Feasibility of Multimodal Prehabilitation to Enhance Preoperative Functional Capacity of Esophageal Cancer Patients During Concurrent Neoadjuvant Chemotherapies
A Pilot Interventional Study

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A Thesis Submitted to McGill University
In Partial Fulfillment of the Requirements of the Degree of Experimental Surgery

Master of Sciences

April 2021

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List of Abbreviations & Initials

6-MWD/6-MWT = 6- Minute walk distance/test

ACSM = American college of sports medicine

ASA = American society of anesthesiologists

ATS = American thoracic society

BIA = Bioelectric impedance analysis

CCI = Comprehensive complication index

CDC = Clavien-dindo classification

CTCAE = Common terminology criteria for adverse events

CTX = Chemotoxicities

CHAMPS = Community Health activity model program for seniors

COPD = Chronic obstructive pulmonary disease

CPET = Cardiopulmonary exercise test

CCI = Comprehensive complication index

CDC – Clavien-Dindo classification

CRP = C-reactive protein

DASI = Duke activity score index

DFS = Disease-free survival

DLT = Dose-limiting toxicities

EAC = Esophageal adenocarcinoma

ESCC = Esophageal squamous cell carcinoma

ED = Emergency department

EMR = endoscopic mucosal resection

ESD = Endoscopic submucosal dissection

ERAS = Enhanced recovery after surgery

ERP = Enhanced recovery pathway

ESAS = Edmonton symptom assessment score

ESPEN = European society for clinical nutrition and metabolism

FACT-E= Functional assessment of cancer therapy - esophagus

FFM(i) = Fat-free mass (index)

GERD = Gastro-esophageal reflux disease

GCP = Good clinical practice

HADS = Hospital anxiety and depression scale

HGS = Handgrip strength

HR = Hazard ratio

HRQoL = health-related quality of life

IMT = Inspiratory muscle training

LOS = Length of Stay

LBM = Lean body mass

MCID = Minimal clinically important difference

NACT = Neoadjuvant chemotherapy

NAT = Neoadjuvant therapy

NCRT= Neoadjuvant chemoradiotherapy

OR = Odds ratio

OS = Overall survival

PG-SGA = Patient generated-subjective global assessment

PHIPA = Public health information protection act

POETTS = Peri-operative testing and training society

RPE = Rated perceived exertion

REB = Research ethics board

SkM(i) = Skeletal muscle (index)

STS = Sit to stand test

TUG = Timed-up and go

VO_2AT = Oxygen consumption at anaerobic threshold

VO_2 peak= peak oxygen consumption

Abstract

Background: The prognosis among patients with esophageal adenocarcinoma (EAC) is poor, moreover the aggressive nature of the disease and treatments often leads to a pervasive decline in functional status throughout the perioperative period. Importantly, prehabilitation has been demonstrated to improve functional trajectories in patients with esophagogastric cancers. Despite the logical rationale, few studies have investigated its clinical potential during neoadjuvant chemotherapy (NACT). The thesis aimed to (1) assess the safety and feasibility of prehabilitation (2) investigate the impact of a multimodal prehabilitation program on preoperative functional status and QoL, and (3) to document the short-term clinical outcomes of EAC patients receiving prehabilitation concurrently with NACT. It was hypothesized that prehabilitation would be feasible even with the challenges of the disease and treatments. Additionally, researchers anticipated an improvement in cardiorespiratory fitness following prehabilitation.

Methods: The current thesis describes a single cohort pilot study operated out of a single high-volume centre. Patients diagnosed with non-metastatic EAC referred to receive NACT prior to an esophagectomy were approached for recruitment. All patients received a personalized multimodal prehabilitation program until surgery, varying with respect to modality of exercise delivery (home-based, in-hospital supervised, teleprehabilitation supervised. Program feasibility was dependent on patients' weekly self-reported adherence to exercise and nutritional interventions. All patients performed a complete battery of functional tests at baseline and before surgery, which included: 6-MWT, CPET, TUG, HGS, STS and 1-arm curl test. Patient reported outcomes included: FACT-E, ESAS, DASI, CHAMPS and HADS.

Results: Between August 1ˢᵗ, 2019 and November 1ˢᵗ, 2020, a total of 23 patients met the inclusion criteria, 56.5% (n=13) were recruited. All received either home-based (n=6), in-hospital supervised (n=5) or teleprehabilitation (n=2). All patients completed the program, performed both evaluations and received their respective surgeries. The cohort reported a satisfactory overall adherence rate to the program (68.9% vs 70%, p=0.7). Cardiorespiratory fitness as determined by the 6-MWD did not significantly change (p=0.6). Conversely, muscle strength improved, as determined by timed-repetitions performed in both sit-to-stand (p=0.004) and 1-arm curl tests (p=0.005). The median compliance to NACT was 100%, with only three

patients ceasing treatments prematurely. The five patients did not experience postoperative complications, the median length of stay was seven days, and the incidence of in-hospital mortality was two.

Conclusion: The thesis confirmed that personalized multimodal prehabilitation programs could be safe and feasibly delivered to EAC patients during NACT. Notwithstanding the lacking functional improvements, the results suggest that prehabilitation may have played a role in preserving cardiorespiratory fitness, functional status and QoL throughout the preoperative period.

Abrégé

Contexte: Le pronostic des patients atteints d'un adénocarcinome de l'oesophage (ACE) est mauvais. De plus, la nature agressive de la maladie et des traitements conduit souvent à une dégradation généralisée de l'état fonctionnel tout au long de la période périopératoire. Néanmoins, il a été démontré que la préadaptation améliore les trajectoires fonctionnelles chez les patients atteints de cancers de l'œsophage. Malgré ce raisonnement, peu d'études ont étudié le potentiel clinique de la préadaptation à la chirurgie pendant les traitements de chimiothérapie néoadjuvante (NACT). La présente thèse vise (1) à évaluer la sécurité et la faisabilité de la préadaptation, (2) à étudier l'impact d'un programme de préadaptation multimodal sur l'état fonctionnel préopératoire et la qualité de vie des participants, et (3) à documenter les variables cliniques à court terme des patients atteints de ACE recevant simultanément une préadaptation et des NACT. L'hypothèse primaire de cette thèse est que la préadaptation serait faisable malgré les défis de la maladie et des traitements. De plus, l'hypothèse secondaire est que la préadaptation engendra une amélioration de la condition cardiorespiratoire chez les participants.

Méthodes: Cette thèse rapporte les résultats d'une étude pilote, opéré à partir d'un seul centre sous forme de cohorte unique a modalités d'intervention variable. Les patients diagnostiqués avec ACE non métastatique référés pour recevoir NACT suivi d'une œsophagectomie ont été approchés pour le recrutement. Tous les patients de la cohorte ont reçu un programme de préadaptation multimodal personnalisé jusqu'à la chirurgie, variant en ce qui concerne la modalité de prestation de l'exercice (à domicile, supervisé à l'hôpital, supervisé par télépréadaptation. La faisabilité du programme dépendait de l'adhérence hebdomadaire à l'exercice et aux interventions nutritionnelles, autodéclarée par les patients. Ceux-ci ont, de plus, participé à une batterie de tests et questionnaires lors de leur recrutement ainsi qu'avant leur chirurgie, afin d'évaluer leur santé fonctionnelle et qualité de vie préopératoires (tests: 6-MWD, CPET, STS, HGS, TUG, flexion à un bras & questionnaires: FACT-E, ESAS, HADS, DASI, CHAMPS).

Résultats: Entre le 1er août 2019 et le 1er novembre 2020, un total de 23 patients répondaient aux critères d'inclusion, dont 56,5% (n = 13) ont été recrutés et alloués aléatoirement à recevoir le programme de préadaptation à domicile non supervisés (n = 6) ou supervisés (n = 5; intervention en hôpital & n=2; par télépréadaptation). Tous les patients ont terminé le programme, effectué les deux évaluations et reçu leurs chirurgies respectives. Le taux d'adhérence moyen de la cohorte était similaire à celui rapporté dans la littérature (68,9% vs 70%, p = 0,7). La capacité cardiorespiratoire telle que déterminée par le 6-MWD n'a pas changé de manière significative (p = 0,6). À l'inverse, la force musculaire s'est améliorée (test assis-

debout; p = 0,004 & test de flexion à un bras; p = 0,005). L'adhérence médiane au NACT était de 100%, avec seulement trois patients arrêtant prématurément les traitements. Cependant, cinq patients n'ont pas présenté avec des complications postopératoires, la durée médiane du séjour à l'hôpital était de sept jours et l'incidence de mortalité hospitalière était de deux.

Conclusion: La thèse a confirmé que les programmes de préadaptation multimodaux personnalisés pourraient être sûrs et réalisables pour les patients ACE pendant NACT. Malgré l'absence d'améliorations cardiorespiratoires, les résultats suggèrent tout de même que la préadaptation peut avoir joué un rôle dans la préservation de la santé fonctionnelle et de la qualité de vie tout au long de la période préopératoire.

Mots clés:

Cancer de l'œsophage, chimiothérapie néoadjuvante, préadaptation, santé fonctionnel, capacité fonctionnelle, aptitude cardiorespiratoire, thérapie multimodale, exercice thérapeutique en oncologie, tolérance aux traitements

Acknowledgements

Contribution of the Authors

The current thesis is the product of a master's research project, evidently, the latter would not have been possible without the support and assistance of several important contributors. In this regard, please find the respective contributions of the student, and supporting staff:

Kenneth Drummond BSc, MSc(c), and CSEP-CEP: Was responsible for oversight, coordination and management of the research project, recruitment, patient baseline and follow-up assessments, provision of exercise prescriptions and regular follow-ups. He coordinated with patients throughout the continuum of care, monitored patient progress, tracked adherence and coordinated with the appropriate team members as needed. He assisted in the development of the amendment and communications with REB. He is also the author of all chapters in the current thesis.

Enrico Minnella, Ph.D., M.D: Was a co-investigator for the project, who assisted in the development of the research protocol, preparation of documents for the research ethics review board, supervision of its execution, oversight of patient health and CPETs revision.

Lorenzo Ferri, Ph.D., M.D.: Was a co-Principal Investigator for the project, assisted in the development of the research protocol and was the primary surgical investigator and reviewed the manuscript. With respect to the clinical study he overlooked perioperative patient care, including diagnosis, staging, surgical interventions and optimizing recovery.

Franco Carli, M.Phil, M.D.: Was a co-Principal Investigator, assisted in the developed the research protocol, documents for the research ethical review board, oversight of the project, patient care, and the graduate student work. This included clinical activities, research publications and manuscript revision.

Chapter 1 - Introduction

1.1 Statement of the Problem

Cancer of the esophagus is a male dominant disease associated with a challenging array of symptoms, complicated management protocols and a poor overall prognosis. Despite ongoing medical advancements and being only the eighth most common cancer, it is one of the leading causes of cancer-related deaths worldwide, having a low overall 5-year survival rate of approximately 18%, varying with respect to geographical location and institution (4-40%).(1)

The daunting clinical outcomes can be largely attributed to advanced disease progression at time of diagnosis. As a result, the majority of patients are deemed ineligible for treatment with curative intent.(2) Like most solid cancers, surgical resections, specifically esophagectomies, are central to the management of esophageal carcinomas, offering the greatest curative potential. The procedure, however, is invasive and is associated with a high incidence of postoperative complications, morbidity, disease recurrence and poor disease-free survival (DFS).(3) To this end, some patients may be precluded from surgery due to significant comorbidities, older age and low performance status.(2, 4)

The unfavourable long-term outcomes associated with surgery alone have compelled several institutions to conduct large-scale randomized controlled trails investigating the impact of preoperative chemotherapy and or radiotherapy. (5-7) The outcomes of these have proved promising, highlighting the therapeutic potential of neoadjuvant therapies (NAT) to reduce tumor activity, improve complete resection rates leading to improved disease-free and overall survival rates. NAT followed by esophagectomy has since been adopted as gold standard for the management of locally advanced esophageal cancers. Notwithstanding its advantages, NAT is a significant stressor. It is not always well tolerated and can negatively affect physiological reserves, physical fitness, overall functional status and health-related quality of life (HRQoL).(8-11)

Globally, esophageal squamous cell carcinoma (ESCC) is the most prevalent histological subtype, however, the incidence of esophageal adenocarcinoma (EAC) has witnessed rapid growth in the more industrialized regions, notably Europe and North America.(2, 12) The latter parallels the rising prevalence in obesity, gastro-esophageal reflux disease (GERD), and Barrett's Esophagus (BE), all of which are known risk factors for EAC.(13)

The clinical manifestations of the disease include but are not limited to dysphagia, gastric

reflux, involuntary weight loss, and anorexia. Unsurprisingly, it is not uncommon for patients to be malnourished, sarcopenic or deconditioned at diagnosis. (14) Moreover, the wasting nature of the disease and its management can exacerbate existing deficits and contribute to further declines in health and functional status. Preoperative fitness has become increasingly appreciated as an important prognostic parameter due to its ability to predict postoperative morbidity and long-term survival in these patients.(15-17) This realization has underlined the importance for preoperative patient optimization and the apparent need for pre-conditioning programs that counter the deleterious effects of both the disease, its management and improve perioperative trajectories.

Prehabilitation involves optimizing a patient's health and functional status prior to a physiologic stressor, such as surgery or NAT, with the aim of improving patient tolerance and subsequent recovery. (18) A multimodal approach is typically preferred, and prioritizes physical, nutritional and psychosocial support, to attenuate the impact of malnutrition, physical deconditioning and anxiety.(19) Additional support may be needed for pharmacological and glycemic optimization, and in select cases for smoking and alcohol cessation. Several studies have investigated the impact of unimodal interventions, such as exercise or nutritional support alone. Christensen et al., recently demonstrated that a high-intensity exercise program was safe and feasible to be implemented preoperatively. Moreover, it produced improvements in in physical fitness and HRQoL.(20) Similarly, a study published by Minnella and colleagues in 2018, demonstrated that with respect to standardized care, a multidisciplinary approach to prehabilitation, in patients scheduled for esophagogastric cancer surgery improved perioperative functional capacity, as assessed by changes in 6-minute walk distance (6-MWD).(21) Despite the increasing evidence for prehabilitation programs, there is a lack of research investigating the impact of personalized multimodal programs in these patients. This holds especially true in the context of patients receiving neoadjuvant therapies (NAT).

1.2 Purpose

The aim of the current thesis is to (1) assess the feasibility of delivering multimodal prehabilitation programs to patients with locally advanced EAC electively referred for disease management with NACT followed by an esophagectomy, (2) investigate the impact of a personalized multimodal prehabilitation program on preoperative health and functional capacity using objective and subjective assessment tools, finally (3) to document the short-term clinical outcomes of EAC patients receiving prehabilitation concurrently with NACT.

1.3 Hypothesis

With respect to the primary objective, it is hypothesized that it would be safe and feasible to deliver a personalized multimodal prehabilitation program to patients with EAC throughout the preoperative period and concurrent cancer therapies. For the secondary objective, it is hypothesized that such a prehabilitation program would result mainly in significant improvements between pre-and post-intervention measures of cardiorespiratory fitness.

Chapter 2 - Literature Review

2.1 Carcinoma of the Esophagus

The Biology of Cancer

The esophagus is a long tubular structure comprising of four layers of tissue that connects the pharynx to the stomach. It is unique in its ability to execute the action of swallowing through timely and coordinated contractions of the surrounding smooth muscle, allowing for the movement of food to the stomach.[22] Esophageal cancer is a disease whereby cells in the esophageal epithelium undergo uncontrolled cellular replication, proliferation and later formation of a malignant tumour.[23] Beginning in the inner mucosa, the lesion can grow medially into the lumen but also laterally to the adventitia, which is often seen in the more advanced stages.[23, 24] In many cases this can negatively affect the mechanical transport of food, resulting in dysphagia, altered dietary patterns and subsequent weight loss.

Epidemiology

The prevalence of esophageal cancer is highest among men and rises with increasing age.[1] There are several pathologic subtypes the incidence varies according to geographical location.[25] ESCC is the most common, followed by esophageal adenocarcinoma, and together they account for over 95% of cases. [23, 26]

ESCC classically originates in the basal cells of the squamous epithelium, often in response to chronic exposure to carcinogens and stressors such as tobacco, alcohol, and hot beverages [2, 27]. Other known risk factors include achalasia, poor dietary habits, male gender, select inherited genetic predispositions and low socioeconomic status. [23, 27] The highest incidences of ESCC are observed in Asian and Eastern countries in what is commonly called the "esophageal cancer belt".[2, 28] China is among them, and alone is responsible for 50% of the global esophageal cancer burden.

EAC is derived from abnormal glandular mucus-producing cells of the inner most layer.[23, 28] Its etiology is less clear than ESCC, nevertheless it is believed to be related to reflux-induced stress along the esophageal mucosa provoking metaplasia of the squamous cells to a columnar morphology.[2, 28] Frequent exposure to acid-related stress is recognized to cause permanent changes in the epithelium resulting in BE and in some cases EAC.[2, 23, 28] The main risk factors for EAC include GERD, BE, obesity, smoking, male gender, and poor dietary

habits.(2, 23) EAC is less common from a global standpoint, yet it appears to have a higher relative incidence in the developed western countries. Over the past four decades industrialized regions, such as North America, Europe and Australia, have witnessed a decline in ESCC with a sustained increase in EAC.(1, 2)

Clinical Manifestations & Prognosis

It is largely a disease of the elderly, with a peak incidence between 60 to 80 years and is therefore not surprising that patients often have several comorbidities at the time of diagnosis.(28) Often asymptomatic during the early stages, later symptoms commonly include heartburn, dysphagia, odynophagia and unintended weight loss.(14) A significant concern with disease progression is dysphagia because it can be especially challenging for patients to self-nourish and maintain nutritional adequacy.(24) In fact, malnutrition and sarcopenia commonly co-exist in esophageal cancer, the combination of which increases the risks of frailty, therefore making these patients an especially vulnerable group.(29) Frailty has been demonstrated to be an strong predictor of increased postoperative morbidity, length of stay and overall recovery.(30)

The symptoms of the disease typically occur with disease progression, therefore the majority of patients with esophageal cancers are diagnosed with advanced stage or metastatic disease, and less than 40% are eligible for treatment with curative intent.(24) Unsurprisingly, esophageal cancer has a high mortality rate, with prognosis influenced by a number of disease-related factors, which include anatomic location, histopathology and staging, but also other patient specific variables, most notably: age, comorbidities, physical performance, nutritional status, and HRQoL.(2, 31-33) Even with improvements in pharmacologic and surgical techniques, the 5-year survival rate remains below 20%. Recognizing the importance of physiologic and phenotypic parameters, Hodari and colleagues used a multifactorial frailty index to assess frailty in surgical candidates for esophagectomies. The results from the 2095 patient cohort highlighted that elevated frailty scores were positively correlated with increased postoperative morbidity and mortality.(34)

Despite significant advancements in cancer care, various therapies often come at a cost to physical, nutritional and psychological health, resulting in a low physiologic and functional reserves.(33) Given that patients with esophageal cancer are already at a high risk for malnutrition, sarcopenia, frailty, and cachexia, the costs are not insignificant.(14)

2.2 Modifiable Risk Factors

Weight loss & Malnutrition

Given the putative risk factors, common comorbidities and symptomatology it is therefore not surprising that patients with esophageal cancers are often significantly physically and nutritionally compromised at diagnosis.(33) One article noted that >70% of patients presented with significant ($\Delta > 10\%$ in body weight (BW)) unintentional weight loss at the time of diagnosis.(35) Bozzetti et al. conducted a large multi-centered study investigating the baseline nutritional status among a diverse oncological population and noted that patients with esophagogastric cancers had the largest degree of weight loss (ΔBW) and the highest reported incidence of malnutrition.(36)

Unintended weight loss is a hallmark feature of malnutrition and is common the result of a sustained nutritional (usually protein and/or energy) disparity and/or increase in energetic expenditure.(37) The latter typically occurs in advanced staged cancers, as a result of tumor-induced inflammation, alterations in metabolism and dietary intake, which ultimately contribute to an overall catabolic state.(14) Preserving nutritional status is especially challenging in patients with esophageal carcinomas, given the anatomical location of the tumor. Disease progression can result in discomfort when swallowing and even complete physical obstructions of the lumen, thereby obliging patients to adopt modified textured diets and altered dietary patterns. In extreme cases, whereby modified texture or liquid diets cannot be tolerated, more invasive nutritional approaches may also be deemed necessary.(38)

Malnutrition is a physiological state resulting from a sustained nutritional imbalances, usually a protein-energy deficit, often characterized by significant weight loss (typically skeletal muscle), altered body composition and reduced muscle function.(38) Handgrip strength and repeated chair stand tests have been recognized as an acceptable measures to assess deficits in muscle strength.(39) The global leadership initiative on malnutrition (GLIM), recently published a consensus statement, endorsing the use of etiological and phenotypic parameters in the clinical setting to comprehensively identify patients at risk of malnutrition. This includes utilizing the standard anthropometric cut-offs: unintended weight loss of >10%, low BMI (<18.5 kg/m^2), low FFMi (<15 kg/m^2 in women or <17kg/m^2 in men) but also reductions in muscle strength and functional performance.(40, 41) Severity is classically stratified according to the observed change in body mass over a defined period of time.(42)

Predictably, malnutrition is correlated with poor prognostic outcomes in surgical candidates as affected patients are more susceptible to physiological stressors.(38) In this regard, malnourished patients may have a lower compliance to NAT, which can adversely affect perioperative morbidity, recovery and overall survival.(14, 42)

Cancer Cachexia

In some cases, severe malnutrition in conjunction with an elevated inflammatory status and catabolic drive, can result in a state of cachexia.(14) In 2011, an international consensus by Fearon et al., defined cachexia as: "a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment".(43) Distinguishing features include, decreased food intake, a hypercatabolic state, reductions in bodily stores and physical function. Cachexia may not be overtly present at diagnosis, however the cachectic drive exists as a continuum, influenced by a number of factors including the disease stage, neuro-endocrine changes, inflammatory and catabolic mediators, anorexia, mechanical changes in the upper gastrointestinal function but also oncological treatments, which may further exacerbate the cachectic pathways.(14)

The prevalence of cachexia is frequently under-reported in patients with adenocarcinomas, as disease-related myopenia and nutritional deficits are often concealed by their elevated BMI and adiposity at diagnosis.(14, 42) In a study cohort of 205 newly diagnosed patients with esophageal carcinomas, 54% were classified as overweight (BMI 25-29.9) or obese (BMI>30), 82% of which had EAC. While there was a high incidence of elevated body mass, 74% of patients were actively losing weight, and 34% had experienced clinically severe weight loss.(44) In order to ascertain a more comprehensive understanding of a patient's status it is important to assess patients with respect to: dietary patterns, anorexia, circulating catabolic factors, skeletal mass and function and HRQoL.(43) The nature of the disease, is such that it increases patient susceptibility for cachexia, and increases their risks of adverse short- and long-term outcomes.(14, 33)

Disease-Related Sarcopenia & Physical Decline

As previously mentioned, esophageal cancer patients are often involuntarily subject to altered dietary habits and weight loss. Reductions in lean body mass (LBM) is a major contributor

to the observed weight changes in these patients and it is not uncommon for most to become sarcopenic at some point.(45) Sarcopenia is similar to cachexia in that it is a syndrome resulting from a multitude of causative factors, but is distinct in that it is specifically defined by a reduction is skeletal tissue and function.(39) Boshier et al., recently published a meta-analysis and systematic review of 29 studies, investigating anthropometrics phenotypes in candidates for esophageal cancer surgeries. They reported that the overall prevalence of sarcopenia was approximately 38% and ranged from 16 to 56%.(46) Similar findings have been reported elsewhere. The prevalence of sarcopenia is exceptionally high in esophageal cancer, with one study reporting an incidence of 75%.(47) Decreased reserves of LBM are often paired with reductions in strength and physical performance.(45) Patients with sarcopenia commonly have reductions in physical performance status, as reflected by their slower gait speeds, lower chair rises and grip strength scores.(39) It is not surprising that these impairments in physical status can adversely affect perioperative trajectories. Additionally, it is well documented that these impairments can be further aggravated by neoadjuvant therapies.(10) To this end, not only is sarcopenia related to declining functional status, but also with reduced tolerance to NACT regimens, access to surgery, and an increased risk of select postoperative complications.(Elliott et al., 2017)

2.3   Disease Management

The majority of patients with esophageal cancers have advanced diseases at time of diagnosis which often makes them ineligible for curative management and frequently results in a poor prognosis.(48) In the case of non-metastatic, the treatment modality will vary according to the histopathology, staging and location. In order to determine and streamline the optimal therapeutic approach for disease management, many institutions have instituted multidisciplinary tumor boards for comprehensive clinical assessments and review.(49)

Disease management interventions can be broadly subdivided into two categories, locoregional or systemic. Locoregional interventions include radiotherapy and surgery, which includes esophagectomies but also the less invasive alternatives such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).(50) Systemic therapies generally refer to intravenous or oral anti-neoplastic chemotherapy, which has a broader distribution than

locoregional interventions.(48) That being said, depending on the clinical context, it is not uncommon to combine both treatment modalities.

