Research Project: Prehabilitation to enhance postoperative functional capacity following esophageal resection.

Principal Investigators: Francesco Carli, Department of Anesthesia and Lorenzo Ferri, Department of Surgery MUHC

Collaborators: Liane Feldman, David Mulder, Chao Li, Department of Surgery, MUHC,
Chelsia Gillis, Department of Anesthesia, MUHC
Eleanor Eckert, Clinical Nutrition, MUHC
Mary Diovisalvi, Nursing, MUHC
Stan Kubow, Department of Dietetics & Human Nutrition, McGill University

Introduction

In 2010, 1,700 new cases of esophageal cancer were diagnosed in Canada and approximately 1,800 people die every year from the disease. The incidence rate of esophageal adenocarcinoma has doubled in the last 20 years, and this may reflect the rising prevalence of obesity and gastro-esophageal reflux disease.

Surgical resection offers the best chance of cure of esophageal cancer although multimodal treatment including neo-adjuvant chemotherapy and chemo-radiation is often part of the standard treatment. Most of the patients (>50%) scheduled for surgical resection are over 65 years of age, most have been smokers, and present with several comorbidities. Medical and surgical complications following esophagectomy range between 20 and 60%, with pneumonia as the most common complication. The latter has been shown to represent the principal cause of death in 55% of patients. In a recent study from this institution, the introduction of an Enhanced Recovery Pathway contributed to a significant decrease in length of stay, but had no impact on the rate of postoperative morbidity (pulmonary complications accounted for 50%), implying that patient related factors might be responsible for high postoperative morbidity.

Esophagectomy, like all major surgery, is associated with a 20% to 40% reduction in physiological and functional capacity which is experienced by the patients as a higher level of fatigue for a period of up to 6-8 weeks after hospital discharge. Fatigue is manifested by muscular weakness, increased need for sleep and decreased ability to concentrate. It is correlated with preoperative health status, preoperative fatigue, weight, and grip strength, the degree of surgical trauma and intensity of metabolic response, and with postoperative deterioration. The elderly, and others with limited metabolic protein reserve, are the most susceptible to the negative effects of surgical stress. In addition a
The great majority of these patients undergo chemo-radiation which causes further loss of muscle mass and fatigue.

Efforts to improve the recovery process have primarily focused on the intraoperative and post-operative periods. However, the post operative period may not be the best time to ask surgical patients to make significant changes in their care, as they are tired and concerned about perturbing the healing process as well as being depressed and anxious as they await additional treatments for their underlying condition. The pre-operative period may in fact be a better time to intervene in the factors that contribute to recovery, beyond the physical, and alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process.

The process of enhancing functional capacity of the individual before an operation to enable him or her to withstand the stress of surgery has been termed prehabilitation. It has been shown that poor baseline physical performance capacity and poor nutritional status increase the risk of complications after major non cardiac surgery and prolong recovery. One would therefore assume that by preparing the patients before surgery, they would have better chance to withstand the surgical stress.

Our group, composed of anesthesiologists, surgeons, kinesiologists, nutritionists and psychologists have started a few years ago to conduct studies on prehabilitation at the Montreal General Hospital. The first and largest trial on surgical prehabilitation, compared two exercise regimens (intense exercise on a stationary bike vs walking and deep breathing) for 4-5 weeks before colorectal surgery. The primary outcome was functional walking capacity measured by the six-minute walk test (6MWT) between 5 to 9 weeks postoperatively. Subgroup analysis identified that patients whose functional exercise capacity improved preoperatively, regardless of exercise technique, recovered well in the postoperative period. However, one-third of patients deteriorated preoperatively despite the exercise regimen, and these patients were also at greater risk of prolonged recovery after surgery. Poor preoperative physical function (fatigue, under/malnutrition and physical performance) and presence of anxiety and depression were also significant confounding predictors of prolonged recovery. These results suggested that exercise alone is not sufficient to attenuate the stress response in all patients. The physical and psychological deterioration observed in a subgroup of patients made us more aware of the role of nutritional status and psychological well-being in surgical recovery.

