# Diet and Exercise Interventions in Patients with Pancreatic Cancer: Effect on Health-related Quality of Life

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A Thesis

In the Department

of

Health, Kinesiology and Applied Physiology

Presented in Partial Fulfillment of the

Requirements For the Degree of

Doctor of Philosophy (Health and Exercise Science)

at Concordia University

Montreal, Quebec, Canada

March 2023

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**CONCORDIA UNIVERSITY**
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Doctor Of Philosophy (Health and Exercise Science)

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## Abstract

Diet and exercise interventions in patients with pancreatic cancer:

Effect on health-related quality of life

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Concordia University, 2023

Pancreatic cancer is a deadly disease with few curative treatment options. Therefore, preserving health-related quality of life (HRQoL) is significant. Factors that may negatively affect HRQoL include malnutrition and muscle wasting, which are prevalent in patients with pancreatic cancer. However, little is known regarding the role of diet and exercise interventions in maintaining HRQoL. A scoping review of the literature was performed to identify what is already known, and the research gaps that remain, surrounding diet and exercise interventions in patients with pancreatic cancer (Chapter 3). Studies (n=62) were heterogenous in the types of interventions investigated and the main outcomes studied. Seven research gaps were identified to guide the design of future studies. In response to the research gaps presented, Chapters 4 and 5 explored HRQoL outcomes in patients undergoing multimodal prehabilitation (prehab) prior to hepato-pancreato-biliary (HPB) surgery. Prehab included a diet, exercise and relaxation intervention that began 4 weeks prior to surgery. A control group (rehab) was observed for the 4-week preoperative period and began the same program right after surgery; both groups were followed for 8 weeks postoperatively. Chapter 4 explored associations between HRQoL and nutritional status, physical strength/function, muscle mass and cancer symptoms in the subset of patients awaiting pancreatic resection. There were strong, negative relationships between cancer

symptoms (r=-0.832) and malnutrition (r=-0.697, p<0.001) at baseline, but not with physical strength/function or body composition. There was no difference in HRQoL outcomes between prehab or rehab over the study period. However, both groups achieved baseline HRQoL levels at 8-weeks postoperatively, quicker than the expected 3 to 6 months. Chapter 5 outlined the effectiveness of dietary counselling to meet protein recommendations and relationships between nutritional status and HRQoL in patients awaiting HPB surgery. In the preoperative period prehab, but not rehab, significantly increased protein intake (+0.3±0.1 g/kg, p<0.001). Additionally, nutritional status was negatively associated with HRQoL only in those who did not experience a minimally important HRQoL improvement (β:-2.83, p<0.001). This dissertation demonstrates a positive effect on HRQoL from diet and exercise interventions in patients awaiting pancreatic resection. Future research directions arising from this study are explored in Chapter 6.

**Acknowledgments**

This work would not have been possible without the support of the following people:

Dr. Robert Kilgour: A supervisor like no other! Always available to help, provide constructive feedback, push me to improve my understanding of research methods, exercise physiology, statistics and overall reasoning. A wonderful mentor, colleague, psychologist, co-conspirator and friend.

Dr. Antonio Vigano: Everything I know about supportive care in cancer, I owe to you. My passion for treating patients with cancer, for interdisciplinary team interventions and for cancer rehabilitation is from watching how you treat patients. Your mentorship has been significant, and I will carry all I have learned with me in my future endeavours.

My committee: Dr. Plourde, my choice to research HRQoL outcomes in patients with pancreatic cancer is all because you once told me, while I was rambling on about muscle mass, “Yes, but what is important to patients?” I think of those words often, both in my research and clinical practice. I am forever grateful. Dr. Cohen, you are my ideal of what a nutrition researcher should be. An amazingly prolific researcher, and a clinician with an incredibly empathetic bedside manner, who I have been privileged to observed and learn from. I consider myself very lucky to have you both as mentors. I am grateful for your belief in me, even when I doubted myself. Thank you for all of the support and for making me a better researcher.

Tram Bui: What a ride! We lived through the COVID shutdown, the navigation of participants through the system as they waited for surgery and the trials and tribulations of recruiting such a challenging patient population. I learned so much from you and admire your work ethic and vast knowledge of restaurants in Montreal. As you complete your own PhD journey, I will be rooting for you, knowing you will excel and achieve all your goals.

My colleagues in the Cancer Rehabilitation Program: I am truly grateful for how supportive you have all been while I pulled my hair out completing this PhD. You were there during my highs and lows, and treated study patients I thought would benefit from further rehabilitation postoperatively without question. I will always be grateful and owe you many cups of Greek coffee.

To my family: Zoe and Adrien, you are my heart and soul. Thank you for supporting me and allowing me to pursue this crazy dream.

To our study participants and family members: Thank you so much for participating in our study during an extremely difficult time. You are not all still among us, but I remember every single one of you. If our prehabilitation program was able to improve your health-related quality of life even in the most minute fashion, I feel eternally grateful.

## Contribution of Authors

Manuscript 1:

Popi Kasvis created the scoping review question, search strategy and inclusion and exclusion criteria for chosen studies, under the guidance of Dr. Robert Kilgour. Popi Kasvis performed the search and extraction of all articles. Both Popi Kasvis and Dr. Kilgour independently screened the articles for eligibility and came to a consensus through discussion when there was disagreement. Popi Kasvis wrote the first draft and all subsequent edits of the manuscript. Dr. Kilgour provided feedback and edits on the manuscript.

Manuscripts 2 and 3:

Popi Kasvis was the study coordinator involved in patient recruitment and scheduling, helped develop the prehabilitation program, and was responsible for the study's ethics approval and renewal with the McGill University Health Centre Research Ethics Board. She was responsible for study tool development (data collection sheets, diet teaching materials), and choosing relevant questionnaires. Additionally, Popi Kasvis provided nutritional counselling to patients, aided in procuring all study measurements (including questionnaires, strength/function tests, 3-day food diaries, anthropometry and body composition measurements). She was responsible for data entry (including all the dietary data) and auditing. Finally, Popi Kasvis was the primary author on both manuscripts, wrote the first drafts and all subsequent edits and performed all statistical analyses.

Dr. Antonio Vigano was the primary investigator and study doctor for this work that took place at the McGill University Health Centre. Dr. Vigano was involved in the development of the prehabilitation program. Dr. Vigano approved all study forms and provided feedback and edits for the manuscripts.

Tram Bui was the research assistant for the study and was involved in patient recruitment, scheduling, providing exercise training to patients and aided in procuring all study measurements (including questionnaires, strength/function tests, anthropometry and body composition measurements). Tram Bui audited all collected data entered into our database to ensure accuracy and provided feedback and edits for the manuscripts.

Dr. Franco Carli was involved in the development of the prehabilitation program. Dr. Carli provided feedback and edits for the manuscripts.

Dr. Robert Kilgour was involved in the development of the prehabilitation program and was the primary investigator for the manuscripts. Dr. Kilgour provided feedback and edits for the manuscripts.

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**List of Abbreviations**

| | |
|---|---|
| AHCC | Active hexose correlated compound |
| aPG-SGA | Abridged Patient-Generated Subjective Global Assessment |
| ASMI | Appendicular Skeletal Muscle Mass Index |
| BMI | Body mass index |
| CI | Confidence interval |
| CT | Computerized tomography |
| EAA | Essential amino acids |
| ECOG-PS | Eastern Cooperative Oncology Group performance status |
| EORTC-QLQ | European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire |
| EPA | Eicosapentaenoic acid |
| ERAS | Enhanced Recovery After Surgery |
| ESAS | Revised Edmonton Symptom Assessment System |
| EWB | Emotional Wellbeing |
| FAACT | Functional Assessment of Anorexia-Cachexia Therapy |
| FACT-G | Functional Assessment of Cancer Therapy-General |
| FACT-Hep | Functional Assessment of Cancer Therapy-Hepatobiliary |
| FITT | Frequency, intensity, time, type |
| FOLFIRINOX | Folinic acid, fluorouracil, irinotecan, oxaliplatin |
| FWB | Functional Wellbeing |
| HGS | Handgrip strength |
| HPB | Hepato-pancreato-biliary |

| | |
|---|---|
| HRQoL | Health-related quality of life |
| MID | Minimally important difference |
| MNUPAL | McGill Nutrition and Performance Laboratory |
| mTORC1 | Mammalian target of rapamycin complex 1 |
| MUHC | McGill University Health Centre |
| Nab | Nanoparticle albumin-bound |
| ONS | Oral nutritional supplement |
| Prehab | Prehabilitation |
| PREPARE | Prehabilitation for palliative pancreatic cancer study |
| PRISMA-ScR | Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews |
| PEI | Pancreatic exocrine insufficiency |
| PERT | Pancreatic enzyme replacement therapy |
| pNET | Pancreatic neuroendocrine tumour |
| PRO | Patient-reported outcomes |
| PWB | Physical wellbeing |
| QoL | Quality of life |
| RD | Registered dietitian |
| Rehab | Rehabilitation |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | 36-item short-form survey |
| SWB | Social wellbeing |

| | |
|---|---|
| TOI | Trial outcome index |
| USFDA | United States Food and Drug Administration |
| WLGS | Weight loss grading scale |

# Chapter 1: Introduction

Pancreatic cancer is the 11th most commonly diagnosed cancer in Canada (1) and the 12th most common worldwide (2). However, 2022 projections rate it as third deadliest due to minimal advancements in both early detection and treatment options (1). Pancreatic adenocarcinoma in its early stage has nonspecific and vague symptoms. It is only in more advanced stages of the disease that patients will present with jaundice, weight loss/cachexia, hepatomegaly, epigastric/back pain, nausea/vomiting and/or diarrhea/steatorrhea (3). At present, screening for pancreatic cancer is limited to high-risk individuals with genetic predisposition, accounting for 10-15% of diagnosed adenocarcinomas (4). Recently, more attention has been given to include screening among adults 50 years and over with new-onset diabetes (diagnosis < 3 years), as associations with the development of pancreatic cancer have been made in this group (5). Given the vague symptoms in early disease and the limited use of screening, diagnosis is frequently made once the tumor is unresectable; only 15-20% of patients are able to receive potentially curative surgery (6). Even with surgical resection, 5-year survival rates remain dismal at 10-25% (6).

The most common technique used in the diagnosis and staging of pancreatic cancer is computerized tomography (CT) (7). In the few patients where diagnosis via CT is unclear, a staging laparoscopy, in conjunction with serum tumor markers such as carbohydrate antigen 19-9, are utilized (7). Once the absence of advanced disease or metastasis is confirmed, and adequate assessment of surgical risk is completed, potentially curative surgery can be performed. Very simply, surgical interventions are determined based on the location of the tumor, and include: 1) pancreaticoduodenectomy (Whipple procedure) for tumours in the head of the

pancreas, 2) distal pancreatectomy for tumours in the tail of the pancreas, and 3) total pancreatectomy (7). Along with pancreatic resection, other organs may also be removed during these surgeries. For example, resection of the duodenum, gastric bulb (pylorus), gallbladder and bile duct, in addition to lymphadenectomy, may be performed as part of the Whipple procedure, while the spleen may be removed in distal or total pancreatectomy (8, 9). Additionally, blood vessels such as the superior mesenteric and portal veins, as well as the superior mesenteric artery, may be dissected depending on tumour involvement/invasion (7). As such, these surgeries, and in particular the Whipple procedure, are complex. A recent review and meta-analysis found a strong association between hospital centres with high patient volume and less postoperative mortality, morbidity and successful achievement of clear margins, compared to centres with very low or low volumes (10).

Unfortunately, most patients are diagnosed with metastatic or locally advanced pancreatic cancer, for which either neoadjuvant or palliative chemotherapy is recommended. The latest American Society of Clinical Oncology guidelines (11) for palliative, first line treatment of pancreatic cancer are as follows:

1. Folinic acid + fluorouracil + irinotecan + oxaliplatin (FOLFIRINOX) for those with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-1 (no to mild performance status deficit),
2. Gemcitabine + nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in those with ECOG-PS 0-1,
3. Gemcitabine monotherapy in those with an ECOG-PS of 2 (moderate deficit in performance status). The addition of nab-paclitaxel or capecitabine or erlotinib may be considered with close monitoring and adjustment of dose/schedule to minimize toxicities.

In patients with a ECOG-PS of 3 (poor performance status), there is no particular treatment recommendation, with decisions made on a case-by-case basis and with a focus on offering best supportive care (11). In all cases, the decision to begin palliative chemotherapy should be based on a review of comorbidity burden, patient preference and access to support given the aggressiveness of certain treatments (11).

Due to the tumour location, type of surgery and/or systemic chemotherapy, patients with pancreatic cancer suffer from many symptoms that have a negative effect on HRQoL, including: pain, insomnia, nausea and vomiting, as well as malnutrition and deconditioning related to cachexia and sarcopenia (12, 13). In patients with resectable pancreatic cancer, fatigue, insomnia, anorexia, trouble digesting food, weight loss, and abdominal pain/cramping are frequently reported both in the pre- and postoperative period (14). It is currently unclear whether interventions that aim to counter malnutrition, muscle loss and reduce symptom burden, are effective in improving HRQoL in patients with pancreatic cancer. Although early referral to palliative care has been deemed important for symptom management and HRQoL (15), rates of referral remain low, especially among surgical candidates (16). It is possible that referral to a prehabilitation program may be more palatable to patients awaiting pancreatic resection with curative intent. Prehabilitation refers to interventions that optimize the physical, nutritional and/or psychological status of patients prior to surgery, in order to hasten return to baseline levels, reduce post-operative complications and length of hospital stay (17). Prehabilitation interventions may include exercise, nutritional counselling and psychological counselling, individually or in tandem (18). Through these interventions, it is feasible that prehabilitation may improve HRQoL by reducing the symptom burden of pancreatic cancer. At present, little is known regarding the effect of diet and exercise on HRQoL in patients both awaiting surgery for

pancreatic cancer and in the postoperative period. Additionally, relationships between function, strength, body composition, nutritional status, cancer symptoms and HRQoL among surgical candidates have not been clearly elucidated. Given the poor prognosis of pancreatic cancer, the maintenance of HRQoL should be of prime concern for healthcare workers involved in the care of these patients. Exploring the effectiveness of diet and exercise interventions to improve the HRQoL of patients with pancreatic cancer can potentially provide clinicians with tools to improve patient care.

### 1.1. Rationale for this thesis

The negative effect of a pancreatic cancer diagnosis on HRQoL is well understood. However, it is unclear how diet and exercise interventions targeting cancer symptoms, malnutrition and muscle wasting may help maintain and/or improve HRQoL in patients with pancreatic cancer. Understanding the determinants of poor HRQoL and the types of interventions that contribute to improvements is primordial, given the importance of HRQoL outcomes in both clinical trials and as a priority for patients. Providing evidence for interventions that improve HRQoL should be of great interest to clinicians, as opportunities to offer curative treatments are limited.

### 1.2. Study objectives and hypotheses

The purpose of this dissertation is to: 1) review the literature and determine research gaps in diet and exercise interventions previously studied in patients with pancreatic cancer, 2) understand the role of a diet and exercise intervention, offered within a prehabilitation program, on HRQoL outcomes in patients with pancreatic cancer awaiting surgery, and 3) assess the

effectiveness of dietary counselling, and how diet and nutritional status impact HRQoL, in patients participating in a prehabilitation program while awaiting hepato-pancreato-biliary (HPB) resection.

Objective 1: Scoping review (Manuscript 1)

The purpose of the scoping review was to assess the current state of knowledge, and to identify research gaps, in diet and/or exercise interventions previously investigated in ambulatory patients with pancreatic cancer. The results of the scoping review reported in manuscript 1 may help inform the design of novel interventions.

Objective 2: The effect of prehabilitation on HRQoL (Manuscript 2)

The aim of this study was to determine the effect of a trimodal prehabilitation program (exercise, diet, relaxation intervention) on the HRQoL of patients with pancreatic cancer awaiting resection, in the both the pre- and postoperative period. Additionally, relationships between HRQoL and anthropometry, body composition, physical strength/function, cancer symptoms, cancer-related fatigue, anxiety, depression and nutritional status were also explored.

Hypotheses: Patients undergoing prehabilitation prior to surgery will have better HRQoL outcomes than patients who received the same intervention, but only in the postoperative period. Negative relationships between HRQoL and nutritional status, body composition and physical/functional status will be observed.

Objective 3: The effect of dietary interventions on HRQoL in patients awaiting HPB surgery (Manuscript 3)

There were two distinct purposes of this study: 1) to understand if nutritional counselling by a registered dietitian (RD), as part of a trimodal prehabilitation program, could achieve preoperative dietary protein intake goals in patients awaiting HPB surgery, and 2) to establish the baseline nutritional status of this cohort and to determine relationships with HRQoL.

Hypotheses: 1) RD-led nutritional counselling will lead to patients meeting protein intake goals over the study period, 2) low BMI, muscle mass, handgrip strength, and malnutrition will be predictive of poor HRQoL in patients awaiting HPB resection, and 3) there will be differences in HRQoL over the study period between those who received prehabilitation (prehab), which included diet and exercise interventions, 4 weeks prior to surgery, and a control group (rehab), who received the same intervention, but only after surgery.

The following literature review will provide background and elucidate the rationale for the hypotheses stated above. This review will present the concept of HRQoL, its definition and importance in studies involving patients with cancer. Additionally, the review will address what is currently known regarding diet and exercise interventions in patients with pancreatic cancer and the effect on HRQoL, as well as the growing role of prehabilitation in surgical cancer care. This review will provide credence to the research questions posed in this dissertation and will identify some knowledge gaps in the literature.

# Chapter 2: Literature review

## 2.1. HRQoL definition

Agreement on a concrete definition of HRQoL remains elusive. However, there seems to be consensus on a conceptual framework; it is agreed that HRQoL is multidimensional, and includes physical, emotional/psychological and social domains as its main pillars (19, 20). In 1990, Aaronson also included disease and treatment symptoms, as particularly important factors affecting the quality of life of patients with cancer (21). Perceived HRQoL is subjective; an individual's impression of their health can have a negative impact on HRQoL domains (22). In 2006, the United States Food and Drug Administration (USFDA) provided guidance on the use of patient-reported outcomes (PRO), and particularly measures of HRQoL, in clinical trials. The addition of PROs to drug trials would help support cancer drug label claims. In order to clarify the meaning of HRQoL, the USFDA offered the following definition:

> "A multidomain concept that represents the patient's overall perception of the impact of an illness and its treatment. A HRQoL measure captures, at a minimum, physical, psychological (including emotional and cognitive), and social functioning (23)."

## 2.2. A history of HRQoL measurement in oncology

The increasing prioritization of HRQoL measurement in cancer care is a fairly recent phenomenon; it is only since the early 1980s that the consideration of patient HRQoL, and not only cure and the extension of life at all costs, gained traction (24). This was the result of a stagnation in the development of life-prolonging treatments at the time; new therapies of that era were not offering positive survival outcomes (25). Instruments used to measure HRQoL were

originally developed for chronic disease and not specific to cancer. As such, the tools were generic in nature, possibly missing symptoms and problems important to individuals with cancer. This led to possible error in understanding measured HRQoL in patients with cancer, and the development of cancer specific tools (24).

HRQoL is a subset of PROs, as it is a subjective perception of the effect of disease and treatment on an individual's overall wellbeing. As mentioned previously, PROs including HRQoL, are now widely recognized by pharmaceutical regulatory agencies, such as the USFDA and the European Medicines Agency, as an important endpoint in clinical trials (23, 26). Although PROs and HRQoL are reported more frequently in cancer drug trials, measuring HRQoL remains difficult due in part to inconsistent reporting, questions regarding the quality of data (e.g., incomplete data due to incomplete survey or missing timepoints) and the perception of data as unreliable due to subjective nature of the HRQoL measures (20). Despite these limitations, much work has been accomplished in developing valid and reliable tools to measure cancer-specific HRQoL; asking enough questions to ensure reliability with the lowest burden to patients, and asking precise questions to ensure validity, have been hallmarks in tool development (24).

### 2.3. HRQoL measurement tools

There are two main HRQoL measurement tools used in cancer research: 1) the European Organization for Research and Treatment in Cancer-Quality of Life Questionnaire (EORTC QLQ) and the Functional Assessment of Cancer Therapy-General (FACT-G). Both tools offer a core HRQoL questionnaire, to which disease, population or symptom-specific modular options can be added on. The following provides specifics related to each tool.

2.3.1. EORTC QLQ-C30

The EORTC QLQ-C30 (core 30) (Appendix 1) questionnaire includes 30 questions for the subjective assessment of HRQoL over the past week (27). Questions provide information covering the following domains: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), individual symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea and perceived financial difficulties), and a global health and QoL (quality of life) status scale (28). The first 28 questions are answered using a four-point Likert scale (not at all, a little, quite a bit, very much); the last two questions, assessing the perception of health and QoL, are scored on a numerical scale ranging for 0 (very poor) to 7 (excellent) (29). A higher score on each item/scale indicates a corresponding high response; therefore, a higher score on a functional, global health or QoL scale represents a high/healthy level of function, global health and QoL, whereas a high score for each individual symptom or scale represents greater symptom burden (29).

Modules specific to a disease, population or treatment-specific problems (e.g., breast cancer, elderly cancer patients, chemotherapy-induced peripheral neuropathy, etc…) can be added to the EORTC QLQ-C30 in order to broaden its ability to measure various problems that may affect HRQoL (28). The validation of these modules is sometimes lengthy, especially in the context of constant development of new cancer treatments, or in rare cancers where too few patients are available to test these tools (28). Therefore, a flexible item list has been developed, whereby researchers can choose individual questions assessing symptoms or issues not included in the core questionnaire or validated modules, that are relevant to the research question posed (28). The EORTC QLQ-C30 is valid and reliable in patients with cancer (27). At present, there

are two modules undergoing validation available for patients with pancreatic cancer: The QLQ-PAN26 and, specifically for pancreatic neuroendocrine tumours, the pNET. Phase III of development has been completed for both modules; testing of psychometric properties among a large, international patient population has not yet been completed (30).

### 2.3.2. FACT-G

The FACT-G is a core, cancer specific, HRQoL questionnaire containing 27 questions that cover four distinct domains of HRQoL: physical wellbeing, social/family wellbeing, emotional wellbeing and functional wellbeing (31) (Appendix 2). Analysis of HRQoL can be performed on all domains individually as subscales, in addition to the total FACT-G score. All FACT-G questions are answered using a five-point Likert scale (not at all, a little bit, somewhat, quite a bit, very much), allowing individuals to report their perceived experience of a symptom/problem over the past seven days. For all subscales and for the total FACT-G score, a higher score denotes better HRQoL (31).

Similar to the EORTC QLQ-C30, there are extensions to the core FACT-G questionnaire that help assess HRQoL specific to diagnosis, symptoms and/or treatments. Additionally, extensions are available that are not specific, but relevant to patients with cancer, including: financial toxicity, palliative care, spiritual wellbeing, and satisfaction with care (32). Also similar to the EORTC QLQ-C30, a searchable library of various individual symptoms/problems that may affect HRQoL was released in 2018 for the creation of custom questionnaires, added to the FACT-G, addressing only what is relevant to a study's outcome (33). The core FACT-G questionnaire is valid and reliable in patients with cancer (31). The FACT-Hepatobiliary (FACT-Hep) questionnaire allows for the assessment of additional concerns specific to patients with

hepatobiliary or pancreatic cancers (Appendix 3). The FACT-Hep is a sensitive and reliable tool with published minimally important differences (MID) to help understand the meaningfulness of changes over time (34, 35). Finally, the FACT-Hep offers the possibility of calculating a trial outcome index (TOI) score, which is the sum of the physical wellbeing, functional wellbeing and hepatobiliary additional concerns subscale scores (34). The TOI is commonly used to evaluate change in physical/functional status; using the TOI is advantageous since the total FACT-Hep score includes social and emotional wellbeing domains not likely to change as quickly over time as the domains in the TOI (36).

#### 2.3.3. EORTC QLQ-C30 versus FACT-G: which one is superior?

In 2011, Luckett et al. (37) performed a literature review to compare the psychometric properties of the EORTC QLQ-C30 and the FACT-G. The authors found no decisive evidence to recommend one tool over the other for global HRQoL scores. The recommendation from the review is that the HRQoL tool chosen for a study should be dependent on the outcomes sought, as there are differences in the tone of the tools, the social domains explored and the structure of each scale (37). Luckett et al. suggested that if the social domain of HRQoL is of interest, and outcomes such as the impact of health on the ability to engage in social activities are being studied, the EORTC QLQ-C30 should be chosen. Whereas, the FACT-G is a better measure of relationships and support within the social/family wellbeing scale (37). King et al. (38) also suggested that the EORTC QLQ-C30 responds to changes in social domains more efficiently than FACT-G. However, change in the FACT-G global score responds better to change over time than the EORTC QLQ-C30. Both King and Luckett reported that sample size using the FACT-G could be smaller, as total HRQoL score is calculated using all 27 questions rather than

a the two global HRQoL questions in the EORTC QLQ-C30. The use of all questions FACT-G leads to a smaller standard deviation compared to that of the two questions used in the EORTC QLQ-C30; King et al. estimate that 5 times fewer participants are required when using the FACT-G (38).

## 2.4. Predictors of HRQoL in patients undergoing cancer treatment

Many studies have attempted to determine relationships between symptoms and/or problems affecting the physical/functional, psychological and social domains in patients with cancer and their overall HRQoL. There is a great variation based on stage of the disease, tumour location, whether treatment is being received, age, sex and various socio-economic factors (e.g., financial toxicity, having a partner). The following will give an overview of some studies that have examined relationships between HRQoL and cancer symptoms, nutritional status, body composition (specifically muscle mass) and physical strength, all relevant to the present dissertation.

### 2.4.1. Cancer symptoms

The detrimental effect of cancer symptoms on HRQoL can be intuitively understood and is corroborated in the literature. Diplock et al. (39) reported on a heterogenous group of patients with cancer attending an outpatient oncology clinic. Patients completed the Edmonton Symptom Assessment System Questionnaire (ESAS) to determine cancer symptom burden and the EORTC QLQ-C30 to measure HRQoL. ESAS is a nine-question tool used to determine the severity of the following common cancer symptoms: pain, nausea, tiredness, anxiety, depression, sleepiness, lack of appetite, wellbeing and shortness of breath (40, 41). A numerical scale is used for each

question allowing patients to rate their current experience of a given symptom; a score of 0 denotes the lack of a symptom, and 10 indicates the worst experience of the symptom. The total ESAS score indicates overall cancer symptom burden (41). ESAS total score was strongly correlated with global health ($r=-0.61$, $p<0.0001$), and emotional function ($r=-0.62$, $p<0.0001$). Regression analysis demonstrated that with every one unit increase in ESAS total score, a 0.91 decrease in global health, 0.64 decrease in physical functioning, 0.71 decrease in role functioning, 0.99 decrease in emotional functioning, 0.73 decrease in cognitive functioning and 0.92 decrease in social functioning (all $p<0.05$) was found (39).

The deleterious effect of cancer symptom burden on HRQoL was corroborated in a study of 76 patients with lung cancer undergoing treatment (42). For every one unit increase in total ESAS score, a decline of 0.83 (standard error (SE): ±0.13, $p<0.001$) was observed in overall HRQoL as measured by the EORTC QLQ-C30. Pain (-2.67±0.81 $p<0.001$) and tiredness (-3.16±0.75, $p<0.01$) were the ESAS symptoms that independently predicted worsening HRQoL in this patient population.

An interesting study by Tagami et al. (43) et al. demonstrated how achieving personalized symptom goals has a positive effect on HRQoL. A heterogeneous group of 140 patients with cancer first reported their personalized symptom goal by choosing the number between 0 and 10 that indicated their highest level of tolerance for each of the 6 ESAS physical symptoms (pain, nausea, tiredness, sleepiness, lack of appetite and shortness of breath). HRQoL was measured using the FACT-G. Results demonstrated that patients who achieved their personalized symptom goal for pain, tiredness, lack of appetite and shortness of breath had significantly better FACT-G scores than those who did not. An individual's perception of relief

from symptoms is variable, thus affecting HRQoL differently, a concept that may be lost in clinical practice where a score of ≤3 on ESAS indicates low symptom burden (44).

### 2.4.2. Nutritional status

Poor nutritional status in patients with cancer has a negative effect on HRQoL. In a study by Daly et al. (45), relationships between the grade of weight loss and HRQoL were explored among a heterogeneous group of 1027 patients with cancer. Table 2.1. shows the body mass index (BMI)-adjusted weight loss grading system (WLGS) as developed by Martin et al. (46). Briefly, the WLGS assigns severity to cancer-related weight loss based on the % body weight lost and BMI; a grade from 0 to 4 is assigned, with 4 describing the most severe weight loss. When EORTC QLQ-C30 scores of patients among the 5 WLGS grades were compared, significant differences were observed between grade 0 and 4 for role functioning (median: 83 versus 41.6, $p<0.001$) and physical functioning (median: 80 versus 60, $p<0.001$). Median scores differed between WLGS grade 0 and 4 for appetite loss, pain, dyspnea, insomnia (all: 0 versus 33.3, $p<0.001$), and fatigue (33.3 versus 56, $p<0.001$); differences were both statistically and clinically meaningful, as indicated by a difference of > 20 points. There were no significant associations with HRQoL at WLGS grade 0 and 1. However, the odds of a negative effect on overall HRQoL score increased as the WLGS grade increased (grade 2: 1.69 (95%CI: 1.04-2.73), $p<0.05$; grade 3: 2.06 (95%CI: 1.37-3.11), $p=0.001$; grade 4: 4.29 (95%CI: 2.44-7.55), $p<0.001$).

Table 2.1.: BMI-adjusted weight loss grading system (46)

| | Body mass index (kg/m$^2$) | | | | |
|---|---|---|---|---|---|
| Weight loss (%) | ≥ 28 | 25 to <28 | 22 to <25 | 20 to <22 | <20 |
| <2.5 | 0 | 0 | 1 | 1 | 3 |
| 2.5 to <6 | 1 | 2 | 2 | 2 | 3 |
| 6 to <11 | 2 | 3 | 3 | 3 | 4 |
| 11 to <15 | 3 | 3 | 3 | 4 | 4 |
| ≥15 | 3 | 4 | 4 | 4 | 4 |

Another large study by de Oliveira et al. (47) identified the nutrition risk of 1039 patients, referred to a specialized palliative care unit (both in- and outpatients), to determine associations with HRQoL. The authors utilized the abridged Patient-generated Subjective Global Assessment (aPG-SGA) to determine nutrition risk; the tool is comprised of 4 boxes that evaluate the following: 1) weight loss, 2) food intake, 3) symptoms, 4) activities and functioning (48). Patients with an aPG-SGA score ≥9 were deemed at nutrition risk. Associations between the EORTC QLQ-C15-PAL (a 15-item palliative care module) and nutrition risk were robust; all functional domains (physical and emotional), symptoms (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation) and overall HRQoL were significantly associated with being at nutrition risk and indicated worse HRQoL.

The relationship between weight loss and HRQoL was corroborated in a systematic review; 23 out of 27 studies reported a negative effect of weight loss on HRQoL (49). The authors of the review called this finding unsurprising, as weight loss leads to muscle wasting in the context of cancer cachexia, and leads to cancer-related fatigue and a decrease in objectively measured functional capacity (49). The relationship between muscle, strength and HRQoL will be examined further in the following section.

2.4.3. Muscle mass and strength

Deficits in muscle strength and mass combined are part of the criteria leading to a diagnosis of sarcopenia, with physical function determining the severity of sarcopenia (50). For the purposes of this dissertation, muscle mass and strength will be examined separately, as there is much inconsistency in the literature that often uses the word sarcopenia to define low muscle mass, and few studies that examine all three components of sarcopenia together.

Two studies demonstrate associations between low muscle mass and poor HRQoL. In a large study of 734 patients with advanced non-small cell lung cancer, Bye et al. (51) demonstrated that EORTC QLQ-C30 physical and role function were negatively associated with skeletal muscle mass index, determined by CT scan at the level of lumbar 3, in both males and females. However, low skeletal muscle mass index was only associated with poor global HRQoL in males. Similarly, fatigue was associated with low skeletal muscle mass index only in males (51). Nipp et al. also demonstrated the predictive nature of muscle mass on HRQoL. In a heterogeneous cohort of 237 patients receiving palliative anticancer treatment, skeletal muscle cross-sectional area was measured using CT at the level of lumbar 3, and HRQoL measured using the FACT-G. Low muscle mass was associated with poor HRQoL [$\beta$=-4.26 (95%CI: -8.49 to -0.03), $p<0.05$] (52).

Handgrip dynamometry is a commonly used measure of strength in patients with cancer, due to its ease of use in the clinical arena. There are several studies that have explored handgrip strength (HGS) as a possible determinant of HRQoL. However, associations between HGS and HRQoL are inconsistent. For example, van Heinsebergen et al. (53) measured the HGS of 295 patients with colorectal cancer just before surgery. Six weeks postoperatively, patients completed the EORTC QLQ-C30 along with the QLQ-CR29 (a colorectal cancer-specific module). No

significant associations were found between preoperative HGS and any of the domains, symptoms or global QoL in the EORTC QLQ-C30. Only the symptom of fecal incontinence from the QLQ-CR29 was significant [β=-9.50 (95% CI:-18.32 to -0.68), $p<0.05$] (53). However, in a group of 163 patients with breast cancer undergoing active treatment, negative associations were found between HGS and EORTC QLQ-C30 physical, role, emotional, cognitive and social function (54). Additionally, worse symptoms of fatigue, pain, insomnia and appetite were associated with poor HGS (54). Of course, the inconsistent results between these two studies are multifactorial, and include examining different cancer types, different treatment modalities, and measures taken at different time points during the cancer trajectory.

While some evidence points to how cancer symptoms, nutritional status, muscle mass and strength may play a role in predicting poor HRQoL in patients with a multitude of cancers at different stages, it is unclear whether the same predictors of HRQoL are relevant to patients with pancreatic cancer. The following section will explore predictors of HRQoL in patients with pancreatic cancer.

### 2.5. Predictors of HRQoL in pancreatic cancer

Specific predictors of HRQoL in patients with pancreatic cancer are not well studied. In patients with advanced pancreatic cancer, HRQoL is less than that of healthy populations at diagnosis, but improves once palliative chemotherapy treatments begin (55). Among surgical patients, who are the focus of this dissertation, two recent reviews of the literature have reported that a decline in HRQoL occurs following surgical resection, and seems to recover to baseline levels 3 to 6 months postoperatively (56, 57). Understanding why this deterioration in HRQoL occurs may lead to pre-emptive interventions to mitigate this decline.

2.5.1. Cancer symptoms

Patients with pancreatic cancer experience many symptoms that may have a negative effect on HRQoL. A review of the literature by Bauer et al. (58) attempted to characterize HRQoL of patients with pancreatic cancer. The authors included 36 studies in the review, and reported the prevalence of symptoms found in patients with pancreatic cancer. For example, moderate to severe pain ranged from 30-37% of patients, and fatigue from 38-63%. The prevalence of many nutrition symptoms were also described, including: weight loss or cachexia (23-72%), indigestion nausea (8-56%), changes in bowel movements (11-17%) and xerostomia (42-50%) (58).

Fong et al. (59) evaluated the HRQoL of 248 patients post Whipple procedure (median 9.1 years, range 5.1-21.2 years postoperative) using the EORTC QLQ-PAN26. Even after such a long period of time, patients reported greater pancreatic pain (41.7±17.6) compared to a cohort of patients awaiting pancreatoduodenectomy (18.1±20.5, $p<0.001$). Postoperatively, patients also experienced more altered bowel habits (37.6±30.6 versus 20.0±24.5, $p<0.001$) and digestive symptoms (26.3±29.5 versus 18.7±27.8, $p<0.01$), compared to control. Additionally, bloating (50.8 versus 40.8%), indigestion (53.1 versus 36.5%) and flatulence (73.4 versus 54.7%) were more prevalent in the postoperative cohort ($p<0.05$) (59). Clearly, there are several gastrointestinal symptoms reported by patients with pancreatic cancer that may affect the ability to eat. The next section will provide a deeper examination of nutritional complications in patients with pancreatic cancer.

