform and record incentive spirometry.
3. Perform and record functional outcome measures as listed above.

7.4 Visit 4 (Post-operative follow-up appointment at 4 weeks)

1. Perform and record incentive spirometry.
2. Perform and record functional outcome measures as listed above.
3. Record participant's self-reported exercise post-operatively.

7.5 Visit 5 (Post-operative follow-up appointment at 8 weeks)

1. Perform and record incentive spirometry.
2. Perform and record functional outcome measures as listed above.
3. Record participant's self-reported exercises post-operatively.
4. Complete subjective questionnaires as listed above.

7.6 Visit 6 (Interviews)

1. Interested participants (n=8) will be invited to participate in individual interviews, which will last up to 75 min. The interviews will be carried out by a PaCER trained researcher (CG).
2. An amendment will be submitted for this ethics proposal which details the nature of the interviews.

8 DISCONTINUATION/WITHDRAWAL OF SUBJECTS

8.1 Early discontinuation and/or withdrawal of subjects from trimodal prehabilitation

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the primary medical team feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by their primary medical team until the abnormal parameters or symptoms have resolved or stabilized.

Subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. A subject may also withdraw their personal study data and in this case, all relevant recorded data will be securely erased, along with any paper files shredded, and the data will be excluded from analysis. This can be done up to the time when the report on study findings is finalized and distributed.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Subjects who withdraw from the study will not be replaced.

9 STATISTICAL METHODS AND CONSIDERATIONS

9.1 Quantitative Analysis

An available case analysis without imputation of missing values will be conducted. All analyses will be performed using Stata 14.1 (2015, StataCorp). All continuous variables will be reported as mean, 95% confidence interval. Categorical variables will be presented as frequency (%) and compared using Pearson's χ^2 test. A mixed effects model will be used to analyze repeated measures, including our primary outcome the 6MWT, because this method had advantages in dealing with missing data and controlling for baseline variables. A P-value <0.05 will be considered statistically significant.

9.2 Power & Sample Size

Power and sample size are limited by the amount of funding available. The grant amount of \$15,000 allows for a total of ~50 patients with 25 being enrolled in the prehabilitation group.

10 DATA COLLECTION, RETENTION AND MONITORING

10.1 Data Collection

All data collected will be anonymized with a locked, password-protected file (available only to the primary investigator) identifying participants to their anonymized data. The research member responsible for statistical analysis will be provided with anonymized data only. Collection will be completed at multiple timepoints as outlined in this document and will be obtained from direct patient interactions, Alberta Health Service's Discharge Abstract Database (DAD), National Surgical Quality Improvement Program (NSQIP) data, and Sunrise Clinical Manager (SCM).

Aside from the clinical data obtained from these sources, qualitative interviews will be completed following the study where participants are invited to talk about their experiences with prehabilitation. Their responses will be anonymized and all direct and indirect identifying information will be redacted prior to analysis by the research team.

Participants will be informed regarding the limits of confidentiality and that all efforts will be made to ensure their clinical data and interview responses are anonymized and kept confidential.

10.2 Data Identifiers

Personal identifiers that we will be collecting include:

- Surname, first name, and initials;
- Address and full postal code;
- Telephone number and email address;
- Full date of birth and age at time of collection;
- Health Care Number;
- Hospital admission and discharge date;

This information will be collected to allow the research team to contact the research participants in order to provide information regarding the study, and to schedule appointments specific to the study. Clinical outcomes such as length of stay are necessary to determine the effectiveness of our intervention.

The researcher responsible for collecting this information and assessing the patients will not be blinded to the patient's treatment group. Their responsibility includes anonymizing all collected data that is to be analyzed statistically. A password-protected spreadsheet will be created that links an anonymous identifier to the above identifying information. A second member of the team, blinded to this process, will be responsible for analyzing the anonymized data statistically.

Once data collection is complete and interviews are completed, all master lists that link identifiers with the anonymized data will be securely deleted.

10.3 Confidentiality and Privacy

In order to maintain the confidentiality of all data all study data will be password-protected and encrypted. The identity of all participants will be maintained in a password-protected, encrypted, spreadsheet. Only the private investigator will have access to this list. Additionally, all staff that are involved with the study will sign a confidentiality agreement. This ensures all personnel are aware of their responsibilities concerning privacy and confidentiality of participant information.