Therefore we conducted a second multimodal prehabilitation program in a group of patients scheduled for colorectal resection of cancer, based on exercise, supplemental nutrition with whey protein, and stress reduction strategies that were initiated 3-5 weeks before surgery and continued postoperatively for 8 weeks.

Functional capacity, as assessed by the 6MWT, increased in the preoperative period by an average of >40 mt, and >81% of patients were at or above their baseline measurement 8 weeks after surgery. At the end of the multimodal prehabilitation program, patients experienced more feelings of vigor and less impairment of activities. Unlike in the previous trial using exercise alone, where one third of the patients...
deteriorated despite prehabilitation, no patients deteriorated from baseline in this new multimodal program.

In view of these results it is appropriate to apply multimodal prehabilitation to patients affected by esophageal cancer in order to enhance the preoperative physical, nutritional and psychological capacities and hopefully impact postoperative functional capacity and morbidity.

We propose a randomized controlled study in patients undergoing esophageal resection for cancer to determine the impact of multimodal prehabilitation on functional exercise capacity and postoperative pulmonary complications. Patients who accept to be enrolled in the study will be randomized to receive either a standard nutritional intervention (including supplements as needed) as per current institution policy or standard nutritional intervention (including supplements as needed) combined with a physical exercise program before and after surgery.

Hypothesis

It is hypothesized that, compared with the group receiving nutrition alone, the addition of physical exercise to nutrition starting before surgery and continuing for 8 weeks after surgery will have a significantly greater impact on functional walking capacity during the prehabilitation period and during the postoperative period, and on the incidence of postoperative pulmonary complications.

Specific aims

The aims of this research project are the following:

1. To determine the extent in which a multimodal prehabilitation regimen optimizes functional recovery in patients suffering from esophageal cancer and the incidence of postoperative pulmonary complications.

2. To understand further which measures of immediate surgical recovery are sensitive to prehabilitation interventions, and predict change in later outcome measures.

Patients and Methods

Patients

The study has been submitted to the McGill University Health Centre Ethics Board for approval. Three previous studies on prehabilitation (see Background, above) were approved and completed by our team in our institution (McGill University Health Centre-Montreal General Hospital Research Ethics Committee REC#02-053, #09-284, #011-004).

Subjects eligible to enter the study include those aged 18 and older who have been referred electively for resection of malignant esophageal lesion. Excluded will be persons with American Society of Anesthesiologists (ASA) health status class 4-5 or co-morbid
medical, physical and mental conditions (e.g. dementia, disabling orthopedic and neuromuscular disease, psychosis), severe cardiac abnormalities, severe end-organ disease such as cardiac failure (New York Heart Association classes I-IV), COPD, renal failure (creatinine > 1.5 mg/dl, and hepatic failure ALT and AST >50% over the normal range), sepsis, morbid obesity (BMI >30), anemia (hematocrit < 30 %, haemoglobin <10g/dl, albumin < 25mg/dl). Patients will be excluded if they cannot swallow and/or are being fed through a percutaneous endoscopy gastronomy or jejunostomy tube. Patients with poor English or French comprehension will also be excluded. In order to participate in this study the patients need to have the ability to complete the questionnaire in French or English.

Recruitment and multidisciplinary evaluation

At the MUHC patients with a diagnosis of esophageal cancer, and scheduled for preoperative neo-adjuvant chemotherapy (mostly docetaxel, cisplatin, and 5-FU based on the recently published results of a local phase II trial) are operated by Drs L Ferri and D Mulder, esophageal surgeons, who perform at the MUHC a total of approximately 50 esophageal cancer resections annually. Patients will be screened by the medical research team for health conditions that would prohibit participation in the program. The following are the steps taken in the recruitment:

1) Patients scheduled for elective esophageal surgery (preceded or not by neo-adjuvant chemotherapy), that also meet inclusion/exclusion criteria, will be identified and initial contact made by their surgeons at a scheduled appointment. The surgeons will introduce the study to the patients.

