Prehabilitation in patients undergoing surgery for hepatobiliary or pancreatic cancer

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Abstract

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In patients with hepatobiliary and pancreatic cancers, surgery is the only potential curative treatment for resection candidates (Benson et al., 2009; Freelove & Walling, 2006). A five-year research experience in patients undergoing surgery for colorectal cancer found that prehabilitation led to faster return to preoperative walking capacity than rehabilitation (Minnella et al., 2017). There has been no studies thus far evaluating the impact of a trimodal prehabilitation program on functional recovery in patients undergoing hepatobiliary or pancreatic cancer surgery. Our goal was to determine the impact of prehabilitation on the functional exercise capacity of these patients. We performed a randomized controlled pilot trial comparing the impact of a prehabilitation program begun four weeks before surgery, to the same program (rehabilitation) initiated right after surgery. The program was maintained by both groups until eight weeks postoperatively. We hypothesized our prehabilitation program would improve 6-minute walk test performance preoperatively. Furthermore, at eight weeks post-surgery, we hypothesized greater 6-minute walk performance in the prehabilitation group compared to the rehabilitation group. Thirty-five participants were randomized to receive prehabilitation or rehabilitation. We found that preoperatively, the prehabilitation group demonstrated a clinically meaningful improvement in 6-minute walk distance. At four-weeks after surgery, the rehabilitation group experienced a statistically and clinically significant decrease in mean 6-minute walk distance from baseline, whereas the prehabilitation group was able to maintain its baseline walking capacity. Our findings suggest that a prehabilitation program in hepatobiliary and pancreatic cancer patients can deliver meaningful changes in pre- and postoperative functional exercise capacity.

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Table of Contents

Chapter I 1

Introduction 1

Hepatobiliary cancer 2

Pancreatic cancer 3

Cancer treatments 4

Rehabilitation for cancer surgery 5

Prehabilitation for cancer surgery 6

Project overview 7

Chapter II 9

Impact of a trimodal prehabilitation program on functional recovery after hepatobiliary or pancreatic cancer surgery: preliminary findings from a randomized controlled pilot trial 9

Chapter III 41

Concluding remarks 41

Chapter IV 43

References 43

Appendix A - Sample pages of aerobic and resistance training from booklet of exercises 52

Appendix B - Compliance 54

Appendix C - Community Healthy Activities Model Program for Seniors - Surgical Version .. 56

Lists of figures

Figure 1: CONSORT diagram for the trial……………………………..………………......... 22

Figure 2: Mean 6-minute walk test change from baseline at the four study time points …..…… 26

Figure 3: Mean 6-minute walk test change from baseline at the four study time points in pancreatic, gallbladder and bile duct cancer resections……………………………..………… 27

Figure 4: Mean 6-minute walk test change from baseline at the four study time points in liver cancer resections…………………………………………….…………………….……...... 27

List of tables

Table 1: Baseline patient demographic and clinical characteristics………………...…………... 23

Table 2: Baseline low muscle based on diagnosis, and based on chemotherapy treatment…..… 25

Table 3: Baseline number of participants who have received neoadjuvant chemotherapy based on diagnosis…………………………………………………………………...…………. 25

Table 4: Changes in outcomes over time………………………..………………..………... 27

Table 5: Mean changes in 6-minute walk test over time compared to baseline…………..…… 28

Table 6: Exercise, nutrition and relaxation compliance……………………………..……..… 31

Table 7: Exercise compliance by diagnosis……………………………………..…..………... 31

Table 8: Nutrition compliance by diagnosis……………………………………..………..... 32

Table 9: Total hospitalization days and rehospitalization days after surgery by diagnosis…...... 32

List of Abbreviations

6MWT - 6-Minute Walk test

ACS - American Cancer Society

ASMI - Appendicular Skeletal Muscle Index

CHAMPS - Community Healthy Activities Model Program for Seniors

CHAMPS-S - Surgical Version of CHAMPS

CONSORT - CONsolidated Standards Of Reporting Trials

DXA - Dual-energy X-ray Absorptiometry

ERAS - Enhanced Recovery After Surgery

HGS - Hand Grip Strength

MET - Metabolic Equivalent of Task

RCT - Randomized Controlled Trial

TuG - Timed Up and Go

VO_2 - Volume of Oxygen uptake

Chapter I

Introduction

Hepatobiliary cancer

Pathophysiology of hepatobiliary cancer

Hepatobiliary cancer includes cancers of the liver, gallbladder and bile ducts. The most common form of hepatobiliary cancer is hepatocellular carcinoma. These carcinomas are usually nodular or massive type. The nodular type is associated with cirrhosis, and is characterized by well-circumscribed nodules. The massive type is rarely associated to cirrhosis, and is characterized by the coverage of a large area and by the addition of satellite nodules in the liver. Hepatocellular carcinomas are usually symptom-free during the majority of the disease progression. Nonspecific symptoms include jaundice, anorexia, weight loss, malaise, and pain of the upper abdomen (Benson et al., 2009).

As for gallbladder cancer, 80% are adenocarcinomas, meaning they are formed from glandular cells (Benson et al., 2009). Gallbladder cancer is often diagnosed once the disease is advanced. This cancer can spread rapidly, and early cancer spread can go to lymph tissue and into the blood circulation (Bartoli & Capron, 2000).

As for bile duct cancers, they are also known as cholangiocarcinomas, and they originate in the bile duct epithelium. The majority of cholangiocarcinomas are adenocarcinomas. Cholangiocarcinomas can be classified based on their anatomic location: intrahepatic or extrahepatic. They can also be classified on the basis of their macroscopic appearance: mass-forming, periductal or intraductal (Benson et al., 2009). Bile duct cancers typically grow slowly and are characterized by late metastasis. As such, cholangiocarcinomas are typically symptom-free in early stages and are often diagnosed once the disease is advanced (Fernández-Ruiz et al., 2009).

Risk factors

For hepatocellular carcinoma, the most common risk factor is cirrhosis from hepatitis B and/or C (Benson et al., 2009). Other risk factors include obesity, diabetes mellitus and chronic alcohol consumption (Janevska et al., 2015). For gallbladder cancer, the most common risk factor is cholethisasis, which is a gallstone disease. Chronic inflammation typically contributes to gallbladder cancer development and progression. As for bile duct cancer, the majority of patients do not present with any predisposing factors (Benson et al., 2009).

Statistics in Canada

Liver cancer is the third deadliest cancer worldwide, with a five-year survival rate of only 20%. In Canada, the number of liver cancer cases could continue to increase. The increase is due to the prevalence of Canadians with chronic hepatitis B or C, which is the main risk factor for liver cancer. An estimated 600,000 Canadians have chronic hepatitis B or C (Benson et al., 2009). Although liver cancer only accounts for approximately one percent of new cancer diagnoses in 2013, mortality associated with the disease has been increasing in Canada. Mortality rates increased from 1.8 to 3.3 per 100,000 males between 1970 and 2009, and from 0.7 to 0.8 per 100,000 females between 1970 and 2009 (Canadian Cancer Society, 2013).

Pancreatic cancer

Pathophysiology of pancreatic cancer

The majority of pancreatic cancers originate in exocrine cells which produce enzymes for digestion and absorption (Canadian Cancer Society, 2017). Pancreatic ductal adenocarcinoma are epithelial tumors originating from the cells of the pancreatic duct or ductules and account for over 90% of pancreatic cancers (Feldmann & Maitra, 2008). These adenocarcinomas evolve through noninvasive precursor lesions, most typically pancreatic intraepithelial neoplasia. Pancreatic intraepithelial neoplasia are abnormal new tissue growths. Along the way, these adenocarcinomas acquire genetic and epigenetic alterations. Epigenetic alterations do not involve changes to DNA sequence. Alternatively, pancreatic cancers can evolve from intraductal papillary mucinous neoplasms or mucinous cystic neoplasms (Vincent et al., 2011).

In its early stages, pancreatic cancer usually goes unnoticed until the tumor invades surrounding tissues or metastasizes to other organs. As such, symptoms only begin to appear once the disease is advanced (Vincent et al., 2011). At the time of diagnosis, at least 80% of patients have positive regional lymph nodes or distant metastases (Halloran et al., 2002). Due to the growth of the tumor pressing on nearby structures, symptoms include mid-back pain, obstructive jaundice, nausea and weight loss (Canadian Cancer Society, 2017). Moreover, 25% of patients have diabetes mellitus and 40% have impaired glucose tolerance (Vincent et al., 2011).

Risk factors

For pancreatic cancer, the main risk factors are cigarette smoking and family history of chronic pancreatitis. Other risk factors include age, masculine sex, diabetes, obesity, non-O blood group, occupational exposures, African ethnic origin, high fat and high meat diet, low vegetables and folate diet (Vincent et al., 2011).

Statistics in Canada

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Canada despite being the 12th most prevalent cancer in the country. This is because the majority of pancreatic cancers are only diagnosed at later stages, resulting in poor prognosis. Furthermore, over 80% of pancreatic cancers cases are diagnosed in patients 60 years of age or older (Canadian Cancer Society, 2017). In Canada, the five-year survival rate for pancreatic cancer is 8%. For those whose pancreatic cancer is resectable, the observed five-year survival rate is between 15 and 20%. These low survival rates translate to high mortality rates. Between 1992 and 2012, mortality rates for men dropped by 0.6% per year, but remain unchanged for females (Canadian Cancer Society, 2016; Canadian Cancer Society, 2017).

Cancer treatments

The choice of treatment depends on the stage of the cancer and the resectability of the tumor. For both hepatobiliary and pancreatic cancers, tumor resection is the only potential cure (Benson et al., 2009; Freelove & Walling, 2006). Resectable tumors can be fully removed with surgery, as would generally be the case in stage 1 or 2 cancers. For hepatocellular carcinomas, less than 30% of patients are eligible for surgery, because of the plurality of associated lesions (Belghiti et al., 2005). For pancreatic cancers, only 15 to 20% are resectable (Freelove & Walling, 2006). The classic Whipple procedure removes tumors in the head of the pancreas or the pancreatic duct opening (Canadian Cancer Society, n.d.-a). This procedure involves removing the head of the pancreas, duodenum, proximal jejunum, gallbladder, common bile duct and distal stomach. The common hepatic duct is anastomosed to the pancreas and the stomach is anastomosed to the jejunum (Freelove & Walling., 2006). After major cancer resections, patients still experience an overall 4 to 11% risk of mortality and 21 to 45% risk of complications despite advances in cancer diagnosis, surgical technology and rehabilitation efforts (Finks et al., 2011; Lucas & Pawlik, 2014).

For liver cancer resection, the particular anatomy and vital functions of the liver intensifies the complexity of the surgery. Common complications include venous catheter-related infection, incisional infection, hemorrhage, bile leakage, liver failure, pleural effusion, urinary tract infection and subphrenic infection, and liver failure. Possible postoperative hemorrhages include intraperitoneal hemorrhage, coagulation disorders, gastrointestinal tract bleeding and biliary tract hemorrhage (Jin et al., 2013). Patients with liver tumors may already have reduced liver function due to chronic hepatitis, liver cirrhosis or chemotherapy-associated steatohepatitis, a fatty liver disease. As such, overall liver resection morbidity rate ranges between 4.1 and 47.7% (Ishii et al., 2014).

For pancreatic cancer resection, major complications are an important factor in postoperative mortality. The rate of complications is approximately 60%. Such a high rate is attributable to the complexity of the surgeries typically involving several anastomoses, poor nutritional status and increased comorbidity of this patient population. After surgery, patients are exposed to the risk of pancreatic exocrine insufficiency, weight loss, anastomotic stricture, bleeding gastritis, adhesions and marginal ulceration. Several complications do not require surgical intervention, however, those that do are associated with a mortality risk ranging between 23 and 67% (Halloran et al., 2002).