### 2.5.2. Nutritional status

Pancreatic cancer and its treatment may lead to endo- and exocrine dysfunction. A particular nutritional problem among patients is the development of pancreatic exocrine insufficiency (PEI), whereby the exocrine function of the pancreas in the digestion and absorption of food becomes impaired. PEI is most prevalent in patients with tumours in the head of the pancreas, or who have undergone a Whipple procedure. Table 2.2. outlines the expected prevalence of PEI in patients with pancreatic cancer. As such, PEI-induced weight loss, gastrointestinal symptoms (e.g., diarrhea, steatorrhea) and overall malnutrition may have a negative impact on HRQoL. These relationships were observed in a qualitative study by Gooden et al. (60) in patients with pancreatic cancer and their caregivers. Dietary management, challenges with eating (anorexia) and gastrointestinal symptoms were the most commonly reported factors negatively affecting HRQoL. Unpredictable bowel movements and increased frequency reportedly led to patients becoming more housebound, thus limiting their social interactions. A lack of information regarding PEI and reluctance of clinicians to prescribe pancreatic enzyme replacement therapy (PERT) is also a cause of distress among patients with pancreatic cancer and their caregivers (61). The use of PERT is indicated for PEI in pancreatic cancer. However, PEI remains an underrecognized problem, with levels of PERT initiation very low (61). The effectiveness of PERT to improve HRQoL in patients with pancreatic cancer remains inconclusive. A recent systematic review and meta-analysis revealed no effect of PERT on HRQoL in patients with advanced pancreatic cancer (62). However, the number of patients included in the analysis was small (n=194), and the studies were not uniform and examined different outcomes. The authors concluded that further studies are warranted. Appropriate use of

PERT is a tool that may help limit weight loss in patients with pancreatic cancer. Davidson et al. (63) previously demonstrated that weight stabilization resulting from an 8-week dietetic intervention in patients with non-resectable pancreatic cancer led to a significantly greater EORTC QLQ-C30 global QoL score than those who lost weight during the study (55.1±18.5 versus 47.2±17.4, $p<0.05$). Although PERT was not part of the Davidson study, any tool that can help mitigate weight loss among patients with pancreatic cancer may translate into better HRQoL outcomes.

Table 2.2.: Prevalence of PEI in pancreatic cancer

| | Resectable (post-operative) | | | Unresectable | |
|---|---|---|---|---|---|
| Tumour location | Head | Body/tail | Total resection (pancreatectomy) | Head | Body/tail |
| Estimated PEI prevalence (%) | 70 | 30 | 100 | 85 | 30 |

Adapted from Pezzilli et al. (64) and Roeyen et al. (61)

Cancer cachexia is an extreme form of malnutrition with an estimated prevalence that ranges between 70-80% at diagnosis and causes one-third of deaths in patients with pancreatic cancer (65). There is no consensus regarding the definition of cachexia or the criteria for its diagnosis at this time. A conceptual framework for cachexia was developed in 2011 by Fearon et al. (66):

> "Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."

Briefly, the altered metabolism observed in cancer cachexia is driven by increased inflammation caused by a cascade of proinflammatory cytokines (e.g., interleukin-6, interleukin-1β, tumour necrosis factor-α) primarily released in response to tumour-immune system crosstalk, but also by the tumour itself (67). This inflammation leads to an energy balance deficit; total energy expenditure (especially resting energy expenditure) increases, while food intake decreases, leading to a deficit causing weight loss of both muscle and fat. The imbalance in energy intake is further exacerbated by the presence of anorexia, caused by inflammation in the hypothalamus, leading to cytokine-inhibited orexigenic centres such as neuropeptide Y. Simultaneously, anorexia is stimulated via the activation of the anorectic melanocortin pathway (67). Proinflammatory cytokines also act within myocytes to stimulate catabolism via the ubiquitin proteosome pathways resulting in the loss of myofibrillar proteins and weakness due to contractile dysfunction of the sarcomere (67). Additionally, catabolism is exacerbated by dysregulation in adipose cell thermogenesis; a futile loop occurs within the mitochondria of fat cells, thus increasing energy expenditure. Meanwhile, lipolysis is exacerbated by the presence of proinflammatory cytokines and decreased food intake (67). There is no cure for cancer cachexia, which becomes refractory to dietary intervention in its late stages. The negative effect of cancer cachexia on HRQoL is profound and should be considered when treating patients with advanced pancreatic cancer (68). Clinical practice guidelines state that interventions in patients with cachexia should be multimodal in nature, and can include: 1) nutritional advice (for example counselling, ONS or nutritional support if appropriate), 2) education about cachexia, 3) treating nutrition impact symptoms, 4) offer psychological and palliative support (69).

2.5.3. Muscle mass and strength

Prevalence of low muscle mass in patients with pancreatic cancer ranges from 14 to 72%, with pooled prevalence at 39% (70). Despite it being a common problem, it is unclear how low muscle mass affects HRQoL. Thus far, a null effect has been reported in the literature. For example, low muscle mass as measured by CT in a small cohort of patients with pancreatic cancer did not influence HRQoL as measured by the EORTC QLQ-C30 (71). Poulia et al. (72) reported that among 97 patients with pancreatic cancer, low handgrip strength was related with lower overall EORTC QLQ-C30 scores, indicating worse HRQoL (normal handgrip strength: $71.35 \pm 27.55$ versus low handgrip strength: $56.12 \pm 24.58$, $p<0.05$). However, there were no relationships between HRQoL and estimated muscle mass via measured mid-arm muscle circumference (72). This was corroborated in a study by Kurokawa et al. (73) in which handgrip strength was associated with global HRQoL, three months post pancreatic resection, as measured by EORTC QLQ-C30 (Estimate: $1.83 \pm 0.60$, $R^2=0.32$, $p<0.05$). Again, skeletal muscle mass index, measured using bioelectric impedance analysis, was not associated with HRQoL at the same time point, this despite being lower than at preoperative evaluation (6.3 kg versus 5.9 $kg/m^2$, $p<0.05$) (73).

There are several reasons explaining the absence of a relationship between muscle mass and HRQoL in patients with pancreatic cancer. First, there is vast heterogeneity in the way muscle is measured, and the cut-offs used. Second, some of the inconsistencies in relationships between muscle mass and HRQoL may be due to increasing evidence that the quality of muscle is more important than the actual amount of muscle. For example, myosteatosis, or fatty infiltration of muscle, has been associated with poor postoperative outcomes (74). Finally, sarcopenic obesity in patients with cancer (i.e., low muscle mass with excessive adiposity), has

also been associated with poor overall survival, recurrence- and disease-free survival, postoperative complication and extended length of hospital stay (75). Further research should be conducted to understand relationships between quality of muscle, strength/functional outcomes and HRQoL in patients with pancreatic cancer.

### 2.6. The role of diet and exercise interventions in HRQoL

Much of the literature examining the role of diet and exercise interventions on HRQoL has been conducted in survivors of cancer, rather than patients undergoing treatment. This despite clinical practice guidelines that suggest nutrition and exercise interventions be included in cancer care, as they may have a positive effect on HRQoL (76, 77, 78). It is hypothesized that by maintaining adequate nutritional intake, staving off weight loss, and prescribing exercise, muscle mass will be maintained, leading to reduced cancer-related fatigue and preserved functional capacity (79). Clinical practice guidelines also suggest that diet and exercise care be conducted within multidisciplinary teams, that can identify and treat possible nutrition and functional deterioration (76).

A very promising study demonstrating the effectiveness of a multidisciplinary intervention in improving HRQoL was recently reported by Bland et al. (80). Patients (n=162) with cancer cachexia (identified based on weight loss and BMI), were referred to a multidisciplinary clinic that included the services of an RD and physiotherapist, along with symptom management by a palliative care physician. The RD provided advice on symptom management and adequate macro- and micronutrient intake; the physiotherapist provided advice on how to increase daily physical activity along with home-based resistance exercises. HRQoL was measured using the EORTC QLQ-PAL15 (palliative module), the FACT-G and the

Functional Assessment of Anorexia/Cachexia Therapy [(FAACT) a FACT-G module] over three visits, each 4 to 6 weeks apart. Over the 3-visit period, 67 % of patients experienced weight maintenance or gain, and no change was seen in handgrip strength or the number of sit-to-stand repetitions. At visits 2 and 3, EORTC QLQ-PAL15 global QoL status was significantly improved compared to baseline (baseline: 52.6, visit 2: 63.3, Visit 3: 61.8, $p<0.001$). Similarly, FACT-G (+8.5±1.9, $p<0.001$), FAACT (+14.6±2.7, $p<0.001$) and TOI (+12.7±2.1, $p<0.001$) significantly improved between baseline and visit 2; the improvement was maintained through visit 3. The authors state that these findings are not only statistically significant, but likely clinically meaningful, as the improvements in HRQoL measures were robust and met the MID for each tool.

An alternate way to apply diet and exercise interventions in cancer care is through prehabilitation. Interest in prehabilitation has been growing over the last decade as a means to prevent and/or lessen morbidity due to cancer treatments, ready patients to begin/tolerate treatments, and improve HRQoL (17). At present, most prehabilitation interventions have been limited to patients awaiting surgical/curative treatment, although interest in examining multimodal prehabilitation interventions in patients awaiting palliative treatments is increasing (for more information, please refer to section 6.4 and Appendix 4). The following section will illustrate some examples of how multimodal prehabilitation, which include diet and exercise interventions, may improve HRQoL.

### 2.6.1. Multimodal prehabilitation and HRQoL

Some data indicating a positive effect on the HRQoL of patients with cancer undergoing multimodal prehabilitation has been published. For example, Gillis et al. (81) recently reported

the results of a pooled analysis of patients awaiting surgery for colorectal cancer who participated in a trimodal prehabilitation program (dietary counselling, exercise training, relaxation techniques). Patients completed the non-cancer specific HRQoL tool, 36-Item Short Form Survey (SF-36) questionnaire at baseline and preoperatively (approximately 4 weeks later). Compared to a control group, patients in the prehabilitation group experienced a significant increase in general health score by the preoperative assessment (+5.2±14.0, $p<0.05$). After the intervention, those with the worst nutritional status at baseline (aPG-SGA ≥9) had the greatest increase in general health score (prehabilitation: +12.1±18.6 versus control: -4.8±14, $p<0.05$). Additionally, a significant difference was observed in the total physical health domain in the prehabilitation group, but not controls, by the preoperative appointment [+3.0 (interquartile range: -3.0 to 9.0), $p<0.05$]. This suggest that improving nutritional and physical status via prehabilitation may also improve HRQoL. Further evidence was reported in a small (n=28), pilot study by Rupnik et al. (82), which demonstrated the effect of a diet and exercise intervention for at least 2 weeks prior to haematopoietic stem cell transplantation. Patients (n=34) engaged in aerobic exercise (4 times/week for 20-30 minutes), strength training (3 times/week for 10-20 minutes) and took a daily whey protein supplement equaling 0.3-0.4 g/kg body weight, along with oral nutritional supplements (ONS) when required. Patients completed the EORTC QLQ-C30 at baseline and 1 day prior to receiving their transplant. Patients experienced a significant increase in global health status (baseline: 56.5±20.5 versus pre-transplant: 65.1±22.4, $p<0.01$). Role functioning, social functioning, fatigue, insomnia and nausea/vomiting also improved significantly ($p<0.05$).

At present, prehabilitation studies in patients with pancreatic cancer have not always been multimodal and have not consistently measured HRQoL outcomes. Results of a recent

systematic review by Bundred et al. (83) revealed only six studies, of which only two offered both a diet and exercise intervention. HRQoL outcomes were mixed; in a case series by Marker et al. (84), all four domains of FACT-G improved in 2 patients during the preoperative period. Conversely, the study by Ngo-Huang et al. (85) demonstrated that prehabilitation did not result in a statistically significant change in FACT-G or FACT-Hep in the preoperative period. Both studies utilized a unimodal prehabilitation model, including only exercise interventions. To date, evidence is lacking to identify the effect of multimodal prehabilitation on HRQoL outcomes in patients with pancreatic cancer.

## 2.7. Conclusion

Measuring HRQoL in patients with cancer has become increasingly important over the past 40 years due to the recognition that quality of life is a primary concern of patients. As such, much research has been undertaken to ensure appropriate tools exist to measure HRQoL, as it pertains to problems related to cancer. Much work has been undertaken to examine domains that may be specific to different types of cancer affecting HRQoL; along with traditional physical/functional, social and psychological domains, tools have been developed to examine specific cancer-related symptoms. This is useful in both pharmaceutical trials, as HRQoL is well-accepted as a secondary outcome in drug testing, as well as lifestyle interventions.

Determining the effect of specific symptoms on HRQoL remains understudied in patients with pancreatic cancer. Both treatments and the cancer itself lead to severe endocrine and exocrine dysfunction, resulting in malnutrition, loss of skeletal mass and physical function. Cancer cachexia is highly prevalent in patients with pancreatic cancer, leading to its own set of factors predicting negative overall wellbeing. Stage of the disease, and whether patients are undergoing treatment for curative versus palliative intent also play a role in HRQoL. Since the

majority of patients with pancreatic cancer are only eligible for palliative therapies, the need to ensure that HRQoL is preserved is of utmost importance. Preliminary evidence demonstrates that diet and exercise interventions can help preserve or improve nutrition/functional status, thus leading to improvements in HRQoL. It is reasonable to believe that combined dietary and exercise therapy would work synergistically to improve HRQoL in patients with pancreatic cancer; this has been demonstrated in studies of patients with a variety of different cancer diagnoses. Exercise to increase physical function, strength and muscle mass, supported by nutrition therapy that reduces nutrition impact symptoms and provides substrate for muscle protein synthesis, should hypothetically lead to improved HRQoL.

Several gaps in the literature regarding both determinants of and therapies to improve HRQoL in patients with pancreatic cancer have been identified. The role of diet and exercise as an effective method to improve HRQoL in this patient population is currently unknown.

## Connecting statement: Manuscript 1

The literature review conducted for this dissertation has revealed a possible promising effect of diet and exercise interventions on the HRQoL of patients with cancer; data on how such interventions may help patients with pancreatic cancer remains scarce. Complicating the matter is that dietary interventions can vary widely, ranging from providing ONS, to ensuring adequate macro- and micronutrient intake, to nutritional support via enteral or parenteral nutrition, or precision nutrition utilizing immunonutrition or anti-inflammatory nutrients. Similarly, exercise interventions can include aerobic or strengthening exercise; aerobic interventions can be as simple as a walking program ranging up to individualized high-intensity interval training programs. Strength training can use body weight, free weights or machines. Additionally, exercise can be supervised or unsupervised, done in groups or individually, and so on. Finally, diet and exercise interventions can be provided simultaneously to provide a synergistic therapy, whether it be to optimize HRQoL, improve nutritional status or increase strength and muscle mass. The diversity of possible dietary and exercise interventions that can be provided to patients with pancreatic cancer is vast, and dependant on the outcome of interest. At present, it is unknown what modality is best.

The manuscript presented in the following chapter attempts, through a scoping review of the literature, to determine what types of dietary and exercise interventions have been studied in patients with pancreatic cancer. The use of a scoping review is preferential to determine research gaps in such a heterogenous view of interventions, and where a meta-analysis would not be possible.

## Chapter 3: Manuscript 1

Published in: Pancreas, 2021 May-Jun 01;50(5):657-666

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# Diet and Exercise Interventions in Patients With Pancreatic Cancer: A Scoping Review

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Conflicts of interest

The authors have no conflicts of interest to declare.

## 3.1. Abstract

Diet and exercise interventions may help reverse malnutrition and muscle wasting common in pancreatic cancer. We performed a scoping review to identify the knowledge gaps surrounding diet and exercise interventions. We searched PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature, Embase, ProQuest Theses and Dissertations and Google Scholar, utilizing the umbrella terms of "pancreatic cancer," "diet/nutrition," and "exercise." Included were articles reporting on ambulatory adults with diagnosed pancreatic cancer. Excluded were studies examining prevention and/or risk, animal or cell lines. Of the 15,708 articles identified, only 62 met the final inclusion criteria. Almost half of the articles were randomized controlled studies (n = 27). Most studies were from the United States (n = 20). The majority examined dietary interventions (n = 41), with 20 assessing the use of omega-3 fatty acids. Exercise interventions were reported in 13 studies, with 8 examining a diet and exercise intervention. Most studies were small and varied greatly in terms of study design, intervention and outcomes. We identified 7 research gaps that should be addressed in future studies. This scoping review highlights the limited research examining the effect of diet and exercise interventions in ambulatory patients with pancreatic cancer.

Keywords: Scoping review, pancreatic neoplasm, diet, nutrition, exercise

## 3.2. Introduction

Pancreatic cancer is a deadly disease, with a 5-year relative survival rate of 9% (86). Canadian projections for 2019 indicate that mortality from pancreatic cancer will surpass that of breast cancer, becoming the third deadliest form of the disease (87). Similarly, it is estimated that in 2020, pancreatic cancer will be the fourth leading cause of all cancer deaths in the United States (86). The most effective curative treatment is surgical resection with systemic chemotherapy (7). However, up to 80% of patients are diagnosed when the tumor has become unresectable (88). As such, the majority of patients with pancreatic cancer receive palliative chemotherapy, which seems to improve health-related quality of life (HRQoL), despite possible treatment toxicities (89).

The positive effect of palliative treatment in advanced cancer may be muted by poor nutritional status, as a direct relationship with HRQoL has been demonstrated (47). This is of particular concern in patients with pancreatic cancer, as up to 85% experience unintentional weight loss and malnutrition (90, 91). The etiology of malnutrition in pancreatic cancer is multifactorial, and includes: Pancreatic exocrine and endocrine disturbances, cytokine-induced catabolism and altered metabolism, increased energy requirements, anorexia leading to decreased oral intake and nutrition impact symptoms related to both treatments and the disease (92). These components of malnutrition are related to both muscle wasting and cachexia, commonly seen in patients with pancreatic cancer. Prevalence of muscle wasting in both resectable and non-resectable pancreatic cancer ranges between 19-68% at diagnosis (93, 94, 95). This is of concern as low muscle mass is associated with worse peri-operative outcomes, decreased survival and increased chemotherapy-induced toxicity (96). There is also evidence that chemotherapy itself

may be responsible for muscle wasting (97). Additionally, the prevalence of cachexia in patients with pancreatic cancer ranges between 70-80% at diagnosis and causes one-third of deaths (65).

While it is evident that malnutrition, muscle loss and cachexia are prevalent in pancreatic cancer, it is unclear if there are interventions that may help counteract these adverse phenomena. It is reasonable to question whether ambulatory diet and exercise interventions, applied either prior to or during cancer treatment, may help stave off malnutrition and muscle loss, and enhance HRQoL. Therefore, we conducted a scoping review to assess the current state of knowledge, and to identify research gaps, in diet and/or exercise interventions previously investigated in ambulatory patients with pancreatic cancer. The outcome of this scoping review may help inform the design of novel interventions.

## 3.3. Materials and methods

The framework of this scoping review was developed based on the method of Arksey and O'Malley (98). Steps for reporting the results of this scoping review follow the 22-items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews (PRISMA-ScR): Checklist and explanation (99).

### 3.3.1. Search

To identify potentially relevant articles, six electronic databases (PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature, Embase, ProQuest Theses and Dissertations, Google Scholar) were searched from inception to August 4, 2020. The fundamental structure of the search strategy utilized was as follows: [(Pancreatic cancer) AND (diet/nutrition OR exercise)]. An experienced subject librarian was consulted to ensure

completeness and refinement of the search terms and strategy (see Table 3.1. for the PubMed search strategy employed). Hand searching of the citations in review articles deemed to be of interest was performed by PK to ensure that no articles were overlooked (48, 65, 68, 90, 92, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119). The subject librarian also guided the organization of articles collected and the tracking of selected articles. Search results were exported into Zotero, and duplicates were removed.

### 3.3.2. Inclusion and exclusion criteria

Articles included in this scoping review were published in English and had a diet and/or exercise intervention administered to ambulatory adult patients with pancreatic cancer. Excluded were articles reporting prevention or risk factors of pancreatic cancer, studies in animals, pediatric populations or cell lines, and studies focusing on non-malignant pancreatic disease (e.g., pancreatitis). It was also decided to exclude non-ambulatory patients, and thus perioperative nutrition support, as the goal of this review was to assess interventions in ambulatory patients. Articles reporting the results of trials, retrospective studies, case studies, review papers and grey literature (e.g., graduate theses) were all considered in this review. Additionally, there were no date limits placed on our search, to ensure the most complete results. Inclusion and exclusion criteria for the final selection of the articles are outlined in Table 3.2.

### 3.3.3. Screening and data extraction

The title and abstracts of all articles were screened independently by PK and RDK. Each article was labelled, “yes,” “no,” or “maybe,” if there was uncertainty. The independent screening results of each reviewer were compared to identify disagreement. The full-text of

disputed articles was accessed to allow for discussion and final consensus on inclusion. Additionally, the full-text of all articles the authors agreed to include in the study were accessed. Data charting tables were developed collaboratively by the reviewers, with variables of interest identified. Data was then charted by PK and reviewed by RDK. Data of interest included: Study design, date of publication, country where the intervention took place, anti-neoplastic treatment modalities, whether the intervention included diet, exercise or both, specifics on intervention type and dose, outcomes and adverse events. Each article was deemed as having a positive or negative result based on whether the primary study objective was achieved. Finally, studies were grouped by the overall intervention type (e.g., diet, exercise or diet and exercise), and then by the specific intervention (e.g., omega-3 fatty acids, resistance exercise, etc…).

### 3.4. Results

A total of 15,708 articles were found: PubMed = 4184, Scopus = 4147, Cumulative Index to Nursing and Allied Health Literature = 1162, Embase = 5876, ProQuest Dissertations and Theses = 149 and Google Scholar = 190. Of these, 8055 articles were duplicates, leaving 7653 articles to be reviewed. After reviewing titles and abstracts, 7489 articles were excluded and the full-text of 164 articles was retrieved and examined for inclusion. Of these, 102 articles were excluded, leaving 62 studies deemed to meet the eligibility criteria of this review. The PRISMA flow diagram outlining the selection process is reported in Figure 3.1.

Of the 62 studies included in this review, 41 reported dietary interventions (120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160) (see Table 3.3.), 13 exercise interventions (161, 162, 163, 164, 165, 166, 167, 168, 169,

170, 171, 172, 173) (see Table 3.4.) and 8 a combination of both (85, 174, 175, 176, 177, 178, 179, 180) (see Table 3.5.). Almost half of the articles were randomized controlled trials (n = 27), followed closely by prospective cohort studies (n = 26). Five case reports described exercise interventions, with one describing a dietary intervention. Most studies were conducted in the United States (n = 20), the United Kingdom (n = 15) and Germany (n = 9). Characteristics of the included studies are reported in Table 3.6.

### 3.4.1. Dietary interventions

*Omega-3 fatty acids*

A total of 20 (54%) of all dietary intervention studies reported findings related to omega-3 fatty acid supplementation (120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139). All studies used products enriched with eicosapentaenoic acid (EPA). Supplementation was delivered in the form of an enriched oral nutrition supplement (ONS) in 12 of these studies (120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131), via peripheral intravenous infusion with chemotherapy in 4 studies (132, 133, 134, 135), and orally in the form of an emulsion or capsule in 4 studies (136, 137, 138, 139). Eicosapentaenoic acid dosing was 2.2 g/day in the studies utilizing ONS (120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131), and 4.3-8.6 g/infusion of combined EPA and docosahexaenoic acid (DHA) (132, 133, 134, 135). Dosage did not vary among the ONS and infusion studies, as they were performed by the same study groups. However, there were conflicting dosages and sources omega-3 fatty acids in the studies providing oral EPA, varying from 300 mg of marine phospholipids and fish oil supplements (137), to studies hoping to achieve a maximum intake of 6-36 g/day of EPA in participants (136, 138, 139). Primary outcomes of the studies varied

widely. The majority of studies reported nutritional status outcomes, such as changes energy expenditure (122, 129), weight (124, 127, 128, 129, 133, 137, 138, 139) and body composition (120, 126, 129). The effect of EPA on various cytokines (e.g., interleukin-6) and acute phase proteins (e.g., albumin, CRP) was reported in 6 studies (121, 123, 125, 131, 138, 139). The anticancer effect of EPA was reported in 3 studies (130, 132, 135). Finally, outcomes on safety and tolerability was the focus of 1 study (134). Reported improvements in nutritional parameters were mixed. Weight stabilization or gain was reported in 5 of the 8 studies with this primary outcome; however, EPA had no effect on body composition. While Barber et al. (122) reported reduced resting energy expenditure and fat oxidation in the fasted state, this was contradicted by Moses et al. (129) who found that total energy expenditure was greater in those with highest EPA intake. There was no effect of EPA on cytokine reduction or acute phase protein modulation. After 3 weeks of fish-oil supplementation, Barber et al. (121) reported a decrease in production of IL-6, but not IL-1β or TNF. Overall, there was no change in albumin (123, 125, 131), or C-reactive protein (123, 131, 138, 139) after supplementation; however, an increase in transferrin was reported by Barber et al (123). Mixed results were also found supporting the antineoplastic effect of EPA. Arshad et al. (132) reported objective response rate in only 14% of patients, a finding corroborated by Ueno et al. (130) who found no significant difference in 1-year survival between those receiving a EPA-rich ONS and controls. In another study, Arshad et al. reported that 85.7% of patients receiving concomitant Gemcitabine and omega-3 fatty acid-rich lipid infusions had stable disease, with partial response of liver metastases in 41% of patients (135).

*Preoperative nutrition interventions (immunonutrition)*

Immunonutrition refers to the modulation of the immune system, and/or the downstream effects of immune activation, by nutrients consumed in amounts greater than what is found in a regular diet (181). These nutrients include: omega-3 fatty acids, amino acids such as glutamine and arginine, anti-oxidants and nucleotides (181). Five studies examined the effect of preoperative oral immunonutrition supplementation on various postoperative outcomes (140, 141, 142, 143, 144). Immunonutrition was delivered *per os* via an ONS in all 5 studies. All studies had a control group, and compared immunonutrition to placebo (140), standard care (141), or to no particular control intervention (142, 143, 144). Primary outcomes of interest were postoperative complications, infections and hospital length of stay for three of the studies (141, 142, 143), with the effect on antioxidant capacity and inflammatory response examined in two studies (140, 144). Results were mostly positive, with reduced length of hospital stay and complications reported in 2 of the 3 studies (142, 143). While antioxidant capacity was greater in the immunonutrition group (140), there was no significant effect on inflammatory markers (140, 144).

*Dietary counselling*

Dietary counselling by a registered dietitian, with or without the use of ONS, was found in 4 of the included studies (145, 146, 147, 148). The goals of the dietary interventions varied greatly and included changes in weight, body composition and HRQoL (145), if patients met their protein needs (146), nutrition status and survival (147), and if a soft diet decreased the occurrence of bowel obstruction (148). Two of the studies were retrospective in design (147, 148). Dietary counselling with the use of an ONS had a positive effect on macronutrient intake and a greater gain of fat mass, compared to only increased protein intake in those who received

counselling alone (145). However, despite improved protein intake, the majority of patients did not meet their protein needs (146). Dietary counselling also either stabilized or improved nutritional status, as evaluated by Subjective Global Assessment, in 70% of patients who received counselling (147). Nutritional status was found to be an independent predictor of survival (147). Finally, dietary counselling promoting a prophylactic soft diet led to no patients developing bowel obstruction, compared to 71% of non-counseled controls (148).

*Vitamin D*

Two studies examined the effect of oral vitamin D supplementation (149, 150). The first examined the effect of taking calcitriol (0.5 μg/kg) on the day before receiving standard Docetaxel treatment, on time to progression (149). Results demonstrated no improvement on time to progression or overall survival. The second study examined whether vitamin D supplementation (various dosages based on disease status and malabsorption), combined with pancreatic enzyme replacement therapy, can normalize serum 25-hydroxy vitamin D levels (150). This time, results were positive with 25-hydroxy vitamin D status normalized in pancreatic cancer patients, albeit with a large dosage required (up to 20,000 IU/day).

*Enteral nutrition*

One prospective, single-arm study examined if weight maintenance could be achieved through peptide-based, jejunal tube feeding in pancreatic cancer patients with cachexia (151). Almost 2/3 (n = 10) of patients maintained their weight after 3 months in this small study.

*Parenteral nutrition*

The effect of overnight, home-based parenteral nutrition on nutritional status was reported in 2 studies (152, 153). Both studies reported weight maintenance or gain in the majority of patients, with Richter et al. (153) reporting these positive results in only those with survival >5 months. Both studies provided ~ 25 kcal/kg, with omega-3 fatty acids administered to 76% of patients in the study by Richter et al (153).

*Supplements and alternative interventions*

The effect of oral curcumin supplementation was examined in 2 studies (154, 155). In both studies, 8 g of curcumin per day was prescribed. The response to the treatment was mostly negative, with the majority of participants exhibiting disease progression. There was an anti-inflammatory effect found due to a significant reduction in inflammatory COX-2 expression and pSTAT3 activation (154). Oral bioavailability was low (154), with significant gastrointestinal toxicity leading to the cessation of treatment in some patients (155).

One study examined the effect of L-carnitine, a molecule derived endogenously or through diet, and involved in the metabolism of fatty acids, on cachexia in patients with pancreatic cancer (156). Participants were asked to consume a liquid formulation of L-carnitine, providing 4 g/day for 12 weeks, compared to placebo. Results were overall negative, as there were no differences between groups in C-reactive protein, albumin, leukocyte count, carbohydrate antigen 19-9 or survival. Body mass index and fat mass increased in the L-carnitine group, but not lean body mass.

Another study looked at the effect of active hexose correlated compound (AHCC), a functional food extracted from the mycelia of the shiitake mushroom, on reducing adverse events related to Gemcitabine (157). Patients were asked to take 6 g of AHCC orally for 8 weeks,

corresponding to 2 cycles of Gemcitabine. Results were mostly positive; although there were no differences in hematological outcomes, grade 3 modified Glasgow Prognostic Scale scores, taste disturbances and C-reactive protein were lower, and albumin higher, in the AHCC group.

The feasibility of administering another functional food, broccoli sprouts, was examined in a placebo-controlled pilot study (158). Patients were asked to consume 15 capsules daily of pulverized broccoli sprouts containing 90 mg sulforaphane and 180 mg glucophanin for 1 year. Results were disappointing, with 21% of the treatment group dropping out within 1 month of starting the intervention, and 72% before the 1-year end-point. Taste, possible gastrointestinal discomfort and the burden of taking numerous capsules each day were some reasons cited for this poor outcome.

A retrospective study of patients who followed an alkaline diet and received bicarbonate therapy reported the effect of this intervention on urinary pH and survival in patients with advanced pancreatic cancer (159). The alkaline diet consisted of patients consuming at least 400 g of fruits and vegetables and the avoidance of meat and dairy products. Participants were also prompted to take 3-5 g/day of oral bicarbonate if their urine pH was <7. Unsurprisingly, urine pH increased with this treatment. The authors also report that patients with urine ≥7 had greater survival than those whose urine was acidic. It is difficult to extrapolate any effect on cancer by this intervention, given the normal acid-base regulation of the lungs and kidneys.

Finally, one pilot case series (160) examined an alternative treatment combining dietary modification (raw or lightly steamed fruits and vegetables, daily vegetable juice, plant-based proteins, with daily yogurt, 1-2 eggs/week, fish 2-3 times/week, red meat/poultry forbidden), vitamin/mineral/trace element supplementation, freeze-dried thymus or liver supplements, 25-40 g of porcine lyophilized pancreas product and detoxification with twice-daily coffee enemas. The

effect of this intervention on survival was positive, with 81% of patients surviving for one year, which the authors state is better than the 25% survival rate for all stages of pancreatic cancer. Compliance by participants to this protocol was not reported by the authors.

### 3.4.2. Exercise interventions

#### *Aerobic exercise*

Two studies reported on the effect of a walking program (161, 162). One study examined safety and feasibility (161) and the other the effect on fatigue, physical function and HRQoL (162). Walking programs were well tolerated, with 68% of patients completing the study, and most dropouts due to declining health (161). Brisk walking for 90-150 minutes per week, divided into 3 to 5 sessions, for a 3 month period, had a positive effect on fatigue and reported physical health compared to usual care controls, but not performance status or symptom burden (162).

#### *Resistance/strength training interventions*

Four studies examined the effect of strength training as a monotherapy (163, 164, 165, 166). One case study described the utilization of ultrasound imaging to guide motor control training in a patient post Whipple surgery (163). Abdominal muscle training, trunk stretching, spine stabilization exercises and progressive strengthening exercises were performed and progressed based on performance to address post-operative impairment and functional limitations. The results were positive, with improvements in pain, muscle performance and functional scores reported at 5 weeks, 12 and 18 months post-operatively. The results of a randomized controlled trial produced two papers that reported outcomes of a supervised versus home-based resistance training program, versus a usual care control group (164, 165). The

intervention lasted 60 minutes, 2 times/week, and included the following exercises: leg press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly reverse and crunch. Each exercise was performed 8 to 12 times for 2 to 3 sets each. Overall adherence to the program was 64.1% in the supervised group and 78.4% in the home-based group, with completion of more than 50% of the intervention in those who completed the study (165). Maximal isokinetic peak torque improved significantly in the supervised group for elbow flexors and extensors compared to the home-based and control group (165). Maximal voluntary isometric contraction improved significantly in the supervised group for elbow flexors compared to control. Both intervention groups improved in knee extensors (165). There was a beneficial effect of the intervention on HRQoL and fatigue in the short-term. At 3 months, physical functioning, global HRQoL, cognitive functioning, sleep problems, physical fatigue and reduced activity were significantly different than controls (164). This was not the case at 6 months. Finally, a resistance training intervention to improve mobility, strength and lean body mass in cachectic patients with pancreatic cancer was explored (166). Over a 12-week period, the intervention group received a twice weekly, 8-exercise, supervised program targeting all major muscle groups, versus a control group who received no intervention. The intervention improved function as measured by the 400-meter walk test, 6-meter usual walk test and chair rise, compared to control. Additionally, peak torque extension of the knee and both elbow flexor and extensors also improved. Appendicular lean mass was also greater in the intervention group after 12 weeks compared to controls.

*Combined aerobic and resistance/strength training interventions*

The majority of exercise interventions included both an aerobic and resistance training component (167, 168, 169, 170, 171, 172, 173). Of the seven studies, 3 were prospective and offered a home-based exercise program (167, 168, 169); of these, 2 were pilot studies (168, 169). The remaining 4 articles were case studies/reports (170, 171, 172, 173), one of which was designed as a randomized controlled trial, but reported as a case series due to poor recruitment (170). All of the case studies offered supervised exercise interventions, whereas the prospective studies examined home-based exercise programs. Frequency of exercise interventions varied from 2 times/week to daily, at a duration of approximately 60 minutes/session. Targeted resistance exercises of both upper and lower body muscle groups were explored in 4 studies (167, 169, 170, 173), with one study only assigning lower body exercises (171), and two studies not reporting which muscle groups were targeted (168, 172). Three studies reported that patients were asked to perform 2 to 3 sets of between 8 to 12 repetitions (167, 171, 172). Aerobic exercises were performed with ergometers (169, 171, 172), gym equipment (treadmill, elliptical, rowing machine) (170) or by bicycling or walking (173). Study outcomes varied widely, and included: feasibility, adherence and safety (167, 169, 170, 172), changes in vascular function (168), improvements in physical function (170, 171, 172, 173), muscle mass (170, 171, 173), HRQoL (170, 171, 172, 173) and fatigue (171, 173). All of these exercise studies had positive results. Exercise can be safely prescribed, with good overall adherence to aerobic programs, but mixed results on reported adherence to resistance exercise (167, 169). In the case studies, both subjective (e.g., patient reported physical function as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, Godin Leisure-Time Exercise questionnaire, Global Questionnaire of Physical Activity) and objective measures (e.g., 400-meter walk test, 12-repetition maximum, 1-repetition maximum, chair sit-to-stand, stair climb) showed

improvement (170, 171, 172, 173). Additionally, muscle mass, as measured by both dual-energy X-ray absorptiometry and bioelectrical impedance analysis, also improved. However, in the study by Marker et al., the positive effect on lean mass was only seen in the preoperative period, with losses experienced post-operatively (170). Health-related quality of life measurements (FACT-G, FACT-Hepatobiliary, EORTC-C30, Short Form-36) improved in all case studies (170, 171, 172, 173). Additionally, fatigue, as reported utilizing the Functional Assessment of Chronic Illness-Fatigue questionnaire, improved over the intervention periods (170, 171, 173).