Early Disease Management

If diagnosed in the earlier stages, esophageal cancers may be treated with either less invasive local endoscopic resection techniques, EMR or ESD, or local radiotherapy.(2, 50) Endoscopic tumor resection may be appropriate if the tumor is sufficiently small, shallow and has not spread to proximal lymph nodes, thereby sparing patients from more invasive interventions.(50) As compared to more extensive surgical procedures there is an increased risk of later disease recurrence.

Locally Advanced Disease Management

a)   Surgical Resections

As for most solid tumor cancers, surgical resections and in this case esophagectomy, have formed the backbone of disease management, offering patients the highest curative potential.(2, 24) The surgery is inherently invasive, as it involves the surgical removal of part of the esophagus and the surrounding tissue, which often includes a portion of the gastric cardia.(24) Although necessary, it imposes a large burden of physiologic stress on patients and is notoriously associated with a high incidence of postoperative complications (50%); the majority consisting of pulmonary complications, laryngeal nerve palsy, anastomotic leaks, and conduit necrosis.(50, 51) The surgical approach will vary between patients and is influenced by numerous factors, including the anatomical location of the tumor, its size, margins and the surrounding nodes affected.(2)

In an attempt to mitigate the iatrogenic stress associated with laparotomies and thoracotomies, there has been a growing shift towards minimally invasive procedures using laparoscopic techniques.(49, 50) The TIME-Trial, an RCT conducted by Biere and colleagues, compared the clinical outcomes of minimally invasive esophagectomy (MIE) to the traditional open approach.(52) Unsurprisingly, they reported less blood loss, postoperative complications, pain, a shorter length of hospital stay (LOHS) and an improved self-reported measures of HRQoL.(52, 53) This was in-line with the results of other comparative studies. More recently, Yerokun et al., performed a population-based analysis of both approaches among 4266 surgical

patients and noted similar surgical outcomes, with improvements in rates of recovery (LOHS, 10 vs. 11, p<0.046). (54) A meta-analysis of 33 studies and 13 269 patients showed further support for MIE over open-esophagectomies, as they were associated with significantly less post-operative pulmonary complications (OR = 0.56, P<0.001), blood loss (SMD = -1.44, p<0.001) and LOHS (SMD = -0.51, p<0.001).(55) Therefore, when applicable MIE is strongly encouraged for surgical resections.

b)   Rationale for Neoadjuvant Therapies (NAT)

Notwithstanding the advancements surgical techniques, MIE or otherwise, is associated with high postoperative morbidity, prolonged impairments in physical status and HRQoL, but also with unfavourable complete resection rates and survival outcomes.(50, 56) Accordingly, adjuvant perioperative therapies designed to promote tumor downsizing, improve resectability and minimizing the metastatic potential, have become increasingly prevalent in the oncological setting with the aim of improving surgical outcomes and DFS.(57) Currently, like many locally advanced solid tumors, they considered to be a standard of practice for the treatment of locally advanced cancers offering improved survival outcomes.

Adjuvant therapies involve the administration of either chemotherapeutic agents alone or in combination with radiation (chemoradiotherapy), which is given either prior to (neoadjuvant) and/or after (adjuvant) attempting a curative surgical resection.(50) The therapeutic approach may vary according to the institution, but is also dependent on the pathologic subtype, size, spread, location and patient tolerability.(57) A robust meta-analysis of 24 RCTs was published in 2011, which reviewed the survival outcomes of patients who received an esophagectomy with or without neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NCRT).(58) The results confirmed that both NACT (HR= 0.87, 95%CI(0.79,0.96), p<0.005) and NCRT (HR= 0.78, 95%CI(0.7,0.88), p<0.0001) combined with surgical resections resulted improved survival outcomes compared to surgery alone, which was held true in the case of both esophageal cancer subtypes, EAC and ESCC.

c)   Neoadjuvant Chemotherapy (NACT)

Chemotherapy is widely recognized as the standard approach to treat most advanced stage cancers minimizing the disease progression and enhancing systemic control. Not surprisingly, chemotherapy has been increasingly utilized to better treat most advanced stage esophageal cancers. A large clinical trial studied the effects of NACT preceding surgery with surgery alone

in 802 patients with esophageal carcinomas of mixed histology.(5) Notwithstanding the mixed subtype distribution, patients receiving preoperative chemotherapy observed a mean improvement in 5-year survival (23% vs 17%) with respect to those receiving surgery alone (HR= 0.84, 95%CI(0.72-0.98), p=0.03). The effects of treatment on both ESCC and EAC histologic subtypes were consistent with the overall findings of the study, confirming the benefit of perioperative chemotherapy.

It is argued that the adenocarcinoma subtype are less sensitive than ESCC to radiotherapy, making NACT a preferred treatment modality in most institutions.(50) Notably, the MAGIC trial underscored the advantage of preoperative chemotherapy regimens in patients with EAC, as opposed to surgery alone. Despite the fact that many of these patients were deconditioned and vulnerable, the majority (90%) were able to tolerate three or more cycles of NACT. Moreover it resulted in significant tumor downsizing, better rates of complete resections, and improved 5-year survival rates (36.3% vs. 23%).(3) Similar results have been observed in other large scale trials, as compared to surgery alone, perioperative chemotherapy resulted in improved curative resection rates (84% vs. 73%, p=0.04) and survival outcomes (38% vs. 24%).(6, 59) While most of the trials investigating NACT regiments have focused on EAC patients, it should be noted that NACT has also been demonstrated to offer comparable benefits in patients with ESCC. A multicentric RCT conducted by the Japanese Clinical Oncology Study Group investigated the impact of preoperative NACT with surgery in patients with ESCC. As compared to surgery alone, the NACT group had better rates of disease-free survival (55% vs. 45%, p=0.037).(60)

d)   Neoadjuvant Chemoradiotherapy (NCRT)

Similarly, combined radiation and chemotherapy has also been widely used in combination with surgery, with the aim of improving surgical and survival outcomes.(2) To date, there have been several large scale clinical trials and meta-analyses confirming the advantages of NCRT with curative esophagectomy over surgery alone.(58) The majority of studies investigating perioperative NCRT had study cohorts of mixed histologic subtypes. Nonetheless, the results have still been promising, highlighting survival improvements in patients with ESCC and EAC.(58, 61). Further analysis of the results revealed that among the esophagogastric patients receiving NCRT, the hazard-ratio (HR) for mortality in ESCC patients was 0.80 (95%CI(0.68,0.98), p=0.004) and 0.75 (95%CI (0.59,0.95), p=0.02) for those with EAC, inferring survival benefits were observed in both subtypes.(58) The results from the CROSS trial

were published afterwards and similarly confirming that NCRT had a profound impact on contemporary esophagogastric cancer care. In the study, esophageal cancer patients received tumor resections with or without NCRT. Among the patients in the NCRT group, they reported a complete pathologic response in 29%, in addition to improved rates of complete resection (92% vs 69%, p<0.001)) and 5-year survival (47% vs. 34%).(62) Furthermore, a complete pathologic response was seen significantly more in patients with ESCC compared to EAC (49% vs. 23%, p=0.008), suggesting a greater sensitivity to the combined treatment modality.(62)

Some studies have compared preoperative chemotherapy with NCRT, however the cohorts have been limited to patients with the adenocarcinoma histologic subtype.(63, 64) Nevertheless, there is support for the use of NCRT or NACT for the management of EAC, as they both have led to appreciable improvements in complete resection rates and 5-year survival rates.(7, 65)

In summary, the optimal neoadjuvant treatment has not been definitively established as trials have differed with respect to agents, dosing and regimens and many have included heterogeneous patient populations.(2) Accordingly, the preferred treatment modality for a given patient is often institution specific.(50) There is some data to suggest NCRT is favorable in the management of locally advanced ESCC, however, NACT and NCRT have both been recognized as acceptable treatment options for locally advanced EAC and ESCC.(58, 62)

2.4 Consequences of Cancer Therapies

Following the results of several large-scale studies (MAGIC, CROSS, OE02) preoperative NACT or NCRT have become integral to the management of esophageal cancers.(3, 5, 7) Although they confer survival benefits, at the same time they impose physiologic stress and, in some cases, exacerbate pre-existing health conditions or deficits in nutritional, physical or psychological status. This can contribute to deterioration in functional status and in-turn reduced independence and HRQoL.(33, 66)

As previously noted, at diagnosis, many patients with esophagogastric cancers present with significant reductions of LBM, and specifically skeletal muscle. This phenomenon is often attributable to the catabolic nature of the disease, energetic imbalances, advanced age and in some cases physical inactivity, and is commonly further compounded by the cytotoxic effects of the chemotherapeutic agents.(14, 45) The latter induce oxidative stress, suppress the activity of

mammalian target of rapamycin (mTOR) kinase and protein synthesis and promote a cascade of catabolic protein pathways.(45)

Weight loss, specifically muscle wasting, is an important consideration in esophageal cancer care, as it contributes to not only persistent decline in physical status but also a lower tolerance to treatments, increasing the risk for dose-limiting toxicities (DLT) and later post-operative morbidity.(33, 42, 45) Compliance to neoadjuvant regimens varies according to the agent used, the dose, frequency and patient-related factors. In esophageal cancer NACT completion rates have been reported between 44 and 95%,(7, 17, 57) however, it has been reported that up to 70% of patients are unable to complete their prescribed perioperative NACT protocols due to DLT.(17, 45)

With respect to skeletal muscle mass, physical fitness is recognized as an important surrogate marker for an individual's physiologic reserves and ability to tolerate metabolic stressors.(17, 45) Also, cardiorespiratory fitness, as determined by VO_2 at the anaerobic threshold (VO_2AT) and peak exercise (VO_2peak), have been shown to correlate with postoperative morbidity and mortality following major elective surgeries.(16)

Recognizing the significance of physical fitness and physiologic reserve in the management of esophagogastric cancers, Jack and colleagues performed cardiopulmonary exercise testing in patients electively referred for NACT followed by surgery.(17)

In the study cohort, 44% of the patients completed the prescribed NACT protocol, and in those patients, there was found to be a significant mean reduction in cardiorespiratory function, as measured by FEV_1 (-0.11 L, p=0.01), FVC (-0.1 L, p=0.03), VO_2 at AT and peak exercise (ml O_2/kg/min = -2.19, p<0.001; -2.51, p<0.001).(17) Furthermore, subgroup analysis revealed that those with a higher baseline aerobic fitness (VO_2 at AT >13.9 ml/kg/min) demonstrated better survival rates at after one year (HR 0.84, 95%CI (0.73,0.97), p=0.014).

Among the patients who completed the NACT protocol, the absolute mean peak oxygen consumption at baseline was significantly greater than that of their counterparts.(17) It suggests therefore, that a greater cardiopulmonary reserve may confer a protective effect to offset the anticipated declines in physical status and treatment-induced side effects.

Similarly, Sinclair and colleagues, noted comparable declines in cardiorespiratory fitness, as determined by preoperative changes in median oxygen consumption at VO_2AT (-2.5ml/kg/min, p<0.001) and peak exercise (-2.1 ml/kg/min, p=0.001), in EAC patients following

NACT.(9) Unsurprisingly, these declines were accompanied with significant DLT, in fact, approximately one third of patients prematurely terminated their NACT regimens due to DLTs. The importance of NAT in the management of advanced disease is clear. However, it is equally important to acknowledge the negative impact NAT can have on functional status, physiologic reserves and physical fitness, and how they might later impact surgical and survival outcomes.(9, 17)

2.5 Perioperative Interventions to Optimize Functional and Clinical Trajectories

Enhanced Recovery After Surgery (ERAS)

An enhanced recovery after surgery (ERAS) pathway was initially designed in the beginning of the 21st century, by a multidisciplinary team of experts with a view towards enhancing perioperative care and recovery.(67, 68) The pathway involves applying a multimodal and coordinated evidence-based intervention in an integrative manner, throughout the perioperative period to minimize the metabolic and physiologic stress associated with surgery and subsequent recovery.(68) The pathway has been shown improve surgical outcomes, minimize postoperative complications and facilitate an accelerated recovery.(67) Depending on the surgical intervention in question, the components of the ERAS pathway may vary, however, most have pre-,peri- and post-operative components. These commonly include; preoperative nutritional and pharmacologic optimization, enhanced anesthetic approaches, minimally invasive procedures, adequate intraoperative hydration, early enteral feeding and physical mobilization.(67, 68) In other cancers, the implementation of ERAS programs have been associated with reductions in both the frequency and severity of complications, as well as the length of stay.(69)

Even without a standardized ERAS protocol for esophagectomies, several institutions have incorporated ERAS elements from other surgical procedures and adapted them to form their own enhanced recovery pathways (ERP), and have observed promising findings.(70, 71) For example, the ERP employed by surgical staff at the Montreal General Hospital, places an emphasis on surgical considerations (procedure, access and conduit), optimization of nutrition (pre and post-operative), multimodal approaches to analgesia, early tube removal, early progressive

mobilization and routine respiratory physiotherapy.(72) When comparing patients matched for age, sex, comorbidities and surgical procedure, those who received ERP on average had a reduced median LOS (days, 8 vs 10; 95% CI, 7-17 vs. 9-17; p=0.01), with no significant changes in rates of complications (59% vs. 62%) and readmissions (6% vs 5%). Similarly, the ERP has allowed for the modification of targeted day of discharge from 7 to 6, with a view towards reducing the burden on patients but also the healthcare system.(73)

The ERAS society recently published their recommendations and graded level of evidence for perioperative management of esophagectomies. Notwithstanding the improvement achieved with ERAS pathways, a significant proportion of patients nevertheless experience postoperative complications, and even in their absence, a full recovery commonly takes several weeks to months.(49) It is apparent that there is a need for a more proactive and pragmatic approach, beyond the confines of the hospital and the operating theatre.(74)

Prehabilitation

Esophageal cancer management is associated with a decline in functional status and an elevated incidence of postoperative morbidity.(10) Accordingly, the importance of postoperative rehabilitation is well recognized as a means to enhance recovery, functional capacity and QoL.(75, 76) However, the preoperative period presents a unique opportunity to address comorbidities and modifiable risk factors, improve functional capacity and address deficiencies in physiologic reserve ,which might otherwise preclude surgery or significantly impede recovery.(18, 74) Specifically, in patients with esophagogastric cancers, low functional status, sarcopenia, malnutrition and mental distress, are known to correlate with poor perioperative outcomes.(33) This underscores the need for preoperative programs to systematically address these risk factors in order to improve patient health and perioperative trajectories.(74)

Prehabilitation describes the process of proactively implementing multidisciplinary interventions, to optimize patient health and physical status to better withstand the anticipated physiological stressors, resulting from either NAT and or surgery.(33, 74) Prehabilitation programs typically focus on providing patients with exercise programs, nutritional counselling and psychosocial support. In some cases, pharmacologic optimization, glycemic control, smoking cessation and alcohol reduction may be also required.(77)

These have been previously demonstrated to be integral to the success of a number of

different surgical ERAS protocols.(74, 78) It reasonably follows therefore, that esophageal cancer patients, who are known to be a high-risk group due to the aggressive nature of the disease and its treatments, should similarly benefit.(79) However, and surprisingly, few studies have investigated the impact of prehabilitation programs in these patients preceding an esophagectomy. Still, even with the limited evidence available to date, the ERAS Society has endorsed the use of prehabilitation in perioperative esophageal cancer care, with moderate strength, acknowledging the pivotal importance of a faster functional recovery following major elective surgeries.(49)

Unimodal intervention

a)   Nutritional Optimization

Poor nutritional status is a central and continuous concern among most patients with upper gastrointestinal cancers. Maintaining adequate oral intake can pose a challenge due to the disease symptomatology, and therefore often results in a negative protein and energy balance and later malnutrition. It is not uncommon for many patients to present with unintentional moderate-to-severe weight loss and sarcopenia at diagnosis, which can persist throughout the preoperative period.(14)

Dysphagia, odynophagia and GERD are common complaints in patients with esophageal cancers. Accordingly, they must often have to alter dietary habits, adopting modified texture diets in some cases and consuming supplements and enhanced nutritional beverages. If oral intake is insufficient, then more invasive feeding alternatives, such as enteral or parental nutrition may be needed.(38, 42). Ultimately, the type of prescribed preoperative nutritional intervention may vary according to the patient's nutritional risk and the institutional protocols in place.(49)

NAT, although an integral component int the management of most cancers, is far from a benign intervention. For example, although NACT can ameliorate nutritional status by reducing tumor volume and the severity of dysphagia, it can also result in nausea, anorexia, stomatitis, diarrhea and vomiting, fatigue, all of which might adversely affect dietary patterns and nutrition.(42) Similarly, radiotherapy is an effective local therapy, can provoke an inflammatory response in the affected tissues, resulting in odynophagia, esophagitis, and in some cases a narrowing of the esophageal lumen.(38)

If nutritional deficits proceed unchecked throughout the preoperative period they can result

in deleterious effects on physiological reserves, functional status, clinical trajectories and HRQoL.(38) Moreover, surgical resections, and in particular, esophagectomies, constitute a significant physiologic stress necessitating increased energetic and nutritional requirements to facilitate healing. Accordingly, nutritional support is paramount in these patients to prevent further weight loss, replenish bodily reserves and physically optimize patients in anticipation of further oncologic interventions.(80) The ESPEN guidelines recommend that patients typically increase caloric (25-30 kcal/kg/day) and high-quality protein intake (up to 1.5 g/kg of actual BW/day or 2g/kg of ideal BW/day) during this time to counter the catabolic drive and support critical anabolic processes.(80, 81) When possible, whole foods consumed orally are typically preferred, although realistically, this is not often always feasible. Depending on the severity of dysphagia, nutritional risk and the discretion of the treating clinical team, feeding via nasogastric, gastric, jejunostomy, or parental routes approach may be deemed necessary.(38) Several studies have investigated the clinical impact of implementing preoperative nutritional pathways in esophagogastric cancer management with the mode of nutritional intervention is dependent on the patient's nutritional risk status. They demonstrated improvements in NAT treatment compliance, hospitalization rates, postoperative morbidity and LOS.(82, 83) Although the level of evidence remains low, both the ESPEN and ERAS societies endorse early nutritional assessments, risk stratification and nutritional optimization in this population.

As it is not uncommon for patients to become immunocompromised as following NAT, immunonutrition has been proposed as a method to improve clinical outcomes through modulation of the inflammatory response and oxidative stress resultant from cancer and its associated therapies.(84) Immunonutrition is defined as the consumption of a combination of nutrients with immune enhancing potential and commonly include: omega-3 polyunsaturated fatty acids (PUFA), select amino acids (arginine and glutamine), nucleic acids, and antioxidants.(80) A meta-analysis by Marimuthu et al., reviewed 26 RCTs to assess the impact of preoperative immunonutritional interventions in patients undergoing gastrointestinal cancer surgeries. They showed strong support for the protective potential of immunonutrition, which was associated with a reduced risk of postoperative infectious (RR=0.64; 95%CI,0.55-0.75), non-infectious complications (RR=0.82, 95%CI(0.71,0.95)) and LOS (RR=-1.88, 95%CI (-2.91, -0.84)).(85) Similarly, a study by Kubota et al., demonstrated that preoperative immunonutrition in patients with esophageal cancers was associated with significant reduction in the incidence of

postoperative infections (19% vs 34.5%, p=0.007), LOHS (34 vs 48 days, p=0.008) and improvement in 6-month survival (92.3% vs 72.4, p=0.028).(86) While several studies have highlighted its therapeutic potential, the literature is admittedly heterogeneous and the strength of the evidence is low. Nonetheless, both the ESPEN and ERAS support early immunonutrition in patients with cancers of the upper gastrointestinal tract who are expected to receive surgery.(80, 84, 87)

Omega-3 PUFAs have unique anti-inflammatory properties and have been previously used in other oncologic populations.(38) It has been suggested that in some advanced-stage cancers, they can reduce basal metabolic rates, inflammatory biomarkers and acute phase proteins. Additionally, they are believed to improve appetite, weight management and preservation of LBM in some advanced stage cancers.(80) Conversely, an RCT by Sultan et al., reported that preoperative supplementation with PUFAs had no effect on postoperative complication rates.(88) This suggests, that the benefits of immunonutrition may not result from the consumption a single ingredient, rather the combined effects of several. Currently there is some evidence, to support the use of immunonutrition in esophageal cancer care, however, further research is needed to better understand the optimal combination of nutrients and their impact on short- and long-term outcomes.(14, 80, 84, 89)

b) **Physical Pre-conditioning**

Physical fitness is an important determinant of functional capacity and independence and HRQoL. Cardiorespiratory fitness, in particular, has become increasingly recognized as an important prognostic parameter in the management of esophageal cancer given its capacity to predict tolerance to NATs, postoperative morbidity and mortality.(9, 16) Furthermore, it is also well known that patients typically experience a decline in fitness resulting from the disease, and the stress of surgery and other therapies.(10)

Therefore, improving preoperative fitness through exercise may be critical in attenuating the functional deficits and morbidity associated with the disease and treatments. The benefits vary according to the exercise prescription, modality and volume, however, aerobic and resistance training are central to most prehabilitation programs.(74, 90) The latter holds especially true, in esophageal cancer care, where given the susceptibility of this patient population to muscle wasting and postoperative pulmonary complications, combined pre-conditioning programs might improve outcomes through optimizing LBM and cardiorespiratory

function.(33)

Resistance training offers unique physiological benefits which include reducing muscle wasting, promoting hypertrophic adaptations in skeletal tissue and thereby increasing muscle mass, strength and function. The ACSM guidelines for oncology patients recommend resistance training two to three times a week with emphasis on exercises targeting the major muscle groups. The exercise prescription should include a minimum of 1 set of 8-12 repetitions per exercise, an initial load that is less than 30% of 1-RM and incremental progress based on the individual's capacity and symptoms.(90)

Resistance training programs have been documented to improve body composition, through an increase in LBM, weight management and strength in all age groups, but more importantly, in the frail and elderly.(14, 18, 91) A meta-analysis by Padilha et al., reviewed 14 RCTs to investigate the impact of resistance training programs in cancer patients receiving either NACT or NCRT. Preoperative resistance training with NAT resulted in a mean increase in lower limb strength (23.43 kg, 95% CI (14.51, 32.36)), with no significant changes in total LBM or adiposity.(92) However, resistance training in the adjuvant period resulted in significant increases in strength, LBM and decreased adiposity. Notwithstanding the heterogeneity of the study population and exercise protocols, the results suggest that resistance training has an important role in countering treatment-related adverse effects on body composition, fitness and physiologic reserves.