After surgery, if cancer cells are found in the tissue removed along with the tumor, radiotherapy or chemotherapy may be administered. Chemotherapy employs cytotoxic drugs to destroy cancer cells. Often, several chemotherapy drugs are administered together. Radiation therapy employs x-rays or gamma rays to destroy cancer cells. For pancreatic cancer, treatment is usually with external beam radiation which directs radiation through the skin (Canadian Cancer Society, n.d.-a). In patients with unresectable and locally advanced cancer, radiation reduces the local progression. However, radiation does not have an impact on survival or metastasis (Freelove & Walling, 2006).

Rehabilitation for cancer surgery

Currently, most physiotherapy and dietary interventions aimed to promote recovery are carried out postoperatively, as part of rehabilitation (Carli et al., 2012). After major surgery, patients with lower preoperative VO_2 at the anaerobic threshold stay hospitalized longer and experience higher mortality and morbidity risk. Rehabilitation exercise in post-surgical cancer patients can improve VO_2max, physical function and quality of life (Dunne et al., 2016).

A rehabilitation pathway that is part of standard care is the Enhanced Recovery After Surgery (ERAS), which is a multimodal and multidisciplinary protocol that targets the optimization of intra- and postoperative care. This protocol promotes guidelines for surgeries and suggests changes to care such as patient education, early mobilization, food on surgery day, carbohydrates drinks two hours before surgery, early removal of drains and catheter, multimodal analgesia, neural blockade and six to eight days of hospital admission (Ljungqvist et al., 2017). In colorectal surgery, early mobilization within ERAS range from any mobilization at all within 24 hours, to eight hours per day by the second postoperative day (Carmichael et al., 2017). In a prospective cohort study in patients with colorectal cancer, greater compliance to the ERAS protocol was related to lower risk of surgical site infections, postoperative complications and shorter length of hospital stay (Li et al., 2017).

However, post-surgery, patients are concerned with wound healing and fatigue. They may also anxiously await their cancer pathology results, and adjuvant treatments (Dunne et al., 2016). As such, rehabilitation occurs during a period where patients are fatigued and emotionally vulnerable which makes it difficult to have them comply with the rehabilitation program (Carli et al., 2012). Few programs target the enhancement of functional capacity and physiological reserves prior to surgery with the same human resources as rehabilitation (Carli et al., 2012). It appears interesting to begin improving functional capacity of patients before acute treatment.

Prehabilitation for cancer surgery

Cancer prehabilitation is a process in the cancer care timeline that starts when a patient is diagnosed with cancer and ends at surgery. Prehabilitation includes assessments to determine the patient's initial function level and to identify impairments, as well as targeted physical, nutritional and/or psychological interventions to reduce these impairments (Carli et al., 2017). By potentially reducing future impairments, prehabilitation can enhance the patient's functional capacity and physiologic reserve prior to acute treatment (Carli & Scheede-Bergdahl, 2015). Prehabilitation may continue throughout survivorship (Silver, 2015). Prehabilitation programs that have been studied in cancer surgery were either trimodal or single mode. Trimodal programs include exercise, nutrition and relaxation as part of the prehabilitation intervention.

The majority of randomized clinical trials in our literature review indicate beneficial outcomes from prehabilitation in colorectal, lung, breast and prostate cancer resections (Bousquet-Dion et al., 2018; Burton et al., 1995; Carli et al., 2012; Cohen et al., 2011; Dronkers et al., 2010; Dunne et al., 2016; Gillis et al., 2014; Gillis et al., 2016; Lai et al., 2017; Larson et al., 2000; Li et al., 2012; Licker et al., 2017; Ngo-Huang et al., 2017; Parker et al., 2009; Stefanelli et al., 2013; Timmerman et al., 2011; West et al., 2015). In patients undergoing colorectal cancer resection, a randomized control trial by Gillis et al. (2014) compared a four-week trimodal prehabilitation program (continued until eight weeks after surgery) to an eight-week rehabilitation program. The prehabilitation group improved their 6-minute walk distance by 25.2 m, compared to a decline of 16.4 m in the control group in the preoperative period. Eight weeks after surgery, 84% of the prehabilitation group was above or at their baseline walking capacity, compared to 62% in the control group. In patients undergoing resection for colorectal liver metastases, a randomized clinical trial by Dunne et al. (2016) demonstrated that an exercise-only four-week prehabilitation program led to improved VO_2 at anaerobic threshold before surgery. In patients undergoing surgery for pancreatic cancer, a trial by Ngo-Huang et al. (2017) indicated patients can adhere to a preoperative home-based exercise program, concurrent with neoadjuvant chemotherapy and/or chemoradiation.

Currently, besides the study by Dunne et al. (2016) in patients undergoing liver resection and the study by Ngo-Huang et al. (2017) in pancreatic cancer resection, no studies on prehabilitation before tumor resection for hepatobiliary or pancreatic cancer has been done. Most prehabilitation studies in cancer patients have described colorectal, breast, lung and prostate tumor resections. Although the majority of studies in our literature review indicated beneficial outcomes for prehabilitation, we do not know whether or not these benefits will be equivalent in patients undergoing hepatobiliary or pancreatic cancer surgery. The one study in liver resection patients employed an aerobic exercise-only type of prehabilitation program and used a narrow range of outcome measures to describe the changes in functional capacity after the program completion, notably VO_2 at anaerobic threshold. Moreover in both liver and pancreatic cancer prehabilitation studies, we do not know how the prehabilitation program impacted functional recovery after surgery because assessments only took place prior to surgery (Dunne et al., 2016; Ngo-Huang et al., 2017). Due to the specific complications related to hepatobiliary and pancreatic cancer resections, we do not know whether or not a prehabilitation program can enhance these patient's functional capacity, and if so, what type of prehabilitation program would be best suited for these patients.

Project overview

Current treatments for cancer are reactive in nature. Due to post-surgical fatigue, pain and emotional vulnerability, it is difficult to carry out rehabilitation programs due to limited compliance (Carli et al., 2012). The benefits of prehabilitation in improving functional recovery are beginning to be established in certain types of cancer surgeries, especially in colorectal cancer. Gillis et al. (2014) demonstrated that four weeks of trimodal prehabilitation in patients with colorectal cancer surgery can result in better functional recovery at eight weeks postoperative, compared to the same program begun postoperatively. More recently, it was reported that adding once weekly supervised exercise training to prehabilitation can further enhance functional recovery in patients undergoing colorectal cancer surgery (Awasthi et al., 2018). As such, significant changes in functional recovery can be obtained with a supervised trimodal prehabilitation program in colorectal cancer surgery.

Despite evidence affirming the role of prehabilitation in enhancing functional exercise capacity postoperatively in colorectal, lung, breast and prostate cancer resections, little is known about the role of prehabilitation in hepatobiliary or pancreatic cancer resections. The objective of this thesis is to provide novel insight on the specific impact of a four-week trimodal prehabilitation program on functional recovery in hepatobiliary and pancreatic cancer surgery patients. We hypothesize that four weeks of prehabilitation will improve 6-minute walk test performance in hepatobiliary and pancreatic cancer patients undergoing surgery. Following a four-week trimodal prehabilitation program, 6-minute walk test, muscle mass, strength, functional capacity and energy expenditure will be assessed and compared to that of participants who underwent the program after surgery (rehabilitation). Findings from this thesis can provide preliminary data comparing the effectiveness of prehabilitation to rehabilitation programs in hepatobiliary or pancreatic cancer surgery, prior to a larger multi-center clinical trial.

Chapter II

Impact of a trimodal prehabilitation program on functional recovery after hepatobiliary or pancreatic cancer surgery: preliminary findings from a randomized controlled pilot trial

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Contribution of Authors

Tram Bui Ngoc: preparation of manuscript, experimental techniques
Robert Kilgour: preparation and editing of manuscript, experimental design
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Abstract

Introduction: It may be possible to improve functional exercise capacity of patients undergoing surgery for hepatobiliary or pancreatic cancer. We are performing a randomized controlled pilot trial assessing the impact of a trimodal prehabilitation program and comparing it to a rehabilitation program.

Methods: A single-center, parallel-arm randomized controlled pilot trial was conducted. Patients were assigned to either a prehabilitation or rehabilitation program. The prehabilitation group received a trimodal program comprising exercise (once-weekly supervised and home-based), nutritional counselling with whey protein supplementation, and relaxation exercises initiated four weeks before surgery. The rehabilitation group received the same trimodal program (minus once-weekly supervised exercise) initiated immediately after surgery. Both study arms continued the program for eight weeks after surgery. The primary outcome was functional exercise capacity measured using the 6-minute walk test.

Results: Thirty-five patients were randomized to receive prehabilitation (n=17) or rehabilitation (n=18). Both groups were comparable in age, gender, appendicular skeletal muscle index and baseline 6-minute walk distance. From baseline to pre-operative assessment, the prehabilitation group demonstrated a clinically meaningful improvement in 6-minute walk distance +19.63 ± 0.25 m ($\bar{x}$ ± SE), p=.061. From baseline to the four-weeks post-operative assessment, the rehabilitation group experienced a statistically and clinically significant decrease in mean 6-minute walk distance (-23.72 ± 0.36 m, p=.035), whereas the prehabilitation group was able to maintain their baseline walking capacity (-0.11 ± 0.3 m, p=.991).

Conclusion: A prehabilitation program in hepatobiliary and pancreatic cancer patients can deliver meaningful changes in pre- and postoperative functional exercise capacity.

Keywords: prehabilitation, 6-minute walk test, functional exercise capacity, hepatobiliary cancer, pancreatic cancer

Introduction

In patients with hepatobiliary - *liver, gallbladder and bile ducts* – and pancreatic cancers, surgery is the only potential curative treatment for resection candidates (Benson et al., 2009; Freelove & Walling 2006). In spite of advances in surgical technology, the five-year net survival rate of pancreatic cancer is 8% only. This is because the majority of pancreatic cancers are diagnosed at stage IV and as such, have metastasized. In Canada, pancreatic cancer is the fourth leading cause of cancer mortality. Liver cancer is also typically diagnosed at later stages, with a five-year net survival rate of 19% (Canadian Cancer Society, 2018).

Despite advances in cancer diagnosis, surgical technology and rehabilitation efforts, patients still experience an overall 4 to 11% risk of mortality and a 21 to 45% risk of complications after major cancer resections (Finks et al., 2011, Lucas & Pawlik, 2014). Specifically for liver resection, the particular anatomy and vital functions of the liver intensifies the complexity of the surgery (Jin et al., 2013). Patients with liver tumors may already have reduced liver function due to chronic hepatitis, liver cirrhosis or chemotherapy-associated steatohepatitis, a fatty liver disease. As such, overall liver resection morbidity rate can be as high as 47.7% (Ishii et al., 2014). At 60%, the rate of complications in pancreatic cancer resections is well above the range typically observed in major cancer resections. Such a high rate relates to the complexity of the surgeries which typically involve several anastomoses, poor nutritional status and increased comorbidity in this patient population (Halloran et al., 2002).

Going into surgery with poor functional capacity leads to higher postoperative complications and mortality risk (Minnella et al., 2017). Recent studies in programs which target the improvement of functional capacity and physiological reserves prior to cancer surgery suggest these programs can help patients achieve meaningful improvements in both preoperative and postoperative functional exercise capacity. Such programs are called prehabilitation. Prehabilitation is a process in the cancer continuum of care that starts when the patient is diagnosed with cancer and ends at surgery (Carli et al., 2012; Carli & Scheede-Bergdahl, 2017). Prehabilitation may also continue throughout survivorship (Silver, 2015). Prior to prehabilitation studies, recovery efforts in cancer surgery have mainly targeted the rehabilitation period, once the patient is discharged from the hospital. Traditionally, more human resources have been put into the rehabilitation period and few programs target the period prior to surgery (Carli et al., 2012). However, post-surgery, patients are concerned with wound healing, fatigue, as well as tumor pathology (Carli & Scheede-Bergdahl, 2017). Based on these concerns, it may be more interesting to begin improving functional capacity prior to surgery.