3.4.3. Diet and exercise interventions

There were eight studies reporting on interventions that included both a diet and exercise component (85, 174, 175, 176, 177, 178, 179, 180). All study participants were awaiting pancreatic surgery, and underwent prehabilitation, with the intervention applied in the preoperative period. Three of the studies were sub-analyses of a larger prehabilitation study (178, 180). The nutrition interventions included: protein supplementation (whey, leucine-rich essential amino acids) (176, 177, 178, 179, 180), EPA-rich ONS (174), 5 days of immunonutrition ONS preoperatively (178, 179, 180), and nutritional counselling (high energy-protein diet, management of nutrition impact symptoms) (85, 175, 176, 178, 179, 180). Protein recommendations and goals varied and included recommending dietary intake of 1.3-1.5 g/kg/day (176, 178, 179, 180), having a protein-rich meal or snack (at least 20 g) within 1 hour of strength training (85, 175), or consuming a leucine-rich amino acid supplement within 30 minutes pre/post exercise (177). The exercise component of the intervention included both aerobic and strength training in all studies but one (174), in which attaining a step count was the goal. The exercise prescriptions were not always detailed; however, 3 studies reported

strengthening exercises included upper and lower body large muscle groups and ranged from 2 to 3 sets of 8 to 12 repetitions of each exercise (85, 175, 177). Primary outcomes of the studies also varied widely, with feasibility and adherence reported in two studies (174, 175). Changes in physical function (measured utilizing the six-minute walk test) (85, 176, 177) and body composition (as measured by bioelectric impedance analysis) (178, 179, 180) were reported in 3 studies each. Nutritional status (177), HRQoL (85) and surgical outcomes (177) were examined in only one study each. Five of the eight studies reported positive results (85, 174, 175, 176, 177). Exercise and nutrition interventions were feasible, with greatest adherence reported for the nutritional and aerobic components of the intervention (174, 175). Prescribed strengthening exercises were least adhered to (175), mirroring the results of other studies (167). Results of functional outcomes were positive, with increased distance walked in the six-minute walk test from baseline to the preoperative assessment in the three studies that examined this outcome (85, 176, 177). However, body composition was not improved in the preoperative period and decreased weight, fat mass and fat-free mass were found 6-weeks post-surgery (178, 179, 180). The study by Nakajima et al. (177) was the only one reporting outcomes on nutritional status beyond body composition; the prognostic nutritional index improved in the treatment group, with preoperative albumin dropping only in the control group. Additionally, Nakajima et al. (177) reported fewer post-operative bile leaks and shorter hospital length of stay in the intervention group compared to controls. Finally, HRQoL as measured by the FACT-G and FACT-Hep, was not different from baseline at the preoperative assessment (85).

## 3.5. Discussion

A summary of dietary and exercise interventions provided to ambulatory, adult patients with pancreatic cancer have been outlined in this scoping review. Our review included articles with a variety of study designs, originating from many different countries and with no date restriction. Despite our wide search criteria, only 62 articles were identified. As a goal of this review was to identify gaps in the literature, specifics on the intervention, assessments and outcomes were examined.

### 3.5.1. Research gaps

Of the 62 articles, the majority described a nutrition-centred intervention (n = 41), of which, the effect of omega-3 fatty acids was most widely examined (n = 20), followed by preoperative nutrition intervention (including immunonutrition), dietary counselling by a registered dietitian, the use of vitamin D supplementation, home-based enteral and parenteral nutrition, supplements such as curcumin, L-carnitine, AHCC and broccoli sprouts and lastly two alternative therapies. It is difficult to determine which, if any, of these dietary interventions should be explored further, for a multitude of reasons: 1) The vast majority of studies were small, single-centre studies, 2) not all studies had a true control group, and 3) the heterogeneity of the patient population (e.g., resectable versus non-resectable, patients receiving antineoplastic treatment versus those who were not). An additional difficulty was identified in the omega-3 studies, as there was a wide variety of doses and/or modes of administration (e.g., ONS versus parenteral versus oral) and/or substances (e.g., EPA-rich versus EPA alone versus marine phospholipids versus fish oil) that were used in each intervention. The greatest amount of evidence seems to suggest that dietary counselling with the use of an ONS (regardless of EPA

content) may improve overall macronutrient intake, nutritional status and body composition (124, 126, 127, 128, 145, 147). The questionable benefit of an EPA-rich ONS was demonstrated by Fearon et al. (128). In a randomized, placebo-controlled trial where almost 200 participants consumed either an EPA-rich or an isocaloric standard ONS, no difference between groups was found in the attenuation of weight loss, improved performance or HRQoL scores. However, these negative results may be due to difficulty in compliance, rather than the EPA-rich ONS being ineffective. Non-compliance to ONS prescription was also reported by Akita et al. (120), due to the poor taste of the supplement. Therefore, it seems clear that a measure of compliance when interventions include ONS should be included in future studies. Additionally, compliance would be improved if care is taken with ONS palatability, and prescribed in small volumes (145). Future interventions should be randomized in nature, with a placebo-controlled group, offering dietary counselling along with an ONS. Furthermore, the ability of immunonutrition to improve surgical outcomes would also require further study, as no study compared immunonutrition to a standard ONS as a placebo-control.

Thirteen studies described exercise interventions, which were a mix of aerobic (n = 2), resistance (n = 4) or combined aerobic and resistance exercise programs (n = 7); there is a paucity of data on all these types of exercise interventions in patients with pancreatic cancer. Available evidence may be considered weak solely based on study design, as five of the studies reported either a case report or series. The types of aerobic (walking, ergometers) exercises prescribed, as well as the tools used to perform resistance training (free weights, elastic tubes, weight machines) varied widely. Additionally, as with the dietary interventions, patients studied were heterogenous in nature, based on treatments and stage of disease. Multiple outcomes were assessed and included adherence, safety and feasibility, physical function, muscle strength and

cardiovascular fitness, body composition, fatigue and psychological wellbeing: Any of these outcomes can be re-examined in future studies to strengthen available evidence. Five studies examined home-based interventions, 6 examined a supervised intervention (only 1 of which was a randomized controlled trial, with the rest being case studies), and 2 comparing home-based to supervised exercise sessions (these two studies reported outcomes from the same cohort). Therefore, with the current state of knowledge, it cannot be determined whether home-based or supervised interventions are best in this patient population. However, clinical practice guidelines recommend that supervised exercise is preferable for people living with cancer (182).

This review demonstrated that very few studies examined a combined exercise and nutrition intervention (n = 8). Of these 8 studies, all described prehabilitation interventions designed to support patients through neoadjuvant treatments and improve functional and nutritional reserves in preparation for surgery. Unlike the previously described nutrition interventions, those combined with exercise often included amino acid/protein supplementation, either with L-leucine or whey protein, to promote muscle protein synthesis. There were a variety of main outcomes reported, including: feasibility, adherence, relationships between physical activity and HRQoL, functional capacity, postoperative complications, length of hospital stay, and body composition. There were no multimodal studies examining the effect of diet and exercise on advanced pancreatic cancer patients, who were not surgical candidates, but receiving palliative chemotherapy. The application of a multimodal intervention in patients whose treatment goals are non-curative is challenging. The presence of both tumour and host derived proinflammatory cytokines in patients with cachexia, leads to metabolic disturbances promoting lipolysis and proteolysis (67). As such, anabolic resistance may be present despite targeted diet and exercise treatments. Recent guidelines by the American Society of Clinical Oncology

suggest only moderate benefit of nutritional counselling and unknown benefit of exercise in patients with cancer cachexia, with the strength of evidence determined to be low (183). Other challenges in designing multimodal studies targeting patients with advanced pancreatic cancer are treatment related. For example, achieving adequate oral intake is difficult for patients receiving palliative chemotherapy due to common treatment side-effects, such as anorexia, dysgeusia, nausea and vomiting. Nutrient malabsorption related to pancreatic exocrine insufficiency, as a side-effect of a Whipple procedure or due to the tumor itself, also leads to malnutrition and wasting. Finally, exercise in this patient population may not be feasible due to pain, which is present in up to 80% of patients with advanced pancreatic cancer (184). Despite these difficulties, it is worth investigating the role of early multimodal interventions as an adjunct to chemotherapy (185). Preliminary evidence suggests an anti-inflammatory benefit of resistance and aerobic exercise (186), and the capacity of resistance exercise and dietary protein, in particular the essential branched-chained amino acid leucine, to stimulate muscle protein synthesis (187). A systematic review recently demonstrated that exercise interventions seem to maintain physical function and may improve quality of life in patients with advanced cancer, although improvements in fatigue remain unclear (188).

### 3.5.2. Implications for future research

This scoping review revealed a scarcity of studies examining the effect of dietary and exercise interventions in patients with pancreatic cancer. Of particular note, we recommend the following be examined more closely, in well-designed, randomized, placebo-controlled (where applicable) trials:

1) A combined nutrition and exercise intervention

2) The nutrition component should include dietary counselling and supplementation (consider ONS, protein)
3) Alternatively, a nutrition intervention examining immunonutrition versus a standard ONS should be examined in patients awaiting pancreatic surgery
4) The exercise intervention should include both aerobic and resistance training
5) Supervised versus home-based exercise programs should be studied specifically in patients with pancreatic cancer
6) The effect of a multimodal intervention in non-surgical patients undergoing palliative chemotherapy has yet to be reported
7) As outcomes measured in all reported studies are very heterogenous, any can be chosen. The following are proposed examples:
    a. Trial design in which patient-reported outcomes and HRQoL measures are outcomes of interest, considering the palliative nature of treatments
    b. Relationships between nutritional status, muscle mass, and chemotherapy tolerance

### 3.5.3. Strengths and weaknesses of the review

The strength of this review was the use of the PRISMA-ScR methodology to identify a research question, create our search strategy and chose the final articles included herein. The clearly defined inclusion and exclusion criteria, and the inclusion of grey literature, allowed for the maximal number of studies and interventions to be identified. The weakness of this scoping review, as in all scoping reviews, is the inability to evaluate the quality of each study. It may also be argued that a weakness of this study was to not include pancreatic enzyme replacement

therapy (PERT) as a sole nutritional intervention. This was done intentionally as the authors felt that PERT may warrant a scoping review of its own, and that our search criteria was not broad enough to ensure the capture of all relevant articles. Interventions with a nutrition intervention that included PERT were reviewed in this study, but not PERT on its own.

## 3.6. Conclusions

This scoping review has helped elucidate the current state of knowledge and identified gaps in the literature regarding diet and/or exercise interventions in ambulatory patients with pancreatic cancer. At the present time, there are a limited number of studies examining such interventions, with a particular lack of information on multimodal approaches. A striking gap in the literature is that a combined diet and exercise intervention in patients receiving palliative treatments has yet to be examined. As such, this may be of particular interest to researchers, given the overall poor survival rate, multiple treatment and surgical side-effects and overall disease burden in these patients. Dietary and exercise interventions may help improve HRQoL, while supporting patients through palliative treatments.

## 3.7. Acknowledgements

The authors with to acknowledge the work of Katharine Hall, subject librarian at Concordia University, for her help in refining the search strategy utilized in this review. Her support and guidance was invaluable.

Table 3.1.: PubMed Search Strategy (Search Performed August 4, 2020)

| | |
|---|---|
| 1. | "Pancreatic Neoplasms"[Mesh] OR ((adenocarcinoma[tiab] OR carcinoma[tiab] OR cancer[tiab] OR neoplasm[tiab] OR tumor[tiab] OR tumour[tiab] OR "Neoplasms"[Mesh:NoExp]) AND (pancreas[tiab] OR pancreatic[tiab])) |
| 2. | Diet, Food, and Nutrition[Mesh:NoExp] OR "Diet"[Mesh] OR diet[tiab] OR dietary[tiab] OR nutrition[tiab] OR nutritional[tiab] OR malnutrition[tiab] OR malnourished[tiab] OR undernourished[tiab] OR undernourishment[tiab] OR undernutrition[tiab] OR anorexia[tiab] OR cachexia[tiab] OR sarcopenia[tiab] OR malabsorption[tiab] OR pancrealipase[tiab] OR "digestive enzymes"[tiab] OR dietetic[tiab] |
| 3. | Exercise[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Physical Fitness"[Mesh] OR "Sports"[Mesh] OR exercise[tiab] OR "physical activity"[tiab] OR "physical fitness"[tiab] OR "physical training"[tiab] OR "aerobic exercise"[tiab] OR "aerobic training"[tiab] OR "weight training"[tiab] OR "resistance training"[tiab] OR "functional capacity"[tiab] OR "physical capacity"[tiab] |
| 4. | 1 AND (2 OR 3) |

Table 3.2.: Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Pancreatic cancer, all stages<br>• Must report on a diet and/or exercise intervention<br>• Adult interventions<br>• All treatment types (chemotherapy, surgery or radiation)<br>• Ambulatory patients | • Non-pancreatic cancer<br>• Non-cancer<br>• Articles not in English<br>• Non-ambulatory patients<br>• Prevention or risk factors of pancreatic cancer<br>• Animal or cell line studies<br>• Interventions that do not include a dietary or exercise intervention |

Table 3.3.: Summary of Evidence From Dietary Interventions

| Author, Year | Study Design | Patient Characteristics | Sample Size | Intervention | Dosing | Primary Objective | Outcomes | Adverse Events | Strengths | Limitations |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Omega-3 fatty acids*** | | | | | | | | | | |
| Akita et al, 2019 (120) | Prospective randomized control trial | Patients with resectable PC scheduled for neoadjuvant CRT | Intervention n =31 Control n =31 | EPA-rich ONS vs normal diet | 2 bottles ONS/day (440 mL, 560 kcal/d) – authors did not indicate amount of EPA in each supplement | Effect on nutritional status | Negative - No significant change in skeletal muscle mass and a significant decrease in psoas area muscle mass post CRT in intervention group. Pre/post ratio of muscle mass and psoas area was better in those who consumed >50% of ONS (n =14) | No difference between groups | Study design, homogenous group, adequately powered | Poor taste of ONS lead to poor compliance. Post-hoc analysis using compliance as a factor when primary outcome not met |
| Barber et al, 2001 (121) | Open-label, single-arm study | Patients with unresectable PC and ongoing weight loss | Data for 18 patients was available for analysis | Fish oil-enriched ONS | Patients consumed 2 x 237 mL cans/day (providing: 620 kcal, 32.2 g protein, 2.2 g EPA and 0.96 g DHA) for 3 weeks | The effect of a fish-oil enriched ONS on cytokine and hormonal mediators | Positive – There was a significant decrease in IL-6, but no other cytokines. There was a significant increase in insulin and decrease in cortisol-to-insulin ratio. There was a significant decrease in the proportion of patients with urinary excretion of proteolysis inducing factor | Not reported | Clear description of laboratory analyses. Compliance monitored | No placebo control group. Small sample size. Reported weight gain could be due to the caloric effect of the ONS, rather than a direct effect of the n-3 on inflammatory cytokines and insulin |
| Barber et al, 2000 (122) | Quasi-experimental study – cachexia versus healthy controls | Intervention: Patients with unresectable PC, with ongoing weight loss, and not receiving any antineoplastic treatments. Controls: Weight stable, healthy individuals | Intervention : 16 Controls: 6 | Fish-oil enriched ONS | The intervention group consumed 2 x 237 mL cans/day (providing: 620 kcal, 32.2 g protein, 2.2 g EPA and 0.96 g DHA) for 3 weeks | To assess the effect of fish-oil enriched ONS on the metabolic response to feeding | Positive - After supplementation, the cancer patients gained weight, had decreased resting energy expenditure, and had reduced fat oxidation in the fasted state, which was not different than the control group | Not reported | The use of a control group. Objective metabolic testing | Small sample size. Healthy control group was significantly younger than cancer patients |
| Barber et al, 1999 (123) | Non-randomized, unblinded trial | Intervention/control: Patients with unresectable PC, with ongoing weight | Intervention : 18 Cancer controls: 18 Healthy controls: 6 | Intervention: Fish-oil enriched ONS Cancer controls: Supportive care | The intervention group consumed 2 x 237 mL cans/day (providing: 620 kcal, 32.2 g protein, 99.4 g carbohydrate; 13 g fat; 2.2 g EPA and 0.96 g | To assess the effect of a fish-oil enriched ONS on acute | Positive - There was a significant difference in negative acute phase proteins, but not positive, between the cancer groups. Patients | Not reported | Objective measures. Control groups | Healthy control group was significantly younger than cancer patients. Unclear what supportive care |

| | | | | | | | | | | |
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| | | loss. Healthy controls: Weight stable, healthy individuals | | | DHA) for ~3 weeks (median 24 days) | phase proteins | receiving the ONS gained weight, while the control group lost | | | the control group received. Unclear if differences in acute phase protein response is due to n-3 fatty acids or improved calorie-protein intake in the intervention group |
| Barber et al, 1999 (124) | Single-arm, open-label trial | Patients with unresectable PC and ongoing weight loss | 20 patients recruited; data available on 18 patients at week 3 and 13 patients at week 7 | Fish-oil enriched ONS | 2 x 237 mL cans/day (providing: 620 kcal, 32.2 g protein; 2.2 g EPA and 0.96 g DHA) for 7 weeks | Weight gain with fish-oil enriched ONS | Positive - Patients experienced significant weight gain, increased lean body mass, and improved performance status at 3 and 7 weeks after the start of the intervention. Energy intake increased significantly at 3 weeks. EPA and DHA content of plasma phospholipids increased after 3 weeks. Resting energy expenditure adjusted for body weight and lean body mass decreased significantly | Two patients developed steatorrhea, and 1 patient had worsening steatorrhea – treated with pancreatic enzyme replacement therapy | Objective measure of compliance through plasma phospholipid fatty acid analysis | No placebo control group. Weight gain due to overall energy intake versus any effect of n-3 fatty acids |
| Barber et al, 2004 (125) | Single-arm, open-label trial | Patients with unresectable PC and ongoing weight loss | 8 patients | Fish-oil enriched ONS | 2 x 237 mL cans/day (providing: 620 kcal, 32 g protein; 2 g EPA) for 3 weeks | To assess the effect of a fish-oil enriched ONS on hepatic synthesis of albumin and fibrinogen | Negative – Increased albumin and fibrinogen synthesis rates between fasted and fed state at baseline. After supplementation, albumin synthesis was not increased in the fed state, while fibrinogen was significantly decreased | None reported | Objective measures of protein synthesis rates. | No placebo control group. Changes in protein synthesis rates are small compared to whole-body protein kinetics |
| Bauer et al, 2005 (126) | Post-hoc analysis of data collected in a multicentre randomized, double-blind study | Patients with unresectable PC who experienced weight loss of >5% in the last 6 months | Intervention : 95 Control: 105 → Final analysis based on compliance (intake of at least 1.5 | Protein, energy-dense, EPA-enriched ONS versus isocaloric, isonitrogenous ONS without EPA | 2 cans/day (providing: 620 kcal, 32 g protein +/- 2.2 g EPA) for 8 weeks | To assess the effect of dietary compliance on intake and body composition (post-hoc analysis) | Positive – Average protein and energy intake, as well as weight were significantly greater in the compliant group vs the non-compliant group. Weight was greater in the | None reported | Large sample size. Homogenous group of patients | 3-day food diaries have limitations in reliability due to fluctuations of intake in advanced cancer patient who experience nutrition impact symptoms. Post-hoc analysis of |

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| | | | cans ONS/d) n = 87 versus non-compliance n = 98 | → Final analysis based on compliance (intake of at least 1.5 cans ONS/d) versus non-compliance | | | compliant group, however there were no differences in body composition | | | data not collected to answer research question |
| Davidson et al, 2003 (127) | Post-hoc analysis of data collected in a multicentre randomized, double-blind study | Patients with unresectable PC who experienced weight loss of >5% in the last 6 months and who had weight data available at baseline and eight weeks | Weight losing patients: 44 Weight stable: 63 | Protein, energy-dense, EPA-enriched ONS versus isocaloric, isonitrogenous ONS without EPA → Final analysis compared group with weight loss >1 kg versus those with no more than 1 kg weight loss | 2 cans/day (providing: 620 kcal, 32 g protein +/- 2.2 g EPA) for 8weeks | To determine if weight stabilization is associated with improved survival and HRQoL | Positive - Survival was significantly greater in the weight stable group. Global HRQoL measures significantly improved from baseline to 8 weeks. Weight stability at baseline was associated with the absence of nausea/vomiting and being female | Not reported | Homogenous group | 3-day food diaries have limitations in reliability due to fluctuations of intake in advanced cancer patient who experience nutrition impact symptoms. Post-hoc analysis of data collected to answer a different research question |
| Fearon et al, 2003 (128) | Multicentre, randomised, double blind trial | Patients with unresectable PC who experienced weight loss of >5% in the last 6 months | Intervention : 95 Control: 105 | Protein, energy-dense, EPA-enriched ONS versus isocaloric, isonitrogenous ONS without EPA | 2 x 237 mL cans/day (providing: 620 kcal, 32 g protein, 11 g fat ± 2.2 g EPA) for 8 weeks | Effect of EPA-enriched ONS on weight, body composition, dietary intake and HRQoL | Negative – Weight and lean body mass was not different between groups at the 8-week assessment. Both groups had attenuated weight loss compared to baseline over the study period. There were no differences in performance or HRQoL scores. No difference in survival between the two groups | No adverse events related to the ONS | Large sample size, blinded design | Patients did not consume the full-dose of 2 cans/d (average 1.4 cans/d) |
| Moses et al, 2004 (129) | Randomized controlled double-blind trial | Patients with unresectable PC who experienced weight loss of >5% in the last 6 months | Intervention : 7 Control: 12 | Protein, energy-dense, EPA-enriched ONS versus isocaloric, isonitrogenous ONS without EPA | 2 x 237 mL cans/day (providing: 620 kcal, 32 g protein, 12 g fat ± 2.2 g EPA) for 8 weeks | To assess effect of EPA-enriched ONS on weight, total energy expenditure and physical activity level | Negative – No change in weight or lean body mass from baseline in either group. Energy expenditure and physical activity level was significantly different from baseline in the intervention group, but not controls. | Not reported | Objective measure of plasma fatty acid to assess compliance | Study underpowered. |

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| Ueno et al, 2013 (130) | Randomized, non-placebo, controlled trial | Patients with PC undergoing chemotherapy | Intervention : 43 Control: 23 | EPA-rich ONS versus no supplement | 2 packs/day (Prosure), providing 2.1 g/day of EPA | Efficacy and safety evaluation | Negative – No significant differences in 1-year survival (hazard ratio) were demonstrated, though delayed effect was found in the intervention group | Toxicities were mild and insignificant in both arms | Homogenous group | No placebo |
| Ueno et al, 2014 (131) | Randomized, non-placebo, controlled trial | Patients with PC undergoing chemotherapy | Intervention : 44 Control: 23 | EPA-rich ONS versus no supplement | 2 packs/day (Prosure), providing 2.1 g/day of EPA | Effect of EPA-rich ONS on albumin and C-reactive protein | Negative – No differences in C-reactive protein or albumin at time of progression | Not reported | Homogenous group | No placebo |
| Arshad et al, 2014 (132) | Single-arm, phase II trial | Patients with advanced PC receiving gemcitabine | Full data in 23 patients | Omega-3 fatty acid-rich lipid infusion | Up to 100g (Lipidem: 200 mg/mL 50% medium-chain triglycerides, 40% long-chain triglycerides, 10% fish oil) delivered at 25g/h via peripheral IV infusion given weekly for 3 weeks with one week off. Provides 4.3-8.6 g EPA and DHA | Objective response rate | Negative - Objective response rate was 3/21 patients with evaluable CT. No difference in overall survival or time to progression in those with baseline low or high mannose-binding lectin. Five patients were classified as mannose-binding lectin responders; they showed no improvement in overall survival, but had significantly improved time to progression, over non-responders | Dose reduction of Lipidem in those with grade 2 bloating or chills – unknown number of patients | Novel examination of the effect of omega-3 fatty acids on the mannose-binding lectin pathway of complement. IV infusion allows for optimal study compliance and accuracy in documentation of dosage administered | No control group. Small sample size leading to possible type I errors |
| Arshad et al, 2011 (133) | Single-arm, phase II trial | Patients with advanced PC receiving gemcitabine | 26 patients recruited, only reporting on 13 patients | Omega-3 fatty acid-rich lipid infusion | Up to 100g over 4 hours. Provides 4.3-8.6 g EPA and DHA | Weight change from baseline | Positive – 10/13 patients completing at least 16 weeks of treatment had stable or increased weight over baseline. Weight stabilization or gain occurred in 7/10 patients who completed 24 weeks of treatment | None reported | IV infusion allows for compliance and accuracy in documentation of dosage administered | No control group. Small sample size. Researchers did not report on patients completing less than 16 weeks of treatment |
| Arshad et al, 2014 (134) | Single-arm, phase II trial | Patients with advanced PC receiving gemcitabine | 22 patients who completed at least 3 | Omega-3 fatty acid-rich lipid infusion | Up to 100g (Lipidem: 4.3 g EPA) over 4 hours via peripheral IV infusion given weekly for 3 weeks, with one- | Long-term uptake of prolonged regular treatment | Positive – Pre/post treatment, there was a significant uptake of EPA and DHA fatty acid methyl esters into | Dose reduction of Lipidem in those with grade | Long duration of trial. IV infusion allows for optimal study | No control group. Small sample size. Target dose not achieved in most patients |

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| | | | infusion treatments | | week rest, for up to 6 cycles | courses of parenteral omega-3 fatty acids | plasma non-esterified fatty acid membranes. EPA increased in erythrocyte cell membrane pellet. DHA and n-6 fatty acid methyl esters decreased in erythrocyte membrane pellet. Over the entire treatment period, increased EPA and DHA was sustained in the erythrocyte membrane pellet, as well as a decrease in the n6:n3 ratio | 1 or 2 vomiting, bloating or chills – unknown number of patients | compliance and accuracy in documentation of dosage administered. | |
| Arshad et al, 2017 (135) | Single-arm, phase II trial | Patients with advanced PC receiving gemcitabine | 36 with full HRQoL data, of these, only 35 patients had evaluable CT scans | Omega-3 fatty acid-rich lipid infusion | Up to 100g (Lipidem: 4.3-8.6 g of EPA and DHA) over 4 hours via peripheral IV infusion given weekly for 3 weeks with one week off for up to 6 cycles | To assess if omega-3 augments the anti-tumor effect of gemcitabine and improves HRQoL | Positive – 85.7% (30/35) of patients had disease control, with partial response of liver metastases in 41% (7/17) of patients. Almost half of patients had a 10% increase in global HRQoL (47.2%), and 52.8% in disease-specific symptom scores. Pain was worse in 58.3% of patients | Most common reason for dose reduction was nausea, bloating and chills | IV infusion allows for optimal study compliance and accuracy in documentation of dosage administered | No control group. Small sample size. Target dose not achieved in most patients |
| Barber and Fearon, 2001 (136) | Open-label, dose escalation study | Patients with unresectable PC | 5 patients | EPA-rich emulsion taken orally everyday with dose increased every 2 weeks for 8 weeks | 25 mL/day (4.5g EPA) for 2 weeks → 50 mL/day (9g EPA) for another 2 weeks → 100 mL/day (18 g EPA) for 2 weeks → 200 mL (36 g EPA) for 2 weeks. Progression based on tolerability | Assessment of tolerance, incorporation and effect of EPA in high doses | Positive - Tolerance: 50 mL/day for 1 patient, 75 mL/day for 2 patients, 100 mL/d for 1 patient and 150 mL/d for 1 patient. Two patients gained and three patients lost weight over the 8 weeks. KPS improved or remained stable in all patients. There was a marked increase of EPA in plasma phospholipid levels at both 4 and 8 weeks, although the increase in red blood cell | Dose limitations related to feelings of fullness in three patients, nausea in one patient steatorrhea in 2 patients and abdominal cramping in two patients. | Novel, high-dose EPA supplement was tolerable in patients who commonly experience malabsorption. | No placebo control group. Small sample size. Very difficult to make any conclusions based on this trial |

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| | | | | | | | phospholipid was more muted. | | | |
| Werner et al, 2017 (137) | Randomized controlled double-blind trial | Patients with PC with weight loss of at least 5% since diagnosis | 15 patients received marine phospholipids<br>18 patients received fish oil | n-3 fatty acids delivered as marine phospholipids versus fish oil supplements | 1 x 500 mg soft capsule of marine phospholipids or fish oil taken 3 times/day with meals for 6 weeks. Both supplements provided 300 mg of n-3 fatty acids/day | To compare the effect on body weight, appetite, HRQoL and plasma fatty-acid profiles | Positive – Meal portions increased significantly in both groups and appetite was stabilized. Weight was stabilized from pre-treatment loses in both groups. EPA and DHA was increased significantly in plasma triglycerides and phospholipids in both groups. Additionally, the n:/n:3 ratio decreased significantly in both groups. CRP and albumin did not change significantly. Plasma EPA was positively associated with global health in the fish oil group only | 4 patients taking fish oil experienced pyrosis, "fishy" regurgitation, loss of appetite, diarrhea and increased bowel movements. 1 patient taking marine phospholipids experienced diarrhea in the last week of treatment | Objective measure of compliance. Study design | Small sample size. Possible differences in antineoplastic treatment. PC stage not reported |
| Wigmore et al, 2000 (138) | Prospective, single-arm study | Patients with unresectable PC | 26 patients | EPA supplement | EPA capsules (500 mg/capsule). Dosing: 1 g/d for first week, 2 g/day second week, 4 g/d third week and 6 g/d thereafter, for 12 weeks | To assess if EPA is the biologically active compound of fish oil with anticachectic properties | Negative - Median rate of weight loss was significantly less than baseline at weeks 4, 8 and 12. Body weight did not change significantly. No change in body composition, C-reactive protein, energy intake or performance status was demonstrated. Plasma phospholipid EPA increased significantly and arachidonic acid decreased | Nausea in 3 patients, steatorrhea in 2 patients | Objective measure of plasma fatty acid to assess compliance | Small sample size. No control group |
| Wigmore et al, 1996 (139) | Prospective, single-arm study with retrospective control | Patients with unresectable PC | Fish oil: 18<br>Gamma-linolenic acid: 20 | Fish oil supplement versus Gamma-linolenic acid | Soft gelatine capsule (1 g fish oil) taken 2 g/day for first week and increasing by 2 g/week until a maximum of 16 g/d. Gammalinolenic | To assess effect on nutritional parameters and the acute | Positive – Significant weight gain or weight stabilization compared to baseline in 14 patients. No significant change in | Offensive tasting regurgitation or transient diarrhea | Objective measure of plasma fatty acid to assess compliance | Small sample size. Compared to another intervention done retrospectively, rather than a control |

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| | | | | | acid administered for 10 days via IV (~7.6 g/day) and followed by an oral capsule starting at 3 g/day and rising to a maximum of 6 g/day | phase response | body composition. C-reactive protein also decreased significantly after 1-month supplementation, but was not maintained after 3 months. There was no change in resting energy expenditure. Those who received gammalinolenic did not experience a reduction in weight loss. | | | |
| ***Preoperative nutrition interventions*** | | | | | | | | | | |
| Braga et al, 2012 (140) | Double-blind placebo-controlled randomized pilot trial | Patients awaiting elective pancreatico-duodenectomy for PC or periampullary cancer | Intervention: 18<br>Control: 18 | Preconditioning ONS (containing glutamine, antioxidants and green tea extract) vs placebo | Three doses taken per os preoperatively: 1) at 3 pm the day before surgery, 2) 6 hours after first dose, 3) 3 hours before anesthesia on the day of surgery | Effect of ONS on postoperative antioxidant capacity and inflammatory response | Negative- There was significantly lower endogenous antioxidant capacity in the placebo group on post-operative day 1, 3 and 7. No significant differences in c-reactive protein or F-2 isoprostanes. Vitamin C was greater than placebo on POD 1 only. There were no post-operative differences in vitamin E, selenium and zinc | No adverse events or reactions to the ONS occurred | Compliance to treatment by 100% of participants | Plasma values provide an estimate of actual endogenous antioxidant defense status. Supplement only given preoperatively |
| Gade et al, 2015 (141) | Single centre, parallel, randomized controlled trial with a balanced randomization | Patients with PC who were eligible to receive potentially curative surgery | Intervention: 19<br>Control: 16 | Immunonutrition ONS versus standard care (pre-operative nutritional screening and counselling by a nurse) | ONS in powder form to be diluted in 250 mL water. 1 package ONS contain 16.8 g protein. Goal protein intake of 1.5 g/kg body weight, with ONS making up protein deficit from diet. | Effect of intervention on postoperative outcomes and hospital length of stay | Negative – No significant difference in complications graded according to severity or length of hospital stay between the groups. No difference in body weight or functional capacity was observed. No differences were found in a subgroup analysis of compliant patients. | Fluctuating glycemia in 1 diabetic participant | Homogenous group, control group | Large and unanticipated variance on overall complication rate likely led to the study being underpowered. Food frequency questionnaire used to estimate protein intake may be inaccurate |
| Martin et al, 2017 (142) | Randomized, non-placebo-controlled trial | Stage 3, locally advanced PC awaiting irreversible | Intervention: 40<br>Control: 27 | Immunonutrition ONS versus no supplement | 3 bottles/day (Nestle IMPACT Advanced Recovery) for 5 days prior to surgery | To assess the effect on length of hospital stay, | Positive – Length of hospital stay was significantly less in the ONS group. Fewer | No adverse effect of the ONS occurred | Homogenous group of patients | Strange randomization scheme based on access to ONS and |

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| | | electroporation surgery | | | | infectious complications and morbidity | complications in the ONS group. There were fewer infectious and gastrointestinal complications in the ONS group, however severity of complications was the same in both groups | | | ability to pay for it. No placebo. No compliance measure for ONS reported |
| Silvestri et al, 2016 (143) | Prospective, single-arm study with a retrospective, matched control group | Well-nourished patients with PC, awaiting surgery | Intervention: 48<br>Control: 48 | Immunonutrition ONS versus no supplement | 3 bottles/day, 750 mL/day (Oral Impact) for at least 5 days prior to surgery. ONS provided: 423 kcal energy, 22.8 g protein, 1.8 g omega-3 fatty acids, 5.4 g arginine | To assess whether immunonutrition improves outcomes | Positive - Infectious complications were significantly more frequent in the group without ONS. Length of hospital stay days were significantly greater in those without ONS. There were no other differences in post-operative complications | 9/48 patients reported adverse events: Abdominal distension (3 patients), nausea (2 patients), vomiting (1 patient) and abdominal cramps (1 patient) | Authors clearly explained how selection bias was avoided in the retrospective control group | Results should be confirmed in a prospective, randomized, placebo-controlled trial |
| Tumas et al, 2020 (144) | Prospective, randomized cohort study | Patients with suspected PC awaiting pancreatoduo-denectomy | Intervention: 30<br>Control: 40 | Immunonutrition ONS versus no supplement | 2 bottles/day (Cubitan Nutricia) providing 6.04 g/day of L-arginine and 4 g/day of polyunsaturated fats | Relationship between immune and nutritional impairments and surgical outcomes | Positive – 40% of patients were cachectic, and low muscle mass in over half of patients. Nutritional status had a large effect on post-operative complications. There were no significant differences in postoperative CRP or IL-6 between intervention and control | Not reported | Well defined nutritional evaluation | Heterogenous population. Most of the analysis did not account for the intervention. No indication of compliance to the intervention. Questionable statistical analysis |
| ***Dietary counselling*** | | | | | | | | | | |
| Kim et al, 2019 (145) | Prospective, randomized, non-placebo trial | Patients with PC and bile duct cancer who were schedule to receive chemotherapy | Final analysis as follows: Intervention: 15<br>Control: 19 | ONS + dietary counselling by a registered dietitian versus dietary counselling alone | Two ONS packs (300 mL) per day (Medifood Miniwell OS providing: 400 kcal, 19 g protein, 12 g fat and 58 g carbohydrates) taken for 8 weeks | To assess weight, body composition, PG-SGA, nutritional intake and HRQoL | Positive – Energy, protein, carbohydrate and fat intake increased significantly from baseline in the ONS group. Only protein intake increased in the control group. Weight, fat-free and skeletal | Not reported | Good compliance to supplement use (90.2%), likely due to small volume. | No placebo. Small sample size. Not all patients began ONS treatment at cycle 1 of chemotherapy. Heterogenous patient population. Almost half of ONS group patients were |

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| | | | | | | | body mass did not change significantly in either group. Only fat mass increased significantly in the ONS group. Overall PG-SGA score improved in both groups. Overall HRQoL did not improve in either group | | | well-nourished at baseline |
| Quashie, 2019 (146) | Secondary analysis from a randomized controlled trial | Newly diagnosed patients with PC awaiting surgical resection | 64 patients | High-protein diet counselling by a registered dietitian to improve protein intake. Whey protein supplement | Recommended protein intake of 1.3 g/kg/day based on actual body weight, or adjusted body weight in those exceeding 125% of ideal body weight. Whey protein was used to make up for dietary protein deficits | To determine whether participants met estimated protein needs at each stage of treatment | Negative – The number of patients who met their protein needs rose from 18.8% at baseline to 52.4% preoperatively. The difference between protein goal and average intake was not significant. At 1-2 months post-operative, only 17% of patients met their protein goals, with mean intake below baseline. At 3-4 months after surgery, only 19.1% of patients met their protein needs | Not reported | Standardized dietary recommendations | Small sample size. The use of 24-hour recall, rather than more accurate intake assessment method |
| Vashi et al, 2015 (147) | Retrospective study | Patients with PC | 304 patients | Registered dietitian-led medical nutrition therapy based on baseline nutritional status determined using Subjective Global Assessment | A minimum of 3 visits in 6 months. In well-nourished patients: Addressed nutrition impact symptoms, healthy eating. In moderately malnourished patients: high energy-protein diet, ONS, ensure adequate nutrient absorption, consider need for enteral feeding and assess need for appetite stimulants/prokinetics. In malnourished patients: Consultation with medical nutrition support team for evaluation of | To assess nutritional and survival outcomes of medical nutrition therapy | Positive – Nutrition status was unchanged in 125 patients and improved in 87 patients. Previous treatment, sex, change in nutritional status and evidence of biological cancer activity were independent predictors of cancer survival. | Not reported | Large sample size | Study design. Heterogeneous treatment modalities in patients. Medical nutrition therapy was applied at different times in the course of patients' treatment |