Cancer therapies uniformly have an adverse impact cardiorespiratory function and predictably result in a progressive decline in aerobic fitness (VO_2peak) that can persist even after termination of treatments.(17) Fortunately, aerobic training also results in several important physiological adaptations that can minimize treatment-induced effects, including increased maximal oxygen uptake, cardiac output, mitochondrial density, oxidative potential and peak power output.(74, 81) The combined results are improved cardiorespiratory function and efficiency and a greater physiological reserve.

Clinicians have long recognized the strain surgery has on the cardiovascular and pulmonary systems, as such, an emphasis been placed to preoperatively optimize aerobic capacity and function. Barberan-Garcia et al. conducted an RCT involving 125 patients undergoing major abdominal surgeries, investigating the impact of preoperative aerobic training on postoperative complications. The intervention group had supervised exercise sessions, 1-3 times per week,

which consisted of high-intensity interval training on a cycle ergometer with an intensity alternating between 40% and 70-85% of maximum work rate (WR).(93) Researchers observed significant improvements in aerobic capacity (endurance time 135%; p < 0.001) in addition to a 51% reduction in the risk of postoperative complications, as compared to non-active controls (RR = 0.5, 95%CI (0.3,0.8), p = 0.001).(93) Similar findings have been noted in other oncological populations. A systematic review published by Vermillion et al, in 2018, analyzed 9 RCTs studying the effects of preoperative exercise in patients with gastrointestinal cancers. Although all of the study protocols included an aerobic component that followed ACSM guidelines, there were significant methodological differences and therefore the results were mixed.(94) Nevertheless, exercise generally improved functional outcomes such as walking capacity, VO$_2$ at AT and peak exercise, postoperative recovery and measures of QoL.(94) With respect to aerobic training, the ACSM recommends that cancer patients perform moderate to vigorous (64-95% of max HR; 12-17 RPE) aerobic exercise 3-5 times per week in bouts of at least 10 minutes. Ideally, patients should accumulate a minimum of 150 minutes per week of moderate intensity exercise or at least 75 minutes per week if the exercise is vigorous. Few studies however have investigated whether these interventions are appropriate for patients with esophageal cancer who are often malnourished, sarcopenic and frail.

Recently, Christensen and colleagues investigated the safety and feasibility of implementing a combined exercise program with concurrent NACT in surgical candidates with esophageal cancer patients.(20) Not only did the authors confirm that it was safe and feasible, but also, contrary to expectations, patients saw improvements physical and functional status despite receiving NACT. Patients in the exercise group reported a significant increase in functional status (mean ΔFACT-E score = 12.6, 95%CI (2.7, 22.9)) and were observed to have an increase in peak power output (12 Watts, 95%CI (0.1, 24.0)) and peak VO$_2$ (1.39 mL/kg/min, 95%CI (0.03, 2.74)). Normally, a continuous decline in weight is observed throughout the preoperative period, however, the exercise cohort did not see a significant change in weight or LBM. Regarding the clinical course, as compared to controls, the exercise cohort had a lesser risk of chemotoxicities (15% vs. 31%, RR=0.45, 95%CI(0.14,1.45)), treatment failure (5% vs 21%, RR= 0.23, 95%CI (0.04,1.29)) and preoperative hospital admission (15% vs 38%, RR= 0.39, 95%CI (0.12,1.23)), suggesting an improved tolerance to treatments.(20) Soon after, Japanese researchers published analogous results from a dual modality physical preconditioning

program. Whereby, compared to the standard of card condition, the intervention group had superior walking scores pre- and post-operatively (p<0.001) but also a lesser incidence of pulmonary complications (4.3% vs. 36%, p=0.007) post-esophagectomy.(95)

In addition to classical aerobic and resistance training, respiratory therapy is another training modality that has been utilized in select patient populations to strengthen the respiratory muscles, improve their function and perceived effort of breathing.(96) It has been shown to be beneficial in patients with chronic obstructive pulmonary disease and those undergoing cardiothoracic surgeries.(97, 98) In a large RCT by Huzlebos et al., inspiratory muscle training (IMT) was provided to patients awaiting coronary artery bypass grafts. As compared to the standard of care, IMT resulted in a lower incidence of serious postoperative pulmonary complications 18% vs. 35% (OR=0.52, 95%CI (0.3,0.92), p=0.02).(99) Given the high incidence of pulmonary complications associated with esophagectomies, it has been postulated that preoperative IMT could also improve postoperative morbidity and recovery in this patient population. Although the rationale is compelling, few studies have investigated the impact of pulmonary prehabilitation in esophagogastric surgical candidates.(100) Inoue et al., retrospectively analyzed the impact of a preoperative multimodal pulmonary rehabilitation program in a cohort of 100 esophageal cancer patients and fount it was associated with a reduced risk for postoperative pulmonary complications (OR= 0.14, 95%CI (0.02, 0.064)).(100) Yamana et al., also reported that as compared to usual care a pulmonary training program significantly reduced postoperative pulmonary complications (OR =3.32, 95%CI(1.1-10), p=0.033).(101) However, other prospective studies have reported improvements in pulmonary function following pulmonary prehabilitation, but without a significant effects on postoperative outcomes and morbidity.(96, 102) While there is currently only limited evidence to support pulmonary training in esophagogastric surgical candidates, many institutions nevertheless still include them in their prehabilitation programs.(102-104)

c)   Mental Health

Following any major cancer diagnosis, it is not uncommon for patients to experience varying degrees of distress, anxiety or depression throughout the preoperative period.(77) In esophageal cancer, the latter is further compounded by the poor prognosis and its challenging symptomology.(105) It has been shown that psychological distress can adversely affect treatment compliance, immune function, disease and treatments-related symptoms, morbidity, and

HRQoL(106) and not surprisingly can influence perioperative trajectories. Notably, it has been associated with impaired wound healing, prolonged recoveries, so increasing healthcare costs.(74, 107, 108)

The importance of psycho-social health has become increasingly appreciated by clinicians and there is some evidence to suggest that prehabilitation programs focused solely on physical health may be insufficient.(74, 81) There has been a greater appreciation for psycho-behavioral interventions geared towards patient empowerment, in addition to anxiety and depression reduction.(108) Given the sensitivity involved when dealing with mental health issues, and the heterogeneous patient response, it is generally advised that practitioners personalize their approach to the individual patient.(105, 109) Most interventions typically involve a consultation with a psychologist or qualified healthcare professional who might utilize an array of different cognitive-behavioral interventions, including: image-guided relaxation, meditation, stress reduction exercises, acceptance and commitment therapy, coping and problem solving strategies.(77, 108) Unfortunately, the scientific support for the use of psycho-social interventions in improving clinical outcomes within oncologic surgical candidates is limited.(81, 109) As such, there is no consensus as to what constitutes the optimal psycho-social prehabilitation program, and thus will inevitably vary between institutions.

Preoperative stress management has been demonstrated to be effective in reducing anxiety and depression in a number of oncologic populations patients, however, there have only been a handful of studies that have specifically reported on the impact in esophageal cancer care.(77, 105) One study conducted Zhang et al., investigated the impact of a perioperative psychological support program in EC patients.(110) The program comprised of a multidisciplinary approach, pre- and post-operative support, with the aim of improving self-reported measures of mental well-being and postoperative outcomes.(110) Psycho-social support throughout the perioperative period was reported to significantly improve postoperative multivariate measures of psychosomatic status but also the LOS (days = 20.06 (3.73) vs. 23.24 (7.37); p=0.041). Similarly, a study by Scarpa et al., investigated the impact of psychological support and sleep management strategies on self-reported postoperative measures of HRQoL and sleep quality. Researchers found that in comparison to usual care, the intervention group had less decline in HRQoL (OR: 0.23, 95%CI (0.06, 0.61), p=0.003) and sleep quality (OR: 0.27, 95%CI (0.1, 0.72), p=0.009).(111) Esophageal cancer is associated with psychological morbidity, and while there is

limited research measuring the clinical impact of cognitive-behavioral interventions, the importance for preoperative psychological support is well-recognized among healthcare professionals.(81, 105)

Combined Multimodal Interventions

To a large extent, prehabilitation has been based on research in patients with lower gastrointestinal cancers. Nevertheless, those of the upper gastrointestinal tract have similar in risk factors, clinical presentations and cancer therapies.(94) However it is important to note, that esophageal cancer notorious infamously known for having a challenging symptom profile and is unfortunately associated with malnutrition, significant perioperative morbidity and a poor prognosis.(2) The disease, treatments and recovery each present their own unique challenges and as such require that therapeutic approaches to be adapted accordingly. While there is mounting evidence to support unimodal preoperative interventions in esophageal cancer care; many of the disease-related morbidities are multifaceted and should therefore be treated similarly.(104) Surprisingly, despite the strong clinical rationale, only a few studies have investigated the impact of combined multimodal prehabilitation programs in this population.(33, 49)

Appraising the literature currently available, albeit limited, there is a growing recognition for the synergistic benefits of combining exercise, nutrition and psycho-social support and the pertinent therapeutic potential in esophageal cancer patients.(112) In 2015, Xu and colleagues, published results from an RCT with a bimodal "Walk-and-Eat" prehabilitation program in esophageal cancer patients. During hospital visits, patients were exercised and given nutritional support in adjunct to their NCRT treatments. The study was uniquely focused on tolerance to NATs and less so on surgical outcomes. Nevertheless, in comparison to the standard of care, the intervention group were able to preserve functional capacity to a greater extent (6-MWD: -18.0m (75.3) vs -118.0m (160.5), p=0.01), handgrip strength (-1.1(2.5) vs -4.1(4), p=0.001), and weight (kg = -0.8(1.8) vs -3.5(2.3), p<0.001).(113)

The results of another RCT were recently published by Minnella et al., in 2018, in which, they investigated the impact of bi-modal prehabilitation on the perioperative changes in functional capacity (6-MWD). A total of 51 esophagogastric surgical candidates were recruited at diagnosis and randomized to either the standard of care or the prehabilitation group that included a personalized home-based exercise prescription and nutritional support. As compared

to the control group, the prehabilitation group demonstrated significant improvements in functional capacity preoperatively (Δ 6-MWD: 36.9(51.4) m vs. -22.8(52.5) m, p <0.001) and postoperatively (15.4(65.6) m vs.-81.8(87.0) m, p<0.001). Although it was not shown to affect surgical or postoperative morbidity, prehabilitation nevertheless resulted in improved functional trajectories, as evidence by the group's superior 6-MWD, which was sustained even after surgery.(21) This is significant given that, under normal circumstances, patients experience a significant decline in physical and functional performance following NAT and especially following surgery.(10) Wynter-Blyth and colleagues prospectively conducted an observational study studying the impact of a home-based multimodal prehabilitation "PREPARE" program in a cohort of esophagogastric cancer patients scheduled to receive NACT and surgery. Unlike the previous study, the patients did not experience any preoperative changes in functional performance or HRQoL.(114) The results could be interpreted that the interventions served to protect against the decline in functional status that is classically witnessed with usual care.

Dewberry and colleagues also attempted to implement their own prehabilitation program for esophagogastric surgical candidates. In the pilot study they recruited 11 patients with esophageal cancers scheduled to receive NAT and surgery provided them with a multidisciplinary prehabilitation "STRENGTH" program throughout the preoperative period. The 11 patients receiving the intervention were retrospectively compared to a similar cohort that received the standard of care. Unfortunately, due to the small sample size and non-randomized nature of the trial precludes the drawing of meaningful conclusions about the intervention's true clinical effectiveness. The underpowered nature of the study, notwithstanding, the results, although not statistically significant, suggest that the STRENGTH program may protect against treatment-related morbidities as reflected by the lesser preoperative (27.3% vs 54.4%, p=0.19), and postoperative admission rates at 30 days (0% vs 18%, p=0.14) and 90 days (18.2% vs 27.3%, p =0.6).(115)

Esophageal cancer care is unusual in that, despite the sound reasoning for multimodal prehabilitation programs, few studies have reported a significant impact on surgical morbidity and recovery, which can be understandable given the heterogeneity between programs, treatment compliance and institutional approaches to disease management.

Recently, Halliday and colleagues, published promising findings from a single-armed, prospective cohort study, assessing the impact of their "PREPARE" program in esophagogastric

oncologic surgical candidates.(116) The program spanned 16-weeks and utilized a home-based approach including exercise, respiratory training, nutritional and pharmaceutical optimization, and mental health interventions. They noted that a higher baseline cardiorespiratory fitness was moderately correlated with patient-reported physical activity levels during NAT and the preoperative period. Aerobic fitness was assessed using the Chester Step Test, which did not change during NACT, but increased significantly thereafter, which is suggestive of an important protective effect on cardiorespiratory function during anti-neoplastic therapies. Of note, this was the first study to recognize that adherence with the prehabilitation program was favorable changes in in cardiorespiratory fitness (p=0.048) and the incidence of postoperative pulmonary complications (p=0.035).(116) The findings from the above mentioned study highlight the importance of enhancing program adherence throughout the preoperative. Additionally, it lends support to the importance of personalized multimodal programs in the context of esophageal cancer care.

2.6 Limitations of Prehabilitation Studies in Esophageal Cancer

The current established standards of care for treating esophageal, as well as most cancers, includes perioperative adjuvant therapies with curative surgery, which has been shown to significantly improve patient prognosis.(6, 57) Despite the improvements in survival outcomes, this results in significant physiological stress and commonly has detrimental effects on acute and long-term functional status.(9, 10, 21) Management of esophageal cancer in particular is complicated by a high risk of malnutrition, postoperative complications, persistent deconditioning and muscle wasting, all of which can contribute to emotional distress and poor HRQoL.(45, 105)

Recognizing the particular susceptibility of these patients to treatment-induced morbidity the importance for supportive preoperative interventions cannot be overstated. Although at present, the strength of the evidence supporting prehabilitation in esophageal cancer is low, this can largely be attributed to the limited number of published RCTs.(49) Furthermore it is important to note that the majority of these, have focused on measuring the impact of single-modal interventions. While unimodal prehabilitation programs have indeed reported benefits, presumably, a greater impact would be expected from a combined and comprehensive approach.(79)

Among the few published multimodal prehabilitation trials, functional benefits were observed, however there did not appear to be a consistent significant impact on clinical and perioperative outcomes.(21, 114, 115) This may be in-part be attributed to the small and therefore underpowered sample sizes, non-randomized controlled study designs, in addition to heterogeneity in disease and management approaches. Accordingly, depending on the cancer's pathology and progression, the type of treatment can vary therefore have different side effects and clinical implications.(50) To better understand the specific impacts of prehabilitation programs, there is a need for standardization of the study population, the type of medical interventions prescribed (ie. NACT vs. NCRT), but also the specific components of the preoperative services provided.

The benefits of preoperative NAT are known, although a physiological stressor that is not always well tolerate.(8) Prehabilitation has been demonstrated to help patients recover after NAT, however there is a surprising paucity of research into its therapeutic potential NAT.(117) As novel programs have been shown to improve perioperative functional and clinical trajectories, modulating the stress response associated with surgery and recovery, similar benefits would be expected during NAT.(118) However, it is uncertain if prehabilitation programs may actually enhance tolerance to NAT regimens, and perioperative morbidity and recovery in these patients. At the present time, although there is some ongoing research, there is only limited data currently available to guide clinicians.(79, 119)

On a separate note, among published RCTs using multimodal prehabilitation the majority of programs were home-based, which makes it difficult to monitor true program adherence, progression and challenges. This is an important consideration given that there is appreciable evidence to support the superiority of supervised training interventions in cancer patients.(120) Additional supervision might prove to be particularly valuable in this patient population in light of the distinctive functional decline anticipated with the disease and concurrent treatments. Conversely, it can also be demanding on the healthcare system with respect to time and resource utilization. Furthermore, frequent commutes to the hospital may also be a burden on patients and negatively affect adherence.(121) There is a need for studies investigating supervised and home-based programs to determine if they result in a meaningful clinical effect. The ACSM has published exercise guidelines for cancer patients, however there is currently no consensus on the optimal exercise prescription (FITT-VP; Frequency, Intensity, Time, Type, Volume and

Progression to effectively counter the detrimental effects of neoadjuvant therapies and surgery in this particularly vulnerable population.(90) Aspects of training that warrant further investigation include the effects of different aerobic intensities (high-intensity interval training vs moderate steady state), supervised vs. unsupervised approaches, in addition to different IMT protocols. The science of prehabilitation as it pertains to esophageal cancer is rapidly evolving, and while there is a paucity of well-designed studies in the literature, there is some promising data to support its use and clinical effectiveness during concurrent adjuvant therapies throughout the perioperative period.(21, 116)

2.7 Concluding Remarks

The prognosis of esophageal cancer is exceptionally poor and is further exacerbated by its challenging clinical manifestations and disease-management approaches. The disease is associated with a multifaceted decline in physical and functional status, which can adversely influence perioperative trajectories.(10) The importance of preserving physical an nutritional status and mental well-being in the context of cancer and perioperative care is widely appreciated among most clinicians. The preoperative period represents a unique window of opportunity to pragmatically intervene and support patients, with the aim to optimize health, mitigate preoperative risk, thereby improving tolerance to interventions and enhancing recovery. Although, esophageal cancer is especially challenging, benefits have been documented following unimodal interventions involving preoperative interventions in the form of exercise, nutritional and support. It follows therefore, that a combined approach would have cumulative beneficial clinical effects. However, at present there is insufficient evidence to support multimodal prehabilitation for perioperative risk reduction. Relative to other cancers, there are limited studies investigating prehabilitation in esophagogastric cancer. As previously stated, several limitations exist with respect to their study designs, interventions and heterogeneity in study populations. Further research is still needed to better define the optimal approach and treatment modalities and also to better understand its impact during concurrent NAT, but also perioperative clinical outcomes.

2.8 Research Questions

This thesis will study the impact of personalized multimodal prehabilitation in patients with EAC scheduled to receive NACT followed by surgery and systematically address the following research questions:

1. Can a multimodal prehabilitation program be safely implemented with these patients while concurrently receiving NACT?
2. What are the impacts of a prehabilitation program on functional and outcomes in these patients over the preoperative period?
3. What would be the clinical parameters of patients receiving NACT and prehabilitation?

Chapter 3 – Methodologies

3.1 Study Design

The current thesis is a prospective cohort study, derived from an ongoing RCT (2019-5387), registered on clinical trials.gov (identifier: NTC04581005), which intended to investigate the impacts of two different (supervised in-hospital vs home-based) multimodal prehabilitation programs on functional and clinical outcomes in patients with EAC receiving concurrent NACT. The original study was initiated in 2019 at McGill University Health Centre's Prehabilitation Unit, located in the Montreal General Hospital, Montreal, Quebec. Its design was a prospective, parallel-group, single-centre, and single-blind RCT. In both study arms patients received multimodal prehabilitation programs that consisted of exercise, nutrition and psychological support varying with respect to the delivered modality and intensity of exercise program prescribed.

Unfortunately, the ongoing Covid-19 pandemic severely impacted the above-mentioned research project, as the active patients randomized to the supervised condition were no longer able to receive in-hospital interventions.

Given that the three modalities (exercise, nutrition, mental well-being) were provided to all patients, differing uniquely with respect to exercise modality and aerobic intensity, the design of the thesis was adapted to combine patients into a single cohort. This will place an emphasis on the feasibility of implementing a multimodal prehabilitation program, its preliminary efficacy in the preoperative period.

3.2 Ethics Committee Approval

The study protocol was approved by the research ethics board (REB) of the McGill University Health Centre in the summer of 2019 under the trial identification 2019-5387. It was also registered on ClinicalTrials.gov, with the following identifier: NTC04581005.

In March of 2020, the MGH hospital restricted access to the public and staff, in response to Covid-19 pandemic. As a result, recruitment and research activities were temporarily ceased. Given the high-risk nature of these patients and their need for continuous support, a protocol amendment, F1-59743, was created to safely adapt the delivery of prehabilitation services while preserving patient safety in the context of the pandemic. The amendment involved adapting the protocol for patients randomized to the supervised (in-hospital) group, providing them with the

option of coming to the hospital for in-person supervised exercise or alternatively virtual supervised exercise facilitated by a teleconferencing platform. The amendment submitted to the REB in May of 2020 and was approved in July 2020. Study recruitment and interventions resumed immediately after acquiring approval from the appropriate governing bodies.

3.3 Participants

In order to be deemed eligible to participate in the study, patients needed to be at least 18 years of age, recently diagnosed with non-metastatic EAC, and electively referred for the disease management with NACT followed by surgery with curative intent. Exclusion criteria for the study were as follows: comorbid medical, physical and psychological conditions whereby exercise or oral nutrition was contraindicated: acute or uncontrolled cardiac conditions, American Society of Anesthesiologists (ASA) physical status classes 4-5, disabling orthopaedic and neuromuscular disease, psychosis, dementia, cardiac failure (New York Heart Association functional classes III-IV), severe COPD (FEV1<50% predicted), end-stage liver or kidney disease, severe anemia (symptomatic or hematocrit < 30%), inability to swallow or presence of feeding gastrostomy/jejunostomy. Patients needed to be literate and have a sufficient comprehension of either English or French. Patients residing beyond 50 km from the hospital were not to be approached due to the anticipated challenges associated with regular commutes if randomized to the supervised group.

At the McGill University Upper GI Cancer Clinic, patients met with surgical staff to discuss the diagnosis and appropriate course of oncologic treatments. During the initial visits, surgical investigators were able to screen for patients that met the inclusion criteria. Patient files were then presented to a multidisciplinary tumor board for a comprehensive case review, staging and to establish the optimal disease management approach. A member of the prehabilitation team (KD) would attend tumor board meetings, where surgical investigators would identify and confirm prospective patients with locally advanced disease scheduled for NACT and surgery.

3.4 Study Procedures

Recruitment & Randomization

A member of our research team would then contact the patient to introduce the study, the purpose, components of the program, implications of patient involvement, and lastly to assess interest in participation. If patients expressed interest, they were invited for an initial visit at the Prehabilitation Clinic at the Montreal General Hospital. During this time, further clarifications were provided of the study, eligibility was re-confirmed, patients were provided with a copy of the informed consent document and pending questions or concerns were clearly addressed. It was made clear that in both study arms patients would have access to comprehensive prehabilitation services including exercise, nutritional and psychosocial support. All prospective participants were reminded that participation was entirely voluntary, it would not affect the quality of care they received, and study withdrawal could be done at any time without justification. It was ensured that research personnel acquired informed written consent in accordance with the international Good Clinical Practice (GCP) guidelines. After having acquired informed consent, the research team reviewed medical history with patients, and a comprehensive baseline health and functional evaluation was subsequently performed.

Following the baseline assessment, they were randomly allocated in a 1:1 ratio to either the supervised (hospital-based or virtual home-based) or the unsupervised (home-based) group (see Figure 1). Random computer-generated blocks of 6 were used and a group assignment was placed in sequentially numbered opaque envelopes in a locked room. A member of the research team not directly affiliated with the study was responsible for opening the envelopes and revealing group assignment.

Timeline

Following recruitment, randomization and the baseline assessment, patients were provided with multimodal prehabilitation services throughout their NAT regimens and the preoperative as a whole. The research team was interested in studying the feasibility of implementing a multimodal prehabilitation program, but also the impact it carries on functional, clinical and patient-reported outcomes throughout the continuum of care, but especially in the preoperative period. Upon recruitment, patients completed an initial evaluation (T1), which involved documenting baseline

patient characteristics and an assessment of functional status. In order to monitor changes in preoperative trajectories, patients were asked to perform the comprehensive evaluations at two timepoints: (T1) baseline and (T2) prior to surgery.