In a randomized control trial by Gillis et al., (2014), patients undergoing colorectal surgery were randomized to receive either trimodal prehabilitation or the same program immediately after surgery (rehabilitation). The improvement between baseline and eight-weeks post-surgery 6-minute walk test was significantly greater in the prehabilitation group compared to the rehabilitation group. The trimodal prehabilitation program consisted of home-based unsupervised moderate aerobic and resistance exercises, nutritional counselling with whey protein supplementation, and relaxation exercises. A recent study by Awasthi et al. (2018) pooled together the results of the Gillis et al. (2014) study with those of a more recent study by Bousquet et al. (2018), that delivered the same trimodal prehabilitation program to colorectal cancer patients as the Gillis et al. (2014) study, but added once-weekly supervised exercise sessions on-site. The conclusion was that the addition of supervised exercise training can accelerate the return to baseline functional exercise capacity. In hepatobiliary and pancreatic cancers, there has been no studies to date employing a trimodal prehabilitation program to determine its impact on functional recovery after surgery. Which patient population can benefit from a multimodal prehabilitation program is still an evolving area of research.

To quantify the effect of prehabilitation on functional exercise capacity before and after surgery in hepatobiliary and pancreatic cancer patients, we conducted a single-center, parallel-arm randomized controlled pilot trial. The purpose of this study was to evaluate the impact of a trimodal prehabilitation program on functional exercise capacity in hepatobiliary and pancreatic cancer patients undergoing surgery. This study compared the impact of the program begun four weeks before surgery (prehabilitation) to the same program (rehabilitation) initiated after surgery. The prehabilitation group's program comprised exercise (once-weekly supervised and home-based), nutritional counselling with whey protein supplementation, and relaxation exercises initiated four weeks before surgery. The rehabilitation group received the same intervention (minus once-weekly supervised exercise) initiated immediately after surgery. Both groups followed the program until eight postoperatively. We hypothesized that a four-week prehabilitation program will improve 6-minute walk test performance, muscle mass, strength, agility and balance, and energy expenditure in hepatobiliary and pancreatic cancer patients scheduled for surgery. Furthermore, post-surgery, we hypothesized greater 6-minute walk distance, muscle mass, strength, agility and balance, and energy expenditure in those patients who followed the prehabilitation program compared to those patients who followed the rehabilitation program.

Methods

This study was approved by the McGill University Health Centre Research Ethics Board, and they were responsible for monitoring this study. Data was collected during four study visits which took place at the McGill Nutrition and Performance Laboratory, part of the McGill University Health Centre. The baseline study visit took place approximately four weeks prior to the surgery. The second study visit, the preoperative visit, took place within a week before surgery. The third and fourth visits took place four and eight weeks after surgery, respectively. Upon completion of the baseline assessment, patients were randomly assigned by computer generated random numbers to either receive either the prehabilitation or the rehabilitation intervention. The scheduling of the surgery was not affected by participation in our study.

Recruitment took place at the Royal Victoria Hospital, part of the McGill University Health Centre. The McGill University Health Centre is a university-affiliated hospital network servicing Montreal. We approached patients at the hospital's hepatobiliary and pancreatic cancer clinic where surgeons see patients for consultations. All patients we identified as fulfilling the inclusion criteria were invited to participate in the study: aged 18 or older and referred electively for resection of hepatobiliary malignancies, either primary or metastatic. The exclusion criteria included medical risk factors and conditions or treatments which could independently alter outcome measures in the weeks before the surgery. These included:

1) conditions interfering with the ability to perform exercise at home or to complete test procedures:
    a) American Society of Anesthesiologists health status class 4 or 5;
    b) comorbid medical, physical and mental conditions (such as dementia, disabling orthopedic and neuromuscular disease, psychosis);
    c) cardiac abnormalities;
    d) severe end-organ disease (such as cardiac failure, chronic obstructive pulmonary disease and hepatic failure);
    e) sepsis;
    f) morbid obesity;

g) anemia;

2) poor English or French comprehension.

Interventions

The prehabilitation group received their interventions at their baseline visit, whereas the rehabilitation group received the same interventions at their preoperative appointment and only started right after surgery. Both groups continued their interventions until eight weeks after surgery. The study visit during which participants received their interventions lasted four hours, and the other study visits each lasted 1.5 hours.

Exercise

A kinesiologist prescribed an individualized exercise program for each participant. Aerobic, strength, and flexibility exercises were comprised in the program. The aerobic portion consisted of walking every day for 30 minutes, including five minutes of warm-up and five minutes of cool-down. The intensity was set to a rating of perceived exertion of 4 to 6 on the modified 0-10 Borg scale, which corresponds to “moderate” to “hard”. Progression of intensity was implemented when the participant’s perceived exertion decreased below the target intensity. The strength portion consisted of exercises performed every other day, three to four times per week, and lasting up to 30 minutes. The kinesiologist prescribed 10 full body calisthenics and elastic band exercises, at 2 sets of 8 to 15 repetitions. Progression of intensity was implemented when the participant was able complete 17 repetitions of a given strength exercise. The flexibility portion comprised six major muscle stretches, at 2 sets of 20 seconds every day, and lasting up to 10 minutes. To pursue the exercise program at home, participants were provided with a standardized booklet containing pictures and details of the exercises (see Appendix A) and a modified Borg scale. They were each given a Thera-Band elastic at a level of resistance deemed suitable for their fitness level. The green Thera-band has the least resistance, the blue has in-between resistance, and the black has the most resistance.

Before surgery, each prehabilitation group participant exercised on-site with the kinesiologist once per week, and at home the rest of the week. The on-site supervised exercise sessions lasted up to 1.5 hours each. During the supervised session, participants trained either on a standard treadmill or a NuStep recumbent stepper for the aerobic portion of their exercise program. The choice of equipment was dependent on each participant’s physical ability. They also performed their resistance and flexibility exercises under supervision. During the eight weeks after surgery, prehabilitation participants were exercising entirely at home.

As for the rehabilitation group, they received a onetime on-site supervised exercise session during their preoperative appointment. The purpose of this orientation session was to allow them to learn and practice the exercises, as well as receive feedback from the kinesiologist on their form. They were instructed to start their program only after surgery. Throughout the eight weeks postoperative, rehabilitation participants were exercising entirely at home unsupervised.

Nutrition

A registered dietitian met each participant on-site during a 45 to 60-minute session to advise them individually. Based on their 3-day food diary filled out in the week prior to their visit, the dietitian assessed their macronutrients intake. Given that the main goal of the overall trimodal program was to expedite functional recovery, protein intake was the macronutrient of primary concern in the nutrition intervention. Participants were advised to increase their intake of animal protein sources. They were also given Immunocal whey protein isolate powder at a quantity matching their estimated dietary deficit. The goal of the supplement was to help participants reach a daily protein intake of 1.5 g per kilogram of body weight. To increase palatability, participants were advised to mix Immunocal with juice, yogurt or applesauce. Participants were instructed to consume the supplement ideally within 30 minutes after exercise. If that was not possible, their second choice was to consume the supplement during a meal containing little protein, and their third choice was to consume the supplement before bedtime. For those participants already meeting the daily protein intake goal of 1.5g/kg of body weight, they were still advised to take one sachet of Immunocal per day to insure consumption of a high quality protein source. Each sachet of Immunocal contained 10 g of whey protein isolate.

The nutrition intervention also focused on managing nutritional impact symptoms issues, blood glucose control, and body weight optimization.

Relaxation

A psychologist met each participant on-site during a 60-minute session to teach them relaxation techniques. During the session, the psychologist explained the goal of the intervention, which is to acquire a tool to better manage stress, anxiety and pain related to the surgery. Participants then practiced deep abdominal breathing exercises with the psychologist.

The exercises were mirrored on a compact disc provided to participants for home-based practice. The compact disc also contained additional exercises such as passive muscle relaxation and meditation. The psychologist instructed participants to perform the exercises on the compact disc once per week. If they found the exercises helpful, they should increase the frequency to two to three times per week. As such, the relaxation intervention was meant to work alongside exercise and nutrition as a separate intervention. The relaxation session was not formulated to improve adherence to the other aspects of the prehabilitation program.

During the session with the psychologist, a referral to psychosocial oncology could be made and signed by the study doctor should the patient and/or his family member request it. Possible reasons for referral could include mood assessment, family issues, need for support, and assessment of coping and/or spiritual questioning.

Outcome measures

The following measurements were taken during each of the four study visits, with the exception of compliance.

Primary outcome

The 6-minute walk test measures the capacity to maintain a physical endurance level considered moderate because it relates to the ability to partake in physically demanding activities of daily living (Gillis et al., 2014). Participants were asked to walk back and forth along a 15-meter stretch delimited by an orange cone at each end. Before the start of the test, the assessor instructed participants to cover the greatest distance possible during the test. Using the Borg Scale of Perceived Exertion, patients were asked to reach a level of breathlessness between "somewhat hard" and "hard". Participants were allowed to rest at any time by sitting on a chair placed at one end of the walkway or by leaning against the wall. They were advised to resume walking as soon as possible because the timer would continue. Each minute, the assessor gave out a standardized motivational message to the participant, as per the American Thoracic Society guidelines. The total distance covered was recorded by multiplying the total number of laps by 15 meters, then adding the distance covered in the final lap. A 2-minute practice test was administered prior to the 6-minute walk test. The 6-minute walk test is valid and reliable in cancer patients, and thus is recommended for use in this patient population (Schmidt et al., 2013). A change in 6-minute walk test that falls within a range of at least 19 to 20 m was considered the minimal clinically meaningful difference. We employed this range based on the use of both 19 m and 20 m in prehabilitation studies of colorectal cancer surgery and the estimated measurement error of this test (Antonescu et al., 2014; Bousquet-Dion et al., 2018; Minnella et al., 2017).

Secondary outcomes

1. Appendicular skeletal muscle index was measured using dual-energy x-ray absorptiometry. The appendicular skeletal muscle index represents the main portion of muscles involved in physical activity and ambulation. The GE Healthcare Lunar Prodigy machine was calibrated each day before any patient measurement. Participants were asked to remove any metals and sit with both legs centered on the scanner bed's midline. Once they laid down supine, their hands were placed in a neutral position with fingers together, thumbs up, and if possible, not touching the thighs. Feet were placed around a rolled up towel, and held in place with a Velcro strap. For female participants, a Velcro strap was placed around the chest. The approximate time for the total body scan is 10 minutes. The test printout indicates the amount in kilogram of lean body mass, fat mass, arm lean mass, leg lean mass and the percentage of body fat. The arm and leg lean mass were added together and divided by the height in meters squared to obtain the appendicular skeletal muscle index. Dual-energy x-ray absorptiometry is valid in estimating appendicular skeletal muscle index (Gallagher et al., 1997).
2. Hand grip strength was measured using a Jamar Dynamometer. This test measures the maximum isometric strength of the hand and forearm muscles and is an indicator of general muscle strength (Hamilton et al., 1992). Each participant's grip strength was measured twice on both hands and rounded to the nearest kilogram. The handle was adjusted to the hand by ensuring the proximal interphalangeal joint of the middle finger was at 90 degrees. Participants were seated and held the dynamometer while keeping their elbow at 90 degrees. The assessor lightly held around the base and the readout dial of the dynamometer, and asked the participant to exhale as they squeeze the handle. During the test, participants were given the instruction to "squeeze as hard as you can, ...harder, ...and relax".
3. 30-second chair stand test was used assess lower body strength needed for activities of daily living (Jones & Rikli, 2002). Participants were asked to fold their arms across their chest while maintaining their feet shoulder width apart and their back straight. The

number of full stands that can be completed in 30 seconds is the test score. If participants were on their way up to stand when the time was up, that stand was credited.