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| | | | | | feeding tube placement or parenteral nutrition | | | | | |
| McCallum et al, 2002 (148) | Retrospective study: convenience sample of randomly selected deceased patients | Patients with PC cancer who had been followed by the Palliative Medicine Program | Intervention: 17<br>Control: 17 | Prophylactic, gastrointestinal/ soft diet, instruction by a registered dietitian versus standard care | One initial nutrition assessment (40 min), one diet instruction (40 min), and one follow-up telephone contact to ensure compliance (20 min). The control group did not receive specific instructions for a soft diet | To assess efficacy of a gastrointestinal/soft on decreasing the occurrence of bowel obstruction | Positive – None of the intervention group developed bowel obstruction prior to their death, whereas 71% of the control group did | Not reported | Specific intervention | No information on dietary intake at baseline. No information on compliance. Retrospective design |
| ***Vitamin D*** | | | | | | | | | | |
| Blanke et al, 2009 (149) | Single-arm, phase II trial | Patients with unresectable PC receiving Docetaxel | 25 patients | Oral calcitriol supplement | Calcitriol 0.5 µg/kg per os, divided into four equal parts and administered every hour over a 4-hour period on the day before receiving Docetaxel. This was repeated weekly for 3 weeks, followed by 1 week of rest | Time to progression | Negative - Partial response, n = 3. Stable disease, n = 7. Median time to progression, 15 weeks. Median overall survival, 24 weeks → this is not different than Docetaxel alone | Hyperglycemia (13%) and grade 3 fatigue (9%) were the most reported toxicities, however they were due to Docetaxel or its pre-treatment and not calcitriol | Homogenous group of patients | Study underpowered. No control group |
| Klapdor et al, 2012 (150) | Prospective, unblinded, single-arm study with unmatched, healthy controls | Patients suffering from exocrine pancreatic insufficiency due to PC or chronic pancreatitis | 103 patients with PC | Oral vitamin D supplement with pancreatic enzyme replacement therapy | Dose varied from 1000 IU per day over 1 x 20,000 IU per week, or 2-3 times 20,000 IU per week, up to 20,000 IU per day | To assess extent and number of patients in which 25(OH)D can be normalized | Positive – At baseline, 94.2% of PC patients and 87% of controls had serum 25(OH)D <30 ng/mL. Vitamin D supplementation increased serum 25(OH)D from 11.9±5.4 ng/mL to 46.6±15.7 ng/mL in PC patients, however they needed larger doses to achieve this (up to 20,000 IU per day) | No adverse events occurred | Large sample size | Data on sun exposure, diet, malabsorption not collected. Dietary advice received by patients not reported. Unclear duration of intervention |
| ***Enteral nutrition*** | | | | | | | | | | |
| Hendifar et al, 2020 (151) | Prospective, single-arm study | Patients with PC with cachexia (unintentional weight loss | From 31 patients, 16 evaluable for primary outcome | Peptide-based, jejunal tube feeding | Intervention lasted 3 months. Method to determine nutrition prescription not detailed | Weight stability | Positive – Weight stability was achieved in 62.5% of participants | Not reported | Heterogenous patient population | Small sample size. Tolerance and compliance to enteral feeds not reported |

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| | | >5% in the previous 6 months) | | | | | | | | |
| ***Parenteral nutrition*** | | | | | | | | | | |
| Pelzer et al, 2010 (152) | Prospective, single-arm trial | Patients with PC with weight loss over 5% in the previous 4 weeks or BMI below 19 | 32 patients | Overnight, home-based, parenteral nutrition | Parenteral nutrition administered nightly on 5 times/week, which provided: 25 kcal/kg, 1.2-1.5 g/kg of amino acids, at least 35% fat of the whole energy content, additional vitamins and electrolytes only if indicated and no additional glutamine or n-3 fatty acids | To assess nutritional status through bioelectrical impedance analysis parameters | Positive – Phase angle as measured by bioelectrical impedance analysis increased by 10% from baseline, with 28/32 patients either demonstrating an increase or maintenance. BMI was stable or increased in 28/32 patients. The ratio of extracellular mass to body cell mass was maintained or decreased in 25/32 patients | No adverse effect of treatment observed | Parenteral nutrition therapy applied in addition to normal PO intake or enteral feeding | Small sample size. Accuracy of bioelectrical impedance analysis unclear, partially due to hydration status, recent physical activity and food consumption which were not controlled for. Authors did not report average energy intake from parenteral nutrition |
| Richter et al, 2012 (153) | Prospective, single-arm study, with post-hoc division of patients into groups based on survival | Patients with PC undergoing chemotherapy | Survival >5 months: 10 Survival of 5 months or less: 7 | Overnight, home-based, parenteral nutrition | Parenteral nutrition was administered between 4 and 7 days/week, with daily indication for those consuming <500 kcal/day per os. Parenteral nutrition compounding based on patient body weight, age and individual needs. Both groups received a median of 24 kcal/kg, lipids were 34% in those who survived more than 5 months and 33% in those with survival less than 5 months. Vitamins, electrolytes and trace elements were added if necessary. N-3 fatty acids were added in 13/17 patients | To assess amelioration in nutritional status | Positive – Weight and bioelectrical impedance analysis parameters increased in those with survival >5 months, but not in those who survived <5 months. There was no difference in energy given per week, and macronutrients provided per day, between the groups. There was no difference in the amount of n-3 fatty acids, electrolytes, vitamins and trace elements provided to the 2 groups. | Transient minor nausea and dyspnoea were reported in 2 patients however it was unclear if this was due to parenteral nutrition or chemotherapy | Individualized composition of parenteral nutrition versus all-in-one bags | Small sample size, post hoc division of patients. Unclear how tolerability or improvement in symptoms/ HRQoL was assessed |
| ***Supplements and alternative interventions*** | | | | | | | | | | |
| Dhillon et al, 2008 (154) | Nonrandomized, open-label, phase II trial | Patients with PC, not receiving antineoplastic treatment, only supportive care | 25 patients, (24 evaluated for toxicity and 21 for tumor | Curcumin supplement | 8 g of curcumin/d (8 x 1g caplets) taken per os for 8 weeks | To determine biological effect of curcumin | Negative – oral bioavailability was poor. One patient had stable disease for >18 months, and one patient had tumor | No treatment-related adverse effects | Levels of circulating cytokines compared to healthy controls | Authors cannot explain biological activity despite measured low bioavailability of curcumin |

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| | | for 8 weeks. Antineoplastic treatment could resume after the 8-week period | response) + cytokine levels measured in 48 to 62 healthy volunteers | | | | regression with significant increase in circulating cytokines. There was only a trend towards decreased in nuclear NF-κB, and a significant decline in COX-2 expression and pSTAT3 activation. | | | |
| Epelbaum et al, 2010 (155) | Open-label, phase II trial | Patients with previously untreated locally advanced or metastatic PC, receiving weekly Gemcitabine | 17 patients enrolled, but only 11 patients were eligible for evaluation | Curcumin supplement | 500 mg capsules, with a 4000 mg dose taken twice a day on an empty stomach for a total of 8000 mg per day | To evaluate activity and feasibility | Negative – Partial response = 1 patient, stable disease = 4, tumor progression = 6. Median time to progression was 2.5 months and overall survival was 5 months | Gastrointestinal toxicity (abdominal fullness, pain) was reported in 7 patients. Toxicity was Grade 3 in 5 of these patients, leading to cessation of the curcumin. One patient developed a coffee-ground emesis and was found to have an active peptic ulcer | Homogenous group | Study design did not include an escalating dose of curcumin, as previous studies demonstrated tolerance of 8000 mg/d. No control group |
| Kraft et al, 2012 (156) | Prospective, multi-centre, placebo-controlled, randomized and double-blinded trial | Patients with advanced, unresectable PC, regardless of concomitant or scheduled chemotherapy | 26 evaluable patients Intervention : 14 Placebo: 12 | L-Carnitine supplement versus placebo | Oral, liquid formulation of L-Carnitine, 4 grams/day for 12 weeks | To investigate the role of L-Carnitine on cancer cachexia | Negative – BMI and body fat increased in the treatment group, but not placebo. No difference was found in CRP, albumin, leukocyte count and CA19-9. Survival was not different. Improved cognitive function, improved global health status and reduction of gastrointestinal symptoms was found | No treatment-related side-effects reported | Placebo controlled | Study likely underpowered |

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| | | | | | | | in the intervention, but not placebo group | | | |
| Yanagimoto et al, 2016 (157) | Open-label, non-randomized prospective cohort study | Patients with unresectable PC receiving Gemcitabine | AHCC group: 35 Control (as per patient choice): 40 | AHCC versus non-treatment control | 6 g of AHCC/day for 8 weeks (2 cycles of Gemcitabine) | The effect of AHCC in the reduction of adverse events due to Gemcitabine | Positive – C-reactive protein was lower and albumin higher in the AHCC group. Taste alterations were less frequent in the AHCC group. There were fewer patients with grade 3 modified Glasgow Prognostic scale in the AHCC group than control. No hematological differences were observed | Not reported | Mix of subjective (patient-reported) and objective measure to assess adverse events | Non-randomized trial, not placebo controlled |
| Lozanovski et al, 2020 (158) | Unblinded, prospective, placebo-controlled, parallel-arm pilot study | Patients with pancreatic cancer receiving palliative chemotherapy | 40 patients; 29 treatment and 11 placebo | Broccoli sprout supplementation versus placebo | Daily intake of 15 capsules with pulverized broccoli sprouts containing 90 mg (508 µmol) sulforaphane and 180 mg (411 µmol) glucophanin for 1 year. Placebo capsule contained methylcellulose | Feasibility | Negative – 21% of participants in the treatment group dropped out within 30 days of beginning the study, with a 72% dropout rate before 1 year | Possible nausea, vomiting, flatulence that could not be distinguished from symptoms of pancreatic cancer | Homogenous group | Unable to blind the study due to smell of broccoli sprouts. Unable to make conclusion of effectiveness of the treatment given poor compliance and high dropout rate – no formal assessment of compliance in patients who remained in the study was reported |
| Hamaguchi et al, 2020 (159) | Retrospective study | Patients with metastatic or recurrent PC receiving chemotherapy | 28 patients | Alkalization therapy: Alkaline diet and bicarbonate therapy | Diet: At least 400 g of fruits and vegetables daily, and avoidance of meat and dairy products Bicarbonate therapy: 3-5 g/d of oral bicarbonate when urine pH was ≤7 or when patients wanted to take it | Effect on urine pH and survival | Positive - Urine pH increased after alkalization therapy. Survival was greater in the patients who achieved urine pH of ≥7, than those with <7 | Not reported | Assessment of dietary compliance with exclusion of patients who were unable to follow alkaline diet | Small sample. No control group. Bicarbonate use was not standardized. Normal renal and pulmonary regulation of pH cause of alkaline urine; difficult to extrapolate any effect on cancer. Questionable statistical analysis |
| Gonzalez and Isaacs, 1999 (160) | Unblinded, single-arm, pilot, prospective case series | Patients with PC | 11 patients | Diet, oral supplementation with nutrients and enzymes and detoxification | Diet: Raw fruits and raw or lightly steamed vegetables + daily vegetable juices. Plant-based proteins. 1-2 eggs/week, daily yogurt, | Length of survival from diagnosis | Positive – 81% survived 1 year, 45% survived 2 years and 36% survived 4 three years. This is greater than the 25% survival | Not reported | Very clear inclusion and exclusion criteria | Some of the patient included in the final analysis did not meet inclusion criteria. Does not report compliance. |

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| | | | | | fish 2 to 3 times/week. Red meat and poultry forbidden.<br>Supplements: Vitamins, minerals and trace elements. Freeze-dried beef or lamb organ supplements (thymus, liver). 25-40 g of porcine lyophilized pancreas product (130-160 capsules/day)<br>Detoxification: twice-daily coffee enemas | | after 1 year and 10% survival at two years for all stages of PC at the time of publication | | | Does not report baseline characteristic of patients' nutritional or functional status. Does not report if any anti-neoplastic treatment was given during treatment period. Does not report duration of treatment for each patient. Small sample size. No control group. Selection bias due to patients being recruited from patient population of the authors, and not from a cancer centre |

AHCC = Active hexose correlated compound; BMI = body mass index; CRT = chemoradiotherapy; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; KPS = Karnofsky performance status; ONS = oral nutritional supplement; PC = pancreatic cancer; POD = post-operative day; HRQoL = health-related quality of life

Table 3.4.: Summary of Selected Articles With Exercise Interventions

| Author, Year | Study Design | Patient Characteristics | Sample Size | Training Intervention | Training Dose | Primary Objective | Outcomes | Adverse Events | Strengths | Limitations |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Aerobic exercise interventions*** | | | | | | | | | | |
| Denlinger et al, 2017 (161) | Randomized, controlled pilot trial | Patients with unresectable PC | 25 out of 37 recruited patients completed the study Intervention: 11 Usual care (control): 14 | Walking program versus usual care | Details of the walking program not reported | Safety and feasibility | Positive – 68% of patients completed the study. Declining health was the primary reason for not completing the intervention. There was a significant increase in average duration of physical activity in the intervention group at follow-up. There was a trend toward improved symptoms | No adverse events were reported by participants | Demonstrates feasibility and safety of such a program in PC | Cannot make any inferences based on these results due to small sample size |
| Yeo et al, 2012 (162) | Two-arm, prospective, randomized controlled trial | Patients with resected pancreatic and periampullar cancer | Walking intervention: 54 Usual care (control): 48 | Home-based graduated walking program | Brisk walking for 90 to 150 minutes per week in 3 to 5 sessions for 3 months | To assess effect on cancer-related fatigue, physical function and HRQoL | Positive – Fatigue decreased significantly in the walking group, but not control at study completion. No differences in performance status were reported. Short form-36 health survey physical component score only improved in the intervention group. No difference in symptom burden was found | Not reported | Validated assessment tools | No stratification for pre-diagnosis physical activity. Less phone follow-up in the control group, which the authors deem important to the success of the intervention group |
| ***Resistance/strengthening exercise interventions*** | | | | | | | | | | |
| Cieslak, 2012 (163) | Case study | 54 y male status-post Whipple procedure | n = 1 | Supervised abdominal muscle training, trunk stretching, spine stabilization | Rehabilitative ultrasound imaging was utilized during abdominal muscle training and exercises were | To describe the results of a comprehensive physical therapy program addressing impairment | Positive - Improvements in pain, muscle performance and functional scores were reported at 5 weeks, 12 and 18-months post-op. | Not reported | Identifies domains that a comprehensive physical therapy program should include following a | Results not generalizable |

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| | | | | exercises, diaphragmic breathing, education for transfer and safe body mechanics, progressive strengthening exercises | progressed based on performance | and functional limitations post Whipple procedure | | | Whipple procedure | |
| Steindorf et al, 2019 (164) | Three-arm, randomized controlled trial | Patients with PC, both resectable or non-resectable | Supervised resistance training: 9 Home-based resistance training: 21 Usual care (control): 17 | Supervised versus home-based resistance training versus usual care (control) | Exercise session in both groups was 60 min, 2 times/week for 6 months. Resistance training targeted major muscle groups of the upper and lower extremities. Session included 8 exercises of 2-3 sets each with 8 to 12 repetitions. Intensities were 60-80% of 1-RM in the supervised group and 14-16 on the Borg scale of perceived exertion in the home-based group | Effect of intervention on HRQoL and fatigue | Positive – At 3 months, physical functioning, global HRQoL, cognitive functioning, sleep problems, physical fatigue and reduced activity were significantly different than controls. This was not the case at 6 months | No adverse events occurred | Randomization strategy with control group | Small sample size, underpowered study |
| Wiskemann et al, 2019 (165) | Three-arm, randomized controlled trial | Patients with PC, both resectable or non-resectable | Supervised resistance training: 9 Home-based resistance training: 20 Usual care (control): 14 | Supervised versus home-based resistance training versus usual care (control) | Exercise session in both groups was 60 min, 2 times/week for 6 months. Resistance exercises in both groups included: leg | To assess feasibility of progressive resistance training during and after chemotherapy (>50% adherence), and potential | Positive - Mean overall training adherence in both intervention groups was 59.2%. Adherence to supervised sessions was 64.1% and home-based was 78.4%. The 22 | No adverse event occurred | Three-armed randomization | Small sample size, uneven sample in each arm |

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| | | | | | press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly reverse and crunch. Sessions included 8 exercises of 2-3 sets each with 8 to 12 repetitions. Intensities were 60-80% of 1-RM in the supervised group and 14-16 on the Borg scale of perceived exertion in the home-based group. | effects on muscle strength and cardiovascular fitness | patients who completed the study performed more than 50% of the intervention. Maximal isokinetic peak torque improved significantly in the supervised group for elbow flexors and extensors compared to the home-based and control group. Maximal voluntary isometric contraction improved significantly in the supervised group for elbow flexors compared to control. Both intervention groups improved in knee extensors. In cardiorespiratory fitness, only work rate peak improve in the supervised group compared to the two other groups | | | |
| Kamel et al, 2020 (166) | Randomized controlled trial | Patients with pancreatic cancer with cachexia (weight loss of >5% in 6 months or weight loss of >2% in those with BMI <20 kg/m$^2$) | 40 patients | Resistance training versus no intervention | Small, supervised group training sessions (1-4 patients) twice weekly for 12 weeks. Machine-based exercises: leg press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly | Improvement in mobility, muscle strength and lean body mass | Positive - Significantly improved 400-meter walk test, 6-meter usual walk test and chair rise test were found in the intervention group compared to control. Peak torque of knee extensors, elbow flexors and elbow extensors was found in the intervention group. | Not reported | Homogenous group. Clearly defined intervention. Robust statistical analysis | Selection bias in that the patients were well functioning and motivated to partake in resistance training |

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| | | | | | reverse and crunch. First 4 weeks: 1-2 sets of the first 5 exercises for 20 reps at low to moderate intensity (50-60% 1-RM). At week 5: Eight exercises, 3 sets of 8-12 repetitions at moderate to high intensity (60-80% 1RM). Progressive weight increase was implemented | | Lean mass of the upper and lower limbs also improved in the resistance training group | | | |
| ***Combined aerobic and resistance/strength training interventions*** | | | | | | | | | | |
| Parker et al, 2019 (167) | Prospective, single-arm study | Patients with PC undergoing chemotherapy or chemoradiation for at least 6 weeks prior to pancreatectomy | 9 patients underwent neoadjuvant chemotherapy and chemoradiation, 13 patients received neoadjuvant chemotherapy only, 20 patients received neoadjuvant chemoradiation and a rest period only | Multimodal, home-based exercise program | At least 60 minutes per week (20 minutes x 3 days per week) of moderate-intensity aerobic exercise. At least 60 minutes per week (30 minutes x 2 non-consecutive days) of 8 exercises including proximal upper body, shoulders, abdominals, back and legs. full-body strength training. 3 sets of 8 to 12 | To assess the amount of exercise that can be realistically and safely prescribed | Positive - 81% met weekly aerobic exercise recommendations. Only 21% met strengthening exercise recommendations. Mean moderate to vigorous activity measured by accelerometer exceeded recommendations in those undergoing radiation and a rest period, but not chemotherapy during exercise intervention, however a wide standard deviation was reported | Not reported | Both objective (exercise logs) and subjective (accelerometer) assessments of compliance | Wide variability in antineoplastic treatments. Small sample size |

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| | | | | | repetitions using resistance tubes | | | | | |
| Florez et al, 2018 (168) | Single-arm, pilot study | Patients with potentially resectable PC receiving concurrent chemotherapy or chemoradiation | 58 patients completed the exercise program, however specimens of only 28 patients examined | Home-based aerobic and strength training | Details of the program not reported, however patients completed an average of 145.8 minutes of moderate to vigorous physical activity/week for an average of 15 weeks prior to surgery | To assess whether a sufficient amount of exercise can be performed to improve vascular function | Positive – Significantly increased vessel density and increased number of elongated vessels | Not reported | Objective measure of change in tumor biology due to exercise | Unclear control group |
| Hile et al, 2018 (169) | Feasibility phase of a pilot randomized controlled trial | Patients with PC awaiting surgery | Intervention: 20 Control: 10 | Home-based exercise program including endurance training (seated ergometer) + 7-8 active range of motion exercises or strengthening exercises (including adjustable arm and leg weights) | Daily goal of 60 minutes at rating of perceived exertion of 13 | Adherence | Positive - 88.9% of patients completed 75-100% prescribed range of motion exercises, 78.9% completed the strengthening exercises | Not reported | Homogenous group | Unclear what the control group did |
| Marker et al, 2018 (170) | Case series (designed as a randomised trial, however reported as a case series due to poor recruitment) | Patients with PC, undergoing neoadjuvant chemotherapy | 3 patients | Supervised, preoperative aerobic and resistance exercise program | 60-minute sessions, 2 to 3 times per week, with an exercise physiologist. 10- minute aerobic warm-up (performed on a treadmill, elliptical, rowing machine or | Feasibility and effectiveness on preserving or improving physical fitness, muscle mass and HRQoL | Positive – Appendicular skeletal muscle mass index, 400m walk test, and patient reported physical function improved in all participants | Not reported | Comprehensive exercise intervention | Cannot generalize findings due to small sample |

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| | | | | | recumbent bike), followed by 45 minutes of combined aerobic, resistance (body weight, free weights and weight machines) exercises targeting major upper, lower muscle groups as well as core stability, and flexibility exercises. Intensity: Heart rate of 85% or less of heart rate reserve | | | | | |
| McLaughlin et al, 2019 (171) | Case report | 47 y male with PC undergoing chemotherapy | n = 1 | Supervised aerobic and resistance exercise sessions | 12-week exercise program administered 2x/week on non-consecutive days, including: 5-minute warm-up and cool-down; 8 lower-body resistance exercises performed for 3 sets of 12 repetitions at 60% of 1-RM based on 12-RM baseline strength testing; 15 minutes of continuous cycling on ergometer at 70% of | To assess the effect of exercise on physical and psychological wellbeing | Positive – decrease in body fat percentage and increase in lean body mass and weight. Lower body strength, aerobic capacity and functional tests improved over the 12-month period. Fatigue and psychological distress, but not sleep quality, improved with exercise | No adverse events from exercise | Objective outcomes and patient reported subjective outcomes assessed | Cannot generalize findings. Exercise intervention excluded upper body due to peripherally inserted central catheter |

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| | | | | | maximum heart rate, cycling was also performed for 40 minutes during chemotherapy infusion | | | | | |
| Niels et al, 2018 (172) | Case report | 46 y male with advanced PC | n = 1 | Supervised aerobic and strength training | 2x/week, Strengthening exercises: two sets of 8-10 repetitions at 70-80% hypothetical 1-RM Aerobic exercise: two sets of 8 minutes each on a bicycle ergometer and cross-trainer-ergometer at 70-80% maximum watt. Concentric resistance exercises were added preoperatively for ~1 month to prepare for surgery (30% hypothetical 1-RM) | Feasibility and effect of intensive exercise program | Positive – Overall maintenance of BMI and weight over the 7-month period. Improved physical performance from baseline to 3 months in all measures. Decline in leg curl, seated row, abdominal crunch at 7 months compared to 3 months, although all measures still greater than baseline. Overall HRQoL improved from baseline to 3 months and remained stable at 7 months. | No adverse effects from exercise | Program adjusted depending on treatment that patient underwent (surgery versus chemotherapy) | Cannot generalize findings |
| Cormie et al, 2014 (173) | Case study | 49 y male with PC | n = 1 | Supervised, group exercise session led by an accredited exercise physiologist. Patient was encouraged to engage in home-based aerobic training to | Supervised sessions were performed twice/week and included: 5-minute warm-up and cool-down + 10 resistance exercises targeting major muscle groups (leg press, leg press, leg curl, | Safety and efficacy to improve clinical outcomes | Positive - Aerobic capacity, muscle strength and physical function improved from baseline at both the 3 month and 6-month assessments. Whole body and appendicular lean mass, as well as whole body and trunk fat mass increased. | No adverse events occurred | Both physical and psychological domains assessed. Long duration of study | Not generalizable to all patients with PC |

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| | | | | supplement supervised sessions | calf raise, hip abduction and adduction, chest press, seated row, triceps extension, bicep curl) + 15-20 minutes aerobic exercise (cycling, walking) | | Improvements were also reported in HRQoL, fatigue, sleep quality and psychological distress | | | |

RM = repetition maximum; PC = pancreatic cancer; HRQoL = health-related quality of life

Table 3.5.: Summary of Selected Articles With Diet and Exercise Interventions

| Author, Year | Study Design | Patient Characteristics | Sample Size | Diet and Training Intervention | Diet and Training Dosing | Primary Objective | Outcomes | Adverse Events | Strengths | Limitations |
|---|---|---|---|---|---|---|---|---|---|---|
| Griffin et al, 2018 (174) | Single-arm, feasibility study | Patients with PC, receiving neoadjuvant chemotherapy prior to surgery | Reporting on 9 patients who have completed the study | Intensive nutritional counselling + pancreatic enzyme replacement therapy + EPA-rich ONS + individualized step target | Not detailed | Feasibility | Positive – 100% of patients attended nutrition appointments, 89% utilized enzymes, 78% took ONS and 67% met step count target. Barriers to ONS included taste aversion/fatigue. Barriers to meeting step count included chemotherapy-induced neuropathies, treatment side-effects and fear of acquiring infection | Not reported | Multimodal intervention | Unclear if patients are cachectic |
| Ngo-Huang et al, 2017 (175) | Single-arm, prospective pilot study | Patients with PC awaiting surgical resection and undergoing neoadjuvant chemotherapy or chemoradiation | Complete data in 15 patients | Home-based exercise program + nutrition intervention | At least 60 minutes per week (20 minutes x 3 days per week) of moderate-intensity aerobic exercise. At least 60 minutes per week (30 minutes x 2 non-consecutive days) of 8 exercises including proximal upper body, shoulders, abdominals, back and legs. full-body strength training. 3 sets of 8 to 12 repetitions | To assess adherence to a home-based exercise program | Positive - 12 of 15 participants met or exceeded the recommendations for aerobic exercise, however only 6 of 15 met or exceeded strengthening recommendations. 80% of patients completed a total of 120 minutes of exercise/week. | Not reported | Program designed based on the American Cancer Society and American College of Sports Medicine guidelines for exercise in cancer survivors | No control group. Wide variation in both oncological treatment and duration of intervention. Subjective measure of exercise compliance. No measure of compliance to nutrition |

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| | | | | | using resistance tubes. Nutrition advice to consume a protein-rich meal or snack (at least 20 g) within an hour of completing strength training. | | | | | |
| Ngo-Huang et al, 2019 (85) | Single-arm, prospective trial | Patients with PC awaiting surgical resection and undergoing neoadjuvant chemotherapy or chemoradiation | Complete data in 45 patients | Home-based exercise program + nutrition intervention | At least 60 minutes per week of moderate-intensity aerobic exercise. At least 60 minutes per week (30 minutes x 2 non-consecutive days) of full-body strength training. Nutrition intervention to meet energy/ protein needs, management of nutrition impact symptoms and advice to consume a high-protein meal, snack or supplement within an hour of completing strength training | To assess relationship between physical activity, physical functioning and HRQoL | Positive - Six-minute walk distance, five times sit to stand and three-meter walk test all improved significantly compared to baseline. No change in HRQoL scores. Patient reported aerobic exercise, accelerometer-measured moderate-to-vigorous and light physical activity were associated with increased 6-minute walk distance | Not reported | Both self-reported and objective measurements of physical activity to assess compliance | No control group. Wide variation in both oncological treatment and duration of intervention. |
| Bui et al, 2019 (176) | Single-centre, parallel-arm, randomized control trial | Hepatobiliary and PC patients awaiting surgery | Intervention (prehab) = 17 Control (rehab) = 18 | Prehab: once-weekly supervised + home-based exercise program + nutritional | Diet: whey supplement and high-protein diet = 1.5 g/kg/day Exercise: Strength and | Effect on functional exercise capacity as determined by the 6-minute walk test | Positive - The prehab group had a clinically meaningful improvement in 6-minute walk test distance compared to baseline | None reported | Trimodal intervention | Small sample size. Heterogenous group of patients |

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| | | | | counselling + whey protein supplement + relaxation exercise started 4 weeks prior to surgery and continued for 8 weeks post-op Rehab: Same intervention (without supervised exercise) for an 8-week postoperative period | aerobic training + stretching. No details on the relaxation intervention provided | | preoperatively. Statistically significant decline in 6-minute walk test distance occurred in the rehab group, but not the prehab group, 4 weeks after surgery | | | |
| Nakajima et al, 2018 (177) | Prospective case with matched-control (propensity score-matching) study | Patients with hepato-pancreatico-biliary cancer awaiting surgery | Intervention: 76 Historical controls: 76 | Preoperative exercise and nutrition intervention versus standard care | Exercise: 60 minutes of home-based 3 times/week. 30 minutes of walking with at least 2 sets x 10 repetitions of squats, calf raises, sit ups bridge ups, upper-limb movements with weight. Nutrition: Leucine-rich essential amino acid supplement taken within 30 mins pre/post-exercise | To assess effect on physical fitness, nutritional status, postoperative complications and length of hospital stay | Positive – There were fewer cases of post-op bile leakage and less hospital length of stay in the intervention group. Both groups lost weight from baseline to pre-op measures. Serum albumin dropped in the control group only. Prognostic nutritional index increased in the intervention group. Six-minute walk test difference improved significantly in the intervention group compared to baseline. | Not reported | Stated methodology on how matched-controls were chosen | No control group to assess functional and body composition outcomes. Variable waiting period for surgery among patients |
| Miles, 2017 (178) | Sub-analysis of a randomized, single-blinded, controlled trial | Patients with PC, related malignancies or related premalignancies who were awaiting pancreatico-duodenectomy. Patients were stratified based | Aerobic intervention: 13 Combined intervention: 16 | Aerobic exercise versus aerobic exercise + strength training. All participants received a nutrition intervention including immunonutrition ONS | Daily exercise or 60 minutes for 2-week pre-op period. Aerobic: Range of motion tasks + cycling on ergometer. Resistance: adjustable-weight | To assess changes in body composition using three time points from baseline to approximately 2 months after surgery | Negative – Weight gain occurred preoperatively in the entire sample, but no significant changes in body composition were found. There was a significant decrease in body weight, fat mass and fat free-mass from | Not reported | Stratified for neo-adjuvant chemotherapy | Small sample size, no control group, short intervention |

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| | | on whether or not they received neoadjuvant chemotherapy | | | dumbbells and ankle weights, with weight and repetitions determined by a physical therapist<br>Nutrition: Whey protein (Beneprotein) supplement and dietary protein counseling to meet 1.3-1.5 g/kg/day + Impact AR x 3/day (237 mL each) for 5 days prior to surgery | | surgery to 6 weeks post-op in the entire group. No differences were found in HRQoL measures. No differences were reported between the two treatment groups, or between stratification groups | | | |
| Warfield, 2018 (179) | Sub-analysis of a larger randomized, single-blinded, controlled trial | Patients with PC, related malignancies or related premalignancies who were awaiting pancreatico-duodenectomy. Patients were stratified based on whether or not they received neoadjuvant chemotherapy and whether they are obese | 18 patients with no neoadjuvant treatment (10 = obese)<br>5 patients with neoadjuvant treatment (0 = obese)<br>5 control patients who underwent assessment only (2 = obese) | Aerobic exercise versus aerobic exercise + strength training. All participants received a nutrition intervention including immunonutrition ONS<br>-all patients received this intervention, although final analysis pooled intervention and control groups together | Daily exercise of 60 minutes for 2-week pre-op period. Aerobic: Range of motion tasks + cycling on ergometer. Resistance: adjustable-weight dumbbells and ankle weights, with weight and repetitions determined by a physical therapist<br>Nutrition: Whey protein (Beneprotein) supplement and dietary protein counseling to meet 1.3-1.5 g/kg/day + Impact AR x 3/day (237 mL each) for 5 days prior to surgery | To determine if there is a difference in lean body mass or HGS changes between groups | Negative - no significant changes were found in body composition or hand grip strength from baseline to pre-operative visit | Not reported | With adequate sample size, stratification for neoadjuvant treatment appropriate | Small sample size further diluted by multiple stratifications. Effect of planned intervention lost due to pooled data |

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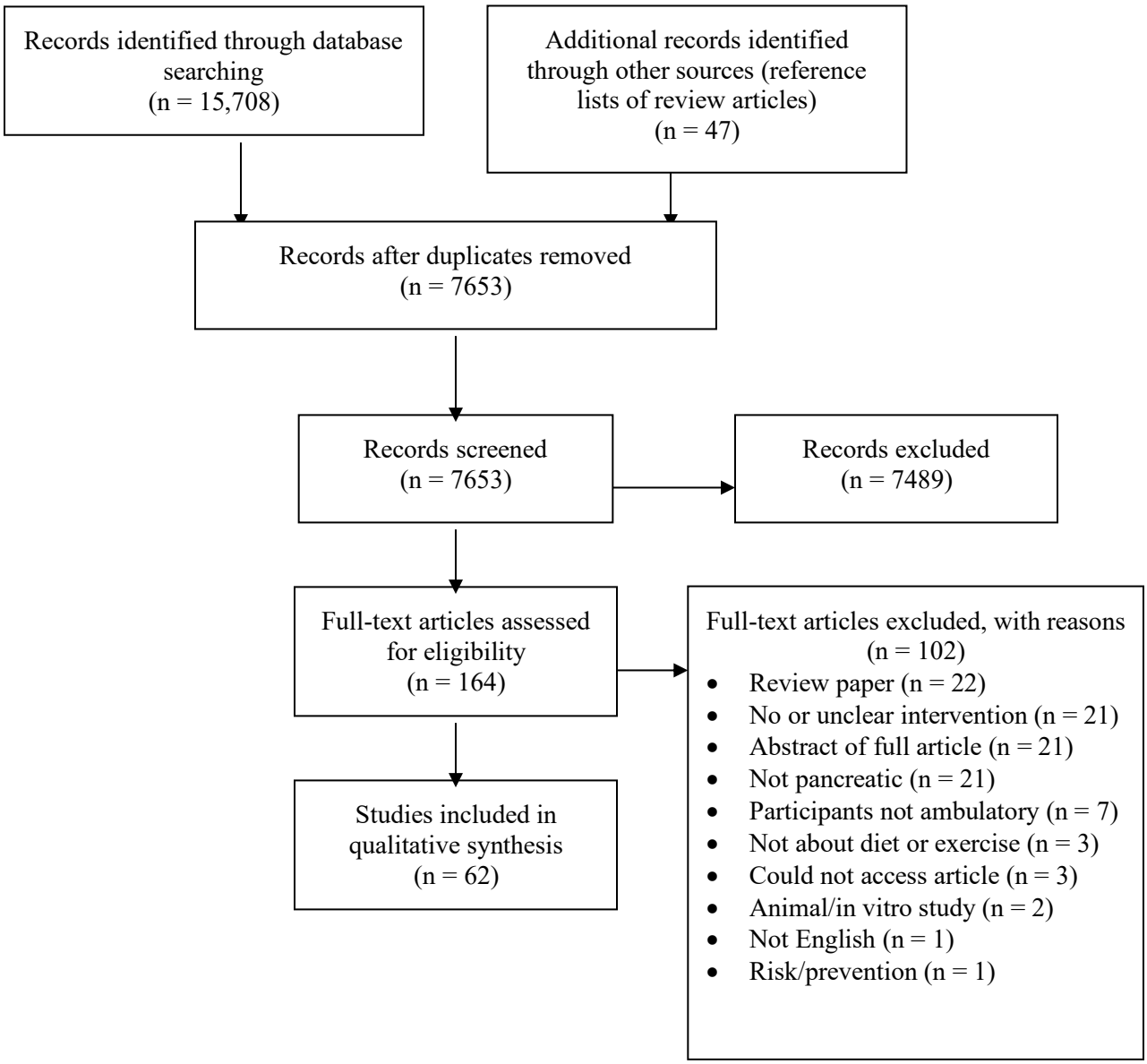
| Zauner, 2017 (180) | Subanalysis of a larger randomized controlled trial | Patients with PC, related malignancies or related premalignancies who were awaiting pancreatico-duodenectomy. Patients were stratified based on baseline measured HGS | Of those above at or above average HGS, 4 received aerobic + strength training, 2 received only aerobic training. Of those below average HGS, 7 received aerobic + strength training, 7 received only aerobic training | Aerobic exercise versus aerobic exercise + strength training. All participants received a nutrition intervention including immunonutrition ONS | Daily exercise of 60 minutes for 2-week pre-op period. Aerobic: Range of motion tasks + cycling on ergometer. Resistance: adjustable-weight dumbbells and ankle weights, with weight and repetitions determined by a physical therapist Nutrition: Whey protein (Beneprotein) supplement and dietary protein counseling to meet 1.3-1.5 g/kg/day + Impact AR x 3/day (237 mL each) for 5 days prior to surgery | Change in FFM at 1-month post-surgery compared to baseline | Negative – No change in FFM between groups or from baseline | Not reported | Multimodal intervention | Small sample size further diluted by multiple stratifications |

BIA = bioelectrical impedance analysis; BMI = body mass index; EPA = eicosapentaenoic acid; FFM = fat-free mass; HGS = handgrip strength; MET = Metabolic equivalent of task; ONS = oral nutritional supplement; PC = pancreatic cancer; HRQoL = health-related quality of life

Table 3.6.: Characteristics of the Selected Articles

| | **All Studies, (n = 62)** | **Diet Studies, (n = 41)** | **Exercise Studies, (n = 13)** | **Diet & Exercise Studies, (n = 8)** |
|---|---|---|---|---|
| Study design | | | | |
| Randomized controlled trial | 27 | 17 | 6 | 4 |
| Prospective cohort study | 26 | 20 | 2 | 4 |
| Retrospective study | 3 | 3 | 0 | 0 |
| Case study/series | 6 | 1 | 5 | 0 |
| Year of publication | | | | |
| 2010-August 2020 | 46 | 25 | 13 | 8 |
| 2000-2009 | 13 | 13 | 0 | 0 |
| 1990-1999 | 3 | 3 | 0 | 0 |
| Country | | | | |
| Australia | 3 | 2 | 1 | 0 |
| Canada | 1 | 0 | 0 | 1 |
| Denmark | 1 | 1 | 0 | 0 |
| Egypt | 1 | 0 | 1 | 0 |
| Germany | 9 | 6 | 3 | 0 |
| Ireland | 1 | 0 | 0 | 1 |
| Israel | 1 | 1 | 0 | 0 |
| Italy | 2 | 2 | 0 | 0 |
| Japan | 6 | 1 | 0 | 1 |
| Korea | 1 | 1 | 0 | 0 |
| Lithuania | 1 | 1 | 0 | 0 |
| United Kingdom | 15 | 14 | 1 | 0 |
| United States | 20 | 8 | 7 | 5 |

Figure 3.1.: PRISMA-ScR flowsheet



## Connecting statement: Manuscript 2

The results of the scoping review detailed in Chapter 3 demonstrates the heterogeneity in diet and exercise interventions and the many different outcomes of interest studied in patients with pancreatic cancer. Additionally, patients themselves were different, ranging from those undergoing treatment with curative intent, to patients with cancer cachexia approaching end-of-life.