Baseline Patient Characteristics

Pertinent health information was first collected to characterize the patient cohort. This included: (1) relevant medical history, (2) an updated list of current medications (3) standardized anthropometrics (height, weight, waist and hip circumference), (4) a bioelectric impedance analysis (BIA) and (5) a basic blood test (hemoglobin, albumin, prealbumin, creatinine, C-reactive protein (CRP), B-natriuretic peptide). Thereafter, a functional assessment was performed to evaluate physical fitness, functional abilities and facilitate personalization of the exercise prescription.

As a part of the evaluation, nutritional status and dietary patterns were also assessed. Baseline nutritional status was formally assessed by a registered dietician, who referred to the patient anthropometric and functional data, a patient-generated subjective global assessment (PG-SGA), and a 3-day food log. The latter was used as the basis to personalize the preoperative nutritional interventions. A patient's nutritional status, anthropometrics and body composition were re-evaluated at T2.

Baseline and Follow-up Functional Status and QoL Assessment

The functional assessment consisted of (1) a 6-MWT abiding to the recommendations of the American Thoracic Society (ATS),(122) (2) an incremental symptom-limited CPET on an electronically braked cycle ergometer,(15) (3) a timed-up and go (TUG) test, (4) a 30 second sit-to-stand test (STS), (5) Handgrip strength (HGS) and (6) a 1-arm curl test.

Patients were also asked to complete several questionnaires to obtain subjective measures of their perceived functional status (CHAMPS, DASI),(123, 124) physical health (ESAS) (125), mental well-being (HADS) (126) and quality of life (FACT-E).(127)

The Prehabilitation Program

   a) **Exercise Component**

During the baseline assessment, the exercise specialist was able to evaluate the patient's fitness, strength, flexibility, mobility, and stability; then created an exercise program adapted to the patient and their abilities. Irrespective of group allocation, the exercise prescription was similar for all patients, in that it included aerobic, resistance and flexibility components, as per the recommendations of the American College of Sports Medicine (ACSM).(90) Beyond the aerobic and resistance components (see options outlined below), the following elements were provided to each patient:

- The exercise specialist ensured to incorporate exercises and movements that sufficiently utilized joint ranges of motion and promoted flexibility. Following each exercise session, either in-hospital or at-home, patients were asked to perform the appropriate static and dynamic stretches for 2 to 3 sets for a cumulative duration of 60 seconds for each movement. All patients were asked to walk regularly and encouraged to accumulate 10 000 steps per day. They were given a pedometer and logbook and asked to track their daily activity levels.

- All patients received inspiratory threshold load training by the exercise specialist following termination of their NACT, at least 2 weeks preceding the surgery. Patients were provided with their own inspiratory threshold spring-loaded trainer (Threshold Inspiratory Muscle Trainer (IMT), Respironics Inc). Patients were instructed to perform 6 sets of 10 breaths daily, 3 sets in the morning and 3 in the evening. As per the recommendations of the ATS, patients were instructed to begin with a low intensity, approximately 30% of maximal inspiratory pressure, then to progress incrementally to perceived moderate the high intensities (spring load) as per tolerated.(128)

- The exercise specialist contacted each patient via telephone patients weekly to monitor adherence, track progress, address any questions or issues, and modify exercises when necessary. They also inquired if further support was needed with respect to nutrition, stress reduction or smoking cessation and coordinated with supportive staff as needed.

Figure 1. Overview of Esophageal Prehabilitation Program

Esophageal Prehabilitation Program

Group Allocation		Supervised		Unsupervised
		Hospital-Based	Virtual, Home-Based	Home-Based
Modality		🏥	🏠 *(Amendment)*	🏠
Exercise	🚴 Aerobic	Cycle ergometer, 28-minutes, HIIT (4:3), 2x/week 4 x (4min 80-85% of AT: 3min @ 85-90% of peak)		Modality of choice, 30 minutes, moderate intensity, RPE 12-13/20 3x/week
	🏋 Strength	8 exercises, 2→3 sets, 8→12 repetitions, RPE 5→6/10, 2x/week		
	🫁 Respiratory	Threshold IMT, 6 sets of 10 repetitions, 30% of MIP progressed daily		
Nutrition	Dietary Recommendations	Nutrition consultation with registered dietician and personalized dietary recommendations based on nutritional status and dietary patterns		
	Whey Supplementation	Whey-based supplements prescribed by dietician based on deficits in protein intake		
Psychological Support		All patients received at least one consultation with psychology trained personnel		
		Personalized relaxation and stress reduction and coping exercises		

Figure 1. The figure above provides a visual overview of esophageal prehabilitation program that was provided to patients in the current study. Patients were randomly allocated to the supervised or unsupervised condition. Patients in the unsupervised condition were provided with an exercise program (differing uniquely with respect to the aerobic component and lack of supervision) to be done at home and were contacted thereafter via telephone on a weekly basis. Patients in the supervised condition were asked to exercise with the kinesiologist at the hospital twice weekly. Following the amendment, they were provided with the option to exercise at their homes virtually supervised by the kinesiologists through a teleconferencing platform.
HIIT, high-intensity interval training; AT, anaerobic threshold; RPE, rating of perceived exertion; IMT, inspiratory muscle training; MIP, maximum inspiratory pressure

Option 1: Unsupervised, Home-Based

Patients allocated to the unsupervised home-based group were given a comprehensive exercise protocol created by an exercise specialist and personalized to the patient's baseline fitness and abilities. Patients reviewed the program, at the hospital, with the exercise specialist who taught them how to properly warm-up, cool-down, self-monitor exercise intensity using their heart rate and the Borg scale.(129) Demonstrations were provided on how to safely and properly execute the movements, corrective feedback was also provided as needed during the exercise prescription. Patients were instructed to perform the moderate intensity aerobic exercise three days per week and the resistance training twice.

- *Aerobic training* consisted of 30 minutes (including warm-up and cool-down) of moderate-intensity continuous steady state exercise of their preferred modality (cycling, swimming, jogging). Patients are to be educated on the Borg rating of perceived exertion scale (range, 6-20) and instructed on how to aim for a self-reported intensity of 12 to 13 rated perceived exertion (RPE).(130)
- *Resistance training* consisted of 8 exercises tailored to their abilities, which they were asked to perform with elastic bands (Thera-band) or their body weight. The exercises targeted the major muscle groups, which they were to perform for 2 to 3 sets of 8 to 12 repetitions at an RPE of 5-6 on a 10-point scale.

Option 2: Supervised, Hospital-Based

Patients allocated to the supervised, hospital-based group were asked to visit the peri-operative clinic twice weekly for 1-hour exercise sessions under the supervision of a qualified exercise specialist (kinesiologist or exercise physiologist).

- *Aerobic training* was performed on an upright cycle ergometer, and consisted of a warm-up, a 28-minute high-intensity interval training (HIIT) protocol, tailored to the individual and determined from their baseline CPET performance (see Figure 2). The HIIT training entailed 4 rounds, alternating between bouts of high-intensity and active recovery, whereby each round involved 3-minutes of high intensity (85-90% of workload at VO_2peak) and 4-minutes of active recovery (80-85% of the workload at VO_2AT).
- *Resistance training* was the second component, and similarly to the first, was supervised by the exercise specialist. Personalized to the individual's fitness level, the exercises were performed using an elastic band (Thera-band), adjustable dumbbells (Bowflex, SelectTech 552) or their respective bodyweight. The resistance training included 8 exercises targeting the major muscle groups (trunk, lower and upper limbs) and were performed for 2 to 3 sets of 8 to 12 repetitions, at a moderate intensity of 5 to 6 on a 10-point modified Borg scale. Exercise intensity and volume was progressed every 1 to 2 weeks as per tolerated by the patient. During the first session, the exercise specialist took additional time to review all the exercises with the patient and provide the appropriate corrective feedback.

Figure 2. Aerobic High-Intensity Interval Training (HIIT) Protocol
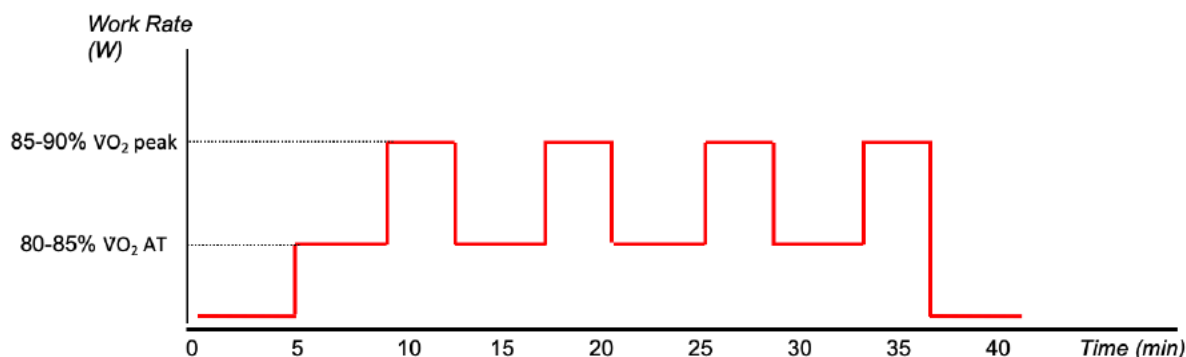
Figure 2. The figure above provides a visual representation of the 4:3 HIIT protocol provided to patients allocated to the supervised condition. Patients were asked to complete a 5-minute warm up followed by 4 intervals: alternating between 4-minute bouts at a work rate of 80—85% of their anaerobic threshold (AT) and 3-minute bouts at a work rate of 85-90% of their peak work rate. The appropriate watts for the above-mentioned AT and peak work rate were derived from a patient's baseline CPET.

Option 3: Supervised, Virtual Home-Based (Teleprehabilitation)

Due to the state of affairs pertaining to Covid-19, many patients were unable or unwilling to visit the clinic for supervised exercise sessions. Therefore, an amendment was done to allow for the remote delivery of prehabilitation services facilitated through a virtual interface, also known as teleprehabilitation, for patients that would have previously been allocated to the hospital-based supervised condition. The latter was able to be realized through the use of a secured videoconferencing platform (Zoom License Pro, Zoom Video Communications Inc., USA) and by providing patients with training watches (Polar Ignite, 2Z, © Polar Electro Oy 2020, Polar FlowSync, Finland). The technology and telehealth platform allowed the exercise specialist to remotely supervise patients at home for training sessions, provide real-time demonstrations and corrective feedback and ensure that the patients were following the exercise program similarly to in-hospital interventions.

Patients allocated to the supervised group who opted for the virtual home-based (teleprehabilitation) option were lent a magnetic upright stationary exercise bicycle (SportOp B900P, © 2020 IVIVA International Corp.) so that they can follow the same aerobic exercise protocol. Patients followed the HIIT aerobic protocol previously described and the resistance

training under the supervision of the exercise specialist. While the protocol amendment was created specifically for the supervised group, the unsupervised home-based group was also provided with smart watches, to provide the exercise specialist with a complementary resource to objectively monitor patient activity levels.

Zoom Platform

Patients who were randomized to the supervised group were asked to download the Zoom.us application on their computer, tablet or cellular devices. Unlike other technologies, the Zoom application is recognized to respect the public health information protection act (PHIPA). The platform facilitated the communication between patient and healthcare professionals in a secured and confidential manner.(131) Regarding the exercise sessions, the exercise specialist and patient agreed on a date and time to schedule the telehealth sessions. Patients would be emailed with a unique session ID, link and password, which allowed them to both access a secure videoconference session.

b) Nutritional Support

Both groups were given personalized nutritional support throughout the preoperative period. Impairments in nutritional status is not uncommon in patients with esophageal cancers, moreover, it can negatively influence functional performance and their care trajectories.(132) Therefore, nutritional optimization has become widely recognized as a critical aspect of esophageal cancer care.(38)

Prior to their baseline assessment, patients were asked to prepare a 3-day food record, comprising of 2 weekdays and 1 weekend. Following the initial baseline assessment and group allocation, patients were scheduled for a private consultation with a registered dietician to assess nutritional status and establish an appropriate dietary approach tailored to the individual. The dietician assessed dietary habits using the food record and carefully evaluate their nutritional status by consulting their anthropometrics (weight, BMI, body composition, waist circumference), functional measures (HGS, 6MWT and STS), blood chemistry measures (hemoglobin, albumin, prealbumin, CRP, HBA1C, creatinine), and the PG-SGA, completed during their initial consultation. Based on this data they can estimate the appropriate amount and distribution of macronutrients and micronutrients to match the patient's dietary requirements. Physiological

stressors such as NACT and surgery can also have important implications on metabolic requirements, therefore dietary recommendations will be adjusted to satisfy the elevated energetic demands.(133, 134)

All the patients received personalized food-based dietary advice, with careful consideration for limiting symptoms, such as reflux, dysphagia and odynophagia. Additionally, whey protein supplementation (ISOlution; Enhanced Medical Nutrition Inc) was prescribed to ensure an adequate daily protein intake of 1.2-1.5g/kg of ideal body weight (or approximately 20% of total energy requirements), as per the recommended ESPEN guidelines for oncologic surgical candidates.(80) Patients were encouraged to consume the nutritional supplements in the morning with breakfast or immediately following exercise. Nutritional support was provided to all patients in the study, even if there were no clinical indications of malnutrition.(14, 41) The dietician is able to monitor adherence to and address dietary issues or concerns through regular telephone follow-ups.

c) **Psychological Support**

Personalized mental-wellbeing support was provided to all patients in the study, irrespective of the group allocation or psychological distress at baseline. Naturally, acquainted with any cancer diagnosis or foresight towards a major elective surgery, anxiety and depression are common psychological responses. Moreover, concerning esophageal cancer, the challenging clinical manifestations of the disease can further exacerbate a patient's psychological distress. Psychosocial well-being is often overlooked in the clinical setting, however importantly, it can affect adherence to medical treatments, surgical recovery and HRQoL.(108, 135)

Following the baseline evaluation, patients were scheduled for a private consultation with a psychology trained personnel. Patients were educated on coping and anxiety reduction techniques, which will include guided-imagery, visualization and breathing exercises. Patients were also provided with a compact disk containing pre-recorded motivational suggestions, breathing exercises and a relaxation audio track. The psychology trained personnel would ask patients to practice the appropriate exercises at home weekly week and to record their frequency in their booklets. Research assistants were able to monitor patient mental wellbeing and perceived distress, address any additional questions or concerns during their regular weekly telephone follow-ups and if needed schedule a follow-up consultation with the psychology trained personnel.

Standard of Care:

All patients received the same standardized perioperative care, in accordance with the recommended guidelines for esophagectomies, recently established by the ERAS Society.(49) The primary components of which include: early patient presentation at a multidisciplinary tumor board, minimally invasive surgical approach when feasible, maintenance of intraoperative fluid balance, use of multimodal analgesics, limited utilization and early removal of drains and tubes, early postoperative oral nutrition, in addition to regular mobilization and respiratory physiotherapy.

3.5 Research Endpoints

Primary - Feasibility

The primary outcome of interest of the thesis was adherence to a multimodal prehabilitation program in the current study cohort. Feasibility was evaluated according to the program's recruitment, completion, and adherence rates, in addition to justification for poor adherence and occurrence of intervention-related adverse events.

Recruitment & Completion Rates

Recruitment rate will be presented as the number of patients consented compared to patients eligible, whereas completion rate will be presented as number of patients completing all evaluations compared to number of patients recruited. Reasons for refusal to participate in the program were also documented.

Adherence Rate

To date, the majority of research on adherence to prehabilitation programs has focused uniquely on the exercise component, and thus adherence to the other modalities has been limited. (136) The current study therefore attempted to measure adherence to both exercise (aerobic and resistance training) in addition to nutritional (dietary recommendations and prescribed whey supplementation) components of the prehabilitation program (refer to Figure 3). Mental wellbeing support was provided to all patients, however adherence to the clinicians' recommendations were not closely monitored, given the variability in each patient's needs, the heterogeneity and personalized nature of the psycho-behavioural approaches in addition to the diversity of interventions provided and exercises recommended.

a) **Adherence - Exercise Component:** In order to assess patient adherence to the exercise program, patients were asked to record their exercise activities and frequency in their personalized logbook. Patients would be contacted weekly by an exercise specialist who would review their activities, adherence and progress. Weekly adherence to the aerobic training was calculated as a percentage of the minutes completed with respect to what was prescribed. Similarly, resistance training was also reported as a percentage of the number of resistance training sessions completed in a given week with reference to what was prescribed.

b) **Adherence - Nutritional Component:** Each patient met with a dietician who provided them with dietary advice specific to them and their respective needs. During weekly follow-ups patients were asked to self-report their adherence to the nutritional recommendations provided on a scale of 1-5 (1=strongly disagree, 5= strongly agree). All patients were also provided with whey supplements, the amount prescribed depended on the patient's dietary patterns, nutritional status and needs. The weekly adherence to nutritional supplementation was also calculated as a percentage, based on the number of pre-measured protein sachets consumed with reference to what was prescribed by the dietician.

Figure 3. Reporting Weekly Patient Adherence

Weekly Step Count	Resistance Training	Aerobic Training	Dietician's Recommendations	Whey Supplementation
Daily steps tracked by pedometer, recorded	Number of resistance training sessions completed (x/2)	Total minutes of aerobic training completed/ minutes prescribed	Self-reported adherence to dietary recommendations (1-5) 1 = Poor; 5 = Excellent	Adherence to supplementation Number of protein sachets consumed/prescribed

Figure 3. Figure provides a visual representation of the data pertaining to adherence acquired by kinesiologists during weekly follow-up phone calls.

With reference to the current literature, adherence to home-based oncological prehabilitation programs have reported to be approximately 70%. Of note, this includes self-reported measures of adherence to exercised programs, none of which include patients receiving NAT.(136) Admittedly, the current study uses a mixed approach to delivering prehabilitation services. In a recent prehabilitation study investigating its impact in esophageal cancer patients receiving surgery, adherence was only measured for exercise and was 64%.(116) To date, no studies have measured adherence to more than one prehabilitation interventions in cancer patients. Given the limited data available, 70% was pragmatically selected to an acceptable score for good overall program adherence.

Reason for Poor Adherence

During the weekly contact between patients and exercise specialists, patients reviewed their week, how they felt about their program and treatments, and raised any questions or concerns. The specialist was able to make the appropriate recommendations to ensure the patient was progressing. If a patient was unable to adhere to the program it was recorded in addition to the supporting rationale.

Adverse events

In the case where adverse events were observed during exercise sessions, or functional evaluations, the following criteria were selected to stratify the severity of the event: type (fall, musculoskeletal and cardiovascular) and severity (minor, moderate or severe).(137)

Secondary– Functional Outcomes

Objective Measures
6-Minute Walk Test (6-MWT)

A secondary outcome of interest was the changes in functional exercise capacity, which was determined by the absolute difference in distances travelled during a 6-MWT, between preoperative and baseline assessments. For the purpose of the test patients were advised to wear

comfortable clothing and running shoes, then to briskly walk back and forth down a 20-meter-long hallway for the total duration of six minutes. Changes in heart rate, oxygen saturation and perceived shortness of breath were recorded at baseline and immediately following the termination of the test. The assessor provided them with standardized instructions on how to perform the test as per the guidelines established of the ATS. The guidelines were published in 2002 to identify test contraindications, to standardize the testing procedures, data collection, minimize error and unintended biases, but also to facilitate its clinical interpretation.

The 6-MWT is a well-known submaximal endurance exercise test that is often used in the clinical setting to assess an individual's functional capacity. It has been demonstrated to be a short, simple and inexpensive assessment tool that has been correlated with CPET-derived measures of cardiorespiratory fitness.(138) According to the literature, a difference of 20 meters has been recognized to represent a clinically meaningful difference (MCID) in 6-MWD, and therefore was used as a reference for the current study.(139) The 6MWT has also demonstrated prognostic value for postoperative morbidity and recovery. (140) Appropriately, it has been particularly important in the perioperative setting to screen for high-risk surgical candidates, but also to measure changes in functional capacity trajectories preoperatively and throughout the period of convalescence.(141)

Cardiopulmonary Exercise Testing (CPET)

CPET is another important clinical tool that has been used to objectively quantify changes in cardiorespiratory function in different pathologic and surgical populations, as determined by change in oxygen consumption at the anaerobic threshold (VO_2@AT) and at peak exercise (peakVO_2). To obtain the measurements of interest, patients were asked to perform a symptom-limited exercise test using the Quark CPET ® testing system (COSMED, Rome, Italy) and was performed in accordance with the recommendations established by the Peri-Operative Exercise Testing and Training Society (POETTS).(15) CPET offers a non-invasive approach to assess a patients physiologic response to an increasing exercise demand and the dynamic changes in cardiovascular, pulmonary, neuropsychologic, haemodynamic, and muscular systems. The bi-directional wind turbine allowed for volumetric air flow analysis. Patients were required to occlude their noses and wear a mouthpiece throughout the duration of the test. This allowed for breath-by-breath measurements of changes in oxygen consumption (VO_2) and carbon dioxide (VCO_2) production, which were analyzed with the assistance of a non-dispersive infrared absorbance

sensor. Results of the tests were then reviewed and interpreted by qualified personnel.

CPET has been widely recognized to be an important clinical tool in perioperative medicine and the gold standard for assessing cardiorespiratory fitness and identifying high-risk surgical candidates, notably in the current demographic.(15, 142) It is known that surgery can impose a stress and increase in metabolic demands, as such CPET can identify potential limitations in the integrative physiologic responses to an progressive physiologic demand.(143)   Exercise is associated with increased metabolic and physiologic demands, and while uncommonly reported it is important to acknowledge that there is an inherent risk for potential adverse events. Fortunately, it is widely recognized as a safe assessment tool. Serious adverse events are rare, the literature reports that the combined morbi-mortality rate as approximately 4 per 10 000 tests.(144)

Timed-Up and Go (TUG)

The TUG is another relevant clinical tool used to functional abilities, based on the time it takes to perform the test.(145) The assessor explained the purpose of the test and its execution following a standardized script. During the test, patients were asked to stand up from a seated position, without using their arms to assist, then to briskly walk around a cone, 3 meters away and return to their original seated position. The assessor ensured the patient completed the test properly and recorded the duration it takes them to complete it.(146) The test has been validated to provide an appropriate assessment of the patient's balance, mobility, gait patterns and walking abilities.(147)

The TUG has been commonly used among the elderly and frail populations to objectively measure their functional mobility and walking abilities. (148) It has also been useful in the clinical setting to assess patients with neurodegenerative and musculoskeletal disorders, and has been significantly correlated with other functional walking tests, including the 2-MWT ($\rho= -0.904, p<0.01$) and 6-MWT ($\rho= -0.925, p<0.01$). (147). Unsurprisingly, it has become increasingly appreciated as a preoperative screening tool for older surgical candidates. To this effect, a multicentric study in onco-geriatric surgical patients confirmed that low preoperative TUG scores were independent predictors of serious postoperative complications (OR =3.43, 95%CI (1.13-10.36), p<0.03). The test is a validated assessment tool that enhances the value of a functional battery, generally, it is regarded as a safe test given that it involves everyday movements and does not require patients to exert a maximal effort.(146)

Sit-to-Stand (STS)

The STS test is another tool of the functional evaluation battery that provides an assessment of strength in the lower extremities, based on the timed-number of repetitions that can be successfully performed.(149) To perform the STS, the assessor followed a standardized script, explained the purpose and execution of the test. Patients were asked to sit in the middle of the chair, with their arms crossed over their chest, then to stand up straight and return to the seated position as many times as possible for a total duration of 30-seconds. The assessor recorded the number of repetitions properly completed.