4. 30-second arm curl test was used to assess upper body strength (Jones & Rikli, 2002). Participants were given a dumbbell: 7 lbs for men and 5 lbs for women. Participants were instructed to complete as many curls as they could in the allotted 30-seconds, moving in a controlled manner. The assessor gave a demonstration to ensure proper technique and use of a supinated grip. Before the start of the test, participants were allowed to practice one or two repetitions without the dumbbell. If the weight was raised about halfway up at the 30-second mark, the curl was counted.
5. Peak knee torque for flexion and for extension were assessed using the Biodex System 3. The purpose of the test is to assess the strength of the muscles of the knee joint that allow its extension and flexion. The Biodex System 3 is an electromechanical machine that can measure the isokinetic action of muscles at multiple major joints. The protocol was "isokinetic unilateral", with only the dominant leg being tested. The angular velocity was set at 60 degrees/second. The machine was calibrated prior to testing each participant. Once seated on the Biodex chair, participants were asked to perform 2 sets of 5 repetitions of knee flexion and extension. The two sets were separated by a 10-second break. The parameter of interest from the test printout was peak torque, which is the highest muscular force output at any moment for each of the sets (Biodex, n.d.). The knee torque is the turning effect of a muscle force around an axis of rotation, in this case the knee. Torque is the product of the muscle force and the force's perpendicular distance from the axis of the lever (Nitschke, 1992). The absolute peak torque is expressed in newton meter (Nm) and rounded to the nearest 0.1 Nm. Peak torque is also expressed relative to body weight in percentage and rounded to the nearest 0.1%. Biodex System 3 has "acceptable" mechanical reliability and validity for torque measurements. Measures are valid at velocities up to 300 degrees/second (Drouin et al., 2004).
6. Timed Up and Go was used to assess agility and balance (Jones & Rikli, 2002). The participant began the test seated, then got up, walked 3 meters, turned around a cone and returned to the initial seated position. One practice trial was permitted to allow familiarization with the test. The results were reported to the nearest 0.01 second.

7. The Community Healthy Activities Model Program for Seniors (CHAMPS) was used to estimate the number of minutes per week participants reported spending on a range of activities. The CHAMPS is a questionnaire that contains 41 questions requiring participants to report the estimated number of hours they have spent on a range of activities in the past week. There is construct validity for the use of CHAMPS as a measure of postoperative recovery (Feldman et al., 2009). We used the surgical version of the CHAMPS, CHAMPS-S, which contains 18 questions and is an abridged version of the original, listing a smaller range of activities than the ones in the original version (see Appendix C). Activities were categorized based on their metabolic equivalents: sedentary (<1 MET), light (1-3 METs), moderate (3-6 METs) and vigorous (>6 METs) intensity (Bousquet-Dion et al., 2018).
8. Compliance to the nutrition, exercise and relaxation interventions was assessed by asking participants standardized questions on a weekly basis (see Appendix B). Open-ended questions in relation to protein supplement ingestion, exercise frequency, intensity and duration, as well as relaxation CD usage frequency were asked. For the prehabilitation group, adherence questions were asked in person when participants were on-site exercising before surgery. After surgery, adherence questions were asked over the phone in both study arms. A score ranging from zero to five, was tabulated weekly for each element of the program. For exercise, a score of zero is no exercise, whereas five is daily exercise. For nutrition, a score of zero is no protein powder intake, whereas five is daily intake. For relaxation exercises, a score of zero is no practice, whereas five is a frequency greater than three times per week. Compliance scores were converted into percentages afterwards for analysis. Weekly compliance calls also served the purpose of clarifying any questions participants had for the dietitian or the kinesiologist. The kinesiologist did the majority of the weekly compliance phone calls and used this opportunity to encourage patients to adjust their exercise intensity whenever possible to promote further exercise adaptations.

Statistical analysis

The study protocol states that the sample size is 60 patients (30 per group). For the purpose of this thesis manuscript however, we analyzed the first 35 participants that joined the study. Our null hypothesis was that the mean 6-minute walk test performance in the prehabilitation group will be the same as the rehabilitation group. Power should usually be greater than 80%, meaning that in 8 of every 10 studies, we would be correctly rejecting the null hypothesis and conclude that prehabilitation improves 6-minute walk test performance. In our study, 6-minute walking test distance between baseline and eight week post-surgery increased by 0.66 m, with a standard deviation of 1.89 m. The calculated standardized effect size is 0.35, obtained from dividing 0.66 m by 1.89 m. Using a table indicating sample size per group for comparing two means, for a level of statistical significance set at an α (two-sided) of 0.05, the sample size per group required to have a power of 80% is 138 participants (Hulley et al., 2013). As such, our smaller sample size means this is a pilot study to collect data for a future trial with greater sample size and sufficient power.

Baseline demographics and clinical characteristics were assessed either with the student t-test, Wilcoxon–Mann–Whitney test, Fisher's exact test or Chi Square test. Whenever baseline data was parametric and non-categorical, the student t-test was used. The Wilcoxon–Mann–Whitney test was used as a non-parametric analysis for the following baseline data: age, fat mass, sit-to-stand, Timed Up and Go, knee extension average peak torque, knee extension average peak torque/body weight, self-reported physical activity from CHAMPS-S, C-reactive protein, hemoglobin, total hospitalization days and rehospitalization. The Fisher's exact test was used to analyze the following categorical data: sex, ethnicity, post-secondary education, radiation prior to baseline visit and low muscle mass based on chemotherapy treatment. The Chi Square test was used to analyze the following categorical data: diagnosis, chemotherapy prior to baseline visit, low muscle mass based on group assignment and low muscle mass based on diagnosis.

For our primary outcome, the effect of our interventions was assessed by calculating the mean difference on the 6-minute walk distance compared to baseline at all subsequent time points. At all time points subsequent to baseline, we also calculated the proportion of patients who improved 6-minute walk distance by at least 20 m compared to baseline, the proportion of patients who stayed within 20 m of baseline, and the proportion of patients who deteriorated by at least 20 m compared to baseline. For our secondary outcome measures, the effect of our interventions was assessed by calculating the mean difference on the measure compared to baseline at all subsequent time points or by calculating the mean measure to analyze differences within and between groups over time. We used a repeated measures ANOVA with post-hoc

Tukey testing to look at differences over time. Covariates included age, sex, diagnosis and total hospitalization days.

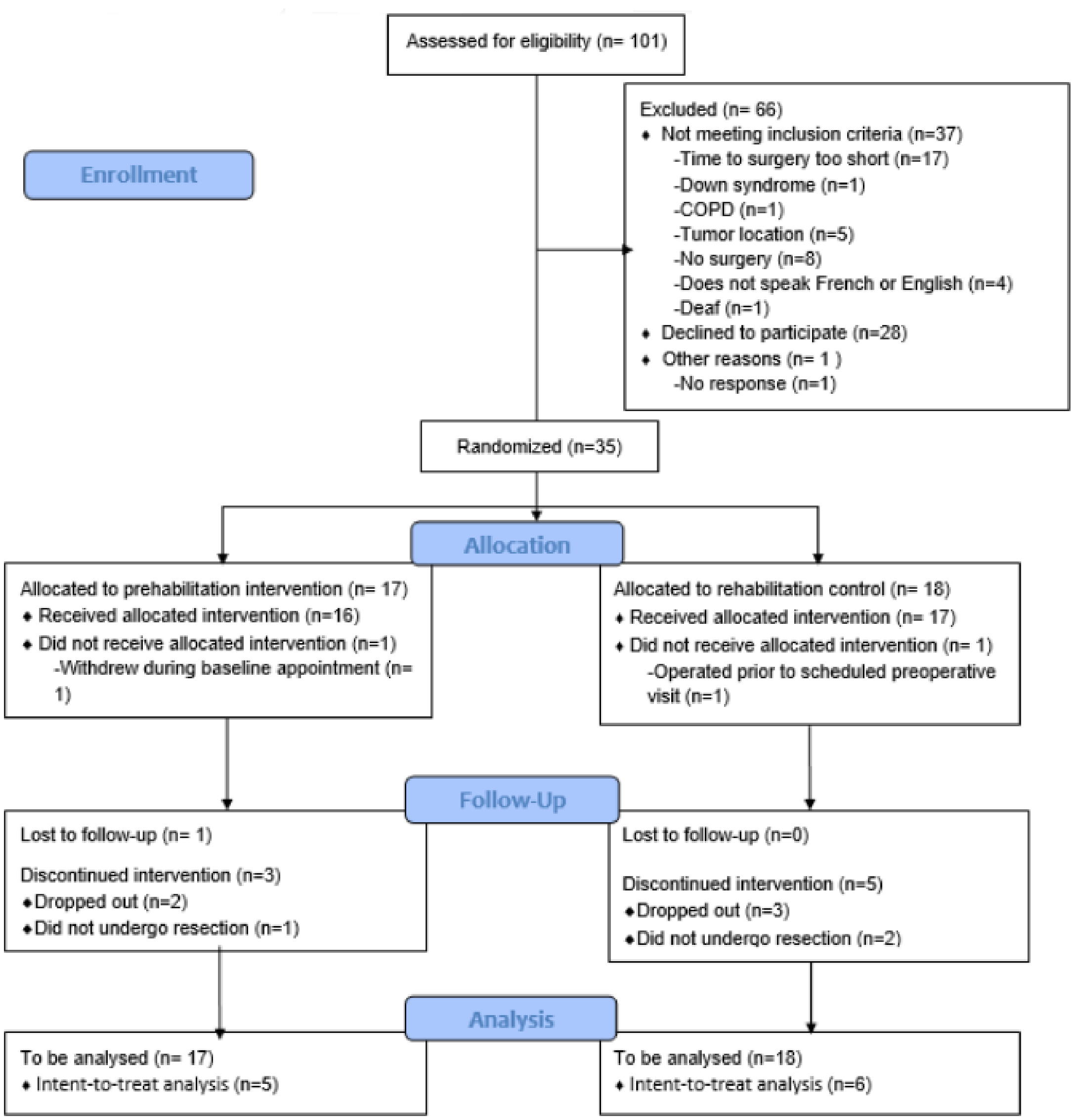
Analyses was performed with SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Subjects

Thirty-five (35) patients schedule for hepatobiliary or pancreatic cancer resection gave their informed consent to participate in our study. At their baseline appointment, 17 participants were randomized to the prehabilitation group and 18 to the rehabilitation control group. All details are presented in the CONSORT diagram in Figure 1.

Figure 1: CONSORT diagram for the trial



Demographic and clinical characteristics were similar at baseline between the two groups, as seen in Table 1. Though there were no statistically significant differences in diagnosis between the groups, the majority of the prehabilitation group was made up of pancreatic, gallbladder and bile duct cancer resections, whereas the majority of the rehabilitation group was made up of liver cancer resections (adjusted p=.238) . No differences were found between groups in regards to having low muscle mass or not; the criteria for low muscle mass being based on appendicular skeletal muscle index cutoffs of 5.45 kg/m^2 for women, and 7.26 kg/m^2 for men (Cruz-Jentoft et al., 2010). In Table 2, we split all participants by diagnosis and observed that at baseline, a significantly higher proportion of participants with liver diagnosis had low muscle mass at baseline (66.7%, p=.015) compared to participants with pancreatic, gallbladder or bile duct diagnosis. We also split all participants based on whether or not they had received neoadjuvant chemotherapy prior their baseline appointment. A higher proportion of participants who had received neoadjuvant chemotherapy had low muscle mass at baseline (63.2%, p=.045) compared to those who had not received neoadjuvant chemotherapy (see Table 2). The majority of liver cancer patients (88.9%) had received neoadjuvant chemotherapy, whereas 23.5% of patients with pancreatic, gallbladder or bile duct cancer patients had received neoadjuvant chemotherapy (see Table 3).

The mean time from baseline to the preoperative visit was comparable between the prehabilitation and rehabilitation groups: 28.0 ± 8.8 days ($\bar{x}$ ± SD) in the prehabilitation and 29.1 ± 9.0 days in the rehabilitation group (adjusted p=.749).