2) If the patient decides he/she would like more information about the study, and is willing to be contacted by the research study coordinator, the surgeon’s secretary will inform the study coordinator.

3) The study coordinator will then contact the patient to explain all the details of the study. If the patient is interested in participating in the study, the coordinator will schedule a time for the patient to come in to the anesthesia lab to complete the informed consent and the preoperative assessments.

4) When the patient arrives at the anesthesia clinic, he/she will once more receive all the study details from the coordinator and be asked to read the informed consent. Once informed consent has been obtained patients will be randomized (computer generated randomization) and the study protocol will be implemented. Patients will then have their physical, nutritional and psychological assessments conducted by a kinesiologist and a nutritionist respectively.

Hospital standards

Routine standard preoperative and postoperative clinical care at the MUHC does not include prehabilitation. Patients are usually seen by their surgeons in the clinic and they are then referred to the MUHC nutritionist for nutritional assessment and counselling/treatment. Psychological support is also provided to patients on an ad hoc basis during the treatment by the hospital psychologist. An Enhanced Recovery Program for esophagectomy has been implemented in 2010 by the SURE committee of the MUHC.
with a standardized perioperative pathway. All patients receive a booklet with the instructions related to the pathway detailing the preoperative, intraoperative and postoperative periods.

**Study Arms**

1. **Standard group**
   Patients in this group will follow standard MUHC protocol of nutritional counselling. This group will receive general instructions on exercises (breathing, ankle rotation) to be done during hospital stay by kinesiologist.

2. **Prehabilitation group**
   Patients in this group will follow the standard MUHC protocol of nutritional counselling in addition to a specific physical exercise program before and after surgery by kinesiologist.

**Randomization**

Patients will be assigned to the two groups using a computer-generated randomization process whereby brown sealed envelopes will be prepared and opened after patients’ consent has been signed.

**Components of prehabilitation**

a. **Nutritional supplementation**
   The nutritional status of patients affected by esophageal cancer is directly influenced by the presence of cancer which has an impact on all aspects of intermediary (protein, carbohydrate, lipid, trace element, vitamin) metabolism, and by other factors such as age, adjuvant cancer therapy and stage of the disease. In addition, a patient who is undernourished before surgery has greater risk of morbidity and mortality. The primary goal of nutrition therapy during the perioperative period is thus to optimize nutrient stores pre-operatively and provide adequate nutrition to compensate for the catabolic response of surgery post-operatively. This includes preventing the loss of lean body mass which is inversely correlated with the survival of critically ill patients.

   The patients’ nutritional status and adequacy of dietary intake will be assessed by a nutritionist using a three day food record and the Subjective Global Assessment tool. Percentage of lean body mass and fat will be measured with bioelectrical impedance. Total energy expenditure will be measured using indirect calorimetry. All patients will be provided with samples of dietary supplements as needed (including Ensure Plus, Boost Plus, Resource fruit beverage, and Beneprotein powder) and will be provided with strategies to optimize dietary energy and protein intake (in accordance with degree of dysphagia) according to current standard hospital protocols. The total amount of supplements (commercial or homemade) the patient is required to take daily will be determined on an individual basis according to the patient’s nutritional status, including degree of dietary energy and protein deficits, as assessed by the nutritionist at baseline assessment.
Compliance will be monitored weekly through phone calls by the study coordinator. The patients will also be asked to complete a journal detailing how much nutritional supplements are consumed each day.

b. Physical exercise program

It has been shown that prehabilitation can improve postoperative physical function in cancer patients undergoing colorectal surgery and lung resection, and these changes are associated with improvements in mental health, vitality, and self-perceived health. Moreover, it appears that subjects whose fitness deteriorated preoperatively have more surgical complications and require intensive care. A recently published systematic review of preoperative physical exercise by Valken et al reported less postoperative complications and shorter length of stay in abdominal surgery patients. Although the role of exercise intensity is unclear, it appears that moderate exercise, carried out in a combination of aerobic and resistance training components, is sufficient to provide adequate physiological reserve and energy, even in patients who receive chemotherapy.