The STS is a validated test to assess the strength of the patient's lower limbs, but also provides important insight regarding their muscular endurance, mobility and balance. The test was been demonstrated to be reliable in assessing muscular strength and functional performance in different clinical contexts.(150, 151) The STS was therefore included in the functional assessment to measure changes in strength of the lower limbs throughout the perioperative period. Admittedly, data is lacking in oncologic surgical candidates, Zanini and colleagues reported that in a cohort of COPD patients receiving pulmonary training programs, changes in repetitions of two or more were recognized to be the clinically significant. (152)

Handgrip Strength (HGS) Test

The handgrip strength is another secondary functional outcome of interest that has been widely used in the literature to assess muscular strength of the arms. The test was performed using a handgrip dynamometer (JAMAR Hand Dynamometer, Jamar Technology Inc., USA), which was able to measure the peak isometric force generated from the muscles of the upper limbs.(153) The assessor followed a standard script to explain the purpose for the test, how to properly perform it and would demonstrate it so that the patient could see. The assessor adjusted the hand-held dynamometer to fir the size of the patient's hand, so that upon flexion of the hand, the middle phalange of the middle finger was resting in parallel on the handle. The patient was asked to remain in an upright seated position, with their back against the chair and feet shoulder width apart. They were then asked to bend the arm that was holding the dynamometer to a 90-degree angle, with the elbows against their side. They were then asked to squeeze as hard as they could while simultaneously exhaling, until instructed to stop by the assessor. The maximal force generated

was rounded down to the nearest kilogram and then recorded by the assessor. The patient was asked to perform the test twice per arm, allowing sufficient recovery time between each attempt.

Grip strength has been used in a number of studies to assess the upper body strength in different populations, including athletes and patients with cancer.(154) Grip strength is a fast, inexpensive and non-invasive was to measure the strength of the upper limbs and which has been demonstrated to be both reliable and reproducible.(153) It has been used as a surrogate measure of overall fitness, effects of interventions, but also to identify impairments and disabilities.(154) Beyond upper body strength, the test also offers important clinical value.

Low grip strength has been recognized to be an independent predictor of nutritional status and has been used in many clinical settings to identify patients at risk of being malnourished. (155) Under normal circumstances decreases in muscle mass are typically accompanied by reductions in strength, however, the reverse is not always observed. Gale and colleagues reported that grip strength was an independent predictor of all-cause mortality in patients with cancers or cardiovascular conditions.(156) The results were compared to normalized scores from a health age- and sex-specific reference population.(157)

1-Arm Curl Test

The 1-arm curl test was the last element of the functional test battery, and was performed to measure muscular endurance in the upper limbs, specifically the biceps. (145) The test required patients with 1 arm curl a fixed weight as many times as they could in a seated position for a duration of 30 seconds. The assessor would follow a standard script, explaining the rationale for the test, explaining and demonstrating its execution. Patients were asked to sit straight in the chair with their feet shoulder width apart, to keep their elbow fixated by their side to avoid swinging the weight. Prior to commencing the test, they were allowed to practice the movement so that the assessor could ensure they were performing it correctly. All females were given a 5-pound weight and while an 8-pound weight is normally used for males, a 7-pound one was used instead due to a lack of resources. During the test, the assessor, started the timer, counted and recorded the number of successfully completed repetitions. Patient were asked to perform the test once for each of their arms.

The curl test measures muscular endurance of the biceps but is also known to be reflective of upper body strength in older adults. The test is short, simple and a reliable assessment tool.(145)

Like most older adults are dependent on their upper limbs for many activities of daily living and such it is important that the strength in their upper body is maintained to preserve their independence.(158) Patient scores were recorded and compared to normalized scores of a healthy age-and sec-specific cohort.(145) The test provided insight as to the changes in upper body strength throughout the perioperative period.

<u>**Subjective Assessments**</u>

Community Health Activities Model Program for Seniors (CHAMPS)

The CHAMPS is a self-reported questionnaire that is used to assess levels of physical activity among the elderly. The questionnaire has good construct validity and has been demonstrated to be a reliable and sensitive tool to measure physical activity patterns.(124) Patients were asked to complete the questionnaire to obtain an appreciation for their current physical activity levels, the types and intensities of the activities they were typically engaging in. The CHAMPS provides a score for the weekly energy expenditure (kcal/kg/week) spent performing light, moderate and vigorous activities. Changes in baseline CHAMPS scores were studies before and after prehabilitation.

Duke Activity Status Index (DASI)

The DASI is another self-reported questionnaire used to subjectively assess functional status in older adults. It is comprised of 12 yes/no questions of perceived functional abilities and was designed to predict an individual's peak oxygen consumption.(123) The DASI was compared with other recognized fitness tests such as CPET and shuttle walk, and has since been validated as a measure of cardiopulmonary fitness in surgical patients.(159) It has become common in the preoperative setting to screen for high risk surgical candidates. A large multicentric cohort study found that low DASI scores were associated with an increased risk of prolonged hospital stay, postoperative complications and mortality.(160) Patients were asked to complete the DASI at all three timepoints to assess changes in perceived functional capacity.

Functional Assessment Cancer Therapy – Esophageal (FACT-E)

The FACT-E is a comprehensive questionnaire that was developed to assess functional status and quality of life in patients specifically with cancers of the esophagus. The questionnaire

includes subsections for perceived health as it relates to physical, functional, emotional and social well-being in addition to cancer specific concerns. The subscales scores were significantly correlated with those of similar questionnaires such as the QLQ-C30 and the OES 24. The FACT-E has demonstrated good test-retest reliability and sensitivity to changes in patient functional status throughout cancer treatments.(127) A MCID has not yet been identified for FACT-E, however, clinicians often refer to that of the FACT-G is a change of 5 or more.(161)

Hospital Anxiety and Depression Score (HADS)

The HADS is a self-reported questionnaire designed to measure levels of anxiety and depression among patients.(126) The tool requires patients to score a total of 14 items, to yield two subscales of anxiety and depression. The HADS been widely used in clinical practice, especially in the context of cancer, and has been validated as a surrogate measure of mental well-being.(162) The cut-off proposed in the literature for anxiety and depression are scores greater than 9 and 7 respectively, which have demonstrated good accuracy and specificity with corresponding areas under the receiver operator curve of 0.9 and 0.84.(163) The HADS was therefore used to assess changes in mental well-being throughout their care continuum.

Edmonton Symptom Assessment System (ESAS)

The ESAS is a self-reported questionnaire with 10 symptom subscales and is used to assess the severity of a patient's symptom profile.(125) The metric has been validated as a clinically relevant assessment metric in cancer patients, demonstrating a good correlation with subscales of other recognized QoL instruments such as the FACT and Memorial Symptom Assessment Scale (MSAS).(164) The minimal clinically important difference to of improvement total decrease in score of three or more points, conversely an increase of 4 or more points reflected a worsening score.(165) Esophageal cancer and its treatments are known to impose a high symptom burden, accordingly it is important to monitor patient perceived symptom trajectories, as it can directly impact their HRQoL.

Tertiary– Short-Term Clinical Outcomes

Tolerance to NACT

Tertiary outcomes of interest include the patient's ability to tolerate NACT. In order to evaluate patient tolerance, the following metrics were recorded, as recommended by the surgical investigators and oncologists: chemotoxicities (CTX, grade: I-IV), the number of cycles the patients received, the frequency of dose reductions, cycles delayed, preoperative ED visits, preoperative hospitalizations in addition to premature treatment terminations. The chemotoxicities were reported by patients directly and graded by the research team members with the assistance of a trained physician using the common terminology criteria for adverse event criteria.(166) The other mentioned parameters were obtained through the revision of medical charts and confirmed by the treating physicians and medical staff.

Surgical Outcomes:

The surgery is also known to be associated with a high incidence of postoperative complications. Accordingly, 30-day postoperative morbidity was also assessed using the Clavien-Dindo classification (CDC) and the Comprehensive complication index (CCI), days in ICU, LOS, 30-day ED visits and readmissions.(167, 168)

Esophagectomies are particularly invasive and associated with a high degree of postoperative morbidity, primarily attributed to cardiopulmonary complications.(10) At our institution the average recovery post-esophagectomy includes eight days of hospitalization, 35.6% of patients reporting major complications (CDC grade >2), 24% of patients experiencing pulmonary complications.(73)

3.6 Statistical Considerations

As previously mentioned, to mitigate the spread Covid-19, the hospital placed restrictions on hospital access and functions, which included most research activities. Inevitably, the current research project was temporarily ceased, and resulted in a study cohort. In order to evaluate if the data was normal, the distribution of the data was firstly visually inspected and analyzed, looking at the inter-quartile ranges. In order to confirm normality of the data, for the outcomes of interest, we performed the Shapiro-Wilk test (n=13).(169) Mean and standard deviations were reported when the data were normally distributed. Alternatively, the median and ranges were used to report nonparametric variables.

Baseline patient characteristics were described using mean and standard deviations for normally distributed data, and median and ranges for those that were not. In the case of categorical variables, the data was reported as absolute numbers and percentages.

Objective 1 – Feasibility

To assess feasibility, the recruitment, completion and adherence rates were recorded and analyzed. Weekly adherence to the exercise (aerobic and resistance training) and nutritional (dietary supplementation and guidelines) components of the prehabilitation program were calculated as a mean percentage with reference to what was prescribed. To obtain a measure for overall individual patient's adherence, an average adherence was calculated for each component of the program (aerobic and resistance training, dietary supplementation and guideline). Once the overall individual patient's adherence was calculated an average cohort's adherence could then be obtained. In order to be conservative in the assessment of the cohort's adherence rate, medians and ranges were favored over means and standard deviations to better portray the data of the small sample, and to avoid unintentionally imposing a bias.

The program adherence rates were assessed to evaluate if they were clinically similar to the literature. A recently published systematic review of RCTs studying prehabilitation in oncologic surgical candidates reported mean adherence rates of 70% in home-based pre-conditioning programs.(136) A Wilcoxon Signed-Rank test was performed on the cohort's combined exercise and nutritional adherence rates with a set threshold of 70%, based on the hypothesis.

Objective 2 – Functional Status & QoL

To determine the effects of the exercise intervention on patient's functional fitness pre- and post-prehabilitation test results from the 6-MWT, CPET, handgrip strength, STS, TUG and 1-arm curl test were compared. A Paired-Samples T-test was performed when data was normally distributed, otherwise a Related-Sample Wilcoxon Signed-Rank test was used. If the change was deemed significant then the change in 6-MWD was compared, using a One-Sample T-test analysis, to the standard error of 20 meters, which as previously mentioned has been recognized as a clinically meaningful change in healthy patients.(139)

Similarly, in order to evaluate if the intervention influenced subjective measures of

functional capacity and HRQoL, baseline and preoperative measures of DASI, CHAMPS, HADS, FACT-E and ESAS were also compared. The same previously mentioned tests were also used depending on the distribution of the results. All the secondary outcomes were analyzed using comparative tests that were 2-sided and with the level of significance set at p=0.05. Variables with a significant difference between baseline and preoperative evaluations were presented in the text as percent change.

Objective 3 – Explore Clinical Outcomes

Descriptive data was reported for tolerance to NACT, as determined by the number of cycles completed, dose reductions, delays or treatment terminations; additional outcomes of interest included postoperative outcomes, such as length of stay, CCI, ER visits and readmissions. As previously described for objective 1: mean and standard deviations were reported for variables that were normally distributed, whereas median and ranges for non-normally distributed variables. Given the exploratory nature of the study and the exceptionally small sample size, outlier data will be clearly identified. All statistical tests were performed using the PASW Statistics software version 24.0, with confidence interval and significance level pre-set at 95% and 0.05, respectively. (SPSS Inc, IBM Corp., Chicago, Illinois).

Chapter 4 – Results

4.1 Baseline Characteristics

A total of 13 patients provided informed consent and were included in the current study cohort. Their baseline patient characteristics can be seen in Table 1. In the current study cohort, the majority were men (76.9%), and 5 (38.5%) were considered elderly. With reference to their BMI, most were classified as either overweight (n=4, 30.8%) or obese (n=5, 38.5%), compared to the remaining patients (n=4, 30.8%) who had normal BMI. With reference to the phenotypic frailty criteria, most (n=11, 84.6%) were classified as either frail or at risk of frailty. Also, at baseline, many patients presented with clinical manifestations that might pose a risk to nutritional status, these include dysphagia (n=10,.76.9%), GERD (n=11, 84.6%), moderate-severe unintentional weight loss (n=6, 46.2%) and elevated mean PG-SGA scores 10(4.5).

Table1. Baseline Cohort Characteristics

	Parameter	Study Population (n = 13)
Demographics & Anthropometrics	Age (years) [a]	60.5 (9.6)
	Male sex (number, %)	10 (76.9)
	Height (cm) [a]	170.2 (6.7)
	BMI (kg/m^2) [b]	30.79 [20.7-37.1]
	Bodyfat (%) [b]	29.4 [26.2-51.1]
	Waist, (cm) [a]	100.2 (11.6)
	LBM, (kg) [a]	56.4 (11.1)
Comorbidities & Risk Factors	**ASA, number**	
	II	10
	III	5
	Charlson Comorbidity Index, (patients)	
	2	1
	3-4	9
	5-6	4
	≥7	1
	Fried Frailty Score (patients)	
	No frailty, 0	2
	Pre-frailty, 1-2	8
	Frailty, ≥3	3
	Tobacco consumption (patients)	
	Never	5
	Former	8
	Current	2
Nutritional Characteristics	**Weight Loss Within 6 months (patients, %)**	
	Moderate, ≥5%	4, (30.7%)
	Severe, ≥10%	2 (15.4%)
	Dysphagia score (number)	
	0	3
	1-2	7
	3-4	3
	Blood Laboratory Values	
	Hemoglobin (g/L)[a]	133 (13.3)

	Albumin (g/L)[a]	41.7 (4.3)
	Prealbumin (mg/L)[a]	257.6 (45.9)
	C-reactive protein (mg/L)[b]	6.8 [0.3-62.4]
Cancer Pathology	**Tumor level (patients)**	
	Thoracic	7
	GEJ Siewart	6
	AJCC pathological stage (patients)	
	I	1
	II	2
	III	7
	IV	3

Data is presented as absolute number of patients (percentage), [a] Mean (standard deviation), or [b] Median [range]. AJCC, American joint committee of cancer; GEJ, gastroesophageal junction; LBM, Lean body mass.

4.2 Feasibility

Feasibility

The recruitment rate for the current study was 56.5%. Baseline and preoperative evaluations were performed by all 13 patients, resulting in a 100% completion rate. Details of the recruitment process of the cohort can be visualized in the recruitment flowchart (Figure 4). The median duration of the program, from baseline to surgery, was 104 days [63-156], which represents 14.9(4.2) weeks. The refusal rate was 43%. Reasons for refusal included: disinterest in the prehabilitation services (n=3, 30%), anticipated challenges with commuting (n=3, 30%), time commitment (n=2, 20%), physical pain and limitations (n=1, 10%), unable to contact (n=1, 10%). The patients that consented were provided with the prehabilitation program at home-based unsupervised (option 1; 46%), in-hospital supervised (option 2; 38%) and teleprehabilitation (option 3; n= 15%).

Figure 4. Recruitment Flowchart
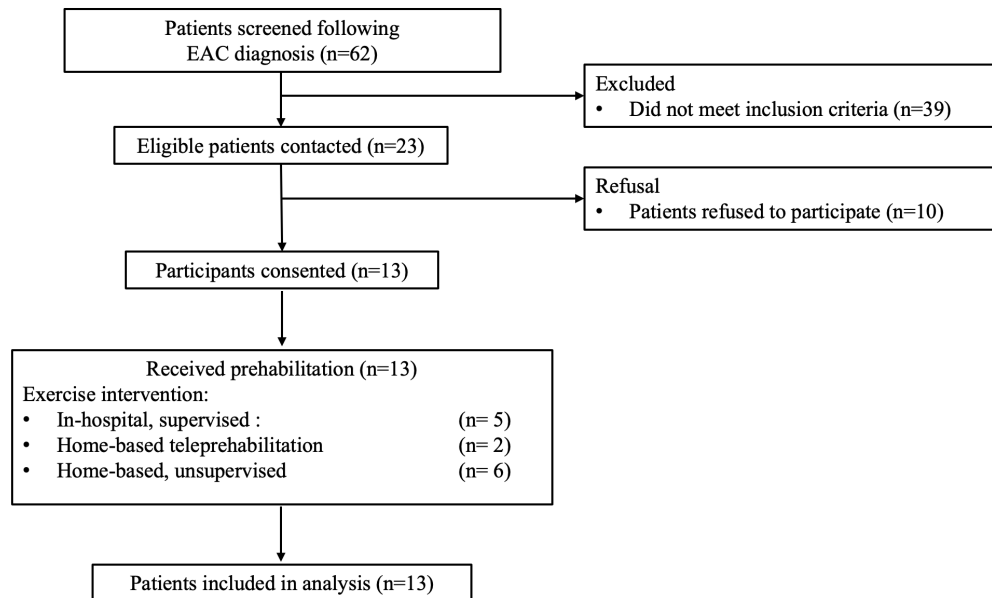
Figure 4. Flowchart for the pilot study describes recruitment, group allocation and patients included in analysis of the results.

The individual patient's adherence rates, to single components and to the overall program recorded during their participation in the multimodal prehabilitation can be seen in Table 2. All patients received a private consultation with psychology trained personnel at baseline, however given the variability of individual patient needs, adherence was not documented. The median cohort's overall adherence to the aerobic and resistance components was 68.7[17.9-100] and 67.3[32-95] percent, respectively. While adherence to the recommended step count was not an outcome of interest, it was also monitored by a kinesiologist throughout the preoperative period; the median daily step count throughout the perioperative period was approximately 5027 [509-8759], representing half of the 10 000 steps recommended. The median cohort's overall adherence to the intake of the prescribed whey supplements and self-reported adherence to personalized nutritional guidelines was 84 [10-100] and 83.5[65.7-93.3] percent, respectively.

The median cohort's adherence to the prehabilitation program was 68.9% [38.8-95.6] and was shown to be statistically similar to the 70% reported in the literature through a One Sample Wilcoxon Signed Rank Test (p=0.7).

Table 2. Patient Adherence

ID	Prehab Group	Preop Duration (weeks)	Mean Daily Steps	Psych Support	Mean Adherence Rates (%)				Overall Adherence to Prehab Program (%)
					Strength	Aerobic	Nutrition	Supplement	
1	1	14.9	8126	✓	73.3	63.0	95.0	97.0	81.3
2	1	20.9	6525	✓	32.5	33.0	70.0	71.0	51.7
4	1	17.9	2401	✓	55.6	71.0	66.7	86.0	69.8
8	1	22.3	7090	✓	67.3	95.3	86.2	42.0	72.7
9	1	13.1	5336	✓	42.9	53.0	65.7	45.0	51.7
11	1	13.1	5096	✓	88.5	79.5	81.5	84.0	83.4
3	2	10	8759	✓	95.0	100	87.5	100.0	95.6
5	2	17.6	5027	✓	70.6	70.6	91.8	86.0	79.8
6	2	17.3	2585	✓	41.0	41.0	83.5	94.0	64.9
7	2	17.1	2317	✓	32.0	17.9	74.3	67.0	47.8
10	2	9	509	✓	68.7	68.7	93.3	91.0	80.4
12	3	12.1	4322	✓	33.3	25.0	86.7	10.0	38.8
13	3	10.6	4465	✓	75.0	75.0	68.0	44.0	65.5

Table 2. The table depicts the different patients receiving different intervention modalities, the duration of the preoperative period and their adherence to different components of the prehabilitation program. Intervention modality: (1) unsupervised, home-based, (2) supervised, hospital-based (3) supervised, virtual home-based (teleprehabilitation). Adherence of each patient's is reported as a mean percentage of their weekly self-reported adherence to each component (refer to methods).

The supporting justification for patient receiving unsupervised home-based prehabilitation (option 1) who were unable to complete the recommended exercise program were: fatigue (n=30, 44.8%), nausea (n=15, 22.4%), dizziness (n=7, 10.4%), medical appointments (n=5, 7.5%) and time constraints (n=5, 7.5%). In the supervised condition, both in-hospital and through teleprehabilitation supervision (option 2 and 3), the most frequently reported reasons for cancellations or poor participation include the commute (n=25, 31.3%), fatigue (n=14, 17.5%), Covid-19 (n=13, 16.3%), medical appointments (n=9, 11.3%), ER visits/admissions (n=8, 10%), nausea (n=7, 8.8%), among other common chemotoxicities (n=4, 5%). Lastly, no intervention-related adverse events were reported throughout the program.

4.3 Functional Status & HRQoL

All functional measures were performed at baseline and during their preoperative visits, of which the objective parameters are presented in Table 3. CPET was not performed for 5 patients due to concerns pertaining to Covid-19 and risk of potential exposures. Additionally, one patient was unable to perform the CPET due to limitations in mobility. Another patient was unable to perform a preoperative BIA, limiting the number of patients to twelve in the pre- and post-intervention results comparison for anthropometric measurements. Still, no significant changes were observed in absolute weight or body compositions. With respect to functional performance, no significant change was observed in TUG or HGS.

Table 3. Preoperative Changes in Functional Status – Objective Measures

	Parameters	n	Baseline	Preop	p-value
Cardiorespiratory Fitness	**6-Minute Walk Test**				
	2-MWD, (meters) [b]	13	199 [52-233]	193 [54-225]	0.86
	6-MWD, (meters) [b]	13	548 [155-696]	549 [140-675]	0.6
	Cardiopulmonary Exercise Test				
	Anaerobic Threshold	7			
	VO_2AT, (ml/kg/min) [a]		13 (1.1)	12.7 (2.0)	0.565
	Workload (watts) [b]		56 [48-94]	65 [38-106]	0.207
	Peak Exercise	8			
	VO_2peak, (ml/kg/min) [a]		20.6 (3.5)	18.1 (5.8)	0.017*
	Workload (watts) [b]		129 [77-165]	115 [47-184]	0.093
	V_E/VCO_2 (ratio) [b]	8	35.3 [25.3-42.5]	38.2 [29.9-54.1]	0.093
	VO_2/WR (ml/kg/watt) [b]	8	10.2 [8.6-11.1]	9.9 [5.3-10.8]	0.237
	RQ (ratio: ml CO_2 / ml O_2) [b]	8	1.0 [1-1.3]	1.2 [1-1.3]	0.046*
Functional Capacity	TUG, (sec) [a]	12	6.1(1.1)	5.5 (1.5)	0.177
	STS, (repetitions) [b]	13	13 [0-16]	14 [0-21]	0.004*
	1-Arm curl test, (repetitions) [a]	13	17 (5.5)	19.8 (5.7)	0.005*
	HGS, (kg) [b]	13	32 [12-50]	32 [10-44]	0.388
Physical Status	Weight, (kg) [b]	13	82.7 [61.4-102.2]	77.5 [63.6-117.9]	0.402
	Bodyfat (%) [b]	12	30.3 [24.4-51.1]	27.7 [21.1-49.1]	0.03*
	FFMi, (kg/m^2) [a]	12	18.9 (3.2)	19.7 (3.6)	0.036*
	SkMi, (kg/m^2) [a]	12	8.8 (1.8)	9 (2)	0.157

Data is reported as [a] Mean (standard deviation), or [b] Median [range]. * Denotes statistically significant difference, $P<0.05$. 2-MWD, 2-minute walk distance; 6-MWD, 6-minute walk distance; VO_2AT, oxygen consumption at the anaerobic threshold; VO_2peak, oxygen consumption at peak exercise; V_E/VCO_2, ventilatory efficiency ratio; VO_2/WR, oxygen uptake to work rate; RQ, respiratory quotient (ratio of the amount of CO_2 produced from metabolism to the amount of oxygen consumed); TUG, timed-up and go test; STS, sit-to-stand test; HGS, handgrip strength; FFMi, fat-free mass index; SkMi, skeletal muscle index.