Table 1: Baseline patient demographic and clinical characteristics

	Prehabilitation (n= 17)	Rehabilitation (n=18)
Age (years)	58.4 (15.8)	61.9 (11.8)
Sex		
Female	6 (35.3%)	4 (22.2%)
Male	11 (64.7%)	14 (77.8%)
Ethnicity		
White	15 (88.2%)	14 (77.8%)
Non-white	2 (11.8%)	4 (22.2%)
Site of resection		
Pancreas, bile ducts and/or gallbladder	10 (58.8%)	7 (38.9%)
Liver	7 (41.2%)	11 (61.1%)
Post-secondary education		
Yes	9 (52.9%)	15 (83.3%)
No	8 (47.1%)	3 (16.7%)
Chemotherapy prior to baseline visit		
Yes	9 (52.9%)	11 (61.1%)

No	8 (47.1%)	7 (38.9%)
Radiation prior to baseline visit		
Yes	2 (11.8%)	1 (5.6%)
No	15 (88.2%)	17 (94.4%)
Body mass index (kg/m²)	26.1 (5.6)	26.0 (3.7)
Body fat (%)	34.3 (9.5)	32.1 (8.7)
Fat mass (kg)	23.6 (10.6)	23.8 (8.9)
Lean body mass (kg)	43.2 (8.3)	48.9 (8.4)
Appendicular skeletal muscle index (kg/m²)	6.58 (1.03)	6.98 (1.14)
Low muscle mass*		
Yes	9 (56.3%)	7 (38.9%)
No	7 (43.8%)	11 (61.1%)
Average hand grip strength (kg)		
Right	35.9 (9.9)	38.4 (9.9)
Left	33.1 (10.6)	35.9 (4.3)
Sit to stand	11.4 (4.1)	10.6 (6.3)
30-second arm curl		
Right	15.6 (3.5)	15.4 (4.2)
Left	15.7 (4.3)	15.8 (4.3)
Timed Up and Go (seconds)	7.47 (1.82)	7.99 (2.23)
6-minute walk test distance (meters)	510.2 (96.8)	479.7 (104)
Knee extension		
Average peak torque (Nm)	83.27 (36.98)	91.08 (53.34)
Average peak torque/body weight (%)	122.13 (44.14)	118.5 (54.72)
Knee flexion		
Average peak torque (Nm)	42.13 (24.61)	40.86 (24.92)
Average peak torque/body weight (%)	60.83 (30.57)	53.06 (27.43)
Self-reported physical activity from CHAMPS-S		
Sedentary (min/week)	783.5 (787)	612.2 (721.6)
Light (min/week)	659.4 (653.8)	644.2 (629.6)
Moderate (min/week)	196.5 (232)	112.8 (195.1)
Vigorous (min/week)	88.8 (139.2)	63.3 (151.5)
Moderate + vigorous (min/week)	285.3 (336.8)	176.2 (322.8)
C-reactive protein (mg/L)	6.54 (5.81)	14.1 (29.5)
Albumin (g/L)	41.4 (4.3)	40.3 (4)
Prealbumin (mg/L)	244.3 (74.1)	212 (62.5)
Hemoglobin (g/L)	129.9 (14.5)	127.7 (13.9)
Total hospitalization days**	11.7 (7.8)	12.1 (7.8)

CHAMPS-S Community Healthy Activities Model Program for Senior-Surgical
Data are presented as mean (SD) or n (%).
*Based on appendicular skeletal muscle index cutoffs of 5.45 kg/m² for women, and 7.26 kg/m² for men (Cruz-Jentoft et al., 2010).
**Includes hospital length of stay and number of rehospitalization days.

Table 2: Baseline low muscle based on diagnosis, and based on chemotherapy treatment

		Pancreatic, gallbladder, bile ducts	Liver	p
Low muscle mass	Yes	4 (25.0%)	12 (66.7%)	0.015
	No	12 (75.0%)	6 (33.3%)	
		Chemotherapy*	**No chemotherapy****	**p**
Low muscle mass	Yes	12 (63.2%)	4 (26.7%)	0.045
	No	7 (36.8%)	11 (73.3%)	

Data are presented as n (%).
Low muscle mass criteria based on appendicular skeletal muscle index cutoffs of 5.45 kg/m^2 for women, and 7.26 kg/m^2 for men (Cruz-Jentoft et al., 2010).
*Have undergone neoadjuvant chemotherapy prior to baseline appointment.
**Have not undergone neoadjuvant chemotherapy prior to baseline appointment.

Table 3: Baseline number of participants who have received neoadjuvant chemotherapy based on diagnosis

	Chemotherapy*	No chemotherapy**
Pancreatic, gallbladder, bile ducts	4 (23.5%)	13 (76.5%)
Liver	16 (88.9%)	2 (11.1%)

Data are presented as n (%).
*Have undergone neoadjuvant chemotherapy prior to baseline appointment.
**Have not undergone neoadjuvant chemotherapy prior to baseline appointment.

Functional walking capacity

The changes in 6-minute walk distance from baseline for both groups over time are shown in Figure 2. At baseline, the mean 6-minute walk test distance was 510.2 ± 96.8 m in the prehabilitation group and 479.7 ± 104.0 m in the rehabilitation group (see Table 1). There were no significant differences between groups (adjusted p=.376). Table 4 shows changes in 6-minute walk distance over time compared to baseline.

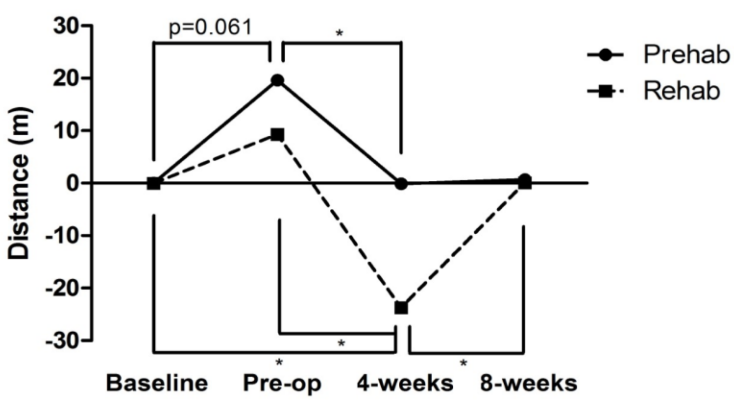
Preoperative period. The mean 6-minute walk distance increased by 19.63 ± 0.25 m ($\bar{x}$ ± SE) in the prehabilitation group and by 9.28 ± 0.24 m in the rehabilitation group. There was a statistical trend in the improvement of the prehabilitation group's distance walked (adjusted p=.061), though it was not significant in the rehabilitation group (adjusted p=.110).

Four weeks after surgery. At four weeks after surgery, both prehabilitation and rehabilitation mean change in walking capacity had significantly dropped since the preoperative appointment. The drop was 19.74 m (adjusted p=.010) in the prehabilitation group versus 33 m (adjusted p<.0001) in the rehabilitation group. Although there were no differences between groups at four-weeks postoperative, the rehabilitation group's mean drop from baseline (-23.72 ± 0.36 m) was statistically and clinically significant (adjusted p=.035), whereas the prehabilitation group was able to maintain their baseline walking capacity. At four-weeks postoperative, 25% of patients in the prehabilitation group remained at least 20 m above their baseline 6-minute walk distance, whereas none did in the rehabilitation group (see Table 5).

Eight weeks after surgery. At eight weeks after surgery, the prehabilitation group remained at its baseline walking capacity, with no change in walking capacity from four-weeks to eight-weeks post-operation (adjusted p=.796). From four to eight weeks post-surgery, the rehabilitation had returned to its baseline walking capacity, with a significant mean increase of 23.80 m (adjusted p=.001).

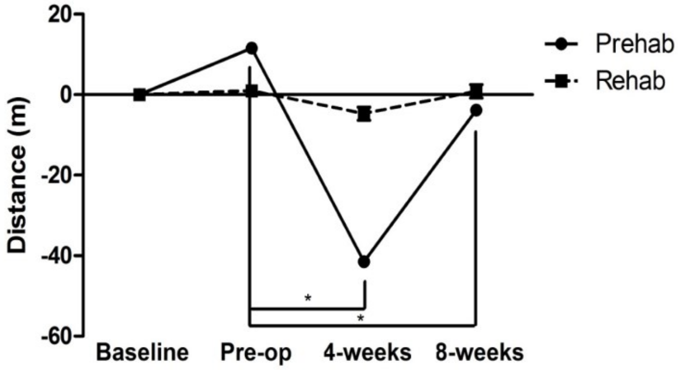
We also analyzed the 6-minute walking test results for each diagnoses separately. For pancreatic, gallbladder bile duct cancer resections, the prehabilitation group's 6-minute walking distance at four-weeks and eight-weeks postoperative had significantly dropped since their preoperative appointment (see Figure 3). These drops were of 53.06 m (adjusted p=.0005) and 15.43 m (adjusted p=.041) respectively. Whereas participants who underwent rehabilitation saw no significant changes in their walking capacity at any time points. For liver cancer resections, at eight-weeks post-operation, the participants who underwent prehabilitation were able to walk significantly greater distances compared to baseline (+56.73 ± 14.97 m, adjusted p=.042), whereas no significant differences were detected in participants who underwent rehabilitation (see Figure 4).

Figure 2: Mean 6-minute walk test change from baseline at the four study time points



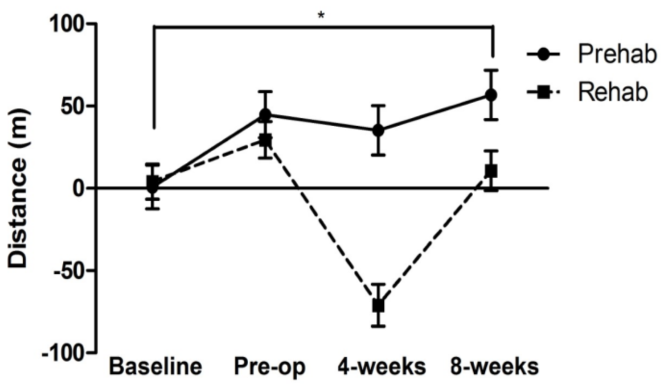
*Significance p<0.05. Repeated measures ANOVA, n=35.
Data transformation to ensure normal distribution.

Figure 3: Mean 6-minute walk test change from baseline at the four study time points in pancreatic, gallbladder and bile duct cancer resections



*Significance p<0.05. Repeated measures ANOVA, n=35.
Data transformation to ensure normal distribution.

Figure 4: Mean 6-minute walk test change from baseline at the four study time points in liver cancer resections



*Significance p<0.05 (not all statistically relevant differences are shown here). Repeated measures ANOVA, n=35.
Whiskers represent standard error of the mean.