Outside of the research team, anonymized data may be provided to the AHS Research Facilitation team for assistance with statistical analysis. If this occurs, the anonymized data will first be encrypted prior to being provided to the Research Facilitation team.

10.3.1 ASA24 System

The ASA24 system consists of a Respondent Website used to collect recall and food record data and a Researcher Website used to manage study logistics and obtain data analyses. The ASA24-2016 Respondent Website is compatible with mobile devices and is available in English and Spanish.

Researchers using the ASA24 system do not provide the National Cancer Institute or the ASA24 system with any identifying data for participants of their studies. Rather, researchers specify a unique numeric identifier for each Respondent and download system-generated usernames and encrypted passwords that they provide to Respondents so that they may access the application.

The ASA24 system also does not collect any identifying data directly from Respondents. However, IP address information is accessed for the purpose of routing information between the server and the respondent's computer—often the IP address is that of the user's Internet Service Provider (ISP). IP addresses are not stored or tracked by the ASA24 system. However, logs of connections are kept in the hosting environment for audit trail purposes. This information is not mined in any way but would be available if there were a legal obligation to release it.

Response data are secured at the hosting site using industry standard security controls, including firewalls and encryption. All data entered into the ASA24 system at the Respondent's computer is encrypted by the internet browser (e.g., Internet Explorer, Firefox) before they are transmitted to our servers using Secure Socket Layer (SSL) Technology. SSL allows for the authentication of the sending and receiving computers.

Only a particular study's investigator(s) and the ASA24 operations team can access response data. Access is gained through usernames and strong passwords.

10.4 Storage, Retention and Disposal

Data will be kept on an encrypted drive on AHS servers. As previously mentioned, any personal identifying information will be individually encrypted and password protected. Paper documentation will be kept in a locked filing cabinet, in a locked room, in the Rehabilitation Department of RGH. At the end of this study, identifying documents and all contact forms will be destroyed.

11 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

11.1 Health Research Ethics Board of Alberta: Cancer Committee

The Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC) provides scientific and ethical review of all cancer-related protocols involving human participants in the province of Alberta. This research proposal with supporting documentation will be submitted to HREBA-CC for review and approval.

11.2 Standard Operating Procedures

HREBA has adopted the Standard Operating Procedures (SOPs) developed by the Network of Networks (N2) and the Canadian Association of Research Ethics Boards (CAREB). These SOPs are compliant with applicable Canadian and US regulatory and ethics guidance criteria. They facilitate the distribution, adoption and maintenance of a single set of standards for REBs in Canada.

Use of SOPs also ensures that the ethics board is constituted appropriately and protects the rights and safety of study participants. They can be found listed on the HREBA-CC website.

11.3 Protocol Amendments

HREBA uses an electronic platform, IRISS, to receive and process all new submissions for ethics review; this program uses the term ‘modification’ to refer to an amendment. Studies that were initially submitted using IRISS will have modifications submitted and reviewed through this system. Step by step instructions on how to modify a study using IRISS are available on the HREBA IRISS resource page. It is important to note that the IRISS application **MUST** also be updated to reflect changes in the protocol and informed consent form (ICF); failure to do so may result in delay in the review of the modification.

11.4 Informed Consent Form

In order to facilitate quicker approval of studies, HREBA-CC has prepared a templated consent form. The Main Consent Form template should be used unless changes are required by the study design. Main informed consent forms which follow the template will go forward for review to the board. If amendments to the template are extensive and/or not reasonably warranted by the

specific study, informed consent forms will be returned at the administrative review stage. Once the revised consent forms have been received and are found to satisfy HREBA – CC requirements, the study will be assigned to the appropriate HREBA – CC full board meeting, as outlined on our meeting dates and deadlines webpage.

11.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Information Act (HIA).