The median change in 6-MWD was -13[-191-69] meters, which is neither clinically (<20m; p=0.152) nor statistically significant (p=0.6). Among patients completing both CPETs (n=7), no significant difference was seen in oxygen consumption at the anaerobic threshold (VO$_2$AT), however a significant reduction was observed at peak exercise reflected by an average decrease of 13% (p=0.017).

Significant improvements were reported in upper and lower body strength, highlighted by an average increase of 19% in 1-arm curls (p<0.005) and 21% in STS (p=0.004) tests respectively. The median change in STS was 3 which also represents a clinically meaningful change. No significant difference was seen in median HGS. These functional improvements were also accompanied by a mean increase in fat-free mass index of 4% (p=0.036).

Beyond the modest improvements in functional performance, it is worth noting that patients saw desirable changes in body composition. Although patient weights did not significantly change between both baseline and preoperative assessments, there was a significant difference in adiposity (percentage: 30.3 vs. 27.7, p=0.03) in addition to LBM (kg: 56.9 vs 59.6, p=0.041) The results lend support to the notion that the prehabilitation interventions may have had a role in facilitating changes in adiposity and lean body mass. This is noteworthy as increased adiposity is known to be a prevalent comorbidity in patients with EAC and ca negatively influence surgical risk.(170) Applicably, in the current cohort 69% of patients at baseline were classified as overweight or obese.

Patient-reported outcomes relating to functional status and HRQoL are presented in Table 4. No significant change was seen in scores for either ESAS or HADS. However, a significant difference was reported in median measures of functional status: an average increase of 14% was seen in scores for the FACT-E (p=0.01), whereas a 158% increase was observed in CHAMPS (p=0.001). No significant difference was reported in preoperative DASI scores.

Table 4. Preoperative Changes in Perceived Health and Functional Status – Subjective Measures

Self-Reported Questionnaire	n	Baseline	Preop	P-value
FACT-E (score)[b]	12	115.5 [87.6-145]	132.4 [101-169]	0.01*
ESAS (score)[b]	13	21 [0-49]	12 [0-45]	0.05
DASI, (score)[b]	13	58.2 [10-58.2]	53.7 [24.2-58.2]	0.767
CHAMPS (kcal/kg/week) [b]	13			
Total		45.6 [6-93.5]	66.8 [39-235]	0.001*
Light		32 [0-74]	45 [15-129]	0.014*
Moderate-Vigorous		8.5 [0-57.5]	34.5 [10-177.5]	0.001*
HADS (score)[a]	13			
Total		12.2 (4.7)	9.8 (5.3)	0.203
Anxiety		7.2 (3.6)	5.5 (3.2)	0.144
Depression		4.9 (3.2)	4.2 (3.5)	0.443

Data is reported as [a] Mean (standard deviation), or [b] Median [range]. * Denotes statistically significant difference, $P<0.05$. FACT-E, functional assessment of cancer therapy – esophagus; ESAS, Edmonton symptom assessment system; DASI, duke activity status index; CHAMPS, community healthy activities model program for seniors; HADS, hospital anxiety and depression scale

4.4 Clinical Outcomes

Data pertaining to the preoperative period, NAT treatments and tolerance are reported in Table 5. The median duration of preoperative therapies was 6.4 [2-11] weeks. All patients but one received NAT, in which case the tumor was in its early stages and therefore systemic therapies were not deemed necessary. The majority of patients were prescribed NACT with either a FLOT (n=6, 50%) or immuno-chemotherapy (mDCF & Avelumab, n =4, 30%) regimen. Common chemotoxicities were experienced by all patients to varying degrees, the most frequently reported side effects reported by patients included fatigue (n=13, 100%), nausea (n=9, 69%), anorexia (n=9, 69%), dyspnea (n=7, 54%) and constipation/diarrhea (n=7, 54%). All patients completed their full NACT regimen, with the exception of three patients who terminated treatments prematurely resulting in completion rates of 25%, 50% and 50% respectively. Among them, two ceased treatments due to serious CTX adverse events (grade: 3-4), whereas the other was due to minor CTX event (grade: 1-2). In each case where a NACT cycle was delayed, the supporting justification was due to neutropenia.

Table 5. Preoperative Clinical Outcomes

	Parameters	Number
Neoadjuvant Therapies (NAT)	Total Duration of NAT (days)[b]	45 [14-78]
	Type of NAT	
	None	1
	NCRT	1
	NACT	12
	NACT Treatments	
	FOLFOX	1
	DCF	1
	mDCF & avelumab	4
	FLOT	6
Tolerance to NACT	Cycles Completed NACT (number) [b]	4 [1-6]
	Compliance to Prescribed Cycles (%)[b]	100 [25-100]
	Treatments Delayed (patients)	4
	Dose Reductions (patients)	3
	Premature Treatment Termination (patients)	3
	Chemotoxicities (CTX)	
	Patients Reporting CTX	13
	Highest Reported CTX Grade (patients)	
	1	2
	2	7
	3	4
	4	0
	Total ED visits	6
	Total days of hospitalized	18

Data is reported as absolute frequency, [a] Mean (standard deviation), or [b] Median [range]
NAT, neoadjuvant therapy; NCRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; FOLFOX, leucovorin, fluorouracil, oxaplatin; DCF, Docetaxel, cisplatin and fluorouracil; FLOT, docetaxel, oxaliplatin, leucovorin and 5-fluorouracil; CTX, chemotoxicity; ED, emergency department;

Data pertaining to postoperative outcomes and recovery can be seen on Table 6. Relating to surgical and postoperative morbidity, all patients received an esophagectomy with curative intent, among which 6 patients did not experience any serious complications. While the median length of hospital stay was 7 days, there were several patients who had complicated clinical trajectories, resulting in prolonged lengths of hospital stay of 73, 38, 30, 21 and 19 days. Pulmonary morbidities were the most commonly reported (n=5, 38.4%) postoperative complications followed by cardiovascular events (n=4, 30.8%).

While several reoperations were necessary in the current cohort (occurrences:9), they were attributed to only three patients who required further surgical interventions. Of note, there were two in-hospital mortalities: the first was 40 days after the primary surgery due to respiratory failure, the second was 19 days due to a self-inflicted fatal injury.

Table 6. Postoperative Clinical Outcomes

Parameters	Number
Surgical procedure	
Ivor-Lewis Esophagectomy	9
3-Hole Esophagectomy	4
Postoperative Morbidity & Recovery	
Patients Without Complications	5
Postoperative Complications	5
CDC (patients)	
I	0
II	1
III	1
IV	5
V	1
CCI (score)[b]	33.7 [0-100]
ICU Stay (days) [b]	0 [0-28]
LOHS (days)[b]	7 [6-40]
30-Day Morbidity (number of occurrence)	
ED visits	1
Readmissions	0
Reoperations	9
Mortality	2

Data is reported as absolute frequency, [a] Mean (standard deviation), [b] Median [range]
CDC, clavien-dindo classification; CCI, comprehensive complication index; ; ICU, intensive care unit;
LOHS, length of hospital stay; ED, Emergency department

Chapter 5 – Discussion

5.1 Main Findings

The primary aim of the current study was to investigate the feasibility of a multimodal prehabilitation program in advanced stage esophageal cancer patients scheduled to receive an esophagectomy with curative intent preceded by NACT. It was hypothesized that prehabilitation was feasible throughout the systemic therapies and the preoperative period, as determine by patient recruitment, adherence, and completion rates, in addition reason for poor adherence and occurrence of prehabilitation-related adverse events. The principal finding of the study supported the initial hypothesis, as a multimodal prehabilitation program was able to be safely and feasibly delivered to this unique clinical population. The cohort's median adherence rate to the program was 68%, for a recruitment rate of 56%, and a completion rate of 100%. All patients consented completed the prehabilitation program and received their respective surgeries, without any prehabilitation-related adverse event. The second objective was to investigate the impact of preoperative interventions on objective and subjective measures of functional status and HRQoL. It was hypothesized that prehabilitation would result in significant preoperative improvements in cardiorespiratory fitness. The secondary hypothesis was rejected based on a lack of significant changes in preoperative measures of cardiorespiratory fitness, as 6-MWD, VO_2AT remained unchanged and as VO_2peak decreased. Complementary functional outcomes such as the STS and 1-arm curl increased, while all other measures remained unchanged. The only self-reported measures that improved were the CHAMPS and FACT-E. The third objective of the study was to investigate the short-term clinical outcomes such as tolerance to NACT and surgery in a patient cohort receiving prehabilitation. To this extent, the cohort demonstrated satisfactory tolerability to NACT (median compliance: 100%), although all patients reported treatment-related side effects, most commonly fatigue, anorexia, and nausea. Regarding surgical tolerance, eight patients experienced serious postoperative adverse events, among them five had pulmonary complications, the median length of stay was seven days, and the total in-hospital mortalities was two.

5.2 Feasibility, Safety & Challenges

The recruitment rate of the current study was 56%, which was not dissimilar from has been previously observed the literature. In fact, the last RCT published by our clinic, involving prehabilitation in surgical candidates with esophagogastric cancers had a recruitment rate of 60%.(21) The study sample of the thesis is considerably small, which can be attributed in part to patients refusing due to disinterest, concerns associated with regular commutes to the hospital. It is also important to recognize that recruitment was temporarily ceased due to concerns relating to Covid-19, potential risks of patient exposures and restricted hospital functions.

During this time, the prehabilitation unit was temporarily closed, while the Upper Gastrointestinal Cancer clinic remained operational, albeit at a reduced capacity. In May the kinesiologist's presence in the Upper GI clinic was requested surgical investigators to pragmatically provide home-based preconditioning programs to high-risk patients with esophagogastric cancers. Between May and July four patients were pragmatically provided with home-based programs, however it remains uncertain how many prospective study patients were missed during this time due to cessation of research activities.

Looking beyond the recruitment challenges imposed by the pandemic, researchers acknowledge that several patients (n=3) refused to participate due to concerns with respect to hospital commutes. Following such a diagnosis and being informed about the many forthcoming medical appointments for gastroscopies, imaging scans (positron emission tomography, computerized tomography), blood tests, port-a-catheter insertions, chemotherapy treatments, among others. With respect to oncologic treatments, all patients are typically asked to visit the hospital at least twice on weeks when receiving NACT, once for a screening blood test and again to receive their respective anti-neoplastic treatments. It is therefore understandable that patients were disinterested in the possibility of more hospital visits for additional services. Although recruitment and adherence rates were acceptable, had patients been provided with the option for remote supervision through teleprehabilitation at an earlier at an earlier stage, it may have proven to be impactful in overcoming the perceived barrier of commuting and overwhelming number of medical appointments, especially for those living far from the hospital.(121)

The study ultimately demonstrated that multimodal prehabilitation programs could be safely provided to EAC patients with locally advanced disease, based on the satisfactory adherence

rates and the lack of intervention-related adverse events during the preoperative period. Due to the vulnerable nature of this demographic, with respect to comorbidities, older age, physical deconditioning and frailty, patient safety remains a relevant concern in studies involving exercise interventions.(33)

The cohort demonstrated satisfactory adherence to the overall prehabilitation program, with overall median rates being 68%, which included both exercise and nutritional components. While the current study utilized both home-based and supervised modalities to deliver prehabilitation services, overall adherence was not statistically different to what has been reported in the literature 70%. The latter represents the average of adherence rates observed in similar studies involving the delivery of home-based surgical oncology pre-conditioning programs.(136) In the current study, the adherence rates to both nutrition and exercise were highly reliant on patient-reported scores and therefore may also inevitably have self-reported measurement bias, which could result in adherence discrepancies.(116, 171) Patients were also asked to fill out an activity log in the work book that was provided to them which was reviewed by the kinesiologist. It was later acknowledged that physical activity monitoring devices might prove to pivotal in providing clinicians with objective data and minimizing the possibility of positive self-reporting biases.

As previously mentioned, all patients received a baseline consultation with psychology-trained personnel, who continued to provide further support as needed throughout the perioperative period. Aptly, the authors decided to not measure adherence to psycho-behavioural interventions given the inter-variability in patient needs and the anticipated challenges with accurately measuring adherence.

A closer examination of the program's modalities revealed that patients reported greater adherence to the nutritional component compared to the exercise prescription. Nevertheless, adherence to exercise was in line with the literature involving home-based exercise programs and supervised in-hospital ones, in which published adherences were, 64% and 68.7% respectively. (20, 116)

NACT represents a significant physiological stressor; predictably, induction therapy commonly prompted CTX, which in turn adversely affected patient adherence to physical activity. Most patients in the current cohort reported a reduction in physical activity levels throughout NACT, albeit to variable degrees. This happening has also been previously documented by

Halliday and colleagues who observed similar reductions in exercise adherence during NACT.(116). In the study, researchers identified that baseline fitness was associated with exercise adherence during NACT; suggesting that a greater aerobic fitness might improve tolerance to NACT and CTX.

Parallel to other studies, fatigue, nausea, dyspnea and dizziness were commonly reported treatment-related effects experienced by the current cohort which and impeded patients from being physically active (see supplemental figures 2 and 3).(20) Within the supervised condition, several patients verbalized concerns with regular hospital visits due to the challenges with commuting, conflicting medical appointments, and later the Covid-19 virus. Fortunately, the protocol was able to be adapted to ensure the continued delivery of prehabilitation services using tele-health platforms. Applicably, a pilot study was recently published, which highlighted the safety and practicality of teleprehabilitation in this demographic.(172) Only two patients in the current study received supervised teleprehabilitation support, however they both stated that they would have been unwilling to participate in the study had interventions been uniquely hospital-based. Few conclusions can be drawn from the two patients that received teleprehabilitation services, nevertheless its clinical application merits further investigation especially in the context of the ongoing pandemic.(121, 173)

Notwithstanding the observed inter-patient differences in adherence to the prehabilitation program, all patients received completed the program throughout NAT and the preoperative period and performed both baseline and preoperative assessments. No patients were precluded from surgery; therefore, the program had a 100% completion rate which is greater than what has been seen in similar studies.(20, 21) Ultimately, the results support the feasibility of personalized multimodal prehabilitation in EAC patients receiving NACT.

Challenges Relating to Covid-19 Pandemic

The Covid-19 pandemic had considerable ramifications on the cohort of the current thesis. As such, the recruitment was ceased for a three-month duration as the prehabilitation clinic was closed and in-hospital interventions were not possible. The latter negatively impacted the delivery of exercise interventions to active patients previously allocated to receive the supervised in-hospital exercise, of which there were three who were unable to receive supervised exercise sessions, as per the protocol. Between them there was a cumulative of 20 missed supervised

exercise sessions due to the clinic's closure. Alternatively, patients allocated to the unsupervised home-based condition continued to follow the exercise program as prescribed.

Therefore, the research team adapted the supervised protocol to facilitate continued support via telprehabilitation. Furthermore, nutrition and psycho-social follow-ups were limited to telephone-based support. Meanwhile, there was an apparent and escalating need for supportive interventions within elderly and oncologic patients during the pandemic.(174)

Beyond the context of the pandemic, esophageal cancers have been widely recognized to be associated with a high morbidity and mortality. The poor prognosis can be further worsened by their comorbidities, challenging symptom burden, and aggressive management strategies.(33) The latter underscores the importance for practical and supportive interventions. This holds especially true in view of the ongoing pandemic, the large surgical backlogs, anticipated deleterious health and functional consequences resultant from self-quarantine, social and physical distancing measures.(121, 173)

A protocol amendment was therefore created to pragmatically implement teleprehabiltiation as a comparable alternative to supervised in-hospital prehabilitation.(175) Teleprehabilitation would facilitate remote patient supervision and delivery of prehabilitation services in a safe and effective manner, similarly to in-hospital care.(121) Understandably, tele-health interventions are imperfect and impose their own unique challenges, as it necessitates familiarization of the appropriate videoconferencing platforms and wearable health monitoring devices.(121)

Upon resumption of recruitment patients allocated to the supervised group were provided with the option of either performing supervised trainings in-hospital or via teleprehabilitation. If they opted for the teleprehabilitation option, they were asked to the videoconferencing platform, and were lent a training watch and upright stationary cycle ergometer so that they could closely follow the aerobic protocol as they would if they were in the clinic.

5.3 Objective Functional Outcomes

Cardiorespiratory Fitness

Minnella and colleagues previously demonstrated that relative to the standard of care home-based prehabilitation programs could significantly improve functional trajectories in patients with esophagogastric cancers.(21) Therefore, researchers anticipated to observe similar

effects in the current cohort. It is important to note, that systemic therapies (NACT/NCRT) have been shown to negatively affect cardiorespiratory fitness in patients with esophageal cancers, as demonstrated by significant decreases in 6-MWD, VO_2AT and VO_2peak.(9, 17, 113). Surprisingly, despite the strong rationale, few studies have investigated the effects of multimodal prehabilitation programs on cardiorespiratory fitness in these patients, nevertheless during NACT.(33) Accordingly, the current thesis was developed to investigate this phenomenon.

Under normal circumstances, patients commonly experience a decline in physical fitness, which persists throughout the perioperative period.(10) Thus, contrary to the secondary hypothesis, patients did not demonstrate improvements in preoperative cardiorespiratory fitness, as reflected by the lack of change in preoperative 6-MWD. This may suggest that patients' cardiopulmonary function did not deteriorate. Cardiopulmonary exercise testing provides additional important insight on cardiorespiratory function, and revealed a significant decrease in VO_2peak, without a change in VO_2AT. The changes in peak oxygen consumption should be interpreted with caution given the effort-dependent nature of the parameter, the lack of paralleled change in anaerobic threshold and the lack of preoperative CPETs performed.(15, 16) Still the results might suggest a preservation of cardiorespiratory function given that prior studies have consistently shown declines in oxygen consumption at peak exercise and at the anaerobic threshold in these patients following NACT. (9, 17)

The thesis had a lacking effect on cardiorespiratory fitness, albeit comparable to what has been observed in the literature. Halliday et al, provided oncologic esophagogastric patients with a similar home-based multimodal prehabilitation program, PREPARE, during NACT. Similarly, researchers reported no significant change in cardiorespiratory fitness during NACT, but an improvement following termination of treatments. (116) Of note, unlike the current thesis, researchers measured cardiorespiratory fitness through the Chester Step Test to predict VO_2peak.(116) While it has been validated as a measure of aerobic fitness in younger populations, it may not be safe for frail and elderly patients due to the potential risk of falls.(176) Xu et al., implemented a pragmatic prehabilitation program, comprising nutritional counselling and supervised aerobic exercise during NCRT. In the study patients prehabilitation did not appear to improve cardiorespiratory fitness, instead resulted in a lesser decline in 6-MWD, suggesting that the interventions had a protective effect on physical deconditioning.(113) Only one study prehabilitation, although unimodal (exercise only), reported significant improvements in aerobic

fitness, as measured by CPET.(20) Unlike the previously mentioned studies, the program of the study in question was supervised and consisted both strength and aerobic training with a high-intensity interval training protocol. Though some of the patients in the thesis cohort did receive with a similar supervised exercise protocol, as a whole, the cohort received exercise programs with variable levels of supervision and different aerobic intensities which inevitably could explain the differences in cardiorespiratory fitness outcomes. Still, the results of the thesis support the notion that prehabilitation was able to prevent significant declines in cardiopulmonary function that would otherwise be anticipated. (9, 177)

Functional Capacity

Prehabilitation did not enhance aerobic fitness, however patients demonstrated significant improvements in complementary measures of functional capacity such as STS and 1-arm curl test. To the knowledge of the authors, it was the first study to investigate the preoperative changes in the above-mentioned parameters in esophageal cancer patients. For the most part, HGS has been used to assess muscle strength in this population.(178) STS, 1-arm curl and TUG are complimentary measures of functional capacity, and provide clinicians with a wholistic appreciation for a patient's functional abilities.(179) They are also fast, inexpensive and can be easily integrated into a clinical setting.

Preoperative reductions in LBM, functional capacity and muscle strength have been repeatedly documented in patients with esophageal carcinomas.(10, 45, 47, 113) Impressively, the findings indicate that prehabilitation programs can increase muscle strength in esophageal cancer patients even when faced with the catabolic stress of NACT. In addition to the improvements in strength, analogous increases in LBM were also recorded. Notably, patients did not experience a reduction in HGS or TUG performance.

With reference to the literature, Christensen and colleagues, were the only other prehabilitation study to report similar findings in preoperative measures of muscle strength during NACT, although without increases in LBM.(20) The discrepancies in body composition might be explained by the unimodal approach with exercise only. The combination of the disease and cancer therapies can potentiate the catabolic drive, therefore necessitating elevated nutritional requirements to resist myopenia and support the anabolic processes associated with resistance training.(14)

Still, the observed functional improvements in the thesis were superior to what has been reported in other multimodal prehabilitation studies, as reflected by their lack of changes in body composition or muscle strength, measured largely by HGS.(95, 113, 180) This may be due to an insufficient duration or intensity of interventions. Although HGS increased in one bi-modal prehabilitation study, patients did not observe improvements in any other functional parameters. The study revealed a potential risk for positive bias as patients did not receive NAT and the exercise program included a specific handgrip training component.(181)

Maintaining LBM and functional strength is a challenge for most patients with esophageal cancers, especially when faced with impairments in nutritional status and systemic therapies which often further aggravate physical deconditioning. (10, 45) The preliminary findings of the thesis nevertheless suggest that prehabilitation, specifically with multidisciplinary preoperative interventions, can sustain and may even improve functional capacity throughout NAT. Due to the mixed intervention modalities it remains unclear which approach provides the greatest functional benefits. Future studies comparing the functional outcomes between the standard of care, supervised, home-based and teleprehabilitation approaches warrant further investigation.

5.4 Patient-Reported Outcomes

The field of oncology has demonstrated an increased appreciation for patient-centered outcomes; recognizing that the disease, NAT and surgery can have acute and chronic consequences that can persist beyond treatments, affecting long-term functional status, independence and HRQoL.(182-184) Neoadjuvant Chemotherapies have been associated with reductions in HRQoL, however, select studies have demonstrated it can be maintained,(185) and even improve in patients, specifically through alleviating symptom burden of the disease.(186)

The current patient cohort reported significant improvements in perceived physical activity, functional status and HRQoL, as determined by the increased CHAMPS, FACT-E and decreased ESAS scores. Self-reported functional measures, although important, are inherently limited in their ability to accurately represent actual physical fitness.(187) With any self-reported data, there is the inevitable risk for a bias. As such, it is recommended that subjective data be combined with objective parameters to better appreciate the effects of the interventions.(171) Predictably, the reported improvements in CHAMPS and FACT-E scores corresponded to the cohort's adherence rates and the objectively measured increases in functional capacity. The results

are in line with what has been seen in other prehabilitation studies.(20, 172)

In the current cohort, patients did not report a significant change in anxiety or depression between baseline and preoperative assessment. The reasons for which cannot be deduced from the HADS to close-ended nature of the questions. It is worth noting that many patients at baseline expressed a great deal of distress with respect to the symptoms of dysphagia impeding nutrition, recent diagnosis and anticipated chemotherapy. As patients received their NACT regimens, dysphagia most often was reduced, thereby improving oral intake. While the following cannot be extracted from the HADS questionnaire, as patients' surgical dates approached, many verbally expressed increasing concern towards their surgeries and the subsequent recovery. Unlike the study cohort, Piraux and colleagues saw a significant improvement in HADS scores. The findings might suggest the need for more comprehensive psycho-social interventions.