Table 4: Changes in outcomes over time

	Baseline		**Preoperative**		**4-weeks postoperative**		**8-weeks postoperative**	
	Prehab	Rehab	Prehab	Rehab	Prehab	Rehab	Prehab	Rehab
6MWT change from baseline, m			+19.63 (0.25)	+9.28 (0.24)	-0.11 (0.32)[3]	-23.72 (0.36)[2, 4]	+0.66 (0.32)	0.08 (0.32)[6]
ASMI change from baseline, kg/m^2			+0.22 (0.11)	+0.06 (0.11)	-0.12 (0.12)	-0.37 (0.12)[4]	+0.09 (0.12)	+0.01 (0.12)
Hand grip strength change from baseline								
Right, kg			0.00 (0.03)	-0.01 (0.02)	-0.60 (0.03)	-1.06 (0.03)	-0.04 (0.03)	0.00 (0.03)
Left, kg			+0.77 (0.89)	-0.49 (0.88)	-2.34 (1.00)	-2.36 (0.97)	-0.03 (0.99)	-0.30 (0.97)
30-second chair stand change from baseline, repetitions			+1.95 (0.68)	+1.76 (0,68)	-0.84 (0.73)[3]	-0.04 (0.78)	+1.74 (0.73)[5]	+2.48 (0.73)[2, 6]
30-second arm curl								
Right, repetitions	15.77	15.79	16.38	17.02	14.64	13.83	16.69	16.86

	(1.15)	(1.14)	(1.17)	(1.17)	(1.22)	(1.22)[4]	(1.21)	(1.21)[6]
Left, repetitions	15.73 (1.16)	15.79 (1.14)	16.59 (1.17)	17.14 (1.17)	14.29 (1.26)	14.18 (1.24)	15.73 (1.22)	15.99 (1.22)
Timed Up and Go, seconds	7.25 (0.01)	7.37 (0.01)	6.60 (0.01)	7.21 (0.01)	7.67 (0.01)[3]	7.72 (0.01)	6.85 (0.01)	6.84 (0.01)
Knee extension								
Average peak torque, Nm	81.28 (12.55)	76.84 (11.54)	102.38 (12.64)[1]	78.41 (11.67)	80.96 (12.90)[3]	72.38 (12.19)	89.01 (12.90)	86.10 (11.77)
Average peak torque/body weight, %	123.85 (12.27)	111.32 (13.08)	153.14 (14.42)[1]	113.09 (13.29)	126.89 (14.85)	108.14 (14.12)	144.35 (14.85)	124.69 (13.45)
Knee flexion								
Average peak torque, Nm	42.67 (6.98)	35.54 (6.42)	47.16 (7.04)	39.41 (6.50)	44.58 (7.20)	32.78 (6.81)	39.31 (7.20)	43.05 (6.56)
Average peak torque/body weight, %*	NA	NA	NA	NA	NA	NA	NA	NA
Self-reported physical activity from CHAMPS-S								
Sedentary change from baseline, min/week			0.00 (4.88)	-1.52 (5.63)	-74.49 (5.98)	+21.45 (6.11)	-51.59 (5.98)	+0.79 (6.11)
Light, min/week	409.58 (10.20)	438.92 (9.73)	545.21 (10.54)	767.16 (10.74)	393.99 (11.52)	551.26 (11.61)	371.31 (11.51)	489.24 (11.61)
Moderate, min/week	31.17 (0.33)	8.64 (0.29)	386.08 (0.37)[1]	130.11 (0.39)[2]	33.70 (0.47)[3]	121.68 (0.48)	271.19 (0.47)[1]	303.42 (0.48)[2]
Vigorous, min/week*	NA	NA	NA	NA	NA	NA	NA	NA
Moderate + vigorous, min/week	51.85 (0.51)	28.99 (0.45)	343.34 (0.55)[1]	148.86 (0.58)	23.93 (0.68)[3]	118.31 (0.69)	234.41 (0.68)[5]	292.39 (0.69)[2]

ASMI appendicular skeletal muscle index, *CHAMPS-S* Community Healthy Activities Model Program for Senior-Surgical. Data are presented as mean (SE).
*Data not normally distributed.
[1] is significantly different (p<.05) from baseline prehabilitation value; [2] is significantly different (p<.05) from baseline rehabilitation value; [3] is significantly different (p<.05) from preoperative prehabilitation value; [4] is significantly different (p<.05) from preoperative rehabilitation value; [5] is significantly different (p<.05) from 4-weeks prehabilitation value; [6] is significantly different (p<.05) from 4-weeks rehabilitation value.

Table 5: Mean changes in 6-minute walk test over time compared to baseline

	Prehabilitation (n = 17)	**Rehabilitation (n = 18)**
Preoperative period		
% of patients exhibiting clinically significant changes in 6MWT		
Improved ≥ 20-m from baseline	9 (64%)	9 (60%)
Within 20-m of baseline	4 (29%)	6 (40%)
Deteriorated ≥ 20-m from baseline	1 (7%)	0 (0%)
4 weeks after surgery		
% of patients exhibiting clinically significant changes in 6MWT		
Improved > 20-m from baseline	3 (25%)	0 (0%)
Within 20-m of baseline	3 (25%)	4 (36%)
Deteriorated > 20-m from baseline	6 (50%)	7 (64%)
8 weeks after surgery		
% of patients exhibiting clinically significant changes in 6MWT		
Improved > 20-m from baseline	4 (33%)	5 (42%)

	Within 20-m of baseline	5 (42%)	3 (25%)
	Deteriorated > 20-m from baseline	3 (25%)	4 (33%)

6MWT 6-minute walk test
Data are presented as n (%).

Secondary outcomes

Muscle mass

Between the preoperative appointment and four-weeks postoperative, there was a significant drop in the appendicular skeletal muscle index in the rehabilitation group (-0.43 kg/m^2, adjusted p=.050), whereas the prehabilitation group were able to maintain their preoperative index (see Table 4).

Strength

Hand grip strength. For both right and left hand, there were no detectable differences between or within the groups (see Table 4).

30-second chair stand. From baseline to eight-weeks postoperative, there was a significant increase in the rehabilitation group of 2.48 ± 0.73 repetitions (adjusted p=.014), but no change in the prehabilitation group (see Table 4).

30-second arm curl. From the preoperative appointment to four-weeks after surgery, the rehabilitation group experienced a significant drop in mean 30-second arm curl in their right arm of 3.19 repetitions (adjusted p=.022). Then between four-weeks and eight-weeks post-surgery, the rehabilitation returned to their baseline number of repetitions (+3.03 repetitions, adjusted p=.035). Patients in the prehabilitation group remained at their baseline 30-second arm curl level throughout the study. In the left arm, we found no differences between or within groups (see Table 4).

Knee torque. For average peak torque of knee extension, from baseline to the preoperative visit, the prehabilitation group had a significant increase of 21.10 Nm (adjusted p=.028), while the rehabilitation group had no improvement. Then between the preoperative visit and four-weeks postoperative, there was a significant decrease of 21.42 Nm (adjusted p=.049) in the prehabilitation group. For average peak torque relative to body weight of knee extension, from baseline to the preoperative visit, the prehabilitation had a significant increase of 29.29% (adjusted p=.025), while the rehabilitation group did not. As for the average peak torque of knee flexion, there were no detectable differences between or within the groups (see Table 4).

Agility and balance

Timed Up and Go. Between the preoperative and the four-weeks postoperative appointments, there was a significant increase in Timed Up and Go duration in the prehabilitation group of 1.07 seconds (adjusted p=.022), but no change in the rehabilitation group (see Table 4).

Energy expenditure

Participants filled out the CHAMPS-S questionnaire at all four study visits (see Table 4). Physical activities listed in the questionnaire were classified into sedentary, light, moderate and moderate plus vigorous intensity activities. Physical activity was analyzed as weekly duration in minutes and classified by intensity. For sedentary activities, there were no detectable differences between or within the groups. For light intensity activities, there were also no detectable differences between or within the groups. For moderate intensity activities, we found a significant increase in the preoperative period in both the prehabilitation group (+354.91 min/week, adjusted p=.001) and the rehabilitation group (+121.47 min/week, adjusted p=.027). Between the preoperative visit and four-weeks postoperative, there was a significant drop in the prehabilitation group of -352.38 min/week (adjusted p=.002), whereas the rehabilitation group saw no change. At eight-weeks postoperative, there was a significant increase in weekly moderate intensity activities from baseline in both groups, by 239.82 min/week (adjusted p=.021) in the prehabilitation group, and by 294.78 min/week (adjusted p=.0001) in the rehabilitation group. For moderate plus vigorous intensity activities, only the prehabilitation group experienced a significant increase in the preoperative period (+291.49 min/week, adjusted p=.017). Between the preoperative and the four-week postoperative appointments, the prehabilitation group had a significant decrease in their moderate plus vigorous intensity activities duration of -319.41 min/week (adjusted p=.002). Then between the four-week and eight-week postoperative appointments, the prehabilitation group significantly improved their moderate and vigorous activities duration by 210.48 min/week (adjusted p=.039). The rehabilitation group had a significant gain in moderate plus vigorous intensity activities duration of 263.39 min/week (adjusted p=.01) between baseline and eight-weeks postoperative.

Compliance

During the preoperative period, the prehabilitation group's compliance to the exercise and nutrition interventions were 87.44 and 93.15% respectively (see Table 6). After surgery, there was no difference in compliance between the groups. However, the prehabilitation group experienced a significant drop in both exercise (-19.68%, adjusted p=.023) and nutrition (-

32.41%, adjusted p=.003) compliance in the period between surgery and four-weeks post-operation, while no change was detected in the rehabilitation group. From four-weeks to eight-weeks post-operation, compliance was above 70% for both exercise and nutrition. As for the relaxation intervention, compliance was similar between both groups and always below 30% at all assessment points.

We also analyzed compliance according to diagnoses. Tables 7 and 8 respectively show exercise and nutrition compliance according to diagnoses. In the period between the preoperative and the four-week postoperative appointments, prehabilitation participants who underwent pancreatic, gallbladder or bile duct cancer resections experienced a significant drop in exercise compliance (-32.71%, adjusted p=.006), whereas prehabilitation participants who underwent liver resection experienced no change. Prehabilitation patients who underwent pancreatic, gallbladder bile duct cancer resections also experienced a significant drop in nutrition compliance over that same period (-57.25%, adjusted p<.0001), whereas liver resections did not. In the period between surgery and four weeks postoperative, prehabilitation patients that had undergone liver resection had significantly higher nutrition compliance than pancreatic, gallbladder and bile duct cancer resections (90.08% vs. 30.61%, adjusted p=.022). Also, in the period between four and eight weeks postoperative, rehabilitation patients that had undergone liver resection had significantly higher nutrition compliance than pancreatic, gallbladder and bile duct cancer resections (91.75% vs. 34.75%, adjusted p=.045).

Table 6: Exercise, nutrition and relaxation compliance

	Exercise		**Nutrition**		**Relaxation**	
	Prehab	Rehab	Prehab	Rehab	Prehab	Rehab
During preoperative period, %	87.44		93.15		9.04	
From surgery to 4-weeks, %	67.76[1]	62.42	60.75[1]	52.00	9.23	28.58
From 4 to 8 weeks, %	78.45	75.02	75.67	72.75	15.31	25.20

[1] is significantly different (p<.05) from preoperative period value.

Table 7: Exercise compliance by diagnosis

	Prehab		**Rehab**	
	Pancreatic, gallbladder, bile ducts	Liver	Pancreatic, gallbladder, bile ducts	Liver
During preoperative period, %	83.45	92.77		
From surgery to 4-weeks, %	50.74[1]	86.01	61.50	62.87
From 4 to 8 weeks, %	68.60	90.01	59.90	82.57

[1] is significantly different (p<.05) from pancreas, gallbladder or bile ducts prehabilitation group preoperative period value.

Table 8: Nutrition compliance by diagnosis

	Prehab		Rehab	
	Pancreatic, gallbladder, bile ducts	Liver	Pancreatic, gallbladder, bile ducts	Liver
During preoperative period, %	87.86	99.33		
From surgery to 4-weeks, %	30.61[1]	90.08[2]	31.00	62.50
From 4 to 8 weeks, %	56.27	95.08	34.75	91.75[3, 4]

[1] is significantly different (p<.05) from pancreas, gallbladder or bile ducts prehabilitation group preoperative period value; [2] is significantly different (p<.05) from pancreas, gallbladder or bile ducts prehabilitation group surgery to 4-weeks value; [3] is significantly different (p<.05) from liver rehabilitation group surgery to 4-weeks value; [4] is significantly different (p<.05) from pancreas, gallbladder or bile ducts rehabilitation 4 to 8 weeks value.