At the baseline assessment all patients’ physical fitness will be evaluated by the kinesiologist (exercise specialist). In the prehabilitation group the exercise component will consist of 20 min of general exercise training, 3 days per week, alternating between aerobic and resistance training. The exercise program will be individualized based upon the baseline fitness test (according to the American College of Sport Medicine, ACMS, standard) and will include: a 5 min warm-up, either 25 min of aerobic exercise (starting at 30-40 of heart rate reserve, HRR), or 25 min of resistance training (5 exercises targeting major muscle groups performed at an intensity of 8-12 repetition maximum), and a 5 min cool-down. All exercises will be clearly explained and demonstrated by the kinesiologist at baseline. Patients will be asked to carry out this program at home, unsupervised, but will be monitored with weekly telephone calls. Training intensity progression will occur when the participant can complete aerobic exercise on mild exertion and/or when the participant can complete 15 repetitions of a given resistance exercise. Participants will be provided with resistance bands, an exercise mat, a pedometer, a heart rate monitor (to monitor compliance) and a log book to report frequency of exercises completed and to record all the activities.

The control group will receive general instructions on exercises during hospital stay while in bed, walking and sitting. All patients will also receive one session on inspiratory muscles training (IMT) and they will be encouraged to perform this exercise every day.

The kinesiologist will follow all the participants on a weekly basis to ensure program compliance and address any barriers that may prevent ongoing participation.

C. Psychological counseling

It is expected that patients undergoing esophageal surgery for cancer are anxious. The patients in both groups will be referred for consultation to the hospital clinical psychologist for counseling as per MUHC policy.
Procedures

To make the two groups as similar as possible, a clear explanation will be made to the patients emphasizing that both groups will be seen by the team and they will receive one booklet on clinical pathway for esophageal surgery prepared by the SURE committee of the MUHC, and a booklet with the study instructions. Both booklets have been developed at the MUHC by members of the MUHC Surgical Recovery (SuRe) clinical pathways committee in collaboration with McGill Molson Medical Informatics with the intention to explain, using many pictures and drawings, all aspects of perioperative care and guide the patient during the period of the study. In addition, patients will receive a journal/log book where all activities related to the prehabilitation will be recorded.

Measures

All measurements will be recorded at baseline (beginning of prehabilitation period), immediately prior to surgery (end of prehabilitation period) and at 4 and 8 weeks after surgery.

The primary outcome is patient-relevant, functional walking capacity as measured by the six-minute walk test (6MWT). The 6MWT evaluates the ability of an individual to maintain a moderate level of physical activity over a time period reflective of the activities of daily living. Subjects are instructed to walk back and forth, in a 20 m stretch of hallway, for six minutes, at a pace that would make them tired by the end of the walk; encouragement and feedback are given according to published guidelines. They are allowed to rest during the test if needed, but this time is included in the 6 minutes. Reference equations are available for calculating percent of age- and gender-specific norms. In community dwelling elderly, measurement error was estimated at 20 meters and this will be used as the threshold value for determining true change. The 6MWT correlates moderately with VO$_2$max indicating that these two tests measure related but not identical constructs. As daily activity is mostly pursued at a sub-maximal level, functional walking capacity is a more direct measure of capacity for daily routine than a maximal test of exercise capacity such as VO$_2$max and is more feasible to perform in the perioperative population. The test-retest reliability has been reported to range from 0.73 to 0.99 among a variety of populations, including the elderly. The 6MWT has been shown to be reliable and valid in many populations including surgical ones, with a recent paper from our group supporting its validity as a measure of recovery after colorectal surgery. The test will be administered at baseline, on the day before surgery to assess the effect of intervention during the prehabilitation phase, and at 4 and 8 weeks after surgery to assess the impact of the intervention throughout the perioperative period.