To the surprise of the authors, there is a lack of research investigating the impact prehabilitation on patient-centered outcomes in this patient demographic, nevertheless during NAT. There is a need for more research on self-reported measures of functional capacity, HRQoL and symptom burden throughout the perioperative period to acquire a better appreciation for patient perspectives and the perceived impact of interventions.

5.5 Tolerance to NACT

The impact of prehabilitation on perioperative functional outcomes have been previously in patients with esophagogastric carcinomas.(21) Notably, the cohort had mixed pathologies, management strategies were heterogeneous, with 69% (n=35) receiving NAT. Esophagectomies preceded by NACT has become a recognized gold standard for the management of locally advanced EAC.(186) In general, albeit variable, NACT is well tolerated (56-95%); still, DLT can negatively affect compliance to treatment regimens and is a frequent concern, especially in patients with malnutrition or sarcopenia.(3, 17, 57, 188) Both malnutrition and sarcopenia were previously discussed, and although they are prevalent among patients with cancers of the upper gastrointestinal cancers, they are modifiable risk factors and can be ameliorated if addressed accordingly by the treating clinical team.(14)

Shockingly, few studies have investigated the implications of prehabilitation during NACT with respect to functional and clinical trajectories in these patients. The cohort demonstrated good tolerability to NACT, as only three patients ceased treatments due to DLT, and all received their

respective surgeries. The median completion rates are superior to what has previously reported by an RCT by our institution.(57) Several studies have clearly demonstrated deleterious effects of NACT on physical fitness.(9, 17) In comparison to a study by Sinclair and colleagues, patients demonstrated a lesser reduction in cardiorespiratory fitness which may in turn have helped them to better tolerate NACT, reflected by the lower incidence of prematurely treatment terminations (25% vs 30%).(9) The observed differences between the thesis and the study, might be explained by the fact that they did not include preoperative interventions during NACT.

Only one other study investigated treatment tolerability during prehabilitation.(20) Relative to the thesis, they reported a higher rate of treatment failure, whereby 14% of the cohort did not receive surgery due to deconditioning, disease progression, or death. Relative to the above-mentioned study, thesis reported a lesser relative incidence of dose reductions (25% vs 33%) but a higher incidence of delayed treatments (33% vs 26%). The findings may underscore the protective potential of preoperative interventions to impede physical deconditioning and optimize patient tolerance.

5.6 Recovery Post-Esophagectomy

Esophagectomies are recognized to be associated with high postoperative morbidity, largely due to the high incidence of postoperative pulmonary complications ranging between 20-50%.(189) A review by Vermillon et al., it was suggested that preoperative exercise-based interventions could improve functional trajectories, postoperative morbidity and recovery in patients undergoing surgical resections for gastrointestinal cancers.(94) Admittedly the review focused primarily on prehabilitation studies in patients with colorectal cancer, however there is a paucity of research to show similar effects in esophagogastric cancer patients. Notably, relative to most colectomies, esophagectomy is known to be a longer and more invasive procedure, therefore naturally is associated with a greater morbidity, length of stay and recovery period.(72, 73)

In the current cohort preoperative interventions did not appear to significantly influence postoperative outcomes as reflected by the incidence of total (n=8, 62%) and respiratory complications (n=5, 38%). The results were not surprising given that most preoperative interventions in this surgical demographic have been unsuccessful in altering postoperative morbidity.(10) A handful of studies have showed support for the therapeutic potential of prehabilitation to improve postoperative trajectories.(101, 116) Still, the data is limited and lacks

consistency.

Although the length of stay was similar, the severity of the complications was higher than what is typically reported by our institution and prior prehabilitation study.(21, 72) Due to the small sample size, the results were likely heavily influenced by a few patients who had challenging postoperative recoveries.

Only one study was able to demonstrate an improvement in postoperative outcomes following prehabilitation, however this finding was only significant in patients who improved cardiorespiratory fitness preoperatively.(116) It remains unclear whether prehabilitation can significantly ameliorate postoperative clinical trajectories; while this phenomenon may necessitate greater improvements in cardiopulmonary fitness, further research is recommended.

Chapter 6 – Limitations & Future Directions

The study revealed promising, preliminary findings with respect to the practicality and clinical utility of implementing prehabilitation programs during NACT. The results should however be interpreted cautiously, as the study did have several pertinent limitations. Notably, the sample size was especially small, also there was no control group (patients not receiving prehabilitation). It is therefore challenging to extrapolate the true impact of the interventions on clinical functional and clinical outcomes in these patients. The thesis described a single prospective cohort receiving prehabilitation via mixed modalities. The mixed approach can make it challenging to systematically monitor adherence, interpret the findings and elucidate the effects of the intervention modality on outcomes. All patients received, exercise, nutritional and psychosocial support, and while rationally they work together synergistically, it is unclear which component might be most attributed for the observed improvements in functional parameters and body composition.

In the study cohort, patients were assessed after diagnosis immediately following recruitment and acquisition of informed consent, they were then re-assessed preoperatively (approximately 1-2 weeks before surgery). Patients were not assessed during NACT treatments or immediately following their termination. It is difficult to accurately quantify the effects of the program on patient functional trajectories during treatments. Future studies should consider increasing the frequency of patient assessments to acquire a greater understanding for changes in functional status during NACT and thereafter.

The optimal prehabilitation program, interventional components and modality of delivery remains unclear, especially for the current demographic. While it is believed that the prehabilitation program can be attributed for a preservation in functional status during NACT, a large-scale clinical trial might be able to provide greater insight into the true impacts and clinical significance of the interventions provided.

Adherence to the program and interventions was highly dependent on accuracy of self-reported data. Naturally, with any patient-reported measures, there is a risk of positive bias. This may certainly explain the lack of increase in cardiorespiratory fitness given the satisfactory reported adherence rates and perceived increases in physical activity levels, quantified by CHAMPS scores. The current study attempted to minimize the potential bias by having patients document physical activity and adherence in their logbooks. To further improve accuracy of remote data collection, wearable physical activity tracking devices may be a practical and effective

alternative to measure patient adherence to exercise.

The functional parameters utilized (6-MWD, STS, 1-Arm Curl, TUG and HGS) can also be a limitation. Despite being recognized measurements of functional capacity, they are also effort dependent and therefore subject to a motivational bias. Alternatively, CPET can provide a more objective measure of physical fitness, however due to circumstances beyond researchers control, preoperative data was unable to be acquired.

There is still a pressing need of more research, specifically large scale RCT, to objectively compare the impact of different prehabilitation programs during NACT on functional and clinical trajectories throughout the preoperative period and the recovery following major elective surgeries.

Chapter 7 – Conclusion

EAC is a lethal disease, associated with a high symptom burden and aggressive management strategies. Surgical resections preceded by NACT have been widely adopted as the gold standard in the management of locally advanced disease. Albeit important to improving the curative potential, cancer therapies can be detrimental to physiologic reserves and functional status, and adversely impact perioperative clinical trajectories. The culmination of all these effects can also negatively impact patient-reported outcomes and later QoL. Applicably, compared to the standard of care, prehabilitation has been shown to be effective in improving perioperative functional trajectories and regaining cardiopulmonary function following NACT.

The thesis investigated the impact of implementing a multimodal prehabilitation program in patients with locally advanced EAC receiving NACT. The program included lifestyle-based modifications interventions, placing an emphasis on exercise, nutritional optimization and stress reduction. Patients were part of a single-prospective cohort, whereby all received the same interventions, differing uniquely with respect to the modality in which exercise was (1, unsupervised home-based; 2, supervised in-hospital; 3, supervised teleprehabilitation). The interventions utilized a similar approach to what has been priorly reported in the literature. Admittedly the cohort was small, and the study design had several notable limitations, therefore the preliminary findings should be interpreted with caution.

The results of the thesis confirmed that prehabilitation was safe and feasible in these patients despite ongoing cancer therapies. Contrary to what was expected, patients did not demonstrate significant improvements in cardiorespiratory fitness nor functional status. A significant difference was however observed in patient-reported outcomes with respect to their physical activity levels and their QoL. The absence of changes in objective functional parameters may suggest prehabilitation conferred protective effect against the physical and functional impairments that might be otherwise expected under the standard of care. There was no control group in the cohort, however the short-term clinical outcomes were consistent with the published literature. Prehabilitation did not seem to elicit any changes on postoperative morbidity, however recent studies have highlighted the promising clinical potential of pre-conditioning programs on postoperative outcomes. Unfortunately, unlike other oncologic tumor resections, prehabilitation has not been consistently shown to improve the recoveries following elective esophagectomies. Further research is still warranted in these patients to objectively investigate its impact on patient

tolerance to NACT and esophagectomy. There is also a lack of consensus with respect to the optimal prehabilitation, the types of interventions and modality of their delivery, especially in higher-risk surgical candidates. The current thesis ultimately demonstrates the importance for prehabilitation in these patients, while underscoring the need for large-scales RCTs comparing different prehabilitation interventions and their impact on functional, clinical and patient-reported outcomes.

Chapter 8 – Supplementary

## Supplemental Figure 1. Overview Adherence Rates to Neoadjuvant Therapies and Prehabilitation Interventions

ID	Prehab Group	Age	Preop Duration (weeks)	NACT			Mean Daily Steps	Psych	Mean Adherence Rates (%)				Preoperative Trajectories & Clinical Remarks
				Type	Pres. Cycles	Completion Rate (%)			Strength	Aerobic	Nutrition	Supplement	
1	1	67	14.9	Immuno	4	100	8126	✓	73.3	63.0	95.0	97.0	Tolerated NACT well, symptoms included nausea & fatigue. Uncomplicated preoperative period.
2	1	72	20.9	FLOT → Rad	4	25	6525	✓	32.5	33.0	70.0	71.0	Patient visited ER twice: (1) hemorrhaging of tumor & anemia, (2) anemia & syncope. Received 6 blood transfusions. Treatment switched to radiation after 1st ER visit. Rads well tolerated.
4	1	57	17.9	FLOT	6	100	2401	✓	55.6	71.0	66.7	86.0	Tolerated NACT poorly, extremely dyspneic, fatigue, nausea, anorexia. 1 ER visit due to syncope & anemia. Declined blood transfusion. Developed edema & pulmonary toxicities
8	1	43	22.3	FLOT	4	100	7090	✓	67.3	95.3	86.2	42.0	Significant dysphagia at baseline & improved after 2nd NACT.
9	1	58	13.1	FLOT	4	100	5336	✓	42.9	53.0	65.7	45.0	Good tolerance to NACT with mild symptoms. Significant dysphagia at baseline. Low initial motivation towards exercise & whey supplementation.
11	1	51	13.1	Immuno	4	100	5096	✓	88.5	79.5	81.5	84.0	Dysphagia at baseline, improved with NACT. Highly motivated towards program. Uncomplicated.
3	2	61	10	DCF	3	100	8759	✓	95.0	100	87.5	100.0	Significant dysphagia throughout NACT. Highly motivated towards program. Excellent tolerance to HIIT protocol.
5	2	50	17.6	Immuno	4	100	5027	✓	70.6	70.6	91.8	86.0	Good tolerance to NACT with minor CTCAEs. Chief complaints were nausea & pain after Gastrofil injections. Uncomplicated.
6	2	74	17.3	FOLFOX	6	100	2585	✓	41.0	41.0	83.5	94.0	Elderly patient with limited mobility due to neurologic condition. Only able to visit prehab clinic 1x/week due to distance and challenges with commuting. Poor tolerance to HIIT protocol.
7	2	58	17.1	FLOT	4	75	2317	✓	32.0	17.9	74.3	67.0	Young patient, low motivation towards program. Refused to visit clinic more than 1x/week. Poor tolerance to NACT. ER visit due to gastric ulcers
10	2	67	9	N/A	0	N/A	509	✓	68.7	68.7	93.3	91.0	Accidently deemed eligible for study investigators. NACT was not needed. Frail elderly patient with significant mobility limitations and was unable to perform CPET or cycle ergometer. Unsuccessful ESD attempt → Esophagectomy
12	3	55	12.1	Immuno	4	100	4322	✓	33.3	25.0	86.7	10.0	Significant dysphagia & malnutrition at baseline. Hospitalized for re-hydration and dobhoff insertion. Agreed to do resistance training only.
13	3	73	10.6	FLOT	4	50	4465	✓	75.0	75.0	68.0	44.0	No dysphagia at baseline, low motivation for program. Moderate tolerance of HIIT due to chronic knee pain.

Supplemental Table 1. Table provides an overview of the different cancer management therapies provided to each patient in addition to the modality of prehabilitation support. Neoadjuvant chemotherapies (NACT) were reported for each patient based on the number of cycles completed with reference to what the oncologist prescribed. Adherence to each component of the prehabilitation program was reported as a mean percentage. Pertinent components of the preoperative clinical trajectory were also documented by the prehabilitation team.

Preop, preoperative period; Pres. Cycles, number of chemotherapy cycles prescribed by the treating oncologist; Psych, psychological support; Immuno, immuno-chemotherapy; FLOT, fluorouracil, leucovorin, oxaliplatin, docetaxel; Rad, radiotherapy; DCF, docetaxel, cisplatin, fluorouracil; FOLFOX, leucovorin, fluorouracil, oxaliplatin; N/A, not applicable; ER, emergency room; CPET, cardiopulmonary exercise testing; ESD, endoscopic submucosal dissection
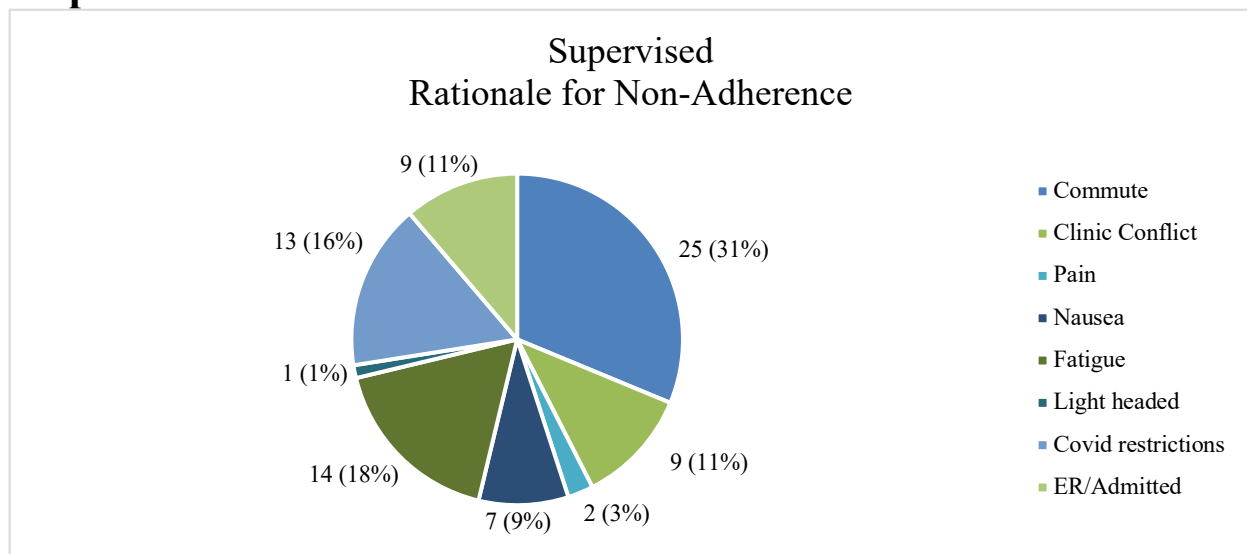
Supplemental Figure 2. Rational for Non-Adherence to Exercise – Unsupervised
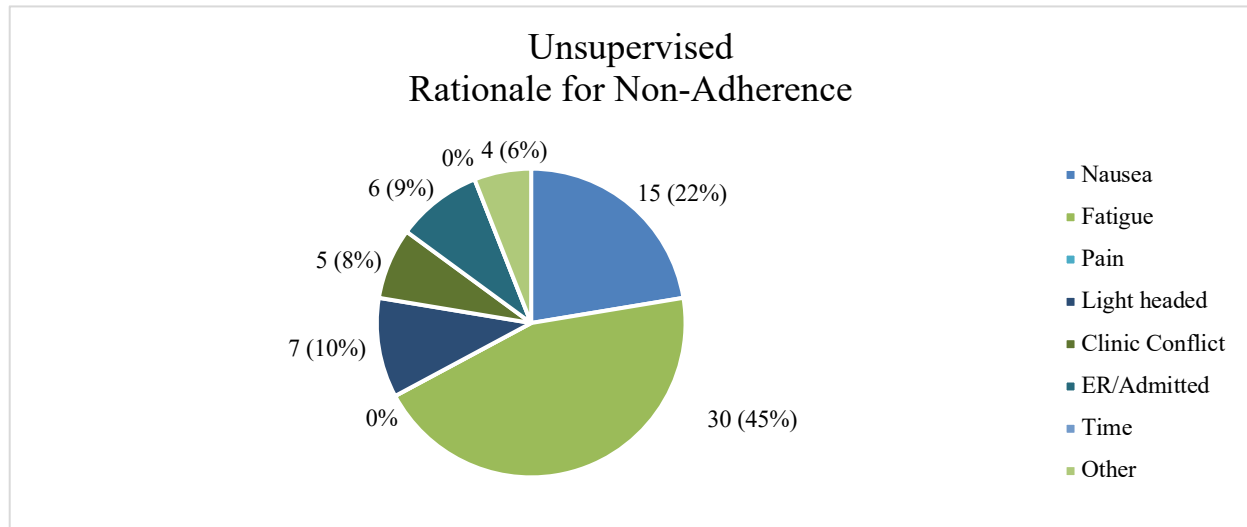

Supplemental Figure2. Pie chart provides a visual representation of patient-reported reasons for being unable to perform the unsupervised exercise prescription. Data is reported as absolute frequency (percentage).

## Supplemental Figure 3. Rational for Non-Adherence to Exercise – Supervised

Supplemental Figure 3. Pie chart provides a visual representation of patient-reported reasons for being unable to attend and/or perform supervised exercise sessions. Data is reported as absolute frequency (percentage).
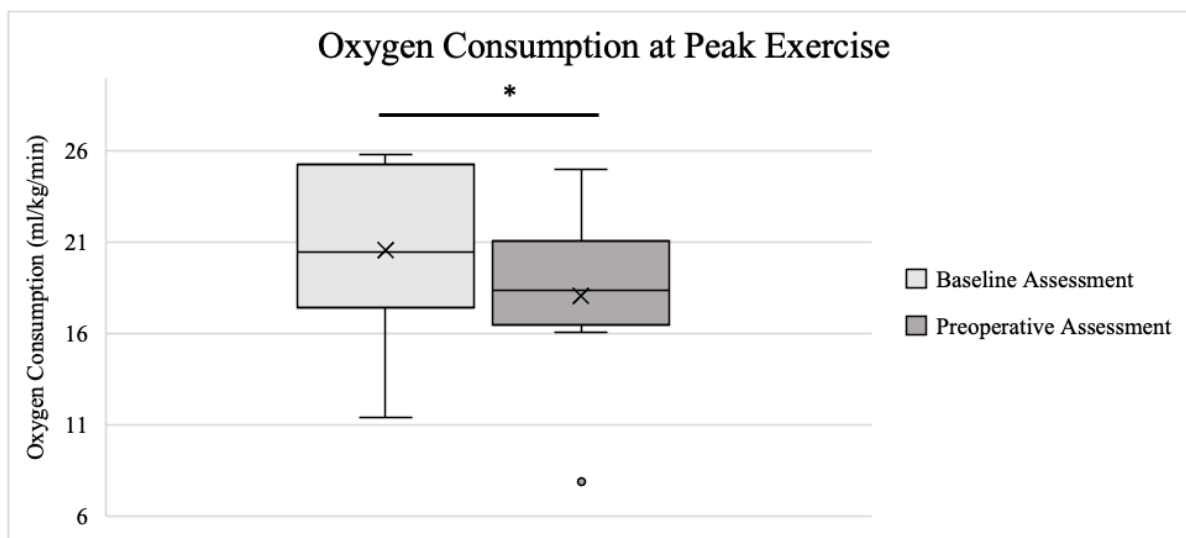
Supplemental Figures. Changes in Cardiorespiratory Fitness
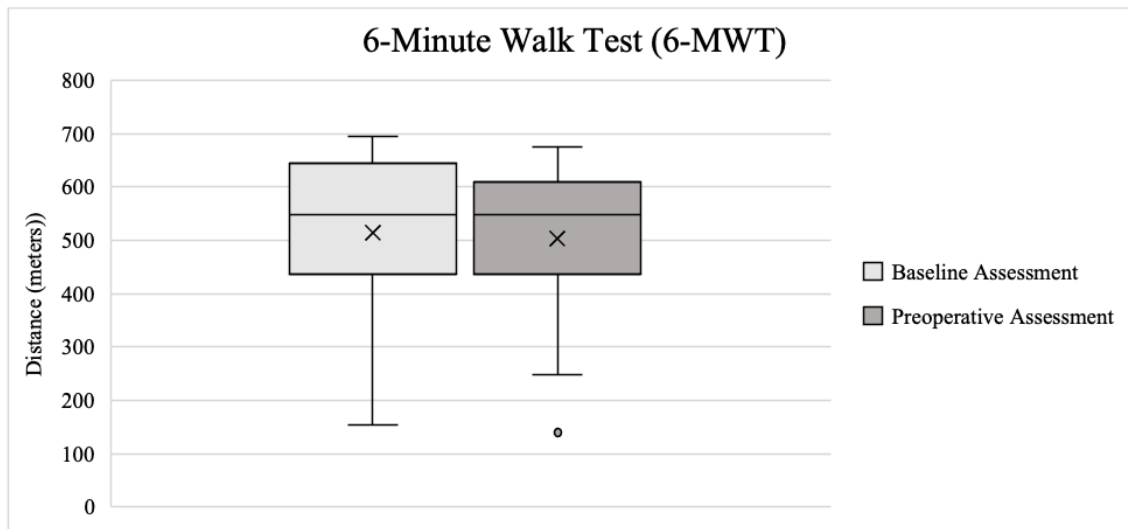
Supplemental Figure 4. Box-and-whiskers plot of 6-MWT distance from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.
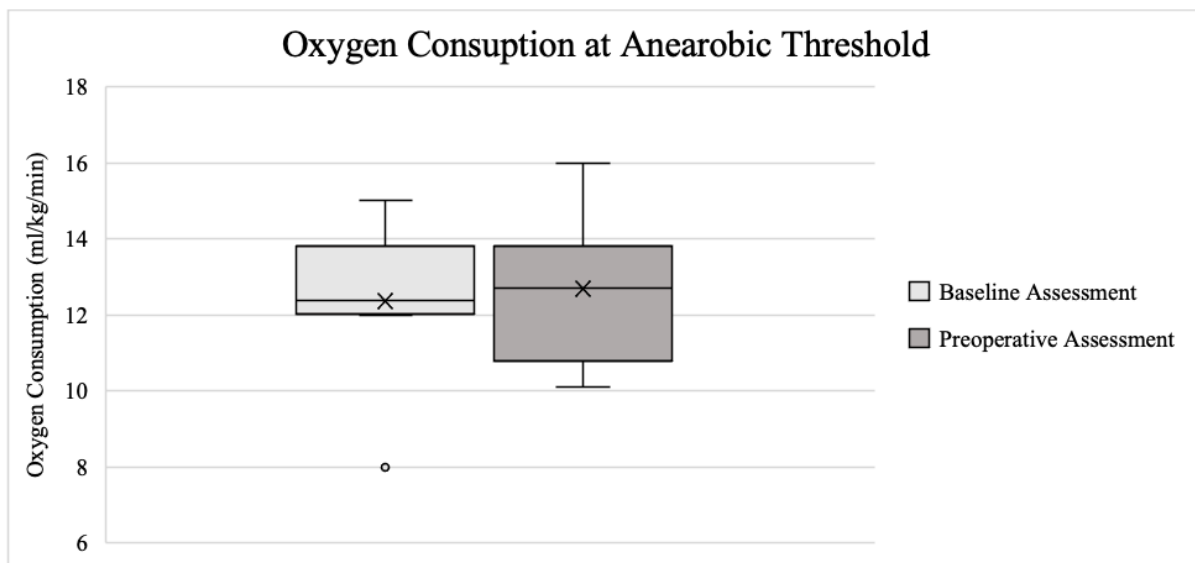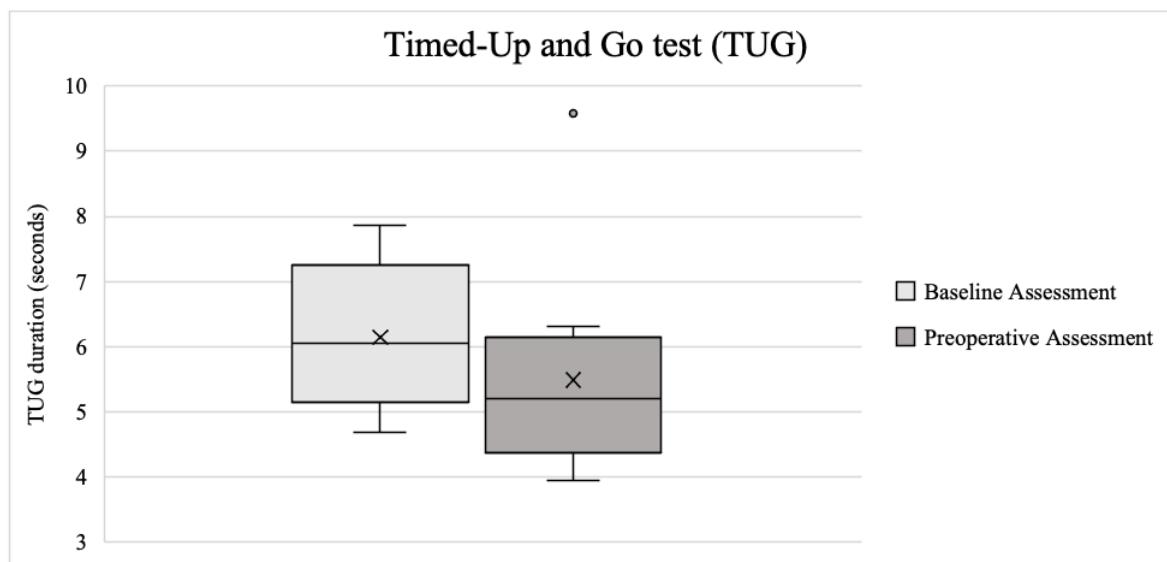