Eight studies described a combined diet and exercise approach within a prehabilitation intervention in patients awaiting surgical resection. Of the 8 prehabilitation studies, only one included HRQoL as an outcome measure. The study by Ngo-Huang et al. (85) was a single-arm study, and did not follow patients throughout the postoperative period. It has previously been demonstrated that, without any interventions, HRQoL returns to baseline levels only 3 to 6 months post pancreatic resection. Therefore, the effect of diet and exercise interventions, within a prehabilitation program, on HRQoL in the post-operative period remains unknown. Additionally, associations between HRQoL and factors hypothesized to decrease wellbeing in both the pre- and post-operative period (e.g., poor nutritional status, loss of muscle mass/strength, decreased physical function, cancer symptom burden), are not well understood.

The purpose of the following chapter is two-fold: 1) to explore the determinants of poor HRQoL in patients enrolled in a prehabilitation program that includes a diet and exercise intervention, and 2) to determine the effect of prehabilitation on HRQoL in the preoperative period and for 8-weeks postoperative, compared to a control group. Understanding the effect of prehabilitation on HRQoL, and what impedes achieving improvements, will allow for better design of future prehabilitation interventions to address the wellbeing of patients.

## Chapter 4: Manuscript 2

Manuscript submitted and under peer review: HPB

Submission number: HPB-D-23-00073

# Health-related quality of life of patients with pancreatic cancer undergoing surgery: correlates and impact of multimodal prehabilitation and rehabilitation

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## 4.1. Abstract

Purpose: It is unclear if trimodal prehabilitation can mitigate postoperative decline in health-related quality of life (HRQoL) in patients with pancreatic cancer awaiting surgery.

Methods: Patients were randomized to prehabilitation (prehab) or rehabilitation (rehab). Prehab started an exercise, nutrition, and relaxation intervention four weeks preoperatively; rehab began the same intervention immediately after surgery. The intervention lasted 8 weeks postoperatively. HRQoL was measured using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep). Baseline relationships between HRQoL and nutritional status were explored using the abridged Patient-Generated Subjective Global Assessment (aPG-SGA), cancer symptoms using the revised Edmonton Symptom Assessment System (ESAS) and fatigue using the Brief Fatigue Inventory (BFI).

Results: This study included 23 patients (prehab: n=11). FACT-Hep score increased in prehab (+11.7±5.6) but was not significant. Only prehab experienced a significant decline in FACT-Hep score 4 weeks postoperatively (-26.6±5.9, $p=0.001$). However, both prehab and rehab FACT-Hep scores remained unchanged from baseline at 8-weeks postoperatively. Strong, inverse relationships were observed between baseline aPG-SGA ($r=-0.691$), ESAS ($r=-0.832$), BFI ($r=-0.732$, $p<0.05$) and FACT-Hep.

Conclusion: Trimodal prehabilitation in patients with pancreatic cancer returned HRQoL to baseline levels 8 weeks postoperatively. Prehabilitation programs that target fatigue, cancer symptoms and nutrition may further optimize HRQoL. Clinicaltrials.gov NCT03475966.

Keywords: prehabilitation, pancreatic cancer, health-related quality of life

## 4.2. Introduction

Pancreatic cancer is the 11th most commonly diagnosed cancer in Canada (189). However, 2022 projections rate it as the third deadliest cancer due to minimal advancements in both early detection and treatment options (189). Only 15-20% of patients are able to receive potentially curative surgery as most diagnoses are made when the cancer is unresectable (6). Even after surgical resection, 5-year survival rates remain dismal at 10-25% (6). Given the poor prognosis related to a diagnosis of pancreatic cancer, a focus on maintaining the health-related quality of life (HRQoL) of patients should be prioritized.

Symptoms arising from pancreatic cancer have a negative effect on the HRQoL of patients, and can include: pain, insomnia, nausea and vomiting, as well as malnutrition and deconditioning related to cachexia and sarcopenia (12, 190). In a study focusing solely on patients with resectable pancreatic cancer, the symptoms of fatigue, trouble sleeping, poor appetite, trouble digesting food, weight loss, and abdominal pain/cramping were most frequently reported both before and after surgery (191). Although early referral to supportive and palliative care services has been deemed important for symptom management and quality of life in patients with pancreatic cancer (15), rates of referral to these services remain low, especially in surgical candidates (16). Prehabilitation refers to interventions that attempt to optimize physical, nutritional and psychological status of patients prior to surgery, in order to hasten recovery, reduce post-operative complications and limit hospitalization length of stay (17). A wide range of interventions have been proposed within prehabilitation, including exercise, nutritional counselling and psychological interventions, individually or combined (192). Through these interventions, prehabilitation may help reduce the symptoms burden in patients with pancreatic

cancer, thus leading to an improvement in HRQoL. At present, little is known regarding the effect of prehabilitation on HRQoL in patients awaiting surgery for pancreatic cancer in both the pre- and postoperative period. Additionally, relationships between function, strength, body composition, nutritional status, cancer symptoms and HRQoL among surgical candidates have not been clearly elucidated. Therefore, the aim of the present study was to determine whether trimodal prehabilitation (exercise, nutrition, psychological counselling) will improve HRQoL in the pre-and postoperative period, and if functional, nutritional, psychological status, body composition and cancer symptoms are predictive of HRQoL.

## 4.3. Materials and Methods

This study is a secondary analysis of data from a randomized, controlled prehabilitation study conducted at the Cedars Cancer Centre of the McGill University Health Centre (MUHC) (clinicaltrials.gov registration NCT03475966). Ethics approval for this study was obtained from the MUHC Research Ethics Board (project number: 2017-2935). Recruitment began in March 2017, with the last patient completing the study in June 2021. The main objective of the present study was to determine the effect of prehabilitation on postoperative functional walking capacity in patients awaiting hepato-pancreato-biliary (HPB) surgery for malignancy. In order to limit postoperative functional decline, a trimodal prehabilitation program was designed and tested. The intervention included: 1) a combined in-person/home-based aerobic/resistance training program, 2) dietary counselling, and 3) relaxation techniques. Patients were eligible to participate in the study if they were at least 18 years old, had an HPB malignancy with a referral for elective surgery, and able to comprehend English or French. Patients were excluded from the study if they had an American Society of Anesthesiologists health status class IV-V.

Additionally, patients were excluded if they could not participate in exercise or complete testing procedures due to any physical or mental co-morbidities. The surgical team determined the eligibility of patients for participation in the study using the aforementioned criteria. If a patient was deemed eligible, the surgeon or an oncology pivot nurse alerted a research assistant to contact the potential trial candidate. The research assistant explained the study to patients and obtained informed consent prior to enrolment. Patients were allocated 1:1 to either the prehabilitation (prehab) or rehabilitation (rehab) study arms, stratified by surgical site (liver versus pancreas), using a computer-generated randomization scheme. While the patients remained blinded to their study arm until all baseline tests were completed, the study team could not be blinded because they were conducting the assessments and providing the interventions. All patient measurements were taken at the McGill Nutrition and Performance Laboratory (MNUPAL) of the MUHC. Patient assessment took place four times over a 12-week period: baseline (~4 weeks before surgery), 1-3 days before surgery (preop), 4-weeks postoperatively (4-weeks) and 8-weeks postoperatively (8-weeks). The prehab group began the intervention immediately following the baseline assessment. However, the rehab group was taught the intervention at the preop appointment and asked to begin right after surgery. The time between the baseline and preop appointment allowed for a ~4-week control period between the prehab and rehab groups. The present study will be a secondary analysis of data collected only from the patients awaiting pancreatic resection.

#### 4.3.1. Materials

*HRQoL measures*

Patients completed the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire to determine HRQoL (12). The FACT-Hep measures HRQoL based on the following domains: Physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and the hepatobiliary subscale (disease-specific symptoms and side-effects of treatment) (193). A trial outcome index (TOI) was calculated for each patient. The TOI encompasses the physical wellbeing, functional wellbeing and hepatobiliary subscale scores of the FACT-Hep, and is likely more responsive to the prehabilitation intervention designed for the present study (194). A minimally important difference (MID) of 8-9 for the FACT-Hep and of 7-8 points for the TOI have been established (193).

Nutritional status measures

*Anthropometry*

Patient weight was measured with an electronic standing scale (Detecto 6855, Cardinal/Detecto, Webb City, MO), and height using a wall mounted stadiometer (Seca 216, Seca North America, Chino, CA, USA). From these measures, body mass index (BMI) was calculated using the following formula: BMI = [weight (kg)]/height ($m^2$).

*Body composition*

Each patient underwent a full-body, dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy Advance, GE Healthcare, Madison, WI). DXA software (Encore 2006 software, GE Healthcare, Madison, WI) provided the output for measured lean body mass (kg), which was used to calculate the appendicular skeletal muscle index (ASMI) for each patient with the following equation: ASMI = [lean arm mass (kg) + lean leg mass (kg)]/height ($m^2$).

*Malnutrition screening*

Patients completed the abridged Patient-Generated Subjective Global Assessment (aPG-SGA) questionnaire. The aPG-SGA is comprised of 4 boxes which describe: 1) weight history, 2) food intake, 3) nutrition impact symptoms, and 4) performance status. Total aPG-SGA scores are classified as follows: 0 to 3 does not require nutrition intervention by a RD, 4 to 8 requires an intervention by a RD, $\geq 9$ indicates a need for improved symptom management and nutrient intervention (195).

*Functional test*

Patients performed the six-minute walk test to assess functional walking capacity (196). A kinesiologist instructed patients to walk up and down a 15m long hallway, pivoting around cones that are placed at the starting point of the test and at the 15m point. Patients walked as far as they could in 6 minutes, without running or jogging. The kinesiologist instructed patients to walk at a BORG rating of perceived exertion of 12-16. The kinesiologist recorded the number of laps the walked in six minutes and calculated the total distance in meters.

*Strength test*

Patients performed dynamometry to measure handgrip strength (HGS). A Jamar hydraulic hand dynamometer (Jamar, Sammons Preston, Bolingbrook, IL) was used for the test. A kinesiologist asked patients to sit in a chair with feet flat on the floor, shoulder width apart. The patients held the dynamometer in one hand, with their elbow positioned at a 90-degree angle. The kinesiologist then asked patients to squeeze the dynamometer as hard as they could

for 3 seconds. Patients repeated the test twice with each hand, pausing for a minute-long rest between squeezes. For the purposes of the present study, we reported the peak measure from the dominant hand.

*Cancer symptoms*

Each patient completed the revised Edmonton Symptom Assessment System (ESAS) (40). The ESAS allows for the assessment of current levels of pain, tiredness, nausea, depression, anxiety, drowsiness, lack of appetite, wellbeing, and shortness of breath. Each symptom is rated from 0 to 10 on a numerical scale based on severity, with 0 indicating that the symptom is absent and 10 that it is the worst possible experience of the symptom. Total ESAS score is the sum of all symptom scores and reflects a patient's total symptom burden.

*Depression and anxiety*

Patients completed the Hospital Anxiety and Depression Scale (HADS), a 14-question instrument measuring both anxiety and depression (197). HADS generates separate scores for anxiety and depression as well as a combined score of psychological distress (198). HADS is accurate in identifying anxiety and depression in patients with cancer; scores of > 9 for anxiety and > 7 for depression are optimal in identifying patients suffering from these psychological difficulties (199).

*Cancer-related fatigue*

Patients completed the Brief Fatigue Inventory (BFI) questionnaire, which measures the level of fatigue and its impact on activities of daily living (200). The BFI has 9 questions: three

questions are designed to assess fatigue during the immediate waking hours and 6 questions address how fatigue has interfered in the patient's life over the previous 24 hours. Each question uses a scale rating from 0 (no fatigue) to 10 (unimaginable fatigue). The total fatigue score is the average score of the nine questions (200).

*Demographic data*

Patients self-reported their ethnicity and education level.

*Diagnosis, surgery, and outcomes*

We collected data on the tumor pathology, surgery type and post-operative length of stay for each patient from the electronic medical record.

*Compliance*

A research assistant contacted participants weekly to determine compliance to the intervention. We measured compliance as follows: 1) percent of recommended exercise program performed (aerobic, resistance), 2) percent of prescribed whey protein supplement consumed, and 3) number of times relaxation techniques performed (100% for >3 times/week).

4.3.2. Methods

Treatment group (prehab)

*Exercise intervention*

A trained kinesiologist prescribed a 60-minute, unsupervised, home-based program for each patient. Additionally, patients in the prehab group came to MNUPAL one day per week to

exercise under the supervision of a kinesiologist. The kinesiologist individualized each exercise program based on the results of baseline fitness tests. The program (both at home and at MNUPAL) included the following: 5-minute warm up, 25 minutes of aerobic exercise utilizing the large muscle groups (e.g.: walking, cycling), 30 minutes of resistance training (8-12 exercises targeting all muscle groups), and a 5-minute cool-down with flexibility exercises.

*Aerobic exercise*

The kinesiologist determined aerobic exercise intensity by calculating 40% to <60% of heart rate reserve (HRR). The kinesiologist adjusted aerobic exercise intensity on a weekly basis based on patients' rate of perceived exertion (Borg Scale) (201). Patients either walked or cycled daily for the home-based component, and walked on a treadmill (Biodex RTM 400, Biodex Medical Systems, Shirley, NY), or used a recumbent cross-trainer (NuStep T5, NuStep, Ann Arbor, MI), during supervised exercise sessions.

*Resistance exercise*

Patients performed resistance exercises using TheraBands (TheraBand, Akron, OH) or their own body weight. Patients completed 1-3 sets of 8-12 repetitions of each exercise, 3-4 times per week (every second day). Resistance exercises included: push-ups, seated row, band pull apart, lateral raises, bicep curl, triceps extension, squats, hamstring curls, standing calf raises, abdominal crunches. Free weights were added to increase intensity of the exercises targeting the biceps, deltoids, and quadriceps (Bowflex Selectech, Nautilus Inc., Vancouver, WA) when Therabands offered insufficient resistance. The kinesiologist had patients lift weights

until they reached volitional fatigue after 8 repetitions to determine appropriate load. The kinesiologist recommended a 48-hour recovery period between each resistance exercise session.

*Flexibility exercise*

Patients performed flexibility exercises after resistance training. Muscles stretched included: chest, biceps, triceps, quadriceps, hamstrings, and calves. Patients repeated each stretch twice, holding for 15-30 seconds.

*Nutrition intervention*

A registered dietitian (RD) determined each patient's protein requirements based on baseline weight. The intervention aimed to achieve dietary protein intake of 1.5 g/kg/day, based on recommendations for both surgery (202) and cancer (203). The RD calculated protein intake at baseline, according to reported intake from a 3-day food diary completed by each patient. The RD subtracted calculated protein needs from estimated baseline protein intake to determine protein deficit. Once the protein deficit was known, the RD made dietary recommendations and prescribe a whey protein isolate supplement (Immunocal, Immunotech, Vaudreuil-Dorion, QC) to achieve the protein target. Patients were encouraged to use the whey protein isolate after resistance exercise to provide substrate promoting muscle protein synthesis (204). Patients were also provided with dietary counselling to manage nutrition impact symptoms.

*Anti-anxiety strategies*

A psychologist met with each patient to provide techniques designed to reduce anxiety, including visualization, imagery, deep breathing exercise and muscle relaxation. The

psychologist asked patients to use these anti-anxiety tools at any time during the day and at least 3 times a week.

Usual care group (rehab)

From baseline to preop, the rehab group received standard care, which does not include preoperative nutrition, exercise, or relaxation counselling. The rehab group then followed the same intervention as the prehab group after surgery.

4.3.3. Statistics

Statistical analysis of the present study was performed with SAS software, version 9.4 (SAS, Cary, NC). The Student's t-test or the Wilcoxon-Mann-Whitney test (for nonparametric data) was used to determine differences between groups at baseline. The Fisher Exact test assessed differences between categorical data at baseline. Pearson's correlations revealed relationships between FACT-Hep, its subscales and TOI (dependant variables) and measures of body composition, anthropometry, functional testing, nutritional status, fatigue, and cancer symptoms (independent variables). Bivariate robust regression analysis determined the predictive value of the aforementioned independent values on both FACT-Hep and TOI. Finally, a mixed model ANOVA was used to examine the interaction between time and treatment group on change in FACT-Hep and TOI. We explored the following covariates for best fit in the model: sex, age, functional testing, nutritional status, fatigue, cancer symptoms and body composition, surgery type, cancer pathology and baseline FACT-Hep/TOI score. We examined the residuals of all robust regression and mixed model ANOVA analyses for normality using the Kolmogorov-Smirnov test, or by examining the skewness and kurtosis of the data, where values

between -1 and 1 are acceptable (205). For each mixed model ANOVA, we used the Bayesian Information Criteria to evaluate best fit, and conducted *post-hoc* Tukey adjustments, which are reflected in reported p-values. Significance for all tests was set at $p<0.05$. We used intention-to-treat analyses to reduce bias related to missing data or patient withdrawal.

## 4.4. Results

Of the 61 patients recruited to the main study, 23 were scheduled to receive pancreatic resection and are included in the present study (prehab n=11, male n=15, mean age: 60.5±15.2 y). A CONSORT flowchart detailing patient recruitment and study completion is included in Figure 1. At baseline, the only significant difference observed between groups was for ESAS anxiety, which was greater in the prehab group (Table 1). This difference was not observed in HADS anxiety results. There were no other significant differences between the prehab and rehab group for demographic data, body composition, functional capacity, symptoms, health-related quality of life, histology, or surgery (Table 1). At baseline, no patients were underweight based on BMI (data not shown). According to sarcopenia criteria cut-offs proposed by Cruz-Jentoft et al. (206), eight patients had low ASMI (35%), one (4%) had low HGS and six (26%) had low six-minute walk test scores (data not shown).

The effect of the intervention on HRQoL over the study period is demonstrated in Figure 2. Both TOI (Figure 2a) and FACT-Hep (Figure 2b) significantly declined in the prehab group between the preop and 4-week appointment ($\Delta$ in TOI: -27.1±5.0, $p<0.001$; $\Delta$ in FACT-Hep: -26.5±5.9, $p=0.001$). The prehab group did not improve TOI or FACT-Hep scores to achieve preop levels by the 8-week visit ($\Delta$ in TOI: -19.1±5.0, $p<0.01$; $\Delta$ in FACT-Hep: -20.5±5.9,

$p<0.05$). However, there was no statistical difference between baseline and 8-week TOI and FACT-Hep in the prehab group (Δ in TOI: -8.7±5.0, $p>0.2$; Δ in FACT-Hep: -8.8±5.9, $p>0.2$). Both TOI and FACT-Hep scores remained unchanged throughout the study period.

Pearson correlations of baseline data demonstrated that strong, negative relationships were present between measures of ESAS total score and FACT-Hep TOI (Figure 3a: r=-0.892), FACT-Hep Total (Figure 3b: r=-0.832), physical (Figure 3c: r=-0.855) and functional wellbeing (Figure 3d: r=-0.831, $p<0.001$). Nutritional status as measured by the aPG-SGA score also demonstrated a strong, negative relationship with TOI (Figure 3f: r=-0.815) and physical wellbeing (Figure 3g: r=-0.855, $p<0.001$). Similarly, BFI measures of fatigue also had a strong, negative relationship with FACT-Hep total score (r=-0.732), TOI (r=-0.745), physical (r=-0.700) and functional wellbeing (r=-0.764, $p<0.001$) (Table 2). The negative relationship was strong between HADS depression and functional wellbeing (r=-0.718, $p<0.001$), but moderate with FACT-Hep (r=-0.632, $p<0.01$), TOI (r=-0.643, $p<0.001$) and physical wellbeing (r=-0.523, $p<0.05$) (Table 2). There were no significant relationships between HADS anxiety and TOI or physical wellbeing, while only moderate, negative relationships were observed with FACT-Hep and functional wellbeing (Table 2). No significant relationships were observed between any HRQoL measures and age, BMI, ASMI, HGS or six-minute walk test (Table 2).

Based on the results of the correlation analyses, we performed robust univariate baseline regression analysis to determine the predictive value of statistically significant symptoms on HRQoL. For every one unit increase in fatigue measured by the BFI, there was a significant decrease of -8.2 points in TOI and a similar -8.3-point decrease in FACT-Hep total score (Table

3). HADS anxiety scores had a greater, significant, negative effect on FACT-Hep (-4.5±1.3, 95% CI: -7.1 to -1.9, $p<0.001$) than TOI (-2.9±1.4, 95% CI: -5.6 to -0.1, $p<0.05$). The difference in magnitude between FACT-Hep and TOI was not observed with HADS depression. Significant decline in both FACT-Hep and TOI with worsening nutritional status (aPG-SGA) and cancer symptom burden (ESAS) was also observed (Table 3).

The prehab group experienced a significant decrease in compliance after surgery to both the diet (preop: 89.0±26.3% versus 4-week: 43.6±28.7%, $p<0.05$) and exercise (preop: 86.1±26.7% versus 4-week: 63.1±29.0%, $p<0.05$) interventions. There was no difference in compliance to any element of the intervention between prehab and rehab in the postoperative period.

## 4.5. Discussion

The present study examined the effect of trimodal prehabilitation and rehabilitation programs on the HRQoL of patients undergoing surgery for pancreatic cancer, and revealed the following notable findings: 1) the trimodal intervention led to stable HRQoL in the rehab group throughout the study period, and a return to baseline at 8-weeks in the prehab group; 2) there is a strong, negative relationship between HRQoL, cancer symptoms and nutritional status; 3) at baseline, fatigue had a large predictive effect on FACT-Hep and TOI (physical wellbeing, functional wellbeing and hepatobiliary symptoms), with a one unit increase in BFI predictive of a deterioration in FACT-Hep and TOI equivalent to the MID; and finally, 4) there is no relationship between HRQoL and anthropometry, body composition, HGS or functional walking capacity.

Patients who participated in the present study experienced a return of HRQoL to baseline levels within the 8-week postoperative study period in both the prehab and rehab groups. Two recent literature reviews demonstrated that patients with pancreatic cancer experience a decline in HRQoL post-operatively that lasts between 3-6 months, before returning to baseline (207, 208). It is significant that the trimodal prehabilitation and rehabilitation intervention used in the present study seems to have expedited the restoration of HRQoL in patients undergoing surgery for pancreatic cancer, with a return to baseline values after two months. Macarulla et al. (207) reported on 11 articles that assessed longitudinal changes in HRQoL, measured at different timepoints pre/postoperatively. Only one study of the 11 articles had a measurement 8-weeks postoperatively; Eaton et al. (209) found a significant decline from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) physical (preop: 91.4±13.8 versus 8-week: 82.8, $p<0.01$), role (preop 86±23 versus 8-week: 74.7, $p<0.01$) and social functioning (preop: 84.3±21.9 versus 8-week: 76.2, $p<0.01$), as well as overall health status (preop: 72.8±22.0 versus 8-week: 69.9, $p<0.03$), which differed from the observed return to baseline values from the present study. James et al. (208) reported the results of a systematic review of 22 studies that assessed the impact of pancreatic resection on HRQoL. Surprisingly, pylorus-preserving pancreaticoduodenectomy did not result in better HRQoL outcomes than a Whipple's procedure, despite fewer intraoperative complications such as blood loss and surgical duration, as well as better cancer-related results from the former intervention (208). Both the Macarulla and James systematic reviews conclude that there is great heterogeneity among chosen studies in HRQoL tool used, timepoint of HRQoL

assessment, surgical type and neoadjuvant and/or adjuvant treatment; as such, neither study reported a meta-analysis of the data from the chosen articles.

The exercise intervention provided to study participants may have contributed the most to the observed maintenance of HRQoL by the 8-week visit. A systematic review with meta-analysis by Chen et al. (210) demonstrated a significant difference in HRQoL between patients with advanced cancer who engaged in an exercise intervention versus those who did not (standard mean difference 0.22, 95%CI: 0.06 to 0.38, p=0.009). Similar to the present study, Ngo-Huang et al. (85) reported maintenance of HRQOL from baseline to preop, resulting from a preoperative exercise intervention in patients with pancreatic cancer undergoing neoadjuvant treatment (FACT-Hep: 137.9±21.0 versus 142.3±21.9, p>0.05).

Despite the overall positive results observed in the present study, there was a significant decline in HRQoL 4-weeks postoperatively in the prehab group. The decline may be related to the significant decline in compliance to the nutritional and exercise components of the prehab intervention. Another possible explanation is that the prehab group experienced more postoperative complications that were not well "captured" by using length of hospital stay; the latter may not be a sensitive enough measure for surgical complications. More accurate assessment of postoperative complications would benefit future HRQoL studies.

The second objective of the present study was to determine to what degree functional, nutritional, and psychological status, in addition to body composition and cancer symptoms, are associated to HRQoL. Understanding these associations is important to better design future

prehabilitation studies in patients with pancreatic cancer. The present study demonstrated that a one unit increase in BFI, denoting increasing cancer-related fatigue, was associated with a decrease in HRQoL equivalent to the MID of the FACT-Hep and TOI. Fatigue has previously been associated with the decline of HRQoL in patients with pancreatic cancer. For example, Müller-Nordhorn et al. (211) demonstrated a significant negative association between fatigue and HRQoL (-0.359, 95%CI: -0.624 to -0.095, p=0.009), in patients admitted to hospital for suspected pancreatic cancer. Fatigue is very common in patients awaiting pancreatic resection, with a recent study demonstrating a 92% (n=131) prevalence rate preoperatively (191). The high prevalence of fatigue in patients with pancreatic adenocarcinoma is greater than in non-malignant pancreatic disease, with patients younger than 50 years of age exhibiting a 2.4 times greater likelihood of having worse fatigue than those aged greater than 65 (212). Additionally, women seem to experience greater fatigue levels than men (212). This may explain the low rate of recruitment among women to the present study, with fatigue being a known barrier to engage in exercise among patients with cancer (213). Managing cancer-related fatigue is difficult, and can benefit from exercise, psychological and medical management (214). Exercise has shown benefit in both patients undergoing treatment and survivors, with most benefit from low-to moderate intensity interventions (215). Best medical management of fatigue remains elusive; a recent meta-analysis revealed mixed results in the effects of psychostimulants (e.g., methylphenidate) and positive results from corticosteroids (216).

The high prevalence of cancer symptoms and malnutrition among patients with pancreatic cancer is well studied. A population-based cohort study by Tung et al. (217) of patients who underwent pancreaticoduodenectomy demonstrated that at 4 weeks post-surgery,

ESAS tiredness, wellbeing and lack of appetite scores were moderate to severe (score of ≥ 4) in > 50% of patients (n=83), and remained moderate to severe in >45% of patients (n=347) at 8-weeks postoperatively. Weight loss, as a surrogate measure of malnutrition, is present in up to 80% of patients with pancreatic cancer at diagnosis (92). The etiology of malnutrition is multifactorial, including the presence of cancer cachexia, as well as endocrine and exocrine derangements that may be exacerbated by surgical resection. For example, pancreatic exocrine insufficiency is known to adversely affect HRQoL in patients with pancreatic cancer (218). Early nutrition intervention by a registered dietitian within a multimodal team, such as what may be offered in the prehabilitation setting, may help optimize the nutritional status of patients with pancreatic cancer (219). Gillis et al. recently provided some evidence of the effect of prehabilitation on HRQoL in a pooled cohort of patients undergoing trimodal prehabilitation (nutrition, exercise, stress-reduction) prior to colorectal surgery (81). Patients in the Gillis study were stratified based on aPG-SGA score denoting their nutritional status: < 4 requiring no real nutrition intervention, 4-8 requiring an intervention by a registered dietitian and ≥ 9 requiring aggressive symptom management and nutrition intervention (81). In the preoperative period, only patients undergoing prehab with an aPG-SGA score of ≥ 9 experienced a significant improvement in the general health domain of the short-form-36 questionnaire (Δ in general health prehab: +12.1±18.6 versus rehab: -4.8±14.0, $p<0.05$).(81)

The lack of relationship observed in the present study between baseline measures of HRQoL and anthropometry, body composition and functional walking capacity was not expected. A recent systematic review and meta-analysis of patients with resectable and borderline resectable pancreatic cancer reported a pooled sarcopenia (low muscle mass)

prevalence of 39% (95%CI: 38-40%) (220). This was similar to the prevalence rate of 35% observed in the present study. Conversely, Poulia et al. (72) found dynapenia in just over 75% of participants included in a prospective, cohort study of patients with pancreatic cancer prior to starting chemotherapy. This is far greater than the prevalence of 4% found in the present study. While there were no relationships between HGS and HRQoL in the present study, Poulia et al. reported a significant difference in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) score between those with dynapenia and without (71.4±27.6 versus 56.1±24.6, $p<0.05$) (72). It is possible that relationships between HGS and HRQoL were not observed due to a selection bias in which stronger, less deconditioned patients enrolled in the present study. Ngo-Huang et al. found that sedentary activity was associated with worse HRQoL as measured by FACT-Hep ($\beta=-0.02$, $p=0.01$) and light physical activity was positively associated to HRQoL ($\beta=0.03$, $p=0.02$) (85). However, moderate to vigorous physical activity was not associated to change in HRQoL ($p>0.05$). It may be that the moderate-to-vigorous exercise intensity necessary to optimize physical reserve prior to surgery, does not improve HRQoL.

There are some important limitations in our study. First, our sample size is small, as we were forced to cease recruitment earlier than expected due to the COVID-19 epidemic. This did not allow for multivariable regression analysis, or analysis by subgroup (based on pathology or surgery type). Second, as previously mentioned, most patients enrolled in the present study were not deconditioned, demonstrating a possible ceiling effect for the outcomes measured. Future studies should screen for more deconditioned patients who would benefit more from such a

program. Nevertheless, the present study was novel in demonstrating a return to baseline levels at 8 weeks postoperatively.

## 4.6. Conclusions

Given the dismal prognosis of patients with pancreatic cancer, even when eligible for curative resection, preserving HRQoL should be at the forefront of all diet and exercise interventions. The present study demonstrated that prehabilitation and rehabilitation may help stabilize HRQoL and hasten the return to baseline levels after pancreatic resection. Future studies should further characterize the role of optimal fatigue management, along with nutritional and functional interventions, to enhance HRQoL in patients with pancreatic cancer undergoing surgery. This study has provided useful information to design adequately powered trials which will show the real effect on HRQoL of both prehabilitation and rehabilitation in this patient population.

### 4.6.1. Acknowledgments

The authors would like to thank the surgical team for their support of this study: Dr. Prosanto Chaudhury, Dr. Peter Metrakos, Dr. Jeffrey Barkun and Daphnée Lamoussenary. Additionally, the authors would like to thank the patients and family members who participated in our study.

### 4.6.2. Funding Statement

Funding for this work was generously provided by the Cedars Cancer Foundation of the MUHC.

### 4.6.3. Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

### 4.6.4. Author Contributions

Franco Carli, Antonio Vigano, Robert Kilgour and Popi Kasvis participated in study conception and design. Popi Kasvis and Tram Bui were involved in material preparation, data collection and analysis. The first draft of the manuscript was written by Popi Kasvis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### 4.6.5. Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the McGill University Health Centre Research Ethics Board (February 1, 2017/2017-2935).