Secondary outcomes will include:

Health-related quality of life (HRQL) as measured by the acute (1 week recall period) SF-36 health survey. The SF-36 is the most widely used HRQL measure and has been validated for surgical population; Canadian norms are also available. It incorporates behavioural functioning, subjective well-being and perceptions of health by assessing, on a 0 to 100 scale, eight health concepts: (1) Physical function (PF) -limitations in physical
activities due to health problems; (2) Role physical (RP) - limitations in role activities due to physical health problems; (3) Role emotional (RE) - limitations in usual role activities due to emotional problems; (4) Social functioning (SF) - limitations in social activities due to health problems; (5) Bodily pain (BP) - pain; (6) General health (GH) - general health perceptions; (7) Vitality (VT) - energy and fatigue; and (8) Mental health (MH) - general mental health. Two summary scores have been developed: the Physical Component Summary (PCS) and the Mental Component Summary (MCS), standardized to have a mean of 50 and a standard deviation of 10. A higher score on the SF-36 sub-scales or component summary measures indicates a better quality of life. A change of as little as two units on the PCS has been shown to be the minimum clinically meaningful change; 5 points is often targeted by medical intervention studies, though surgical interventions can have an impact as large as 10 points. The SF-36 will be measured at baseline, before surgery, and at 4 and 8 weeks after surgery.

Quality of life will be also assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ – esophagus-18 questionnaire (an OLQ designed for esophageal disease). This outcome measure has been in esophageal cancer and shown to be reliable and has face validity. All scales range from 0 to 100. A higher score for each functional scale represents high/healthy level of functioning.

Physical activity level will be measured through the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire. The CHAMPS is a self-reported measure of physical activity, comprising 41 activities evaluated according to the total number of hours done during an average week. Each physical activity is assigned a MET (metabolic equivalent) value yielding average weekly caloric expenditure for the listed physical activities. There is evidence for the validity of CHAMPS as a measure of postoperative recovery. CHAMPS will be measured at baseline, before surgery, and at 4 and 8 weeks after surgery.

Depression and anxiety will be assessed by The Hospital Anxiety and Depression Scale (HADS), a 14-question measure with seven items each for depression and anxiety. HADS generates separate scores for anxiety and depression as well as a combined score of psychological distress has been shown to have good psychometric properties for factor structure, sub-scale intercorrelation, homogeneity, and internal consistency and has been used in studies of patients with a variety of healthcare problems. Psychological tests will be used both as predictors of postoperative functional restoration, and as guides for psychological intervention. HADS will be measured at baseline, before surgery, and at 4 and 8 weeks after surgery.

Nutritional status will be assessed at baseline by measuring body mass index (BMI), body weight loss over the preceding three months, and serum albumin. Patients will also be assessed for malnutrition according to Subjective Global Assessment, administered by the nutritionist. Hand grip strength and body impedance will be also measured.

Postoperative complications grading, will be defined a priori according to the system proposed by Seely.

Fatigue score using the Fatigue Index.
Process measures will include adherence to the protocol (as recorded in a journal), in addition to safety.

Assessment of glutathione in blood will be measured at baseline, end of prehabilitation period, and 4 weeks after surgery. The glutathione measurement involves taking 0.5ml of blood, and will provide an index of glutathione (antioxidant) status within the body.

Assessment of CRP in blood: CRP will be assessed to provide a marker of inflammation. The measurement will be taken at the same time as the glutathione blood measurement is taken, and requires 1ml of blood.

The research assistant performing the 6MWT and helping the subjects with the questionnaires and forms will not be aware of the study hypothesis, randomization, and will not have access to the patients’ data.

Patients will return to the hospital at 4 weeks to see the surgeon, and will be asked to come at 8 weeks after surgery to collect the postoperative data. Patients coming to the hospital for the latter visit will be reimbursed for their expenses incurred in parking their car.