Supplemental Figure 5. Box-and-whiskers plot of oxygen consumption at anaerobic threshold at baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 6. Box-and-whiskers plot of oxygen consumption at peak exercise at baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figures. Changes in Functional Capacity

Supplemental Figure 7. Box-and-whiskers plot of TUG performance (seconds) at baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 8. Box-and-whiskers plot of STS repetitions from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 9. Box-and-whiskers plot of 1-arm curl repetitions from baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.
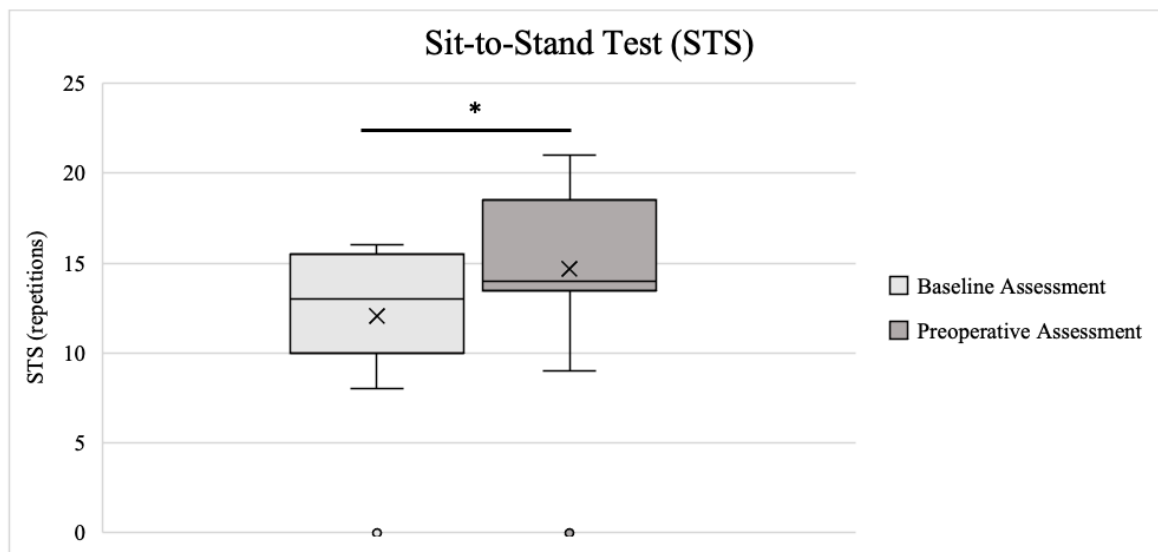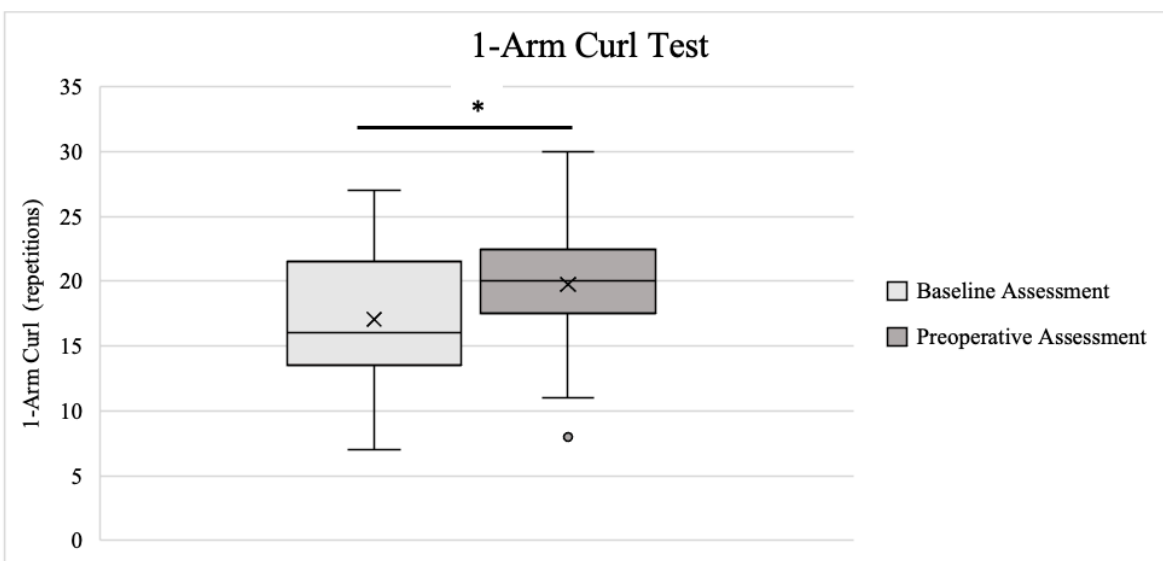
Supplemental Figure 10. Box-and-whiskers plot of HGS results (kg) from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.
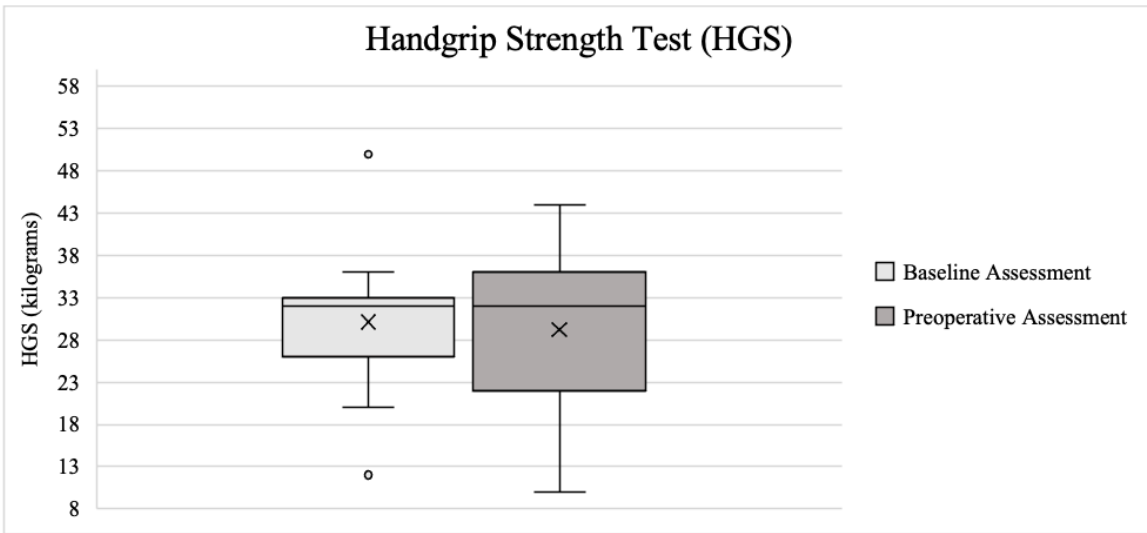
Supplemental Figures. Changes in Patient Reported Outcomes

Supplemental Figure 11. Box-and-whiskers plot of FACT-E scores from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 12. Box-and-whiskers plot of ESAS scores from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 13. Box-and-whiskers plot of DASI scores from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.
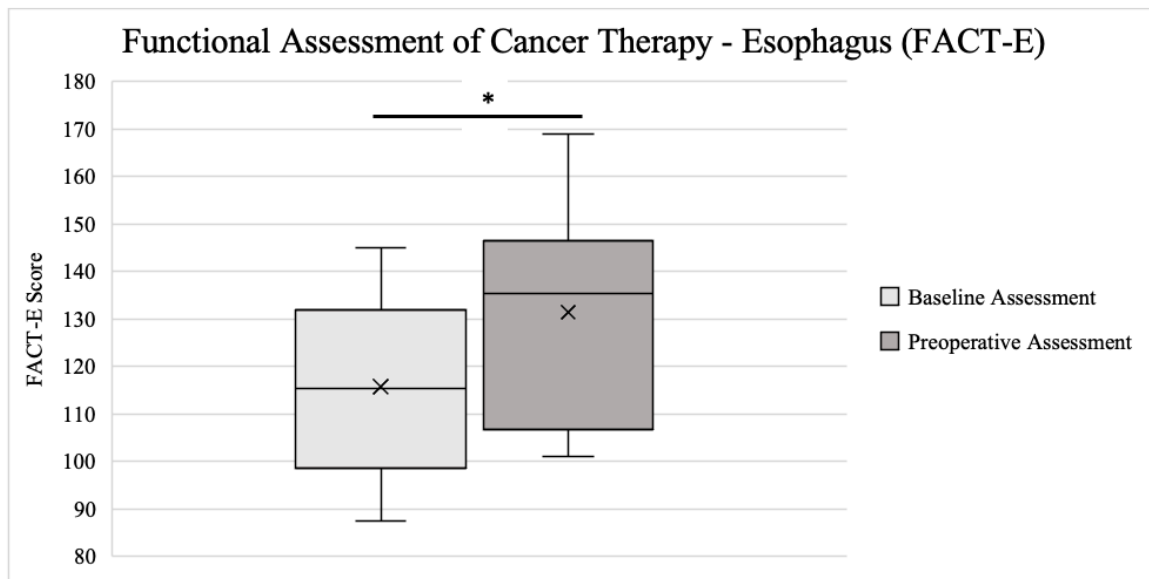
Supplemental Figure 14. Box-and-whiskers plot of CHAMPS scores (kcal/kg/week) from baseline and preoperative assessments. Related-sample Wilcoxon signed-ranked test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

Supplemental Figure 15. Box-and-whiskers plot of HADS scores from baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.
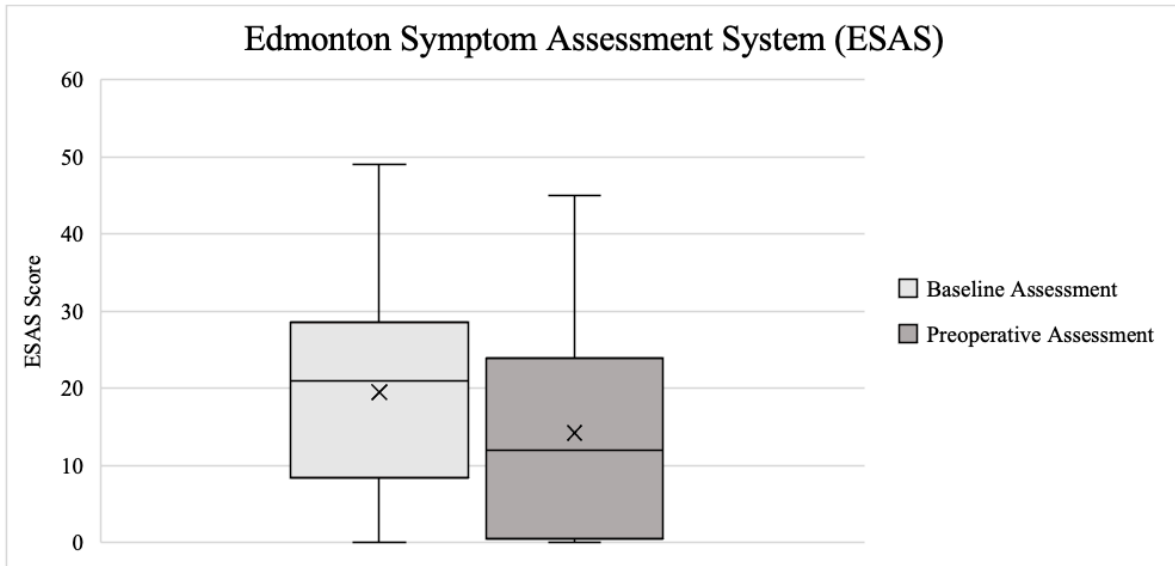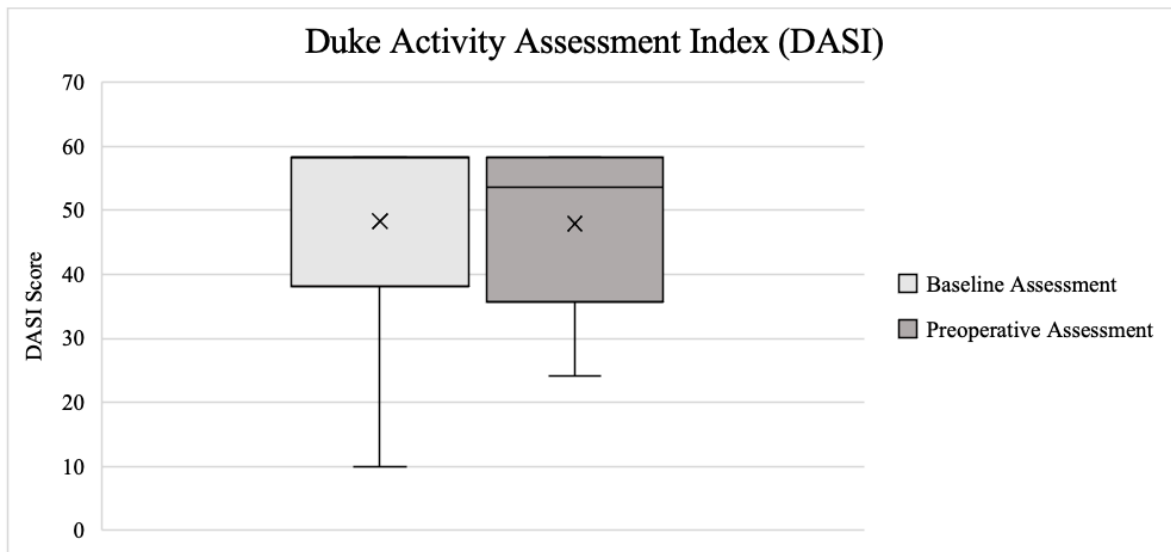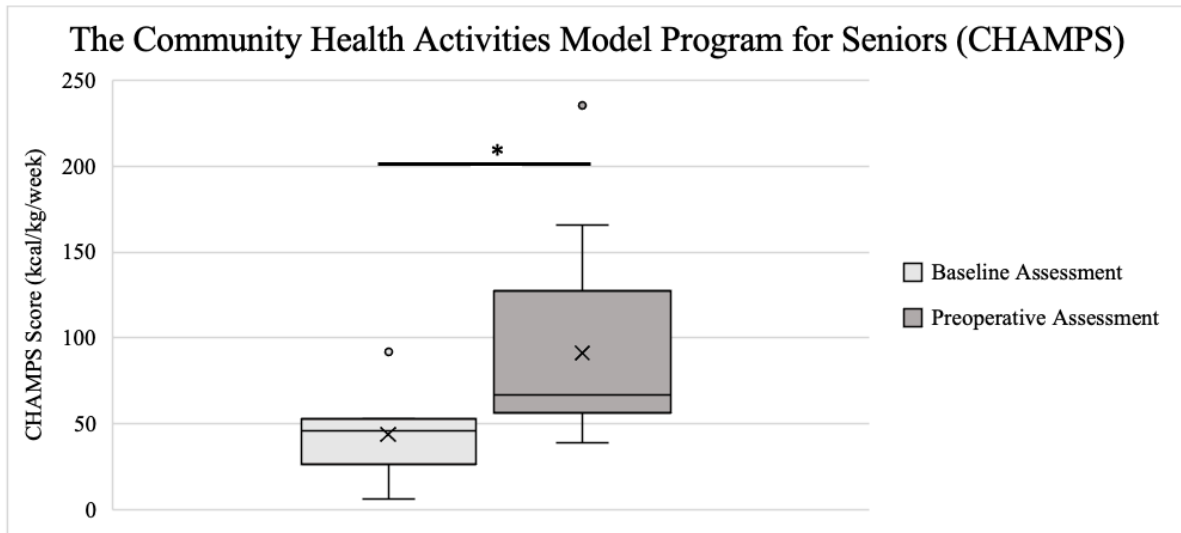
Supplemental Figure 16. Box-and-whiskers plot of PG-SGA scores from baseline and preoperative assessments. Paired-sample T- test, significance threshold of test at P=0.05. * Denotes statistically significant difference.

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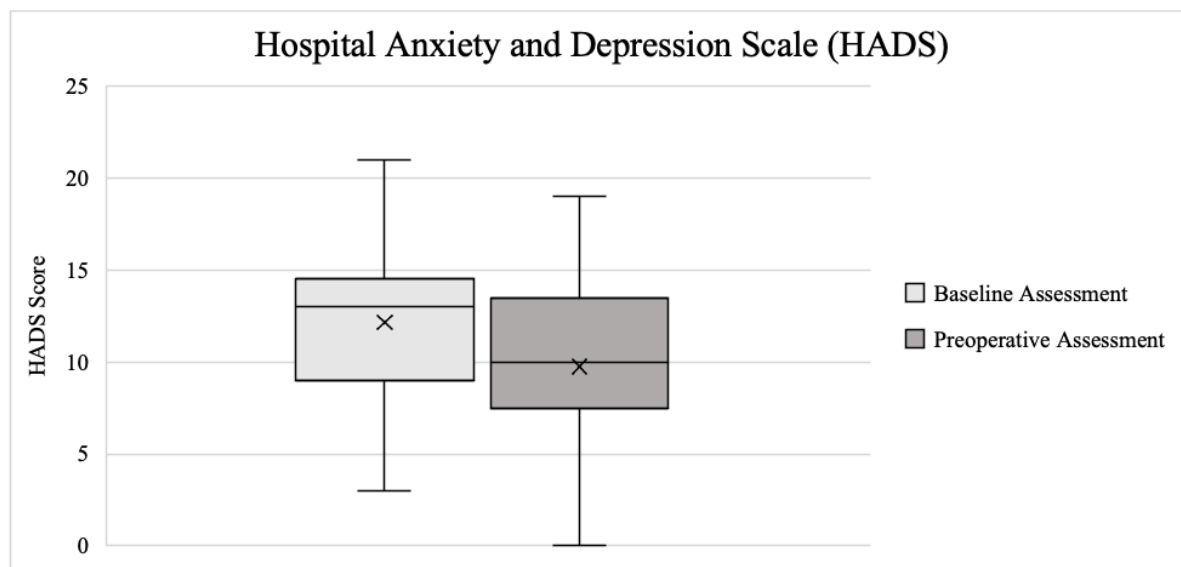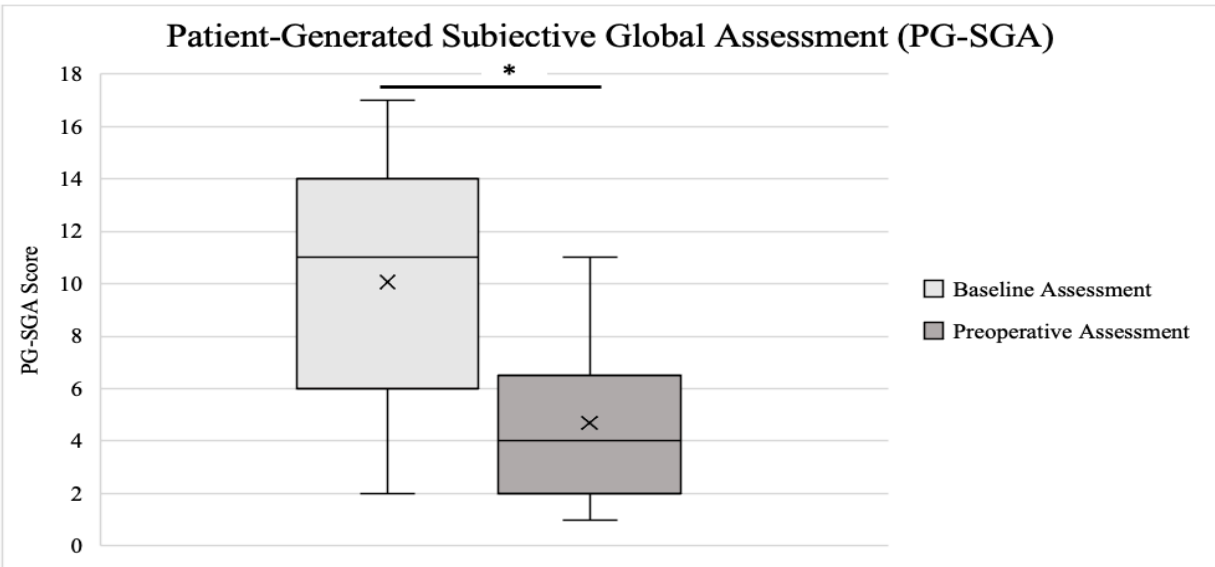1.   Malhotra GK, Yanala U, Ravipati A, Follet M, Vijayakumar M, Are C. Global trends in esophageal cancer. Journal of Surgical Oncology. 2017;115(5):564-79.

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