### 4.6.6. Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Table 4.1.: Baseline patient characteristics

| | Prehab (n=11) | Rehab (n=12) | p |
|---|---|---|---|
| Age (y) | 57.1±17.8 | 63.7±12.3 | 0.311 |
| Male | 7 (30.4) | 8 (34.8) | 1.000 |
| White race | 9 (39.1) | 9 (39.1) | 1.000 |
| University educated | 6 (26.1) | 6 (26.1) | 1.000 |
| *Body composition and functional capacity* | | | |
| Body mass index (kg/m$^2$) | 27.0±5.9 | 26.9±3.6 | 0.930 |
| Appendicular skeletal mass index (kg/m$^2$) | 6.7±1.2 | 7.2±1.2 | 0.346 |
| Six-minute walk test (m) | 492.8±98.4 | 486.6±100.6 | 0.882 |
| *Symptoms* | | | |
| ESAS total | 19.5±15.9 | 13.3±15.9 | 0.123 |
| ESAS pain | 2.0±2.4 | 1.6±2.6 | 0.387 |
| ESAS nausea | 1.0±2.2 | 0.7±2.0 | 0.963 |
| ESAS tiredness | 4.2±2.6 | 2.5±3.3 | 0.127 |
| ESAS anxiety | 2.4±2.2 | 1.1±2.4 | **0.028** |
| ESAS depression | 1.5±2.2 | 0.4±1.2 | 0.070 |
| ESAS drowsiness | 1.9±2.1 | 1.3±2.8 | 0.183 |
| ESAS appetite | 2.1±2.1 | 2.4±3.4 | 0.899 |
| ESAS wellbeing | 2.9±2.2 | 2.7±3.0 | 0.553 |
| ESAS shortness of breath | 1.5±2.0 | 0.6±0.9 | 0.246 |
| Brief Fatigue Inventory | 3.5±2.5 | 2.4±2.7 | 0.177 |
| HADS anxiety | 6.0±2.8 | 5.2±4.1 | 0.576 |
| HADS depression | 4.8±2.6 | 2.9±2.8 | 0.060 |
| aPG-SGA | 8.5±6.4 | 6.8±7.8 | 0.386 |
| *Health-related quality of life* | | | |
| FACT-Hepatobiliary | 130.4±23.1 | 138.8±28.8 | 0.356 |
| FACT TOI | 92.1±20.0 | 100±24.8 | 0.206 |
| Physical wellbeing | 21.1±6.3 | 22.2±6.8 | 0.386 |
| Social/family wellbeing | 22.0±3.8 | 21.8±7.8 | 0.535 |
| Emotional wellbeing | 16.3±4.5 | 17.0±4.6 | 0.705 |
| Functional wellbeing | 17.5±5.7 | 19.6±6.4 | 0.431 |
| *Pathology* | | | |
| Adenocarcinoma | 5 (23.8) | 9 (42.9) | 0.183 |
| IPNM | 2 (9.6) | 1 (4.8) | 0.587 |
| Neuroendocrine tumor | 3 (14.3) | 0 (0) | 0.090 |
| Other | 0 (0) | 1 (4.8) | 1.000 |
| *Surgery/neoadjuvant treatment* | | | |
| Received neoadjuvant chemotherapy | 3 (13) | 1 (4.4) | 0.317 |
| Pancreaticoduodenectomy | 5 (23.8) | 8 (38.1) | 0.387 |
| Subtotal pancreatectomy | 3 (14.3) | 1 (4.8) | 0.311 |
| Partial pancreatectomy | 1 (4.8) | 0 (0) | 0.476 |
| Total pancreatectomy | 1 (4.8) | 0 (0) | 0.476 |
| Other | 0 (0) | 2 (9.5) | 0.476 |
| *Surgical outcomes* | | | |
| Post-op length of stay (days) | 11.6±6.8 | 11.3±3.0 | 0.317 |

Mean±SD or N (%) reported; significance set at $p<0.05$.
Legend: aPG-SGA=Abridged Patient-generated Subjective Global Assessment; ESAS=revised Edmonton Symptom Assessment System; FACT=Functional Assessment of Cancer Therapy; HADS=Hospital Anxiety and Depression Scale; IPMN=Intraductal papillary mucinous neoplasm; TOI=Trial Outcome Index

Table 4.2.: Relationships between health-related quality of life measures and cancer symptoms, body composition and functional status

| | FACT-Hep TOI | FACT-Hep total | PWB | SWB | EWB | FWB |
|---|---|---|---|---|---|---|
| Age | NS | NS | NS | NS | NS | NS |
| BFI | -0.745 *** | -0.732 *** | -0.700 *** | NS | -0.431 * | -0.764 *** |
| HADS anxiety | NS | -0.527 ** | NS | -0.501 * | -0.490 * | -0.505 * |
| HADS depression | -0.643 *** | -0.632 ** | -0.523 * | NS | NS | -0.718 *** |
| ESAS pain | -0.814 *** | -0.777 *** | -0.782 *** | NS | NS | -0.706 *** |
| ESAS nausea | -0.635 ** | -0.576 ** | -0.686 *** | NS | NS | -0.487 * |
| ESAS tiredness | -0.766 *** | -0.726 *** | -0.713 *** | NS | NS | -0.758 *** |
| ESAS anxiety | -0.752 *** | -0.775 *** | -0.648 *** | NS | -0.537 ** | -0.780 *** |
| ESAS depression | -0.578 ** | -0.585 ** | -0.462 * | NS | -0.549 ** | -0.644 *** |
| ESAS drowsiness | -0.574 ** | -0.534 ** | -0.540 ** | NS | NS | -0.624 ** |
| ESAS appetite | -0.593 ** | -0.440 * | -0.664 *** | NS | NS | -0.419 * |
| ESAS wellbeing | -0.617 ** | -0.602 ** | -0.544 ** | NS | -0.467 * | -0.671 *** |
| ESAS shortness of breath | -0.709 *** | -0.634 ** | -0.748 *** | NS | NS | -0.503 * |
| BMI | NS | NS | NS | NS | NS | NS |
| ASMI | NS | NS | NS | NS | NS | NS |
| Six-minute walk test | NS | NS | NS | NS | NS | NS |

Pearson correlations. Correlation coefficient (r) reported. *<0.05, **<0.01, ***<0.001, NS=not significant.

Legend: aPG-SGA=Abridged Patient-generated Subjective Global Assessment; ASMI=appendicular skeletal muscle index; BFI=Brief Fatigue Inventory; BMI=Body mass index; ESAS=revised Edmonton Symptom Assessment System; EWB=Emotional Wellbeing; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Hep=Functional Assessment of Cancer Therapy-Hepatobiliary; FWB=Functional Wellbeing; HADS=Hospital Anxiety and Depression Scale; PWB=Physical Wellbeing; SWB=Social/family Wellbeing; TOI=Trial Outcome Index.

Table 4.3.: Robust regression analysis of predictors of health-related quality of life

| | TOI | | | | FACT-Hep | | | |
|---|---|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p |
| BFI | -8.2 | 1.3 | -10.6 to -5.7 | <0.001 | -8.3 | 1.8 | -11.9 to -4.8 | <0.001 |
| HADS anxiety | -2.9 | 1.4 | -5.6 to -0.1 | 0.042 | -4.5 | 1.3 | -7.1 to -1.9 | <0.001 |
| HADS depression | -2.4 | 9.1 | -5.1 to -1.6 | <0.001 | -5.6 | 1.5 | -8.5 to -2.7 | <0.001 |
| aPG-SGA | -2.7 | 0.5 | -3.6 to -1.8 | <0.001 | -2.5 | 0.7 | -3.8 to -1.2 | <0.001 |
| ESAS total score | -1.3 | 0.1 | -1.5 to -1.1 | <0.001 | -1.3 | 0.2 | -1.7 to -1.0 | <0.001 |

Significance set at $p<0.05$.

Legend: aPG-SGA=Abridged Patient-generated Subjective Global Assessment; BFI=Brief Fatigue Inventory; ESAS=revised Edmonton Symptom Assessment System; FACT-Hep=Functional Assessment of Cancer Therapy-Hepatobiliary; HADS=Hospital Anxiety and Depression Scale; TOI=Trial Outcome Index.

Figure 4.1.: CONSORT diagram of patient flow

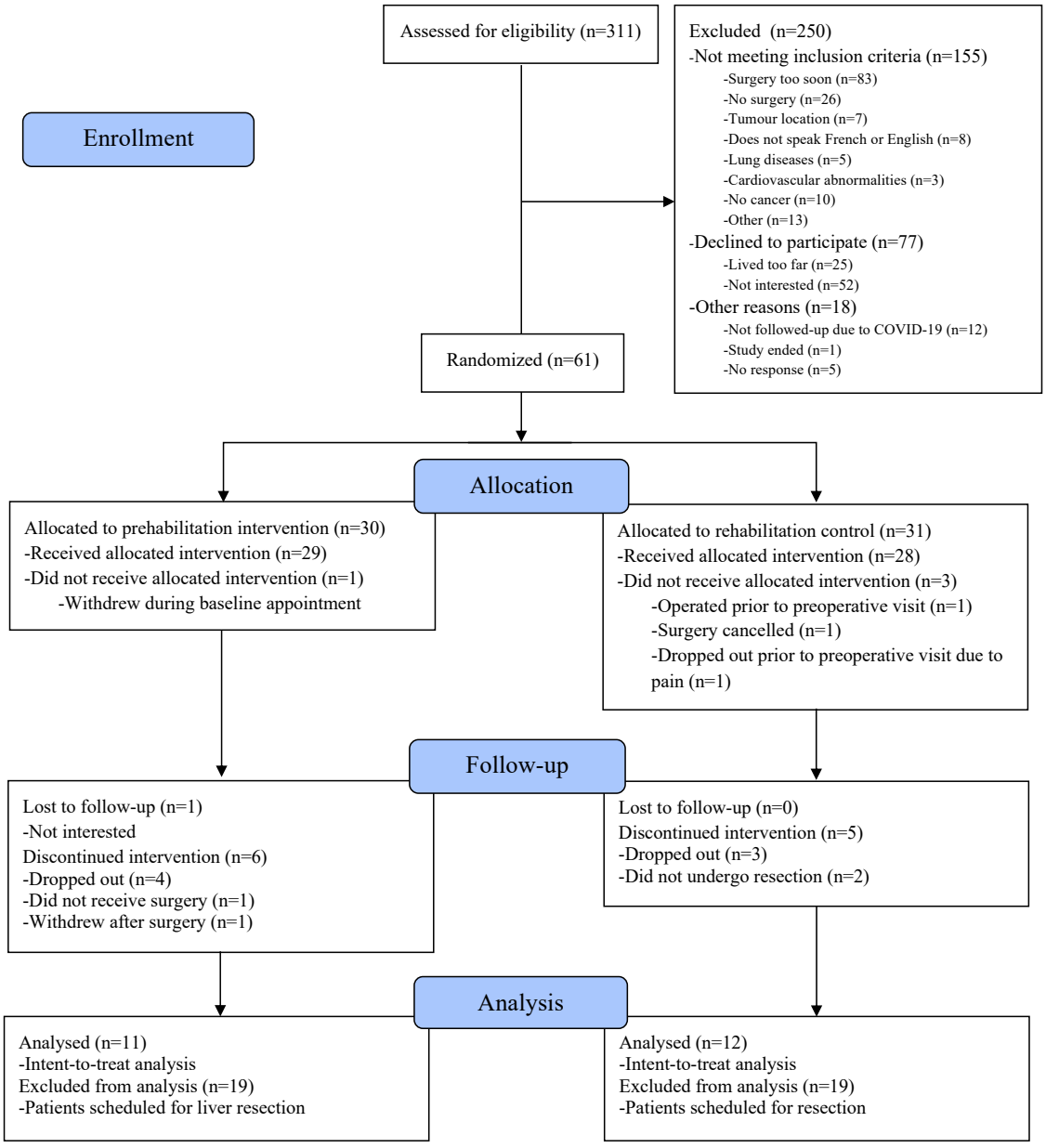
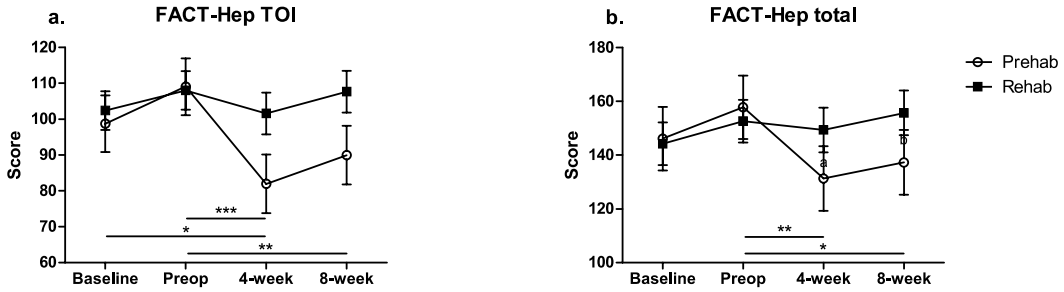


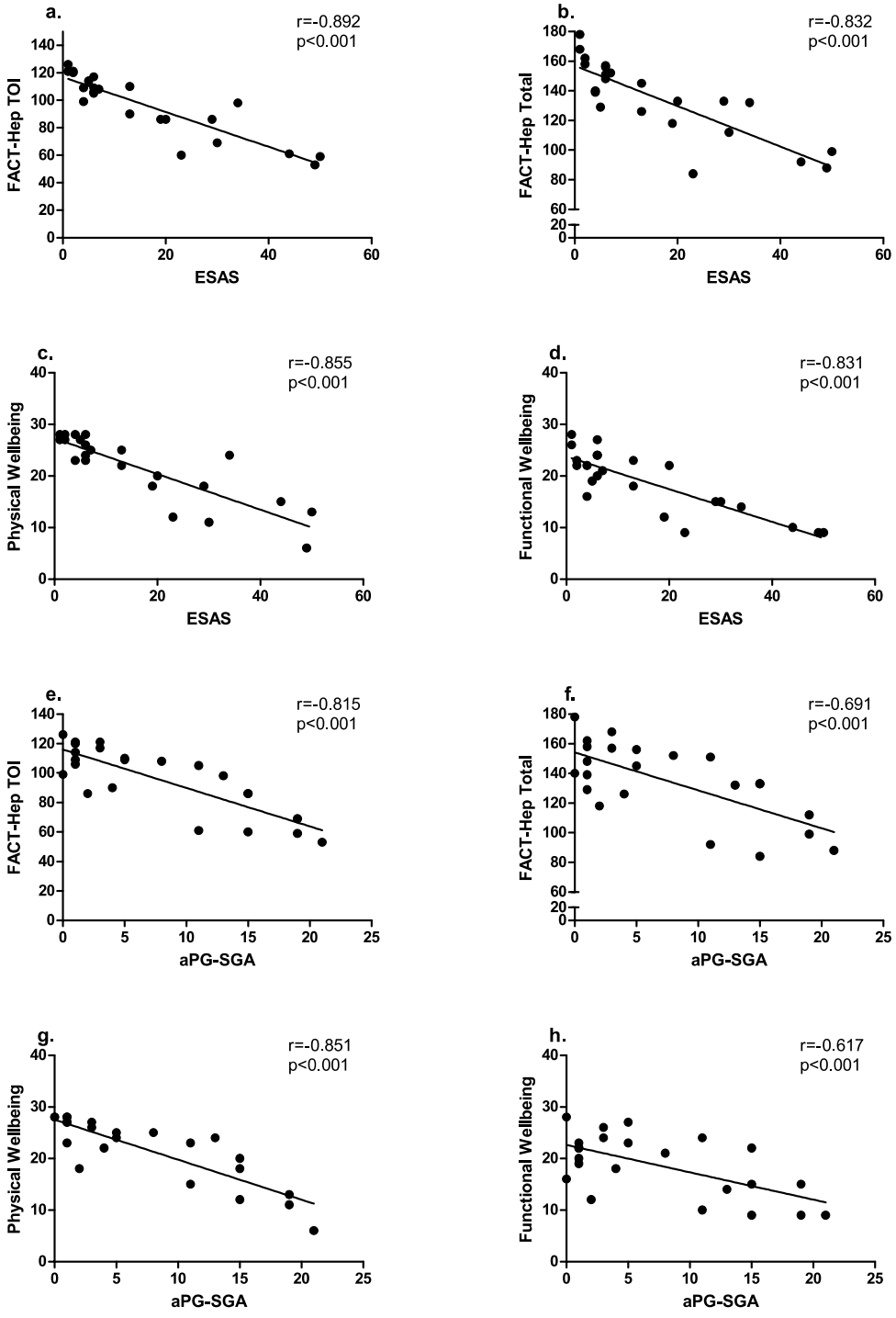
Figure 4.2.: Health-related quality of life over time and by treatment




Mixed model ANOVA, interaction between treatment and time explored. Covariates include: age, sex, baseline FACT value, histology and type of surgery. Significance: *<0.05, **<0.01, ***<0.001.

Legend: FACT-Hep=Functional Assessment of Cancer Therapy-Hepatobiliary; TOI=Trial Outcome Index.

Figure 4.3.: Relationships between health-related quality of life measures, cancer symptoms and nutritional status




Pearson correlations. Correlation coefficient (r) reported, significance set at $p<0.05$. Legend: aPG-SGA=Abridged Patient-generated Subjective Global Assessment; ESAS=revised Edmonton Symptom Assessment System.

## Connecting statement: Manuscript 3

The results presented in chapter 4 are surprising; there were no relationships between ASMI, HGS or 6MWT and HRQoL in patients with pancreatic cancer entering a prehabilitation program. As described in the literature review of this dissertation and the discussion provided in chapter 4, results regarding previously reported relationships between HRQoL and body composition, physical strength and function have been mixed in patients with pancreatic cancer. Chapter 4 provides evidence that the multimodal prehabilitation intervention described in this study hastens return to baseline levels of HRQoL by 8 weeks postoperative, compared to 3-to-6-month average time previously reported in the literature. Additionally, factors such as malnutrition and cancer symptoms (including fatigue) have a significant, negative relationship with HRQoL in patients awaiting surgery for pancreatic cancer.

Malnutrition is significant in predicting HRQoL in patients with pancreatic cancer, entering a prehabilitation program. This finding corroborates what was previously seen in the literature review provided in this dissertation. Although many studies have included dietary interventions, the success of these interventions in reaching nutritional goals to prepare for surgery have not been reported. Additionally, it is unknown if dietary counselling helps improve HRQoL through the amelioration of nutritional status. The following chapter will address these diet-specific questions. Additionally, it will allow for comparison with patients who are awaiting liver resection and may have fewer nutritional impediments, than those in patients with pancreatic cancer.

**Chapter 5: Manuscript 3**

Published in: Nutrition and Cancer, 2023 Mar 3;:1-14.

doi: 10.1080/01635581.2023.2178961, Epub ahead of print

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# Impact of dietary counselling on health-related quality of life in patients with cancer awaiting hepato-pancreato-biliary surgery

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## 5.1. Abstract

We examined the effectiveness of dietary counselling performed within a trimodal prehabilitation study for patients with cancer awaiting hepato-pancreato-biliary (HPB) surgery. Additionally, we explored relationships between nutritional status and health-related quality of life (HRQoL). The dietary intervention aimed to achieve protein intake of 1.5 g/kg/day and reduce nutrition impact symptoms. Patients received dietary counselling 4 weeks prior to surgery (prehabilitation group); the rehabilitation group just before surgery. We used 3-day food journals to calculate protein intake and the abridged Patient-generated Subjective Global Assessment questionnaire (aPG-SGA) to determine nutritional status. We utilized the Functional Assessment of Cancer Therapy-General questionnaire to measure HRQoL. Sixty-one patients participated in the study (30=prehabilitation). Dietary counselling achieved a significant increase in preoperative protein intake (+0.3±0.1 g/kg/day, $p=0.007$), with no change in the rehabilitation group. Dietary counselling did not mitigate a significant increase in aPG-SGA postoperatively (prehabilitation: +5.8±1.0; rehabilitation: +3.3±1.0; $p<0.05$). aPG-SGA was predictive of HRQoL ($\beta=-1.77$, $p<0.0001$). HRQoL remained unchanged in both groups over the study period. Dietary counselling within a HPB prehabilitation program improves preoperative protein intake, but not aPG-SGA, which is predictive of HRQoL. Future studies should examine whether specialized medical management of nutrition impact symptoms would improve HRQoL outcomes within a prehabilitation model.

Keywords: dietary counseling; prehabilitation; nutrition; health-related quality of life; cancer

## 5.2. Introduction

The prevalence of malnutrition among patients with cancer ranges from 20 to 70%, and is dependent on a variety of factors, including cancer diagnosis, stage of the disease and patient age (221, 222). Malnutrition in patients with cancer is related to poor outcomes including treatment toxicity, postoperative complications and mortality (223), as well as poor health-related quality of life (HRQoL) (224). Clinical practice guidelines promote early detection of malnutrition through screening (77). Patients at risk of malnutrition should undergo nutritional assessment by a registered dietitian (RD) to confirm the presence of malnutrition, followed by nutrition therapy where an RD is integrated within a multidisciplinary team (77, 219, 225).

A multidisciplinary approach is commonly seen in prehabilitation programs that aim to improve physiological reserve prior to surgery, and may include some or all of the following multimodal interventions: exercise, diet, psychosocial interventions (226). A common objective of prehabilitation interventions is to reduce post-operative morbidity, which is of particular importance in cancers where surgery is a curative treatment option (227). For example, patients with hepato-pancreato-biliary (HPB) cancers are often considered for surgery as part of standard care (228). However, patients diagnosed with HPB cancers may also exhibit functional impairments or malnutrition that may increase the risk of poor surgical outcomes. A classic example is the significant weight loss seen up to 80% of patients with pancreatic cancer at diagnosis (229). At present, HPB prehabilitation programs seem to have a positive effect on postoperative functional capacity, but not on complications or length of stay (228). Rarely examined is the effect on HRQoL of multimodal prehabilitation in patients with HPB cancers awaiting surgery. Examining how physical and functional domains affect HRQoL is of particular interest in prehabilitation programs that use exercise to improve functional capacity (230). Even

less understood is the role of nutritional status and the effect of dietary intervention on HRQoL in the context of prehabilitation among patients with HPB cancers.

Therefore, our study aimed:

1) To establish baseline nutritional status in patients with HPB cancer (BMI, malnutrition screening (abridged patient-generated subjective global assessment), handgrip strength, dietary intake (3-day food diaries),
2) To determine relationships between baseline nutritional status and HRQoL,
3) To assess whether dietary counselling can achieve nutritional recommendations for surgical optimization, and,
4) To assess whether patients with HPB disease, provided with preoperative nutritional counselling approximately 4 weeks prior to surgery, will have better HRQoL outcomes than those who receive counselling just prior to surgery. Predictors of HRQoL will also be examined.

## 5.3. Materials and methods

We used data from a randomized, controlled prehabilitation study conducted at the Cedars Cancer Centre of the McGill University Health Centre (MUHC) (clinicaltrials.gov registration NCT03475966) to meet the objectives of our study. The original prehabilitation study ran from March 2017 to June 2021 and received ethics approval from the MUHC Research Ethics Board (project number: 2017-2935). The primary objective was to assess the effect of prehabilitation on postoperative functional walking capacity in patients awaiting HPB surgery for malignancy. The prehabilitation intervention was trimodal, and included combined in-person/home-based aerobic/resistance training, dietary counselling and relaxation techniques.

Patient eligibility included: 1) age ≥18 years old, 2) HPB malignancy, 3) referred for elective surgery, and 4) be able to comprehend English or French. Exclusion criteria included an American Society of Anesthesiologists health status class IV or V, or any physical or mental co-morbidities that would limit the ability of participants to perform exercise or to complete testing procedures. The surgical team screened patients for participation in the study based on the aforementioned criteria, and alerted a research assistant to possible candidates for the trial. The research assistant then contacted patients, explained the study and obtained informed consent prior to enrolment. We used a computer-generated randomization scheme to allocate patients 1:1 to either the prehabilitation (prehab) or rehabilitation (rehab) study arms, stratified by surgical site (liver versus pancreas). Patients remained blinded to their study arm until all baseline tests were completed; the remaining study team was not blinded, as the assessors were also providing the interventions. We performed all patient assessments at the McGill Nutrition and Performance Laboratory of the MUHC, at four time points over a 12-week period: baseline (~4 weeks before surgery), right before surgery (preop), 4-weeks postoperatively (4-weeks) and 8-weeks postoperatively (8-weeks). The prehab group began the intervention immediately after the baseline assessment, whereas the rehab group only received the intervention at the preop appointment to begin right after surgery, thus allowing for a ~4-week control period. The principles of Enhanced Recovery After Surgery (ERAS) are part of standard perioperative care in this patient cohort at the MUHC (231, 232).

### 5.3.1. Materials

*HRQoL measures*

Patients completed the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire (31) to determine changes in HRQoL. The FACT-G measures overall HRQoL based on four domains: physical wellbeing, social/family wellbeing, emotional wellbeing and functional wellbeing. We recorded scores for each of these domains, as well as the FACT-G total score; in all cases, a higher score indicates better HRQoL. Patients were categorized as meeting a minimal important difference (MID) in improvement at the preoperative appointment for the FACT-G (score of +3-7) and each subscale (score of +2) (35).

*Nutritional status measures*

i. Anthropometry

We measured patients' weight with an electronic standing scale (Detecto 6855, Cardinal/Detecto, Webb City, MO), and height using a wall mounted stadiometer (Seca 216, Seca North America, Chino, CA, USA). From these measures, we calculated body mass index (BMI) using the following formula: BMI = [weight (kg)]/height ($m^2$). We classified patients based on BMI using the following cutoffs: <18.5 kg/$m^2$=underweight, 18.5 to <25 kg/$m^2$=normal weight, 25-<30=overweight, ≥30=obese.

ii. Body composition

Each patient underwent a full-body, dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy Advance, GE Healthcare, Madison, WI). DXA software (Encore 2006 software, GE Healthcare, Madison, WI) provided the output for measured lean body mass (kg), which we used to calculate the appendicular skeletal muscle index (ASMI) for each patient utilizing the following equation: ASMI = [lean arm mass (kg) + lean leg mass (kg)]/height ($m^2$). DXA is

precise in measuring lean body mass in advanced cancer patients (233). Published cut-offs used to confirm the presence of sarcopenia are as follows: males=7.0 kg/$m^2$, females=5.5 kg/$m^2$ (50).

iii. Malnutrition screening

Patients completed the abridged Patient-Generated Subjective Global Assessment (aPG-SGA) questionnaire. The aPG-SGA is a validated questionnaire used to assess the nutritional status of ambulatory cancer patients (195). The aPG-SGA is comprised of 4 boxes which describe: 1) weight history, 2) food intake, 3) nutrition impact symptoms, and 4) performance status. Total aPG-SGA scores are classified as follows: 0 to 3 does not require nutrition intervention by a RD, 4 to 8 requires an intervention by a RD, $\geq 9$ indicates a need for improved symptom management and nutrient intervention (195).

iv. Handgrip strength

All patients performed handgrip dynamometry to measure grip strength, which is significantly associated with nutritional status (234, 235) and is predictive of poor HRQoL (236), in ambulatory oncology patients. Patients used a Jamar hydraulic hand dynamometer (Jamar, Sammons Preston, Bolingbrook, IL). Patients sat in a chair with feet flat on the floor and shoulder-width apart. Patients held the dynamometer in one hand, with their elbow positioned at a 90-degree angle, and squeezed as hard as they could for 3 seconds. Patients repeated the test twice with each hand, pausing for a minute-long rest between squeezes. We used the peak measure (kg) from the dominant hand for our analysis. Published cut-offs used to assess for the possible presence of sarcopenia are as follows: males= <27 kg, females= <16 kg (50).

v. Assessment of food intake

Patients completed a 3-day food diary prior to each study visit. The 3-day food diary contained detailed information about the quantity and type of food and beverages consumed during a non-consecutive, 3-day period. A RD reviewed the food diary with each patient to ensure completeness and entered the data into Food Processor SQL Nutrition Analysis software (ESHA Research, Salem, OR), utilizing the Canadian Nutrient File (2015 version) database, to calculate overall energy and protein intake, as well as macronutrient distribution at each meal.

### 5.3.2. Methods

*Dietary intervention*

All patients met with a RD once during the study period; at the baseline appointment for the prehab group, and the 4-week appointment for the rehab group. The RD determined protein requirements for each patient based on baseline weight. The intervention aimed to achieve protein intake of 1.5 g/kg/day, based on recommendations for both surgery (202) and cancer (77). The RD calculated protein requirements utilizing 1) current body weight in patients with under/normal weight, 2) the BMI midpoint (22 $kg/m^2$), in patients with overweight or obesity. The RD estimated protein intake at baseline, based on the 3-day food diary completed by each patient. The RD subtracted calculated protein needs from estimated protein intake to determine protein deficit. Once the protein deficit was known, the RD then made individualized dietary recommendations based on preferences and tolerance and provided a whey protein isolate supplement (Immunocal, Immunotech, Vaudreuil-Dorion, QC) in order to achieve protein target. Patients were encouraged to use the whey protein isolate after resistance exercise to provide substrate promoting muscle protein synthesis (204). The RD also provided counselling to

patients experiencing weight loss to achieve adequate energy intake. Estimated energy requirements were calculated using 25 kcal/kg current body weight in patients with overweight/obesity, and 30 kcal/kg current body weight in under/normal weight patients (76). Finally, the RD provided dietary advice to alleviate nutrition impact symptoms.

*Exercise intervention*

A trained kinesiologist prescribed a 60-minute, unsupervised, home-based program for each patient, with an additional, weekly, supervised session for the prehab group. The kinesiologist individualized each exercise program based on the results of baseline fitness tests. The program (both at home and supervised) included the following: 5-minute warm up, 25 minutes of aerobic exercise utilizing the large muscle groups (e.g.: walking, cycling), 30 minutes of resistance training, and a 5-minute cool-down with flexibility exercises.

The kinesiologist determined aerobic exercise intensity by calculating 40% to <60% of heart rate reserve (HRR). The kinesiologist adjusted aerobic exercise intensity on a weekly basis based on patients' rating of perceived exertion (Borg Scale) (237). Patients either walked or cycled daily for the home-based component, and walked on a treadmill (Biodex RTM 400, Biodex Medical Systems, Shirley, NY), or used a recumbent cross-trainer (NuStep T5, NuStep, Ann Arbor, MI), during supervised exercise sessions. Patients performed resistance exercises using TheraBands (TheraBand, Akron, OH) or their own body weight. Patients completed 1-3 sets of 8-12 repetitions of each exercise, 3-4 times per week (every second day).

Resistance exercises included: push-ups, seated row, band pull apart, lateral raises, biceps curl, triceps extension, squats, hamstring curls, standing calf raises, abdominal crunches. Free weights were added to increase intensity of the exercises targeting the biceps, deltoids, and

quadriceps (Bowflex Selectech, Nautilus Inc., Vancouver, WA) when TheraBands offered insufficient resistance. The kinesiologist had patients lift weights until they reached volitional fatigue after 8 repetitions in order to determine appropriate load. The kinesiologist recommended a 48-hour recovery period between each resistance exercise session.

Finally, patients performed flexibility exercises after resistance training. Stretching exercises included the following muscle groups: chest, biceps, triceps, quadriceps, hamstrings, and calves. Patients repeated each stretch twice, holding for 15-30 seconds.

*Anti-anxiety strategies*

A psychologist met with each patient to provide techniques designed to reduce anxiety, including visualization, imagery, deep breathing exercise and muscle relaxation. The psychologist asked patients to use these anti-anxiety tools at any time during the day and at least 3 times a week.

*Usual care group (rehab)*

From baseline to preop, the rehab group received standard care, which does not include preoperative nutrition, exercise or relaxation counselling. The rehab group then followed the same intervention as the prehab group after surgery.

*Adherence to intervention*

A research assistant spoke with patients on a weekly basis to determine whether patients took the prescribed dose of whey protein isolate supplement, followed their exercise prescription and performed anti-anxiety techniques.

5.3.3. Statistical analysis

We used the Student's t-test or the Wilcoxon-Mann-Whitney test (for nonparametric data) to determine differences between groups at baseline. The chi-square or Fisher's exact test allowed for the examination of differences between categorical data at baseline. We calculated means and 95% confidence intervals (95%CI) for protein intake in grams at each meal to assess improvements in protein distribution.

Mixed model ANOVA allowed us to determine the interaction between time and treatment group, as well as time, treatment group and surgery type, on change in protein intake (g/kg), while controlling for age and sex. The same test allowed us to assess changes in aPG-SGA over time and between treatment groups, while controlling for age, sex, surgery type, neoadjuvant chemotherapy treatment, and total days admitted in the 8-weeks postoperatively. Finally, mixed model ANOVA testing allowed us to determine the effect of the time and treatment interaction on FACT-G/subscale scores while controlling for age, sex, surgery type, aPG-SGA score and baseline FACT-G/subscale scores.

Pearson correlations examined relationships between FACT-G and subscale scores with nutritional status measures at baseline. Results of these correlations allowed for the building of robust regression models to determine predictors of HRQoL. Baseline nutritional status measures that were significantly correlated to the FACT-G total and subscale scores were then used in bivariate/multivariate robust regression analysis to determine the predictive strength of these relationships. We also applied robust regression analysis to data from the preop appointment to determine predictors of achieving or not achieving the MID for FACT-G.

We examined the residuals of all mixed model ANOVA and robust regression analyses for normality using the Kolmogorov-Smirnov test, or by examining the skewness and kurtosis of

the data, where values between -1 and 1 are acceptable (205). For each mixed model ANOVA, we used Bayesian Information Criteria to evaluate best fit, and conducted post-hoc Tukey adjustments, which are reflected in reported p-values. We performed intent-to-treat analysis to reduce bias from missing data or patient withdrawal. We used SAS software, version 9.4 (SAS, Cary, NC) for all statistical analyses. Significance was set a $p<0.05$.

## 5.4. Results

### 5.4.1. Baseline characteristics

We enrolled and randomized a total of 61 patients (male=44, prehab=30) in our study. Figure 5.1. shows a CONSORT flow diagram indicating patients progression through the study. There were no significant differences between the prehab and rehab group at baseline (Table 5.1.). The majority of patients (61%) were overweight or obese (Table 5.1.). Almost half of the patients in this study did not require nutrition intervention at baseline (46.6% with aPG-SGA score <4) (Table 5.1.). When examined by sex, average ASMI and handgrip strength measures were above cut-offs established for the diagnosis of sarcopenia (206), with only 1 male participant with confirmed sarcopenia (data not shown). Two prehab patients and 1 rehab patient did not receive surgery due to metastases discovered prior to surgery.

### 5.4.2. Protein intake over the study period

At baseline, the prehab group met the protein goals for surgery (1.5±0.1 g/kg) protein intake, while rehab did not (1.3±0.1 g/kg) (Figure 5.2-A). In the preoperative period, we observed that prehab had a significant increase in protein intake (+0.3±0.1 g/kg, p=0.007), while rehab remained unchanged (+0.2±0.1 g/kg, p=0.121). However, there was a significant increase

from baseline in the rehab group at the 4-week (+0.4±0.1 g/kg, p=0.008) and 8-week (+0.4±0.1 g/kg, p<0.001) visits (Figure 5.2-A). With the exception of rehab at baseline, mean protein intake exceeded 1.5 g/kg/d in both groups and throughout the study period (Figure 5.2-A). At baseline, patients awaiting pancreatic resection in the prehab group had the lowest protein intake (1.2±0.1 g/kg) and had a significant increase by the preop visit (+0.6±0.2 g/kg, p=0.03) (Figure 5.2-B). Patients awaiting liver resection in the rehab group experienced a significant increase in protein intake from baseline to 4-week follow-up (+0.4±0.1, p=0.04) (Figure 5.2-C). The prehab group compliance to whey supplementation was as follows: preop=90±22%, 4-week: 68±34%, 8-week: 84±22%; rehab group compliance: 4-week: 50±38%, 8-week: 76±30% (data not shown).

### 5.4.3. Protein distribution over the study period

At baseline, prehab and rehab did not meet the protein distribution goal of 25-30 g/meal at breakfast (prehab: 20.4±10.6 g/meal (Figure 5.3-A); rehab: 17.7±8.9 g/meal (Figure 5.3-B)). By the preop visit, the prehab group achieved the protein distribution goal (Figure 5.3-A), while rehab did not (prehab: 31.9±13.4 g/meal; rehab: 22.9±6.8 g/meal) (Figure 5.3-B). Protein intake remained >25 g/meal in both groups for all meals at the 4- and 8-week visit (Figure 5.3.).

### 5.4.4. Energy intake over the study period

Baseline evaluation of energy intake for body weight demonstrated that both groups fell within range of energy intake goals for patients with cancer, and was not significantly different between groups (prehab: 28.5±1.8 kcal/kg; rehab: 30.1±1.8 kcal/kg, p=0.998) (Figure 5.4.). Energy intake in the prehab group increased in the preoperative period but this was not statistically significant (+3.7±1.8, p=0.470) (Figure 5.4.). Over the study period, energy intake

remained >25 kcal/kg in both groups with no significant difference between or within the prehab and rehab groups (Figure 5.4.). We found no differences by surgery type (data not shown).

### 5.4.5. aPG-SGA over the study period

Both the prehab and rehab groups had an average aPG-SGA score ≥ 4 at baseline. While aPG-SGA score decreased (improved) in both groups prior to surgery, the observed change was not significant (Figure 5.5-A). Both groups experienced a significant worsening of aPG-SGA score between the preop and 4-week visit (prehab: +5.8±1.0, $p<0.0001$; rehab: +3.3±1.0, $p=0.038$) (Figure 5.5-A). This increase was magnified by patients in the prehab group who underwent pancreatic resection (+10.6±1.7, $p<0.0001$) (Figure 5.5-B), whereas patients who underwent liver resection experienced no significant changes at any time point, nor in either treatment group (Figure 5.5-C).

### 5.4.6. Relationships between HRQoL and nutritional indicators

Baseline relationships between FACT-G, its subscales and markers of nutrition (i.e., BMI, ASMI HGS, aPG-SGA score, protein and energy intake by body weight) revealed that a strong, negative relationship exists between physical wellbeing and aPG-SGA score ($r=0.746$, $p<0.0001$) (Figure 5.6-B). Medium, negative correlations were found between aPG-SGA, total FACT-G score ($r=0.487$, $p<0.001$) (Figure 5.6-A) and functional wellbeing ($r=0.486$, $p<0.001$) (Figure 5.6-C). There were no significant relationships between any other nutritional indicators and FACT-G or its subscales (data not shown).

### 5.4.7. Predictors of HRQoL

Baseline robust regression testing demonstrated that aPG-SGA significantly predicted FACT-G score, in both univariate ($\beta$=-1.33, $p<0.0001$) and multivariable analyses ($\beta$=-1.77, $p<0.0001$) (Table 5.2.). The negative, significant predictive value of aPG-SGA remained in multivariate analysis of physical wellbeing ($\beta$=-0.84, $p<0.0001$) and functional wellbeing ($\beta$=-0.72, $p<0.0001$), but not social/family wellbeing and emotional wellbeing ($p>0.05$) (Table 5.3.).

#### 5.4.8. Changes in HRQoL over the study period

Over the study period, there were no significant changes in FACT-G score, within or between the treatment groups (Figure 5.7.). In both univariate and multivariable analysis, aPG-SGA score was a significant predictor of FACT-G in those who did not meet the MID (Univariate: $\beta$=-3.33, $p < 0.0001$; multivariate $\beta$=-2.83, $p<0.0001$), but not in those who met the MID ($p>0.05$) (Table 5.4.).