Hospitalization

For total hospitalization days (see Table 1), which includes hospital length of stay and rehospitalization days related to the surgery, no differences were found between prehabilitation and rehabilitation groups (prehabilitation = 11.7 ± 7.8 days ($\bar{x}$ ± SD) vs. rehabilitation = 12.1 ± 7.8 days, p= .567). We also analyzed hospitalization according to diagnoses (see Table 9). The number of rehospitalization days was significantly greater in patients who had undergone pancreatic, gallbladder or bile duct cancer resections compared to patients who underwent liver resection (pancreatic, gallbladder or bile duct = 5.5 ± 6.8 days vs. liver = 1.3 ± 4.9 days, p=.018). Total hospitalization days was also significantly greater in patients who had undergone pancreatic, gallbladder or bile duct cancer resections compared to patients who underwent liver resection (pancreatic, gallbladder or bile duct = 16.5 ± 8.2 days vs. liver = 8.3 ± 5 days, p=.001).

Table 9: Total hospitalization days and rehospitalization days after surgery by diagnosis

	Pancreatic, gallbladder, bile ducts	Liver	p
Total hospitalization days*	16.5 (8.2)	8.3 (5)	0.001
Rehospitalization days	5.5 (6.8)	1.3 (4.9)	0.018

Data are presented as mean (SD).
*Includes hospital length of stay and number of rehospitalization days.

Discussion

Our preliminary findings suggest that a trimodal prehabilitation that comprises aerobic, resistance and flexibility exercises, nutritional counselling with whey protein supplementation and relaxation exercises begun four weeks prior to surgery can lead to a clinically significant improvement of walking capacity and can lead to the maintenance of baseline walking capacity at four-weeks post-surgery in hepatobiliary and pancreatic cancer patients. Whereas starting the program postoperatively is not sufficient to maintain baseline functional walking capacity at four-weeks post-surgery. The decline in walking capacity at four-weeks post-surgery in the rehabilitation group was on average 23.72 ± 0.36 m ($\bar{x}$ ± SE). This distance is greater than the range of 19 to 20 m, regarded as the minimal clinically meaningful difference (Antonescu et al. 2014; Bousquet-Dion et al., 2018; Minnella et al., 2017). We also observed that at four weeks post-surgery, 64% of participants in the rehabilitation group had experienced a deterioration in their functional walking capacity by more than 20 m, compared to 50% of participants in the prehabilitation group. From four to eight-weeks post-surgery, the rehabilitation group significantly improved (p=0.001) and returned to baseline levels, while the prehabilitation group stayed at their baseline level.

We had hypothesized that prior to surgery our prehabilitation group would improve their 6-minute walk test performance. We observed a total trimodal compliance of 63.21% in the preoperative period, which is an average of the preoperative period compliance to the exercise, nutrition and relaxation interventions. This led to a clinically significant improvement of 19.63 ± 0.25 m in the prehabilitation group's preoperative walking capacity. Though it was not statistically significant, there was a statistical trend in improvement of distance walked. No difference in 6-minute walk distance was detected between groups at the preoperative visit. In comparison, a study in colorectal cancer patients that employed a similar four-week trimodal prehabilitation reported 53% of compliance in the preoperative period, which is comparable to our total trimodal compliance for the same period (Gillis et al., 2014). The prehabilitation group in the Gillis et al. (2014) study experienced a statistically and clinically significant improvement in its preoperative walking capacity, and had better walking capacity than the rehabilitation group at their preoperative visit. Since our study is underpowered, we are currently unable to determine whether or not there was truly an absence of effect. Possible reasons for our hypothetical absence of effect include our relatively small sample size and unequal randomization by diagnosis in our study. Although there were no statistical differences in diagnosis between our groups, the majority of our rehabilitation group was made up of patients undergoing liver resection. At baseline, there were 88.9% of liver resection patients that had received neoadjuvant chemotherapy, compared to 23.5% of the pancreatic, gallbladder bile duct cancer resections patients. Given that our randomization did not take into account the type of cancer diagnosis, the differences that could have been observed between groups might have been attenuated. This is because the four-week prehabilitation period of our study also coincided with the period of chemotherapy washout. When we split our participants at baseline into those who had received neoadjuvant chemotherapy and those who had not, we observed a significantly higher proportion of patients with low muscle mass in those who had received chemotherapy (63.2%, p=.045). The cutoffs for low muscle mass were based on the appendicular skeletal muscle index, which represents the main portion of muscles involved in physical activity and ambulation (Cruz-Jentoft et al., 2010). Because the chemotherapy washout period coincided with our prehabilitation period, it could be that liver resection patients were able to improve their walking capacity, independently of the trimodal prehabilitation intervention. If we had used a randomized block design, this unequal sample as a result of our study randomization could have been avoided.

Another explanation for the absence of differences between groups at the preoperative visit could be the potential bias that ensued from awareness by participants in both arms at recruitment of the potential benefits of prehabilitation. Instead of providing our rehabilitation group with no intervention or a sham intervention, we provided them with the same intervention as the prehabilitation group, but started after surgery. The purpose of our design was to improve patient participation, as this approach lowers the refusal rate (Gillis et al., 2014). Because of our study's positive bias towards prehabilitation, we observed a significant increase in CHAMPS-S self-reported moderate physical activity prior to surgery in the rehabilitation arm (+121.47 min/week, adjusted p=.027). It is also possible that during the preoperative period, our rehabilitation group participants sought out psychological support or dietary advice. On the other hand, it can also be said that despite the fact that our prehabilitation and rehabilitation programs are no part of standard care, there is already a focus on physical activity and nutrition at our institution. Enhanced Recovery After Surgery (ERAS) is implemented at our institution as part of standard care, and is a multimodal protocol that targets the optimization of intra- and postoperative care, such as early mobilization, food on surgery day, carbohydrates drinks two hours before surgery, etc. (Ljungqvist et al., 2017). This means that without our intervention, participants in our control group would have been already somewhat aware of the benefits of mobilization and nutrition. In a future study, the consent form should not be positively biased towards the prehabilitation program. It may be better to say that both prehabilitation and rehabilitation programs have been shown to be effective, and that our study is testing the effectiveness of both programs.

Another reason for the absence of differences between groups at the preoperative visit is related to the organization of the hospital. For a complexity of reasons, it is commonplace for patients to be confirmed for surgery without having a surgery date provided. This has made coordinating the recruitment of patients difficult. Some patients ended up having prehabilitation periods that lasted less than four weeks, while others had their surgery scheduled beyond four weeks from their initial baseline. This has caused us to ask certain participants to come back for a new baseline assessment. Prehabilitation participants who had to redo their baseline assessment were likely to progress at a slower rate given that their new baseline functional capacity was greater than before.

We had also hypothesized that at eight-weeks post-surgery, the prehabilitation group would have walked greater distances in the 6-minute walk test compared to the rehabilitation group. The lack of difference between groups and within group at eight-weeks post-surgery was not what we would have anticipated, given that a previous colorectal cancer study employing a similar trimodal prehabilitation had found differences in favor of prehabilitation (Gillis et al., 2014). This could be explained by the fact that our study's randomization was not designed to take into account differences in diagnosis. From our literature review, it was observed that the rate of complications in pancreatic cancer resections is on the higher end, compared to liver resections (Halloran et al., 2002; Ishii et al., 2014). Although we found no difference in total hospitalization days between our prehabilitation and rehabilitation groups, the number of rehospitalization days was significantly greater in patients with pancreatic, gallbladder or bile duct cancer resections compared to liver cancer resections, respectively 5.5 ± 6.8 days ($\bar{x} \pm$ SD) vs. 1.3 ± 4.9 days, p=.018. The mean total number of days participants with pancreatic, gallbladder or bile duct cancer resections were hospitalized (hospital length of stay plus additional rehospitalization) was 16.5 ± 8.2 days. Although there was no statistical differences in diagnosis between our prehabilitation and rehabilitation groups, the majority of our prehabilitation group was made up of patients undergoing pancreatic, gallbladder or bile duct cancer resections. Again, the fact that our randomization did not take into account diagnosis could have attenuated the differences that could have been observed. Because of total number of days the pancreatic, gallbladder or bile duct cancer resections were hospitalized, we observed significant drops in both their exercise and nutrition compliance in the first four weeks after surgery.

Another possible reason for the lack of difference at eight-weeks post-surgery could be the difficulty in getting participants with pancreatic, gallbladder or bile duct cancer resections, who made up the majority of our prehabilitation group, to optimally progress their exercises. Between four and eight-weeks post-surgery, the prehabilitation group experienced a plateau in their 6-minute walk test. This could be due to the difficulty in getting patients who had undergone pancreatic, gallbladder or bile duct cancer resections to want to exercise given their concerns with pain and wound healing. For resistance training, if those participants were unwilling to split up their resistance training on two days (one day upper body and one day lower body), they were instructed to do at least one set instead of two. If patients were still not compliant, they were told to do a least some of their exercises rather than nothing. As for aerobic training, if participants could not tolerate walking at the prescribed intensity, duration and frequency, they were first told to split up their walking in smaller bouts of 10 minutes. If they were still not compliant, they were told to do even smaller bouts or to reduce their intensity. If they were still not compliant, they were told to do at least some walking rather than nothing. As such, continuous negotiations between the kinesiologist and participants took place to get them to do as much as they could of their program rather than completely avoid exercising. Progression was thus challenging to implement in those patients with pancreatic, gallbladder or bile duct cancer diagnoses.

In regards to our secondary outcome measures, we observed that at four-weeks post-surgery, our prehabilitation group was able to maintain its baseline appendicular skeletal muscle index, whereas the rehabilitation was not able to. These results are promising and indicate that the main portion of muscles involved in physical activity and ambulation did not atrophy after surgery in those who followed the prehabilitation program. It can also be inferred that maintaining this muscle mass could have contributed to the maintenance of baseline walking capacity observed in the prehabilitation group at four-weeks post-surgery.

As for strength, we observed a significant improvement in the 30-second chair stand from baseline to eight-weeks postoperative in the rehabilitation group, but not in the prehabilitation group. It is possible that pancreatic, gallbladder or bile duct resection patients, who made up the majority of the prehabilitation group, were concerned with complications and/or pain from their surgery and did not perform to the best of their ability in order for us to really measure lower body strength. When we analyzed average peak torque of knee extension, the prehabilitation group achieved a significant improvement before surgery. However, that improvement was lost in the first four weeks following surgery, which coincides with the drop in 30-second chair stand we also observed in the prehabilitation group. For upper body strength, we observed in the rehabilitation group a significant drop of the right side 30-second arm curl in the four-week period after surgery, followed by a return to baseline at eight weeks post-surgery. It could be that although our rehabilitation program was not sufficient to maintain preoperative arm strength at four-weeks postoperative, it allowed a return to baseline arm strength at eight-weeks postoperative. In the prehabilitation group, no changes were observed at any assessment points in the right side 30-second arm curl. As such, maintenance of preoperative right side upper body strength was achieved with prehabilitation. No differences were found in left side 30-second arm curl.

As for agility and balance, we observed a significant increase in the prehabilitation group's Timed Up and Go duration during the first four weeks after surgery. Given that pancreatic, gallbladder or bile duct resection patients made up the majority of the prehabilitation group, concerns with complications and/or pain might have caused some participants to take more time to get up from the chair and sit back down.

Another secondary outcome measure was energy expenditure assessed with the CHAMPS-S questionnaire. The American Cancer Society (ACS) publishes guidelines encouraging adults to engage in at least 150 minutes of moderate intensity exercise or 75 minutes of vigorous intensity exercise per week in order to reduce cancer risk (Kushi et al., 2012). In the preoperative period, both prehabilitation and rehabilitation group significantly increased their amount of moderate physical activity. Only the prehabilitation group reached the weekly ACS recommendation for moderate activity, with a mean of 386.08 ± 0.37 min/week ($\bar{x}$ ± SE). Then between surgery and four-weeks postoperative, the prehabilitation group experienced a significant decrease in weekly moderate physical activity, whereas the rehabilitation group did not. We believe this drop can be partly explained by the fact that our prehabilitation group was mainly composed of patients who had undergone pancreatic, gallbladder or bile duct cancer resection and were thus rehospitalized for significantly longer durations than patients who had undergone liver cancer resection. At eight-weeks postoperative, both prehabilitation and rehabilitation groups' weekly moderate physical activity was significantly greater than their baseline levels, both groups exceeding the ACS weekly recommendations of 150 minutes of moderate intensity exercise. Considering participants in both study arms were below the ACS recommendations at baseline, both our prehabilitation and rehabilitation programs were successful in providing our patients educational and motivational tools to reach the ACS physical activity guidelines. We were unable to analyze data for vigorous physical activity alone because the data was not normally distributed.