Statistical Analysis

To determine if differences exist between groups, patient characteristics will be analyzed using student’s t-test and chi squared test, as appropriate (i.e. categorical vs continuous variables). Measurements of the dependent variables are repeated multiple times per patient under different conditions, thus the data will be analyzed using repeated measures anova. If the data is not normally distributed, a non-parametric equivalent, Friedman’s Test, will be used.

Clinical pathway for perioperative care

Surgery will be performed by Dr Ferri and Dr Mulder at the Montreal General Hospital. Surgical approach, including laparoscopic or open surgery, will be at the discretion of the surgeon. Perioperative care will follow the McGill Surgical Recovery Pathway, also called Enhanced Recovery Program (ERP), which is an evidence-based care plan set up by the Surgical Recovery (SuRe) multidisciplinary committee of the McGill University Health Centre. The ERP for esophageal surgery has been operational since June 2010 and includes standardized patient education, preoperative feeding, laparoscopic approach, multimodal analgesia, maintenance of perioperative normothermia, early oral intake, early mobilization, early removal of catheters and drains, and a planned 7-day hospital stay.

Feasibility and time line

Approximately 50 esophageal cancer resections are performed annually at the Montreal General Hospital. If 75% of patients are eligible, and 75% of them agree to participate, we would enroll 1 patient each week (20 to 30 weeks for enrolment). In our institution, time from decision for surgery to the operation currently ranges from three to four weeks (it depends whether they receive neo-adjuvant chemotherapy), which will allow for the time required for prehabilitation. Thus, a period of one and a half years for completion of this project is a feasible time.
Power and sample size calculation

There is currently no data on the effect of prehabilitation for esophageal surgery on functional capacity after surgery. We therefore use an estimate based on our previous trials on prehabilitation. The estimator of effectiveness is the change in functional walking capacity from baseline 6MWT to 8 weeks after surgery. In our previous clinical trial, the control group receiving a recommendation for walking and breathing were on average -15 (66) meters below baseline. In a recent pilot trial where exercise, nutrition, and psychological care were given, patients were on average +37 (68) meters above baseline. The difference to be detected by independent t-test is thus 53 meters with pooled standard deviation of 68.5 and an effect size of 0.77. With a sample size of 56, (28 patient per group), we will have 80% power (with an alpha level of 0.05) to detect a difference of the same magnitude. Owing to differences between esophageal and colon surgery patient populations, a conservative estimate to avoid underpowering would be an effect size of 0.7, yielding a total sample size of up to 68, (34 per group).

Significance

There is a strong realization that many side effects associated with surgical stress can be attenuated, thus facilitating the recovery process. 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 esophageal surgery as well as contributing to our understanding of which outcome measures represent a valid index of recovery and are sensitive to changes. The model of esophageal surgery for cancer was chosen because of the extensive impact this cancer has on postoperative outcome, therefore determining whether a multimodal intervention, timely based, could increase preoperative reserve and therefore attenuate the surgical stress response leading to reduced postoperative complications is indicated. The results of this randomized study will form the basis for studies in other surgical conditions and aimed at optimizing the perioperative period and minimizing morbidity, thus improving recovery and quality of life in surgical patients.

Facilities available

The investigators are all located at the Montreal General Hospital. The project will be run out of the laboratory in the Department of Anesthesia at the Montreal General Hospital. This lab is equipped for physiologic measurements and staffed with a research associate, a research assistant and fellows. Computer facilities for data collection and management will be available through the Thoracic surgery patient database and Steinberg-Bernstein Centre for Minimally Invasive Surgery at the Montreal General Hospital.

Confidentiality

The information collected for the purpose of the research study will be kept strictly confidential and locked in a cupboard in a locked room. All staff, including students, have signed a confidentiality agreement. The computer where data are entered is located in a locked room and not accessible.
Registration

The proposal has been registered for Clinical Trials.

References