## 5.5. Discussion

Our study examined the effectiveness of a nutritional intervention on meeting overall preoperative protein intake and distribution goals, and the relationships between nutritional status and HRQoL. We reported these notable findings: 1) a single dietary counselling session with a RD elicited a significant preoperative improvement in both protein intake and distribution, and a trend toward decreasing malnutrition risk, but was inadequate to maintain improvements postoperatively, 2) there were no significant relationships between anthropometry, body composition, HGS, protein or energy intake and HRQoL at baseline, 3) aPG-SGA was predictive of overall HRQoL at baseline, and of its improvement preoperatively, 4) significant relationships

exist between aPG-SGA and the physical and functional wellbeing domains of HRQoL, but not the social/family and emotional wellbeing domains.

RD counselling led to patients in the prehab group meeting protein intake goals and improving protein distribution through three meals in the preoperative period. The rehab group achieved the same protein goals in the postoperative period. The positive response to dietary counselling is important, as inadequate protein intake and distribution is commonly seen in patients with cancer. In a longitudinal study, Toberupp et al. (238) found that patients with non-small cell lung cancer starting first-line chemotherapy and no dietary counselling, had protein intake of <20 g at breakfast and lunch, and >30 g with dinner at cycles 1, 2 and clinical follow up after three cycles. Overall protein intake relative to body weight remained < 1.5 g/kg throughout the Toberupp study (cycle 1: 1.14±0.47 g/kg; cycle 2: 1.14±0.35, clinical follow-up: 1.32±0.46) (238), and was lower than the patients in the present study at all study points, with the exception of rehab at baseline visit. In another study of patients with pancreatic cancer undergoing a home-based exercise intervention, Clauss et al. (239) found that mean protein intake was 1.22±0.50 g/kg. These findings were similar to the patients in our prehab group with pancreatic cancer, who had baseline protein intake of 1.2 g/kg. Despite progressive resistance training over a 6 month period, Clauss et al. found no significant changes in protein intake and surmised that exercise alone had no effect on nutritional intake (239). These data provide further evidence that the addition of RD counselling to improve dietary protein intake, thus providing adequate substrate for muscle protein synthesis, should be an essential part of any prehabilitation program. Dietary counselling in our study led to a significant increase in protein intake, which exceeded 1.5 g/kg by the preop appointment. The individualized RD counselling performed in this study to meet the 1.5 g/kg protein goal, included advice to enrich the protein content of foods already

consumed, all while considering nutrition impact symptoms affecting oral intake; this approach is considered best practice in supporting patients with cancer at risk of or experiencing malnutrition (240). Additionally, the RD was able to help patients meet protein goals through the provision of a whey protein supplement to enhance the both the quality and quantity of dietary protein consumed. Decreased protein intake after surgery observed in the present study is not surprising, and is expected. In a study of 50 patients who underwent major abdominal surgery for cancer, average daily protein intake was 0.61±0.44 g/kg in the first week post-operative, with insufficiency seen in 90% patients (241). RD counselling in the preoperative period may help mitigate post-operative insufficiency in protein intake, as our study demonstrated that dietary education focused on increasing protein intake in the rehab group during the postoperative period was adequate to meet 1.5 g/kg goal. Preoperative nutrition counselling is in line with ERAS guidelines. For example, ERAS recommendations for patients undergoing pancreaticoduodenectomy includes the use of nutritional supplements as part of a multimodal prehabilitation program (evidence level: moderate; grade of recommendation: strong) (232).

The present study did not show significant improvement in aPG-SGA score in the preoperative period, despite dietary counselling. Our findings were consistent with a study by Hall et al. that measured changes in aPG-SGA score over time in a diet and exercise rehabilitation program for patients with advanced cancer (242). Despite RD-led dietary counselling, there were no significant differences in aPG-SGA score between the intervention or control group ($p=0.249$) (242). Current guidelines suggest that mitigation of nutrition impact symptoms is best treated using a multidisciplinary team approach to identify, prevent and treat any reversible cause of malnutrition (76). It may benefit future prehabilitation studies to integrate

a physician specialized in cancer supportive care, in conjunction with RD-led dietary counselling, to help reduce symptoms hindering optimal dietary intake.

The absence of any significant relationships between anthropometry, body composition, HGS, protein or energy intake and HRQoL at baseline was surprising. We believe this is the result of high baseline values in all these measures among our participants. As previously mentioned, average ASMI and HGS were above the norms for sarcopenia diagnosis, with only 1 patient presenting with sarcopenia at baseline. Additionally, average protein and energy needs were being met at baseline, reflecting a possible selection bias whereby patients who were already eating well and understood the importance of nutrition, agreed to enrol in the present study. Finally, baseline average FACT-G scores (81.2±14.9) were slightly greater than normative data for the general population (80.1±18.1) and among people living with various cancers (80.4±15.9) (243), although the difference was not clinically meaningful (difference less than MID of 3 to 7).

To the authors' knowledge, only one other study has been published reporting the effect of prehabilitation on HRQoL, adjusting for nutrition status as measured by aPG-SGA. Gillis et al. (81) demonstrated that patients with colorectal cancer and an aPG-SGA of ≥ 9 undergoing prehabilitation demonstrated a significant preoperative improvement in the SF-36 domain of general health (prehab: +12.1±18.6; rehab: -4.8±14.0, $p<0.05$). Additionally, the same study demonstrated that SF-36 bodily pain scores improved in patients with an aPG-SGA score of 4 to 8 (prehab: +5.2±21.2; rehab: -5.1±18.7, $p<0.05$) (81). However, no improvements were found in the SF-36 physical function domain among those with aPG-SGA ≥9 (prehab: +1.8±20.5; rehab: +0.6±8.01, $p>0.05$) or those with aPG-SGA score between 4 and 8 (prehab: +7.2±16.5; rehab: +4.4±22.4, $p>0.05$). Gillis' findings differed from our study where aPG-SGA score negatively

predicted meeting the MID of physical and functional wellbeing in the preoperative period. The discrepancy between our study and that of Gillis et al. and may be partially due to the use of two different HRQoL assessment tools used, making it difficult for comparison. Additionally, there were proportionally fewer malnourished (aPG-SGA ≥9) prehab patients in the Gillis et al. study than in the present study (16% versus 20% respectively), this likely due to the malnutrition associated with pancreatic cancer upon diagnosis. Finally, participants in our study were on average 10 years younger and differed in cancer diagnosis, leading to different treatments and side-effects. The present study was similar to Gillis et al. in that no improvements were noted for overall HRQoL in the preoperative period.

Relationships between nutritional status and HRQoL in patients with a variety of cancers and different stages of disease have previously been reported. Kaya et al. (244) conducted a retrospective study of 166 patients undergoing chemotherapy, in which the Nutrition Risk Screening-2002 (NRS-2002) tool was used to determine risk of malnutrition, and the European Organization for Research and Treatment of Cancer Quality of Life questionnaire-C30 (EORTC-QLQ-C30) to determine HRQoL. Those with malnutrition (NRS-2002 score ≥3) had worse functional ($p=0.003$), physical ($p=0.004$) and general health status ($p>0.001$) than those who were not malnourished (244). This reflected the negative relationship between aPG-SGA score and the total FACT-G score and the physical and functional wellbeing scores found in our study. Ravasco et al. (245) found significant relationships between nutritional markers and global function scores as measured by the EORTC-QLQ-C30 in patients with head and neck, esophageal, gastric and colorectal cancers. Energy intake (effect size (ES): 10%, $p=0.01$), protein intake (ES: 10%, $p=0.01$) and weight loss (ES: 30%, $p<0.0001$) had a significant, low to moderate effect on global function. Our study did not find any relationships between energy or

protein intake and functional wellbeing, possibly because most patients were meeting their energy and protein needs at baseline.

Deprato et al. (246) published a systematic review of surgical and HRQoL outcomes following prehabilitation in patients awaiting HPB surgery; only two of the six studies included in the review reported data on HRQoL, and none on nutrition status. The unimodal prehabilitation study by Dunne et al. (247), in patients awaiting liver resection from colorectal cancer metastasis, saw patients engage in a 4-week, high-intensity interval training (cycling) program. Over the study period, the prehabilitation group experienced improved overall HRQoL, as measured by the SF-36 (+12, 95%CI: 5-19, p=0.002), with this increase being significantly different from the control group (+11, 95%CI:1-21, p=0.028)(247). In contrast, Wang et al. (248) described a multimodal, prehabilitation program for patients awaiting liver resection, which included: 1) preoperative deep breathing exercises taught by a physiotherapist, 2) preoperative nutrition counselling by a registered dietitian, and 3) a case manager intervention to mentally prepare patients/caregivers for surgery. Surprisingly, no overall effect on FACT-Hep HRQoL was demonstrated (248). No information regarding nutrition outcomes was published or analyzed for the effect on HRQoL.

Heterogeneity of tools used to measure HRQoL is a limitation in measuring the effect of prehabilitation on HRQoL. This was demonstrated in a recent systematic review by Chou et al. (249) examining the effect of prehabilitation programs on the HRQoL of patients with cancer. Only 5 of the 10 articles included in the review had HRQoL as the primary outcome, with either the EORTC QLQ-C30 or the SF-36 to measure HRQoL. Chou et al. were unable to make comparisons between studies because 1) the time period patients are asked to reflect on when reporting on HRQoL differs between tools (EORTC QLQ-C30 : past week versus SF-36: past

month) and 2) different domains from each tool were reported on. Future prehabilitation studies should reduce heterogeneity of tools used to measure HRQoL, although the tool that best measures HRQoL in a prehabilitation setting remains unknown.

There are some important limitations to this study. First, there are different nutritional implications in patients awaiting pancreatic versus liver resection. For example, possible surgical complications in patients with pancreatic cancer include pancreatic exocrine insufficiency and diabetes, which may have profound effect on nutritional status. Our study was not designed to address these post-operative complications. Large studies among patients awaiting pancreatic surgery should include nutritional interventions to treat pancreatic exocrine and endocrine disruptions, with closer follow-up both in the pre- and postoperative period. Second, the majority of patients who enrolled in this study had an aPG-SGA score < 9, were not underweight, had normal muscle mass, and did not have dynapenia. This may partially explain baseline FACT-G scores that matched those seen in healthy population. Therefore, it is possible that within- or between-group differences in HRQoL outcomes were not observed because of a ceiling effect. It would likely benefit future studies to screen patients entering a prehabilitation program for malnutrition and physical/functional impairments, thus ensuring the provision of such an intervention to those with the greatest need. Conversely, an important strength of this study was that it identified the unique and essential role that nutritional status and dietary intervention plays in the HRQoL of this patient population, especially during the 4-week postoperative period. Additionally, a strength of this study was the multimodal design that included randomization to a control group.

## 5.6. Conclusions

Our study demonstrated that high aPG-SGA score, indicating increasing risk of malnutrition, was predictive of poor HRQoL in patients awaiting HPB surgery. Prehabilitation programs that include dietary counselling can improve protein intake and distribution to enhance muscle protein synthesis and reserve in the preoperative period. RD-led nutrition counselling should be included in all future HPB prehabilitation programs. Future studies should also examine whether the addition of a supportive care physician to manage symptoms negatively impacting nutrition in the preoperative period, would improve HRQoL outcomes within a prehabilitation model.

### 5.6.1. Acknowledgments

The authors would like to thank the surgical team for their support of this study: Dr. Prosanto Chaudhury, Dr. Peter Metrakos, Dr. Jeffrey Barkun and Daphnée Lamoussenary. Additionally, the authors would like to thank the patients and family members who participated in our study.

### 5.6.2. Author Contributions

PK coordinated the study, wrote/edited the manuscript, performed the statistical analysis and administered the dietary intervention. AV conceptualized the study and reviewed/edited the manuscript. TB coordinated the study, administered the exercise intervention and reviewed/edited the manuscript. FC conceptualized the study and reviewed/edited the manuscript. RK conceptualized the study and reviewed/edited the manuscript.

### 5.6.3. Declaration of Interest Statement

The authors report there are no competing interests to declare.

### 5.6.4. Funding Statement

Funding for this work was generously provided by the Cedars Cancer Foundation of the MUHC.

Table 5.1.: Descriptive characteristics of study participants

| | Prehab | Rehab | p |
|---|---|---|---|
| Age (y) | 58.8±15.7 | 64.4±11.9 | 0.199 |
| Male | 21(70.0) | 23 (74.2) | 0.715 |
| Weight (kg) | 74.7±17.2 | 76.5±13.9 | 0.652 |
| BMI (kg/m$^2$) | 26.4±5.6 | 26.6±3.7 | 0.867 |
| Underweight | 2 (6.7) | 0 | 0.238 |
| Normal weight | 11 (36.7) | 11 (35.5) | 1.000 |
| Overweight | 10 (33.3) | 13 (41.9) | 0.488 |
| Obese | 7 (23.3) | 7 (22.6) | 1.000 |
| ASMI (kg/m$^2$) | 6.95±1.41 | 7.15±1.16 | 0.396 |
| ASMI males (kg/m$^2$) | 7.45±1.35 | 7.41±1.11 | 0.874 |
| ASMI females (kg/m$^2$) | 5.86±0.83 | 6.28±0.92 | 0.397 |
| Peak HGS (kg) | 38.6±10.9 | 37.9±11.6 | 0.816 |
| Males (kg) | 42.7±9.2 | 40.3±10.8 | 0.440 |
| Females (kg) | 29.3±8.7 | 31.3±11.7 | 0.710 |
| aPG-SGA score | 5.8±5.6 | 5.6±5.9 | 0.725 |
| aPG-SGA <4 | 11 (39.3) | 16 (53.3) | 0.284 |
| aPG-SGA 4 to 8 | 11 (39.3) | 6 (20.0) | 0.107 |
| aPG-SGA ≥ 9 | 6 (20.0) | 8 (25.8) | 0.641 |
| Energy intake (kcal/d) | 1839.9±574.1 | 1836.9±706.3 | 0.986 |
| Energy intake (kcal/kg) | 29.8±8.9 | 28.7±10.7 | 0.668 |
| Protein intake (g/d) | 94.9±37.6 | 82.5±31.2 | 0.246 |
| Protein intake (g/kg) | 1.5±0.6 | 1.3±0.5 | 0.097 |
| Pancreas surgery | 10 (33.3) | 12 (38.7) | 0.662 |
| Liver surgery | 18 (60.0) | 18 (58.1) | 0.878 |
| No surgery | 2 (6.7) | 1 (3.2) | 0.614 |
| Neoadjuvant chemotherapy | 14 (46.7) | 17 (54.8) | 0.523 |
| FACT-G total | 81.2±12.9 | 81.3±16.7 | 1.000 |
| Physical wellbeing | 22.3±5.0 | 21.8±5.9 | 0.908 |
| Social/family wellbeing | 22.3±4.4 | 22.4±6.4 | 0.446 |
| Emotional wellbeing | 16.9±4.7 | 18.5±4.2 | 0.212 |
| Functional wellbeing | 16.9±4.7 | 18.5±4.2 | 0.173 |

Data reported as mean±SD or n (%). Significance set at $p<0.05$. aPG-SGA: abridged patient-generated subjective global assessment, ASMI=appendicular skeletal muscle index, BMI=body mass index, FACT-G= functional assessment of cancer therapy-general, HGS=handgrip strength.

Table 5.2.: Baseline robust univariate and multivariate regression analysis of FACT-G predictors

| | Univariate | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p |
| Age | 0.08 | 0.14 | -0.20 to 0.36 | 0.576 | 0.26 | 0.13 | 0.01 to 0.51 | **0.044** |
| Male | -3.01 | 4.62 | -12.06 to 6.03 | 0.514 | -8.26 | 4.05 | -16.19 to -0.32 | **0.041** |
| Neoadjuvant chemotherapy | -1.41 | 4.22 | -9.68 to 6.85 | 0.737 | -3.33 | 3.58 | -10.36 to 3.69 | 0.352 |
| aPG-SGA | -1.33 | 0.33 | -1.98 to -0.68 | **<0.0001** | -1.77 | 0.34 | -2.45 to -1.10 | **<0.0001** |

Robust regression analysis. aPG-SGA=abridged patient-generated subjective global assessment, CI=confidence interval, FACT-G=functional assessment of cancer therapy-general, SE=standard error.

Table 5.3.: Baseline multivariable robust regression analysis of FACT-G subscale predictors

| | **PWB** | | | | **SWB** | | | | **EWB** | | | | **FWB** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p |
| Age | 0.06 | 0.03 | 0 to 0.12 | 0.059 | 0.09 | 0.04 | 0 to 0.18 | **0.049** | 0.06 | 0.05 | -0.03 to 0.15 | 0.210 | 0.10 | 0.05 | 0 to 0.20 | **0.045** |
| Male | -1.95 | 0.91 | -3.73 to -0.17 | **0.032** | -2.43 | 1.42 | -5.21 to 0.35 | 0.086 | 0.52 | 1.43 | -2.28 to 3.31 | 0.718 | -4.26 | 1.54 | -7.26 to -1.25 | **0.006** |
| Neoadjuvant chemotherapy | -2.24 | 0.82 | -3.86 to -0.63 | **0.006** | -0.13 | 1.25 | -2.59 to 2.33 | 0.917 | 1.40 | 1.28 | -1.12 to 3.91 | 0.276 | -2.87 | 1.38 | -5.57 to -0.17 | **0.037** |
| aPG-SGA | -0.84 | 0.08 | -0.99 to -0.69 | **<0.0001** | -0.12 | 0.12 | -0.36 to 0.11 | 0.305 | -0.14 | 0.12 | -0.38 to 0.10 | 0.242 | -0.72 | 0.13 | -0.99 to -0.46 | **<0.0001** |

Robust multivariable regression analysis. aPG-SGA=abridged patient-generated subjective global assessment, CI=confidence interval, EWB=emotional wellbeing, FACT-G=functional assessment of cancer therapy-general, FWB=functional wellbeing, PWB=physical wellbeing, SE=standard error, SWB=social/family wellbeing.

Table 5.4.: Robust regression of **preoperative** FACT-G predictors, stratified by meeting the FACT-G MID

| | **Met MID** | | | | | | | | **Did not meet MID** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Univariate** | | | | **Multivariable** | | | | **Univariate** | | | | **Multivariable** | | | |
| Predictor | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p | Estimate | SE | 95%CI | p |
| aPG-SGA | -1.25 | 0.68 | -2.59 to 0.08 | 0.066 | -1.43 | 0.77 | -2.95 to 0.08 | 0.064 | -3.33 | 0.83 | -4.94 to -1.71 | **<0.0001** | -2.83 | 0.67 | -4.15 to -1.51 | **<0.0001** |
| Age | 0.18 | 0.15 | -0.13 to 0.48 | 0.252 | 0.22 | 0.18 | -0.13 to 0.57 | 0.215 | 0.16 | 0.21 | -024 to 0.56 | 0.437 | 0.10 | 0.13 | -0.15 to 0.36 | 0.434 |
| Male | 2.47 | 4.73 | -6.79 to 11.7 | 0.601 | -0.71 | 5.13 | -10.76 to 9.34 | 0.890 | -6.66 | 7.73 | -21.80 to 8.49 | 0.389 | -8.19 | 5.19 | -18.38 to -1.99 | 0.115 |
| Prehab | 2.09 | 4.56 | -6.85 to 11.04 | 0.647 | 3.04 | 4.85 | -6.46 to 12.54 | 0.530 | -7.76 | 5.90 | -19.33 to 3.80 | 0.188 | -6.72 | 3.88 | -14.32 to 0.89 | 0.084 |
| Pancreatic surgery | -6.09 | 4.84 | -15.58 to 3.40 | 0.209 | -4.50 | 5.24 | -14.76 to 5.76 | 0.390 | 9.40 | 6.21 | -2.77 to 21.57 | 0.130 | 6.44 | 4.32 | -2.02 to 14.90 | 0.136 |

Robust univariate/multivariable regression analysis. aPG-SGA=abridged patient-generated subjective global assessment, CI=confidence interval, FACT-G=functional assessment of cancer therapy-general, MID=minimal important difference, SE=standard error.

Figure 5.1.: CONSORT flow diagram

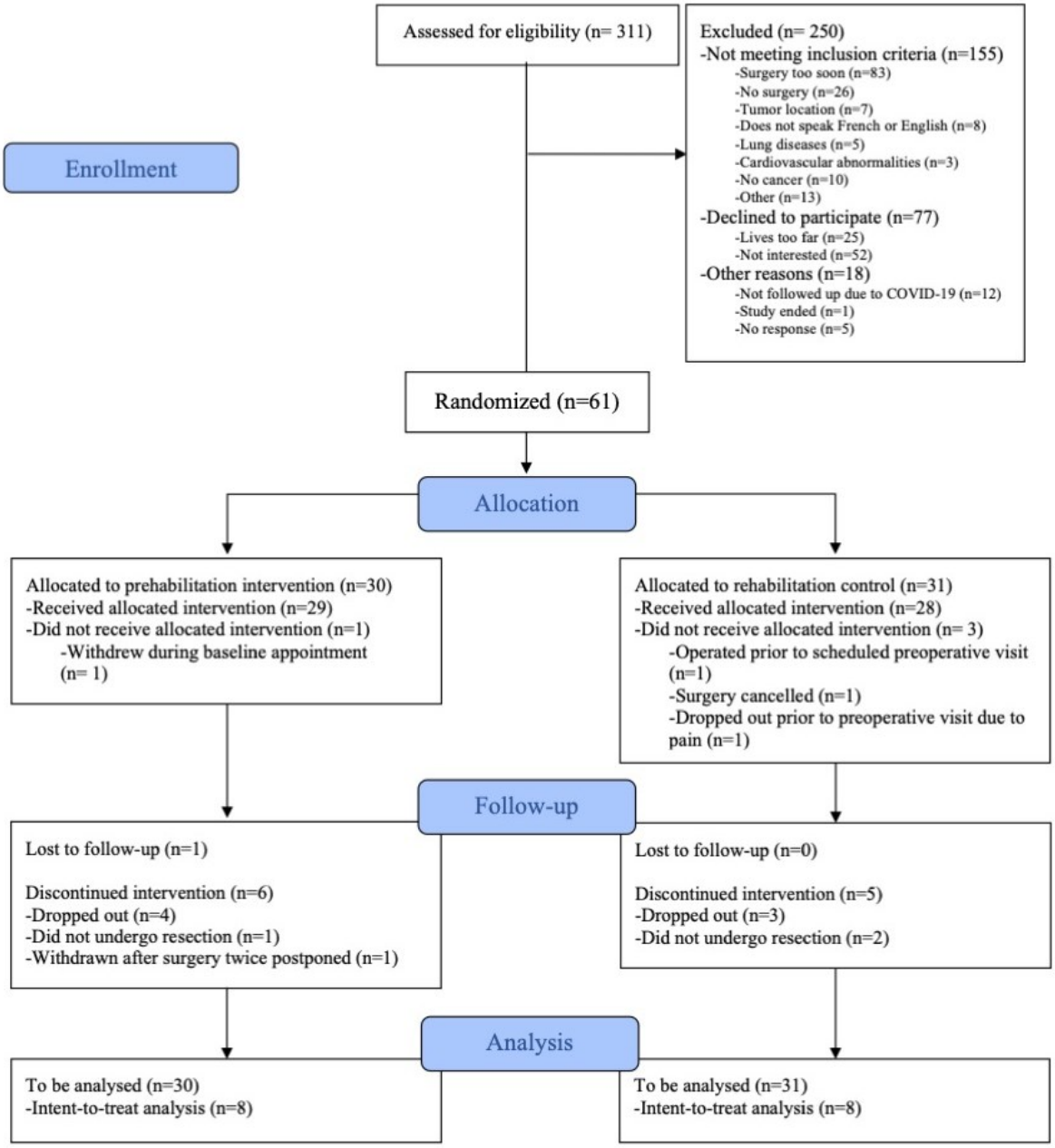
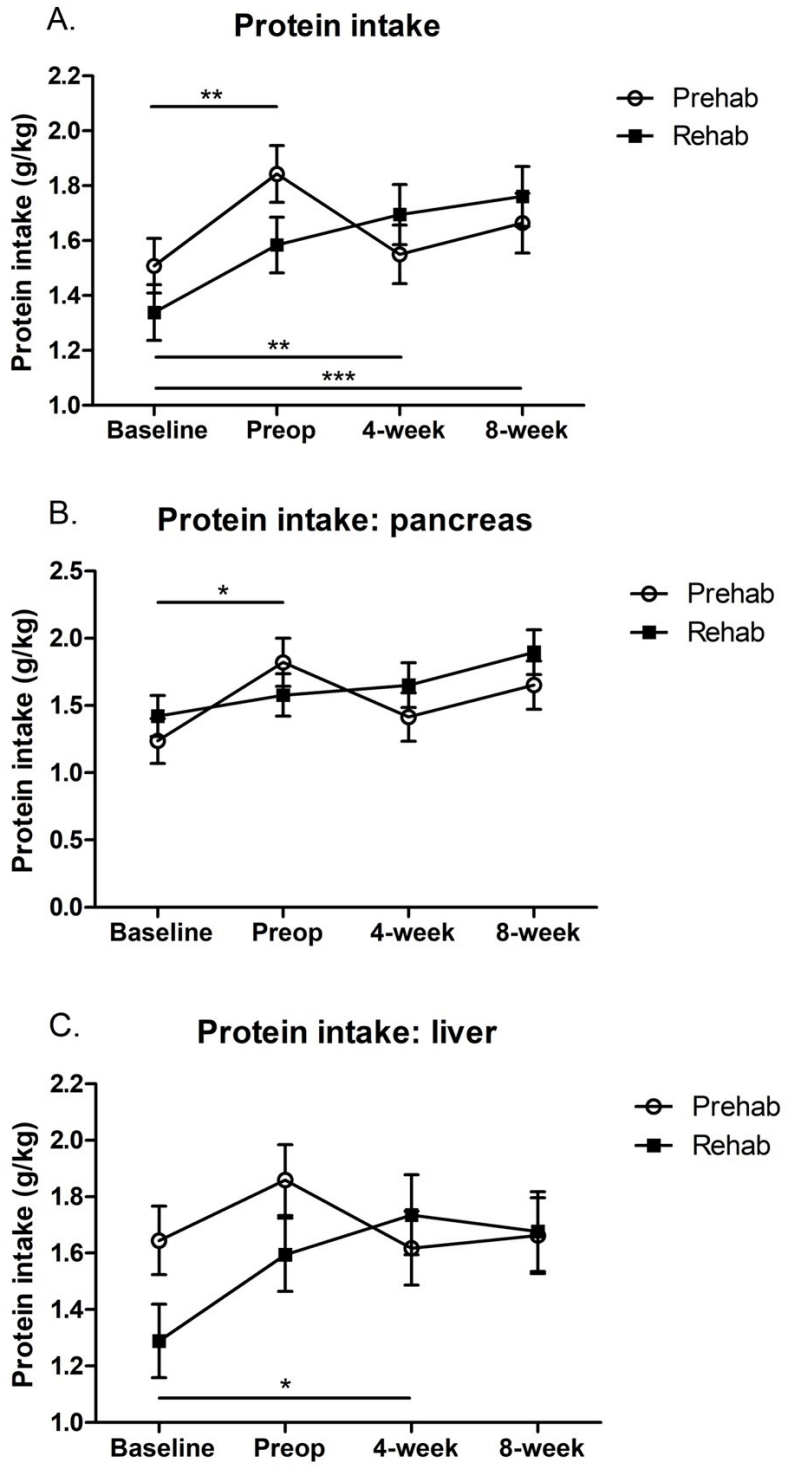
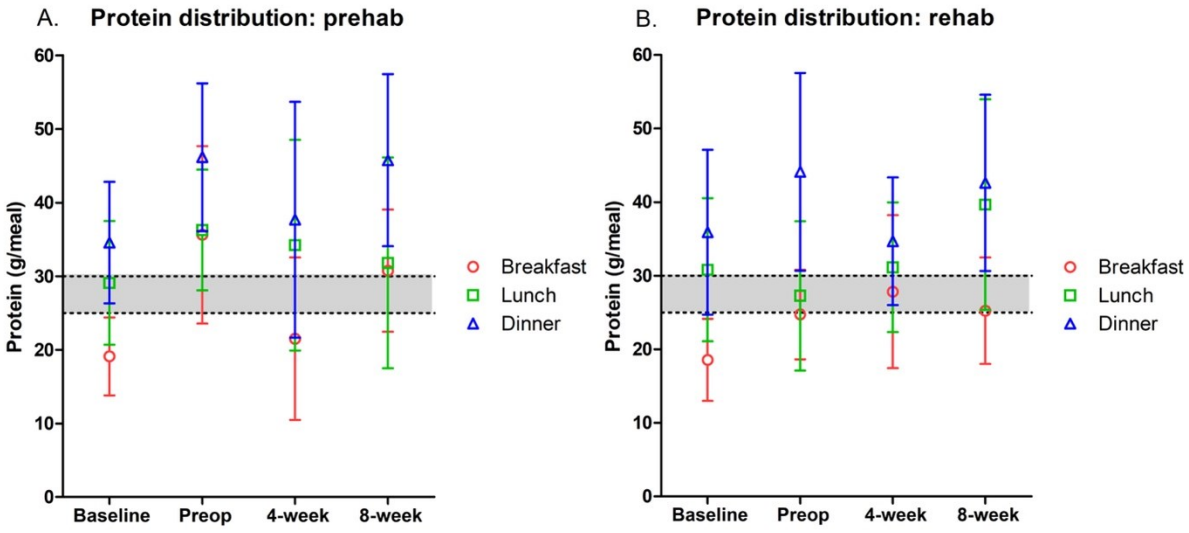


Figure 5.2.: Dietary protein intake by treatment, time and surgery type



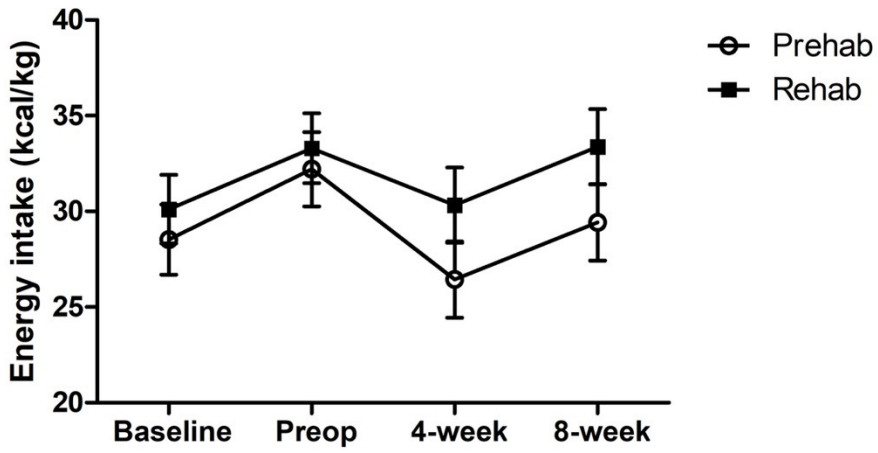

Mixed model ANOVA: interaction of treatment, time and surgery. Covariates include age and sex. Mean±SEM reported. Significance *p<0.05, ** p<0.01, *** p<0.001.

Figure 5.3.: Baseline protein distribution, by meal, treatment group and time



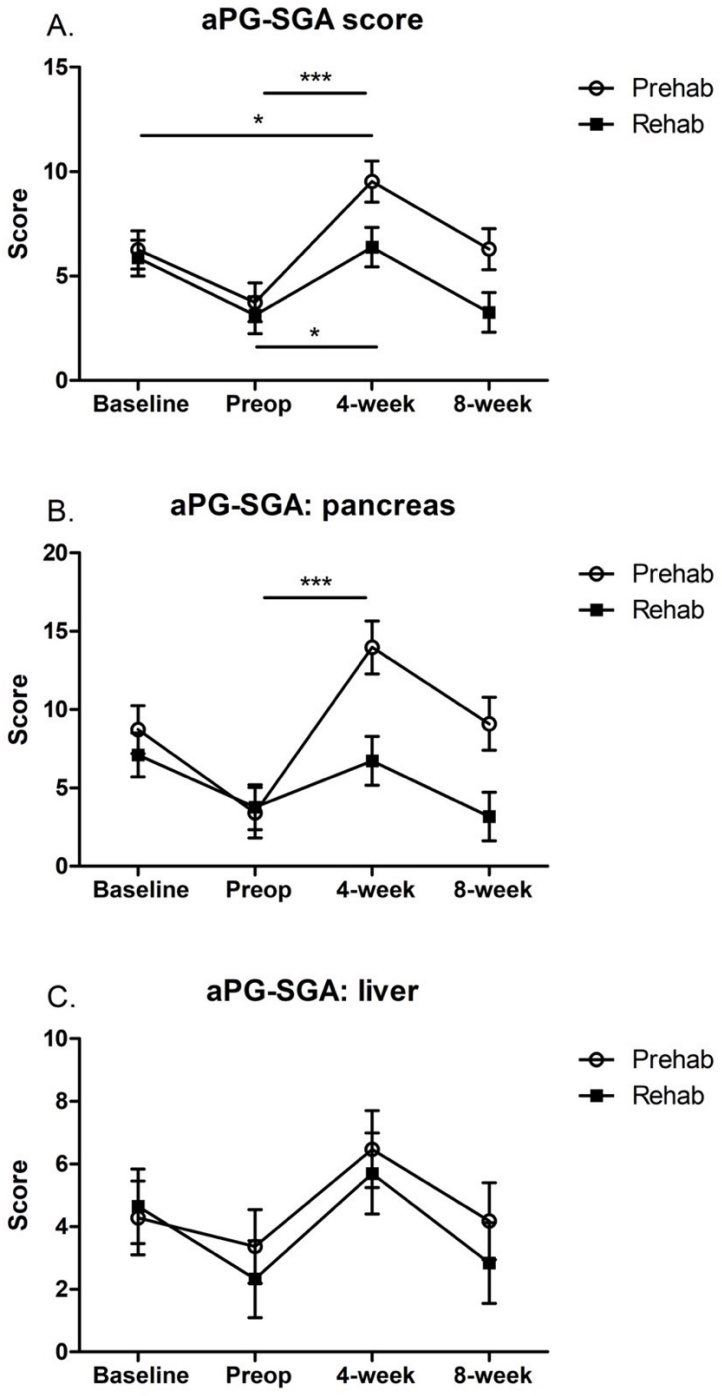

Mean and 95% confidence interval reported. Shaded area between 25 and 30 g/meal denotes target protein intake for each meal.

Figure 5.4.: Energy intake by treatment, over time



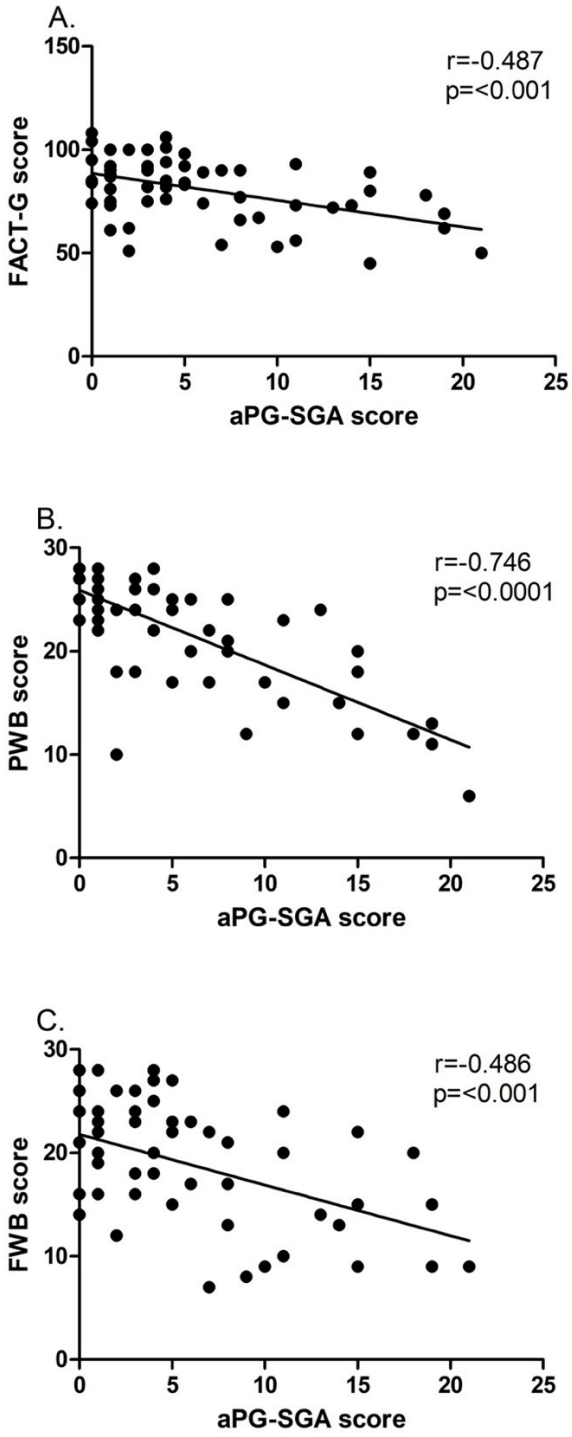

Mixed model ANOVA: interaction of treatment and time. Covariates include age and sex. Mean±SEM reported. Significance *p<0.05, ** p<0.01, *** p<0.001.