REFERENCES

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2017). Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society.
2. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, Raj G, Bochner BH, Dalbagni G, Herr HW, Donat SM: Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2009;55(1):164-74.
3. van Hemelrijck M, Thorstenson A, Smith P, Adolfsson J, Akre O: Risk of in-hospital complications after radical cystectomy for urinary bladder carcinoma: population-based follow-up study of 7608 patients. *BJU Int* 2013;112(8):1113-20.
4. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, Kassouf W, Muller S, Baldini G, Carli F, Naesheimh T, Ytrebo L, Revhaug A, Lassen K, Knutsen T, Aarseth E, Wiklund P, Patel HR: Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations. *Clin Nutr* 2013;32(6):879-87.
5. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman A.S, Kaneva P, Augustin B, Wongyingsinn M, Gamsa A, Kim DJ, Vassiliou MC, Feldman LS: Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy* 2013; 27(4):1072-1082.
6. Cheema FN, Abraham NS, Berger DH, Albo D, Taffet GE, Naik AD: Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults. *Ann Surg* 2011; 253:867–74.
7. 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; 92:715–27.
8. Carli F, Zavorsky GS: Optimizing functional exercise capacity in the elderly surgical population. *Curr Opin Clin Nutr Metab Care* 2005; 8:23–32.
9. Gillis C, Carli F: Promoting perioperative metabolic and nutritional care. *Anesthesiology* 2015;123(6):1455-72.

10. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Liberman AS, Stein B, Charlebois P, Feldman L, Carli F: Prehabilitation vs rehabilitation: A randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 2014;121(5), 937-47.
11. Carli F, Awasthi R, Gillis C, Kassouf W: Optimizing a frail elderly patient for radical cystectomy with a prehabilitation program. *Can Urol Assoc J.* 2014;8(11-12):E884-7.
12. Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M: Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand J Urol* 2015;49(2):133-41.
13. Schilling PL, Dimick JB, Birkmeyer JD: Prioritizing quality improvement in general surgery. *J Am Coll Surg* 2008;207(5):698-704.
14. Thompson, P. D., Franklin, B. A., Balady, G. J., Blair, S. N., Corrado, D., Estes, N. M., ... & Maron, B. J. (2007). Exercise and acute cardiovascular events. *Circulation*, 115(17), 2358-2368.
15. Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Current opinion in psychiatry*, 18(2), 189-193.
16. Van Custem E, Arends J: The causes and consequences of cancer-associated malnutrition. *European Journal of Oncology Nursing.* 2005;9: S51-S63
17. Mackenzie M, Baracos VE: Cancer-associated cachexia: altered metabolism of protein and amino acids, Metabolic and therapeutic aspects of amino acids in clinical nutrition. Edited by Cynober LA. Boca Raton, Florida, CRC Press, 2004
18. Carli F, Silver JK, Feldman LS, McKee A, Gilman S, Gillis C, Scheede-Bergdahl C, Gamsa A, Stout N, Hirsch B. Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts. *Phys Med Rehabil Clin N Am.* 2017 Feb;28(1):49-64. doi: 10.1016/j.pmr.2016.09.002.
19. Celli, B. R., Rodriguez, K. S., & Snider, G. L. (1984). A Controlled Trial of Intermittent Positive Pressure Breathing, Incentive Spirometry, and Deep Breathing Exercises in Preventing Pulmonary Complications after Abdominal Surgery 1–4. *American Review of Respiratory Disease*, 130(1), 12-15.

20. Pecorelli N, Fiore Jr JF, Mappin-Kasirer B, Niculiseanu P, Gillis C, Awasthi R, Fried GM, Carli F, Feldman LS: The six-minute walk test as a measure of postoperative recovery after colorectal resection: Further examination of its measurement properties. *Surg Endosc* 2015 [Epub ahead of print].
21. Montero-Odasso, M., Schapira, M., Soriano, E. R., Varela, M., Kaplan, R., Camera, L. A., & Mayorga, L. M. (2005). Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 60(10), 1304-1309.
22. Studenski, S., Perera, S., Wallace, D., Chandler, J. M., Duncan, P. W., Rooney, E., ... & Guralnik, J. M. (2003). Physical performance measures in the clinical setting. *Journal of the American Geriatrics Society*, 51(3), 314-322.
23. Kim, D. (2016). The effects of hand strength on upper extremity function and activities of daily living in stroke patients, with a focus on right hemiplegia. *Journal of physical therapy science*, 28(9), 2565-2567.
24. Bauer, J., Capra, S., & Ferguson, M. (2002). Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *European journal of clinical nutrition*, 56(8), 779.
25. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN. Return to intended oncologic treatment (RIOT): A novel metric for evaluating the quality of oncosurgical therapy for malignancy. *J Surg Oncol* 2014 110(2):107-14.
26. Lee L, Tran T, Mayo NE, Carli F, Feldman LS. What does it really mean to "recover" from an operation? *Surgery* 2014, 155(2), 211-216.