It is not clear to us which component of our program had the greatest impact on functional recovery. Given the low compliance range of 9 to 29% we observed for our psychological intervention in both study arms, we believe that the weekly practice of relaxation exercises might not have been considered a priority by the majority of participants in our study. However, simply knowing they had a tool to control stressors could have helped certain participants alleviate some distress and thus facilitate their participation in the exercise and nutrition interventions. As for our exercise and nutrition interventions, compliance was respectively 87.44% and 93.15% in the preoperative period. Our preoperative exercise compliance score is consistent with a recent study reporting that patients undergoing neoadjuvant chemotherapy for pancreatic adenocarcinoma are willing to participate in exercise prior to surgery (Ngo-Huang et al., 2017). Although our prehabilitation participants were willing to comply with the exercise and nutrition interventions before surgery, compliance significantly dropped in the first four-weeks postoperative period. For exercise, this drop can be partly explained by the fact that there were no supervision after surgery as participants exercised entirely at home. This made the exposure to supervised training unequal between the preoperative period and the postoperative period. Supervised exercise at participants' home would not have been feasible with one kinesiologist given that there can be multiple participants to be seen and some participants live far. On-site supervised exercise sessions would not have been feasible for all participants either, given that some were instructed by their surgeons not to drive for several weeks after surgery. Also, in our participants that had undergone pancreatic, gallbladder or bile duct cancer resection, compliance to the exercise and nutrition interventions was particularly difficult after surgery because these resections lead to poor nutritional status and their complication rates that are well above average (Halloran et al., 2002). Pancreatic cancer patients who undergo the classic Whipples procedure commonly experience postoperative side effects such as rapid gastric emptying, insufficient digestive enzymes, pancreatic juices or bile, which can cause poor appetite, poor fat absorption, diarrhea and indigestion (Canadian Cancer Society, n.d.-b). Despite significantly longer rehospitalizations in pancreatic, gallbladder and bile duct resections than in liver resections, the overall exercise compliance in our prehabilitation group was 67.76% during the first four-weeks after surgery, which is comparable to the 72% observed in colorectal cancer surgery. However, the overall nutrition compliance of 60.75% in our prehabilitation group during the first four-weeks after surgery is lower than the 91% observed in colorectal cancer surgery (Bousquet-Dion et al., 2018). This indicates that in our studied population, nutritional issues might have played an important role in the absence of differences between prehabilitation and rehabilitation groups post-surgery, unlike colorectal cancer patients (Gillis et al., 2014).

Our study has several strengths. First, the time between baseline and the preoperative assessment was not only similar between both groups, but also close to the four weeks we had wanted. Moreover, our study had a rehabilitation arm, which allowed the comparison of our outcome measures to those of a control group, thus minimizing the impact of confounding factors. Also, our groups were well matched at baseline both for demographic and clinical characteristics.

In light of our present discussion, we suggest that our study results be interpreted in view of several limitations. First, it is possible that we did not apply ideal randomization in the design stage of our research. Our results might have been diluted as a consequence of mixing together study populations with distinct pre- and postoperative clinical characteristics. Secondly, our study is not sufficiently powered to determine the impact of prehabilitation on the 6-minute walk test. As such, our preliminary results are intended to serve as a proof of concept prior to a larger randomized study that could perhaps confirm the results we have obtained here. Lastly, it is possible that during the preoperative period, our rehabilitation group participants sought out on their own to exercise, get psychological support and/or modify their diet after being informed of the potential benefits of our prehabilitation program during recruitment. We did observe an increase in self-reported moderate physical activity in the rehabilitation arm prior to surgery. However, it is unclear based on our currently analyzed data if diet and relaxation behaviors were also modified.

Conclusion

This study suggests that a trimodal prehabilitation program might be superior to a rehabilitation program in delivering meaningful changes in preoperative functional exercise capacity and in limiting decline of functional exercise capacity at four-weeks postoperative in hepatobiliary and pancreatic cancer surgery patients. A sufficiently powered block randomized design study could confirm the generalizability of our preliminary findings.

Chapter III

Concluding remarks

Conclusion

The objective of this thesis was to evaluate the impact of a trimodal prehabilitation program on functional exercise capacity in hepatobiliary and pancreatic cancer patients undergoing surgery. Our research provides novel insight on the ability of a four-week prehabilitation program to deliver meaningful changes in pre- and postoperative functional exercise capacity in this patient population. However, the pancreatic, gallbladder and bile duct resection participants were different from our liver resection participants, in terms of having received neoadjuvant chemotherapy or not prior to their first study visit, and in terms of surgical complications which resulted in significant differences in rehospitalization and compliance. A block randomized study design would have allowed a more equal distribution of groups within each diagnosis and could have led to more significant differences between and within groups.

Our preliminary results are intended to serve as a proof of concept prior to a larger randomized study that could confirm the results we have obtained here. Given that nutrition compliance in the first four weeks after surgery was particularly low in our studied population, more work needs to be done to evaluate whether or not our nutrition intervention needs to be modified given the severity of nutritional complications. We also demonstrated that our study's positive bias towards prehabilitation may have led to an accrued interest in exercise prior to surgery, whether the participant was randomized to prehabilitation or rehabilitation. As for relaxation, given that it was the intervention with the least compliance, it might not have played a major role in the improvements we observed in functional recovery. Consequently, a subsequent randomized trial should consider these elements to determine the most resource-efficient prehabilitation program for hepatobiliary and pancreatic cancer resection patients. If a larger randomized trial can confirm our results, prehabilitation could become part of standard care. Given the rising cases of cancer in the upcoming years, prehabilitation could potentially improve the quality of life of numerous hepatobiliary and pancreatic cancer patients who must face above average surgical complication rates and five-year survival rates that are less than 20% (Benson et al., 2009; Canadian Cancer Society, 2016).

Chapter IV

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Appendix A - Sample pages of aerobic and resistance training from booklet of exercises

week 1 before surgery

Aerobic Training

	SUN	MON	TUES	WED	THUR	FRI	SAT
Resting Heart Rate							
Type of Exercise							
Duration							
Exercise Heart Rate							
Perceived Effort (BORG scale)							
Post Exercise Heart Rate							
Pedometer : number of steps							

Dates ______________ to ______________
Target Heart Rate: ________________
% of Heart Rate Reserve: __________

Duration: ________________
Frequencey: _____________
Number of Steps: _________

Notes:

week 1 before surgery

Resistance Training

	SUN	MON	TUES	WED	THURS	FRI	SAT
Nutrition - Protein Powder							

Exercises	p.	SUN sets	SUN reps	MON sets	MON reps	TUES sets	TUES reps	WED sets	WED reps	THURS sets	THURS reps	FRI sets	FRI reps	SAT sets	SAT reps
Wall Push-Ups	17														
Modified Push-Ups	17														
Full Push-Ups	18														
Seated Row	18														
Chest	19														
Deltoids	19														
Biceps Curls	20														
Triceps Curls	20														
Chair Squats	21														
Touch Squats	21														
Hamstring Curls	22														
Standing Calf Raises	22														
Abdominal Crunches (chair)	23														
Abdominal Crunches (floor)	23														

Flexibility		SUN	MON	TUES	WED	THURS	FRI	SAT
Chest	24							
Biceps	24							
Triceps	25							
Quads	25							
Hamstrings	26							
Calfs	26							

Nutrition - Protein Powder							

Notes:

Appendix B - Compliance

Weekly phone follow-up Date:____________________

Participant: _________ Week: _____________

Nutrition

1. Are you taking the protein? Y / N
   a. If yes, how many pouches, when and how?
   ____
   b. If no, why?
   ____

2. How is your appetite?
   a. If poor, why? (GI distress, lack of energy, etc…)
   ____

3. Have you made any of the changes that the nutritionist recommended?
   a. If no, why?
   ____

4. Nutrition phone consult with dietitian required? Y / N

Nutrition compliance in the past week – based on consumption of protein powder

Compliance	Score out of 5
Daily, none missed	**5**
Missed one day	**4**
Missed 2-3 days	**2**
Missed > 3 days	**1**
Is taking only half the prescription (eg: 1 instead of 2 pouches)	**3**
Is not taking at all	**0**

Exercise

1. Are you walking every day? Y / N
   a. How long are you walking for (or how many steps)?
   ____

2. Are you doing the resistance exercises? Y / N
   b. How many reps/sets are you doing, how many times per week?___________________
   c. Any difficulty with the exercises?____

Exercise compliance in the past week

Compliance	Score out of 5
Daily, none missed (aerobic and resistance)	**5**
Only walking	**3**
Only resistance/flexibility	**3**
Missed > 3 days	**1**
Walking < 4 days	**2**
Walking 4 days, resistance 3 days per week	**4**
None	**0**

Relaxation techniques

1. Since meeting with the psychologist, have you listened to the CD or have you gone online at least once? Y / N
2. What has gotten in the way of practicing?

____

____

Relaxation compliance in the past week

Compliance	Score out of 5
Have you practiced once	**2**
Have you not practiced at all	**0**
Have you practiced twice	**3**
Have you practiced three times	**4**
More than three times?	**5**
Started once, but did not complete	**1**

Do you have a surgery date yet? If yes, when?______________________

Appendix C - Community Healthy Activities Model Program for Seniors - Surgical Version

Surgical Physical Activity Questionnaire (CHAMPS-S)

:______________________________

Note: If not done fill in: 0

	During the past week, how many TOTAL hours a week did you	Hours a week?	
1	Do light work around the house (such as sweeping, vacuuming,work on your car or other machinery) or light gardening (such as watering plants)?	..........(hrs)	
2	Do heavy work around the house (such as washing windows, cleaning gutters) or garden (such as spading, raking)?	..........(hrs)	
3	Use a computer and/or read(book, newspaper ect…) ?	..........(hrs)	
	Walking, Running, Jogging.. (include the use of Treadmill).		
4	Jog or run; walk uphill, or hike uphill(count uphill part only)?	..........(hrs)	
5	Walk fast or briskly for exercise (do not count walk leisurely or uphill)?	..........(hrs)	
6	Walk leisurely or walk to do errands (such as to/from store or take children to school, count walk time only)?	..........(hrs)	
	Dancing, Aerobic Dancing, Aerobic Machines		
7	Dance (such as square, folk, line, ballroom)?	..........(hrs)	
8	Do aerobics or aerobic dancing?	..........(hrs)	
9	Ride a bicycle or stationary bike?	..........(hrs)	
10	Do other aerobic machine such as rowing or stepping machines (do not count treadmill or stationary cycle ?	..........(hrs)	
	Play musical instrument - if Yes what:...............(eg.guitar, piano, drums)..	..........(hrs)	
	Strength training, stretching and flexibility		
11	Moderate to heavy hand-held weights of more than 5 lbs., weight machines, or push-ups?	..........(hrs)	
12	Light strength training (such as hand-held weights of 5 lbs. or less or elastic bands?	..........(hrs)	
13	Do stretching or flexibility exercises, Yoga or Tai-chi?	..........(hrs)	
	Water exercises and swimming..		
14	Swim moderately or fast?	..........(hrs)	
15	Swim gently?	..........(hrs)	
16	Do water exercises (do not count other swimming)?	..........(hrs)	
	Sports (circle the sport you played)		
17	Basketball Single tennis Downhill Ski Soccer Double tennis Hockey Other	..........(hrs)	
	Other (including physical activity done at work)		
18	Other types of physical activity not previously mentioned (please specify)?...	..........(hrs)	