Figure 5.5.: aPG-SGA score by treatment, time and surgery



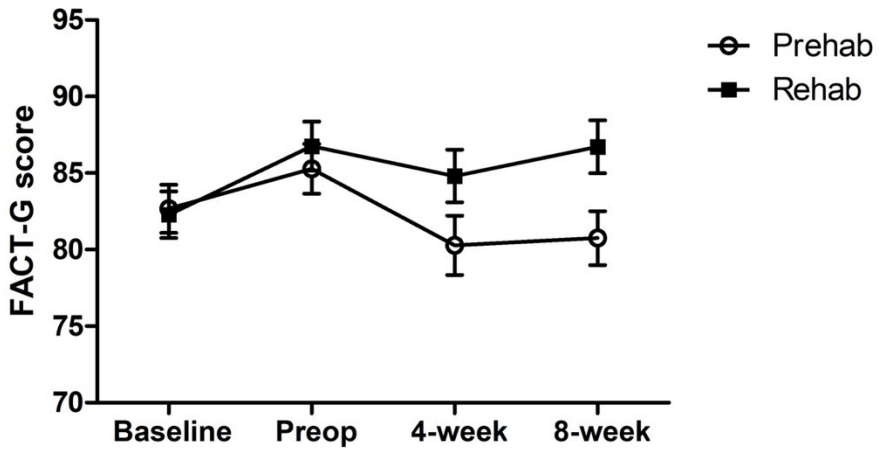

Mixed model ANOVA: interaction of treatment, time and surgery. Covariates include age, sex, neoadjuvant chemotherapy and length of hospital stay. Mean±SEM reported. Significance *p<0.05, ** p<0.01, *** p<0.001. aPG-SGA: abridged Patient-Generated Subjective Global Assessment; higher score denotes increased risk of malnutrition.

Figure 5.6.: Baseline correlations between FACT-G/subscale scores and aPG-SGA




Pearson correlations. Significance set at $p<0.05$. aPG-SGA=abridged Patient-Generated Subjective Global Assessment, FACT-G=Functional Assessment of Cancer Therapy-General, FWB=Functional Wellbeing, PWB=Physical Wellbeing.

Figure 5.7.: Changes in FACT-G score over the study period, by intervention




Mixed model ANOVA: interaction of treatment and time. Covariates include age, sex, neoadjuvant chemotherapy, surgery type, aPG-SGA score and baseline FACT-G score. Mean±SEM reported. Significance *p<0.05, ** p<0.01, *** p<0.001. aPG-SGA=abridged Patient-Generated Subjective Global Assessment, FACT-G=Functinal Assessment of Cancer Therapy-General; higher score denotes better health-realted quality of life.

# Chapter 6: General Discussion

The purpose of this dissertation was to examine the effect of diet and exercise interventions on HRQoL in patients with pancreatic cancer. The question was tackled by moving from a holistic view of diet and exercise interventions via a scoping review of the literature (Chapter 3: Manuscript 1), to a more pointed view examining the effect of a diet and exercise intervention, within a prehabilitation program, on HRQoL (Chapter 4: Manuscript 2), to the very specific role of a dietary intervention and nutritional status in a cohort of patients awaiting HPB surgery (Chapter 5: Manuscript 3).

The literature review performed for the purposes of this dissertation has provided a framework to support the view that diet and exercise interventions may help improve the HRQoL. However, the review has also revealed numerous gaps in knowledge; these gaps were further illustrated in the scoping review of literature presented in chapter 3. Despite limitations, the 2 manuscripts in chapters 4 and 5 provide some evidence to fill gaps in knowledge and provide direction for future study designs.

## 6.1. Scoping review (Manuscript 1)

The purpose of manuscript 1, published in the journal Pancreas and presented in chapter three of this dissertation, was to present a comprehensive overview of the body of literature examining diet and/or exercise interventions among ambulatory patients with pancreatic cancer. The choice to perform a scoping review was made in order to allow for a broad view of the topic, which would help identify how previous studies were conducted and what research gaps remain. The scoping review presented in this dissertation identified 7 research gaps, three of which were

relevant to the work presented in this dissertation. First, the scoping review found that more work examining the combination of diet and exercise is warranted. The principle behind integrating both diet and exercise in interventions designed to help patients with pancreatic cancer is sound. As evidenced in the literature review of this dissertation, there is a high prevalence of malnutrition and sarcopenia among this patient population. As such, providing an anabolic stimulus through exercise, and providing substrate for muscle protein synthesis via dietary interventions is likely best to combat sarcopenia. However, there is very little known regarding whether interventions aiming to achieve dietary energy and protein goals are successful. Furthermore, compliance to exercise interventions is the most commonly reported outcome.

Second, the combination of aerobic and strength training is likely best to counteract sarcopenia and fight the effects of cancer-related fatigue, which is an important symptom negatively affecting the HRQoL of patients with pancreatic cancer (250). The results of the scoping review demonstrated that the majority of exercise-only interventions (7 of 13 studies), while almost all of the combined diet and exercise interventions (7 of 8 studies), included both aerobic and strength training. The heterogeneity among the combined exercise interventions in the scoping review, in terms of the FITT (frequency, intensity, time, type) principle, leaves many unanswered questions as to what is best for patients with pancreatic cancer. Additionally, the need to adjust one or more elements of the FITT principle based on patients with curative or metastatic disease, as the cancer symptom burden and anabolic resistance in advanced pancreatic cancer may not allow for a benefit of intense exercise. At present, recommendations for exercise in patients with cancer undergoing active treatments are not well defined, and are similar to that of healthy populations (251). In manuscripts 2 and 3, we studied a combined aerobic and

resistance training program is part of a trimodal intervention, with our outcome of interest being HRQoL.

Third, there was great heterogeneity in the outcomes of interest among the studies included in the scoping review. As such, very little data exists to confirm the effect of diet and exercise interventions on a multitude of aspects that can be improved by such interventions. A proposed outcome measure that is of particular interest to patients with pancreatic cancer is the effect of diet and exercise on PROs, and HRQoL in particular, given the poor prognosis of the disease and palliative nature of treatments. As demonstrated in the introduction to this dissertation, even in patients undergoing surgery as a curative treatment, 5-year survival remains low at 10-25% (6). As mentioned, the outcome of interest in manuscripts 2 and 3 was to examine the effect of trimodal prehabilitation on HRQoL, and to describe associations with physical strength, functional capacity, nutritional status and cancer symptoms. HRQoL, as described in the literature review of this dissertation, is multifaceted and is affected in part by physical and functional domains of HRQoL, as well as cancer symptoms. Diet and exercise interventions embedded within a prehabilitation program may address problems that pertain to these domains of HRQoL. For example, exercise may help patients maintain or increase strength and functional capacity, leading to better functional and physical domains of HRQoL; dietary interventions can help reduce nutrition impact symptoms of cancer and its treatments, as well as providing substrate to enhance the effect of exercise.

As described in this section, the scoping review on diet and exercise interventions in patients with pancreatic cancer identified many gaps in the literature. The following section will describe how the results of manuscript 2 attempted to add to the evidence that diet and exercise

provided in a prehabilitation program may help improve HRQoL in patients with pancreatic cancer awaiting surgery.

### 6.2. The effect of prehabilitation on HRQoL (Manuscript 2)

The first hypothesis set for manuscript 2 was that patients who participated in a diet and exercise intervention, within a prehabilitation program prior to surgery, would have better HRQoL outcomes than a control, rehabilitation group. Results of the study revealed that in patients who underwent a 4-week prehabilitation intervention showed no significant increase in FACT-Hep score at the preoperative evaluation. Additionally, it was only the prehab group who experienced a significant decline in FACT-Hep at the 4-week postoperative evaluation (-26.6±5.9, p=0.001), whereas maintenance was observed in the rehab group. By the 8-week postoperative visit, no difference from baseline in FACT-Hep scores was observed in either group.

The drastic decline in HRQoL in the prehab group 4 weeks after surgery is not what was expected. A few reasons for this observation can be put forth. The small sample size in this study may exacerbate the effect of a few patients who had complicated postoperative courses; the COVID-19 pandemic forced the cessation of patient recruitment prior to achieving the goal of 30 participants. Additionally, length of hospital stay in the postoperative period was used as a surrogate measure of complications; longer length of stay would indicate more postoperative morbidity. However, there were no significant differences between groups for length of stay. It is possible that using length of stay in place of a more detailed description of surgical complications may have lacked sensitivity to detect the detrimental effect on HRQoL in those who had a difficult postoperative course. Beyond surgical morbidity, the long-term effects of

pancreatic resection were not well considered in HRQoL outcomes. Patients who became diabetic, or experienced PEI postoperatively may have driven the decline in HRQoL. While a possible negative effect of PEI on HRQoL has been documented and discussed in the literature review of this dissertation, pancreatogenic diabetes (type 3c) caused by the cancer or surgery has not been considered and was beyond the scope of the study. Research into relationships between type 3c diabetes and HRQoL is sparse. One study by Kuo et al. (252) demonstrated that patients with pancreatic cancer who had a more recent diagnosis of diabetes (in months), experienced worse HRQoL than those with more longstanding diabetes ($r = 0.3$, $p = 0.026$). It is reasonable to expect that learning to manage diabetes with diet and medications in the postoperative period may be a significant burden to patients, causing a decline in HRQoL. Finally, the observed maintenance of HRQoL by the rehab group at the 4-week postoperative evaluation provides some evidence that the diet and exercise intervention offered may have a positive effect on HRQoL; by the 4-week assessment, all study patients were engaged in the intervention. Additionally, the return to baseline HRQoL levels at 8 weeks postoperatively was quicker than the expected 3 to 6 months, as illustrated in the literature review of this dissertation.

The second hypothesis of this manuscript was that strong, negative relationships between HRQoL and nutritional status, body composition, strength and functional status would be observed. While nutritional status as measure by the aPG-SGA had a strong, negative relationship with HRQoL (Figure 4.2.), and was predictive of poof HRQoL outcomes (Table 4.3.), the results of the study did not demonstrate any relationships between muscle mass, strength or function. However, conclusions cannot be drawn from this negative finding. A major limitation of the study beyond the small sample size, was the presumed bias inherent in this type of study. For example, there may have been an element of performance bias on the part of

patients; most patients who enrolled in the study wanted diet and exercise advice prior to surgery and may have been disappointed to be randomized to the rehab group. Patients knew what the diet and exercise intervention entailed, due to the description of the study included in the informed consent document. As such, they may have started exercising or trying to increase their protein intake prior to receiving the actual intervention. External validity may have been affected by a selection bias in patients who agreed to enrol in the study. Most of the patients in the study were both well-nourished and not sarcopenic, a large deviation from the prevalence of both problems as discussed in the literature review of this dissertation.

### 6.2.1. Future research directions resulting from manuscript 2

Work to improve understanding on how to best address HRQoL concerns in patients with pancreatic cancer entering a prehabilitation program is necessary, given the poor prognosis these patients face. The following three suggestions may improve future studies. 1) A screening effort to determine which patients would benefit most from prehabilitation may mitigate any ceiling effect of the intervention due to high baseline levels. The elements that should be included in such screening are dependent on the outcome of interest and have yet to be elucidated. However, they may include screening for the presence of malnutrition, cancer symptom burden, fatigue or sarcopenia. 2) As cancer symptoms are associated with worse HRQoL in this patient population, examining the role of specialized medical management of symptoms, possibly via the inclusion of a palliative care physician within the prehabilitation team, may be warranted. 3) The specific burden of type 3c diabetes and PEI on HRQoL in the postoperative period should be examined, with the effectiveness of dietary interventions to support patients postoperatively designed and

tested. All of these gaps in our knowledge regarding the role of diet and exercise on HRQoL in patients with pancreatic cancer should be tested in prospective, randomized controlled trials.

### 6.3. The effect of dietary interventions on HRQoL in patients awaiting HPB surgery (Manuscript 3)

The first hypothesis of manuscript 3 stated that RD-led nutritional counselling will result in patients meeting goals necessary for optimization of preoperative nutritional status (e.g., energy-protein intake, protein distribution). At present, no other study has examined the effectiveness of such a treatment, compared to a control group. Results demonstrated that there was a significant increase in protein intake in the preoperative period while rehab remained unchanged (prehab: +0.3±0.1 g/kg, $p<0.01$ versus rehab: +0.2±0.1 g/kg, $p>0.05$). Additionally, only prehab achieved the protein distribution goals of at least 25 g protein at breakfast by the preoperative period (prehab: 31.9±13.4 g/meal versus rehab: 22.9±6.8 g/meal). Both prehab and rehab met the 1.5 g/kg daily protein recommendation and protein distribution goals of 25 g/meal at both 4- and 8-weeks postoperative. These findings supported the hypothesis and provided evidence to advocate for RD-led nutritional interventions within prehabilitation programs. The scoping literature review presented in manuscript 1 showed that of the 13 exercise interventions found, 7 were undertaken in patients in the preoperative period and 1 immediately after surgery, all without a dietary intervention. It is reasonable to question whether those studies would have had more robust, positive findings, if a nutrition intervention had been included. Cancer causes anabolic resistance, in part due to inflammatory cytokines produced by both the tumour and host-tumour crosstalk (67). The anabolic stimulus of exercise, combined with a diet rich in protein, may help stimulate muscle protein synthesis. Protein sources rich in the essential amino acids

(EAA), and particularly the branched-chain amino acid leucine, may be beneficial in overcoming the anabolic resistance observed in patients with cancer. Leucine is a principal trigger for protein synthesis; it stimulates the mammalian target of rapamycin complex 1 (mTORC1) pathway, leading to muscle protein synthesis (253). Another anabolic effect of leucine is its role in stimulating insulin production, which is also responsible for activation of the mTORC1 pathway (254). As observed in the scoping review provided in manuscript 1, and as done in the studies described in manuscripts 2 and 3, whey protein is often provided to increase EAA intake in patients with cancer. Deutz et al. (255) compared two ONS for their effectiveness in promoting muscle protein synthesis in patients with cancer: the first contained 40 g protein (whey and casein) enriched with 4 g free leucine and 8 g fish oil; the second was a conventional ONS containing 24 grams of protein from casein alone. Muscle protein fractional synthesis post-ingestion of the oral nutritional supplements demonstrated a significant increase in patients who consumed the leucine-enriched ONS (+0.023±0.031 %/hour, $p<0.05$), but not in patients taking conventional ONS (-0.008±0.044 %/hour, $p>0.05$). It is unclear if simply providing less protein in the control ONS hindered protein synthesis, or whether leucine and fish oil had an additional anabolic effect (255). In older adults where anabolic resistance due to aging is observed, bolus ingestions of 10-15 g of EAAs, of which at least 3 g are leucine, promotes an anabolic response (256). At present, the exact protein needs of patients awaiting surgery is unknown (257).

The second hypothesis of manuscript 3 was to determine relationships between BMI, appendicular skeletal muscle mass, handgrip strength, malnutrition and HRQoL in patients awaiting HPB resection. Our findings revealed that a strong, negative relationship exists between FACT-G physical wellbeing and aPG-SGA score ($r=0.746$, $p<0.0001$), with medium, negative correlations between aPG-SGA, total FACT-G score ($r=0.487$, $p<0.001$) and functional

wellbeing ($r=0.486$, $p<0.001$). Baseline robust regression testing demonstrated that aPG-SGA significantly predicted FACT-G score, in both univariate ($\beta=-1.33$, $p<0.0001$) and multivariable analyses ($\beta=-1.77$, $p<0.0001$). The negative, significant predictive value of aPG-SGA remained in multivariate analysis of physical wellbeing ($\beta=-0.84$, $p<0.0001$) and functional wellbeing ($\beta=-0.72$, $p<0.0001$). There were no significant relationships between any other nutritional indicators, namely anthropometry, body composition, strength or energy/protein intake, and FACT-G or its subscales. Once again, the burden of nutrition impact symptoms may have a greater effect on patients' perception of HRQoL, than low strength or muscle mass *per se*. The inclusion of patients awaiting liver resection, in addition to pancreatic surgery, for a variety of HPB cancers did not diminish the effect of nutritional status on HRQoL seen in manuscript 2. However, nutritional status was more greatly impaired in patients after pancreatic resection and drove postoperative decline. The study design did not offer adequate support in managing nutritional concerns postoperatively. As in manuscript 2, baseline values of the patients included in this study were very high, with only 1 patient presenting with sarcopenia at baseline. This may be partially due to the relatively young average age of participants in the study. Additionally, average protein and energy needs were being met at baseline in the prehab group, reflecting a possible selection bias whereby patients who were already eating well and understood the importance of nutrition, agreed to enrol in the present study. Along with the absence of impairment in nutritional status of this patient population, baseline FACT-G scores met normative data for the general population (243). As in manuscript 2, identifying a screening method to understand who would best benefit from such a program needs further examination. A weakness in the study presented in manuscript 3 is the choice to not use a cancer symptom module along with the FACT-G, thus not allowing for a calculation of TOI. The participants of

this study included a large number of patients with colorectal cancer who were awaiting surgery for liver metastases. Cancer symptoms in these patients would best be described by a module specific to colorectal cancer, rather than hepatobiliary concerns. Therefore, the effect on HRQoL of these specific concerns, and the relationships with markers of nutritional status, could not be examined.

The final hypothesis of manuscript 3 was that differences in HRQoL would be observed between prehab and rehab over the study period. Contrary to this hypothesis, no within or between group differences were observed ($p>0.05$). However, the importance of nutritional status on HRQoL was demonstrated in the preoperative period; change in FACT-G that did not meet MID was negatively associated with aPG-SGA ($\beta=-2.83$, $p<0.0001$). This suggests that nutritional status may hinder improvements in HRQoL. Therefore, better control of nutrition impact symptoms, through medical management and more frequent RD follow-up, should be studied.

### 6.3.1. Future research directions resulting from manuscript 3

There are many research gaps that remain in describing the effectiveness of dietary interventions, within a prehabilitation study, on HRQoL outcomes. The following four suggestions should be considered when designing future trials. First, dietary interventions should include close follow-up in both the preoperative period, and immediately following surgery. Manuscript 3 was based on outcomes from one dietary counselling session, with no formal follow-up beyond measures of compliance in the postoperative period. The lack of follow-up may have exacerbated the decline in aPG-SGA scores at 4-week postoperatively in the patients with pancreatic cancer. Second, as described in the background section of this dissertation, the

use of PERT should be included in any intervention involving diet in patients with pancreatic cancer, with its role in improving HRQoL closely examined. Landers et al. (258) demonstrated that after 1 week of PERT initiation in patients with metastatic pancreatic cancer (dose of 50,000 lipase units/meal and 25,000 lipase units/snack), there was a significant improvement in EORTC QLQ-PAN26 diarrhea scores (-18, $p < 0.01$), pancreatic (-14, $p<0.05$) and hepatic pain (-13, $p<0.05$). After 3 weeks of PERT, pancreatic pain decreased further from baseline levels (-21, $p<0.01$); additionally, bloating/gas symptoms improved (-20, $p < 0.01$). As PEI is also present in patients prior to surgery and especially in patients after a Whipple procedure, it is reasonable to include PERT as part of a protocol examining nutrition outcomes and HRQoL in this patient population. At present, no studies examining relationships between PERT and HRQoL in the prehabilitation of patients awaiting surgery for pancreatic cancer have been conducted. Third, more research is necessary to determine what protein supplementation is best for the prehabilitation of patients awaiting HPB surgery. The literature review for this dissertation demonstrated that several different types of proteins have been studied in the context of pancreatic cancer (e.g., whey, leucine, standard ONS, immunonutrition). Relationships between protein supplementation and muscle protein synthesis in the preoperative period need to be elucidated. Additionally, the palatability and volume of supplement prescription should always be considered; compliance to the whey protein supplement, especially in the postoperative period, was 68% in the prehab group and 50% in the rehab group. A recent review reports compliance of ONS use in patients with cancer ranges from 35 to 81% (259). Palatability of ONS is often a deterrent to compliance due to off-putting flavours, viscous texture and large volumes (259). Finally, as in manuscript 2, screening for malnourished or sarcopenic patients may lead to a greater response to prehabilitation and more robust HRQoL results than what was

observed in the resent study. All of these gaps in our knowledge regarding the role of diet on HRQoL in patients with HPB cancers awaiting surgery should be tested in prospective, randomized controlled trials.

### 6.4. Future directions: PREPARE study protocol

Although beyond the scope of this dissertation, it was important to highlight that a study has already been designed based on what was learned from the results of manuscripts 1 to 3. The PREPARE study (Prehabilitation in Palliative Pancreatic Cancer) is a three-armed, prospective randomized controlled trial examining a prehabilitation program for patients with advanced pancreatic cancer awaiting chemotherapy. A window of opportunity exists between referral to a surgical oncologist and the beginning of chemotherapy, in which patients with pancreatic cancer can experience weight loss, deconditioning and multiple cancer symptoms, all of which may affect HRQoL. Using this time to address these difficulties and optimize nutritional and physical status prior to the start of chemotherapy may help improve, or at the very least maintain, HRQoL outcomes over time. Patients will be recruited after their first visit to a surgical oncologist, who will be diagnosing patients. A screening process has been designed to assess patients for either malnutrition, sarcopenia, heavy cancer symptom burden or combinations of these problems. If patients screen positive, they will be randomized to one of the study arms. A multidisciplinary team intervention will address physical, functional and nutritional impairments through a diet (including PERT) and exercise program, and provide medical management of cancer symptoms, to prepare patients for chemotherapy. We will compare prehabilitation to: 1) a rehabilitation group, who will receive multidisciplinary diet, exercise and cancer symptom management once chemotherapy begins, and 2) a usual care arm who will receive nutritional counselling (once

chemotherapy begins), possible symptom management (only if patients are referred for a specific symptoms, such as pain), but no exercise intervention. HRQoL as measured by the FACT-Hep will be the primary outcome. Patients will be followed for 2-3 weeks before chemotherapy, and for 8 weeks once chemotherapy begins. For further details, please refer to Appendix 4. The study protocol as published has been conditionally accepted by the MUHC research ethics board (MUHC Research Ethics Board study number 2023-9117).

## 6.5. Conclusion

This dissertation presented the results of a scoping review into diet and exercise interventions in pancreatic cancer. Additionally, the body of work presented here showed the impact of a prehabilitation program on the HRQoL in patients with pancreatic cancer, and how a dietary intervention affected HRQoL in patients awaiting HPB surgery. Prehabilitation, including a diet and exercise intervention, seems to precipitate a return to baseline levels of HRQoL more quickly than what has been reported in the literature among patients observed in the postoperative period. Dietary counselling by an RD is effective in increasing protein intake in the preoperative period and should always be included in prehabilitation programs. However, the possibly severe nutrition impact and cancer symptoms this patient population may experience, would likely best be managed by a palliative care physician, who may be a valuable addition to prehabilitation teams. Of note, cancer symptoms, particularly fatigue and malnutrition are inversely associated to HRQoL in patients with pancreatic cancer entering a prehabilitation program. This patient population is challenging, given the significant morbidity they experience both via the cancer and surgical intervention. Tailoring interventions to improve HRQoL in individuals should be examined as a main outcome of interest in patients with pancreatic cancer. This dissertation adds to the body of literature describing predictors of HRQoL and offers direction to both clinicians and researchers in next steps to improve HRQoL, using diet and exercise, in patients with pancreatic cancer.

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Appendix 1: EORTC QLQ-C30 questionnaire

ENGLISH

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

**During the past week:**

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

SPECIMEN

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

SPECIMEN

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Appendix 2: FACT-G questionnaire

## FACT-G (Version 4)

**Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

English (Universal)
Copyright 1987, 1997

## FACT-G (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

English (Universal)
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Appendix 3: FACT-Hep (Additional concerns)

## FACT-Hep (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| C1 | I have swelling or cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C3 | I have control of my bowels | 0 | 1 | 2 | 3 | 4 |
| C4 | I can digest my food well | 0 | 1 | 2 | 3 | 4 |
| C5 | I have diarrhea (diarrhoea) | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| Hep 1 | I am unhappy about a change in my appearance | 0 | 1 | 2 | 3 | 4 |
| CNS 7 | I have pain in my back | 0 | 1 | 2 | 3 | 4 |
| Cx6 | I am bothered by constipation | 0 | 1 | 2 | 3 | 4 |
| H17 | I feel fatigued | 0 | 1 | 2 | 3 | 4 |
| As7 | I am able to do my usual activities | 0 | 1 | 2 | 3 | 4 |
| Hep 2 | I am bothered by jaundice or yellow color to my skin | 0 | 1 | 2 | 3 | 4 |
| Hep 3 | I have had fevers (episodes of high body temperature) | 0 | 1 | 2 | 3 | 4 |
| Hep 4 | I have had itching | 0 | 1 | 2 | 3 | 4 |
| Hep 5 | I have had a change in the way food tastes | 0 | 1 | 2 | 3 | 4 |
| Hep 6 | I have had chills | 0 | 1 | 2 | 3 | 4 |
| BN 2 | My mouth is dry | 0 | 1 | 2 | 3 | 4 |
| Hep 8 | I have discomfort or pain in my stomach area | 0 | 1 | 2 | 3 | 4 |

English (Universal)
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Appendix 4: PREPARE protocol

**Prehabilitation for palliative pancreatic cancer: The PREPARE study**


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List of abbreviations and terminology

| | |
|---|---|
| aPG-SGA | Abridged Patient-generated Subjective Global Assessment |
| BFI | Brief Fatigue Inventory |
| CAREPRO | Cancer Rehabilitation Program |
| CBC | Complete blood count |
| COPD | Chronic obstructive pulmonary disease |
| DXA | Dual-energy X-ray absorptiometry |
| ECOG-PS | Eastern Cooperative Oncology Group performance status |
| eGFR | Estimated glomerular filtration rate |
| EMR | Electronic medical record |
| ESAS-r | Edmonton Symptom Assessment System-revised |
| FACT-Hep | Functional Assessment of Cancer Therapy-Hepatobiliary |
| HRQoL | Health-related quality of life |
| HRR | Heart rate reserve |
| LBM | Lean body mass |
| MDT | Multidisciplinary team |
| MID | Minimal important difference |
| MSSS | Ministère de la santé et des services sociaux |
| MUHC | McGill University Health Centre |
| PaC | Pancreatic cancer |
| PERT | Pancreatic enzyme replacement therapy |
| PG-SGA | Patient-generated Subjective Global Assessment |
| Prehab | Prehabilitation |
| Rehab | Rehabilitation |
| RHR | Resting heart rate |
| TOI | Trial outcome index |
| UC | Usual care |

Background information

Prognosis in patients diagnosed with pancreatic cancer (PaC) is grim. Canadian Cancer Statistics for 2021 report a 5-year relative survival rate of 10% 1. Additionally, PaC will be the third deadliest cancer in both sexes, following lung and colorectal cancer, and will account for 6.7% of all cancer deaths in 2022 2. The most effective curative treatment is surgical resection with systemic chemotherapy 3. However, up to 80% of patients are diagnosed when the tumor has become unresectable 4. As such, the majority of patients with PaC receive palliative chemotherapy, which seems to improve health-related quality of life (HRQoL), despite possible treatment toxicities 5.

There is growing evidence that early referral to supportive/palliative care in the management of PaC, concurrent with antineoplastic treatments, improves the physical and psychosocial wellbeing of patients 6. Specifically, a multidisciplinary team (MDT) approach to address the great symptom burden experienced by patients with PaC is essential 7. Symptoms may include pain, fatigue, changes in appetite, weight loss, anxiety and depression, which can be most efficiently addressed by a team of specialists 8. If not attended to, these symptoms translate into decreased ability to engage in daily activities, functional decline and disability, leading to poor HRQoL 9. Particularly distressing to patients with PaC is unintentional weight loss, which is experienced by up to 85% of patients at diagnosis 9. The etiology of malnutrition in PaC is multifactorial, and includes: pancreatic exocrine and endocrine disturbances, cytokine-induced catabolism and altered metabolism, increased energy requirements, anorexia leading to decreased oral intake and nutrition impact symptoms related to both treatments and the disease 10. Muscle wasting and cancer cachexia are exacerbated by these components of malnutrition. Loss of skeletal muscle mass is of concern as it is associated with decreased survival and increased chemotherapy-induced toxicity 11. Additionally, the prevalence of cachexia in patients with PaC ranges between 70-80% at diagnosis and contributes to one-third of the mortality rate 12.

Little is known about the impact of early referral to a supportive care physician-led MDT, as a form of prehabilitation, on the management of symptoms, nutritional status, functional status and HRQoL, in patients with PaC awaiting palliative chemotherapy. It is reasonable to ask whether a MDT prehabilitation intervention started at diagnosis in patients with advanced PaC will provide better overall HRQoL outcomes that usual care alone.

Hypothesis

We hypothesize that an MDT prehabilitation (MDT-prehab) intervention, by a team that includes a supportive care physician, registered nurse, registered dietitian, physiotherapist, kinesiologist and occupational therapist, will lead to better HRQoL, symptom management, nutritional status and functional status in patients with PaC awaiting palliative chemotherapy. We hypothesize that MDT-prehab will outperform MDT rehabilitation (MDT-rehab) and usual care (UC) in all outcomes examined in this study.

Primary Objective

1) To assess HRQoL at baseline and determine changes over time, in MDT-prehab versus MDT-rehab and UC groups

Secondary Objectives

1) To assess nutritional status in patients at baseline, determine changes over time and examine associations with HRQoL, in MDT-prehab versus MDT-rehab and UC groups
2) To assess functional performance at baseline, determine changes over time and examine associations with HRQoL, in MDT-prehab versus MDT-rehab and UC groups
3) To determine differences between the MDT-prehab, MDT-rehab and UC groups in tolerance to treatment, progression-free survival and overall survival
Participant inclusion and exclusion criteria

Inclusion criteria:
- Adults aged ≥18 y
- Newly diagnosed, locally advanced or metastatic, pancreatic adenocarcinoma
- Scheduled to receive palliative or neoadjuvant chemotherapy for the first time
- Must demonstrate symptoms that require the attention of a MDT, including high symptom burden [revised Edmonton Symptom Assessment System (ESAS-r)], poor nutritional status [abridged Patient-Generated Subjective Global Assessment questionnaire (aPG-SGA)] and/or probable sarcopenia (handgrip dynamometry, sit-to-stand), based on the following screening tests:
  - ≥3 symptoms on the ESAS-r scoring ≥ 4, OR
  - An aPG-SGA score ≥ 9, OR
  - 1 ESAS-r symptom ≥ 4 PLUS a score of ≥ 4 on the aPG-SGA, OR
  - 1 ESAS-r symptom ≥ 4 PLUS handgrip dynamometry < 16 kg in females/< 27 kg in males OR 5-times sit-to-stand > 15 seconds, OR
  - aPG-SGA score ≥ 4 PLUS handgrip dynamometry < 16 kg in females/< 27 kg in males OR 5-times sit-to-stand > 15 seconds

Exclusion criteria:
- ECOG-PS of ≥ 3
- Severe mental condition (e.g., dementia, psychosis)
- Severe end-organ disease such as decompensated heart failure, chronic kidney disease (eGFR < 30) or COPD
- Anemia (hemoglobin < 80 g/L), neutropenia (absolute neutrophil count < 1.5 x 109/L), thrombocytopenia (platelets < 20 x 109/L)
- Resting oxygen saturation ≤88% on room air
- Other conditions interfering with the ability to perform exercise safely or to complete the testing procedures
- Porcine allergy, or avoidance of pork products
- Inability to speak/understand English or French enough to comprehend the informed consent and comply with study protocols

Additionally, patients will be required to have access to the internet and a device with a camera and microphone in a place where they can perform the prescribed exercises for remote interventions. We are planning to limit patient contact through remote interventions due to current Covid-19 pandemic.

Patients who meet the inclusion criteria and decide to participate in the study can withdraw at any time, for any reason, without compromising their care. Data collected from patients who withdraw from the study will be used in intent-to-treat analyses. No formal follow-up of patients will continue upon withdrawal from the study, although standard nutrition follow-up will continue in both the treatment and usual care groups in the Cedars Cancer Centre.

This study will be conducted in compliance with Good Clinical Practice standards established at the MUHC (https://muhc.ca/cae/muhc-research-ethics-board-reb-standard-operating-procedures-sops).

Study Design

This is a randomized, controlled, parallel-arm study. Blinding is not possible, as the assessors are also conducting the interventions. A computer-generated randomization scheme will be generated, to randomize 1/3 of the patients to MDT-prehab group, 1/3 to MDT-rehab and 1/3 to UC group. Patients will be stratified by disease severity, (e.g., locally advanced versus metastatic) and ECOG-PS (e.g. 0-1 versus 2).
Intervention

Patients with a diagnosis of PaC who are not surgical candidates and require palliative treatment, will be identified by a surgeon or gastroenterologist. Patients will be screened by the medical team for health conditions that would prohibit participation in the program. Once a patient is identified as meeting the study inclusion criteria, a research assistant will meet with the patient at the same appointment, to explain the study, obtain informed consent, and perform the screening tests (ESAS-r questionnaire, aPG-SGA questionnaire, sit-to-stand, handgrip dynamometry). If a patient meets the screening criteria, the patient will be asked to participate in the study, will be randomized to either the MDT-prehab, MDT-rehab or UC group.

MDT groups:

All patients in the MDT groups will be seen in the Cancer Rehabilitation Program (CAREPRO) of the MUHC, prior to beginning treatment. The CAREPRO MDT includes a supportive care physician, a registered nurse, a registered dietitian, a physiotherapist, a kinesiologist and an occupational therapist. MDT patients will undergo baseline assessments that include: anthropometric measurements, a full nutritional evaluation (Patient-Generated Subjective Global Assessment and 24-hour recall), further function and strength tests and symptom assessment. Once the assessments are complete, MDT-prehab will receive immediate counselling from CAREPRO. The same counselling will be provided to MDT-rehab, but only after 4 weeks from the beginning of chemotherapy.

Based on the assessments, each professional will create an individualized plan for the patient that is congruent with that of the overall MDT plan. Treatment includes the following:

- Physician/nurse: assess cancer symptom severity
    - medical management of symptoms

- Registered dietitian: assess nutrition impact symptoms and current food intake
- Ensure adequate energy and protein intake to meet the needs of each individual patient.
    - Protein requirements will be determined via 24-hour dietary recall. Dietary advice supporting a protein-rich diet will be provided in order to achieve the recommended requirement of 1.5 g/kg/day.

o A whey protein isolate supplement (Beneprotein), to be used after resistance exercise in order to stimulate muscle protein synthesis, will be recommended.
o Energy deficits will be determined based on weight change in the past 6 months and the 24-hour dietary recall. Dietary advice to increase energy density of the diet will be suggested, and oral nutrition supplements recommended if adequate oral intake with food cannot be achieved.
o Management of nutrition impact symptoms will be addressed with dietary advice.
o Finally, to ensure adequate absorption of nutrients, all MDT patients will undergo pancreatic enzyme replacement therapy (PERT). Patients will be prescribed a small dose of pancrelipase (50,000u/meal, 25,000u/snack), with increased dosage recommended if overt signs of malabsorption are present. A recent metanalysis showed benefit of this dose of pancrelipase on HRQoL in PaC patients13
o Patients will be advised to take a vitamin D supplement (10000 IU/week), if not already receiving supplementation

• Physiotherapy: assess strength/safety to perform exercise; prescribe the following based on baseline assessments:
o Tier 1 (sarcopenia/deconditioned)
 Aerobic: Small bouts of walking (1-5 minutes), several times/day
 Resistance: wall push-up, wall plank, chair squats, toe stand, leg curls, twice per week
o Tier 2 (low muscle mass, but normal strength/function tests)
 Aerobic: 10 minutes walking, 5x/week, moderate intensity
 Resistance: seated row, wall push-up, wall plank, squats, glute bridge, twice per week
o Tier 3 (no sarcopenia)
 Aerobic: 20 minutes walking, at least 3x/week, moderate intensity
 40-60% HRR – as above
 Resistance: seated row, wall push-up, plank, squats, glute bridge, twice per week

• Kinesiologist: supervise exercise sessions, adjust exercise intensity
o Resistance training:
o All resistance exercise sessions will be supervised remotely, via the Ministère de la santé et des services sociaux (MSSS) Microsoft Teams platform.
o Patients will be asked to perform 1-3 sets of 8-15 repetitions. For isometic exercises such as wall plank and glute bridge, the position will be held for 5-10 seconds, for 1-3 sets. Patients in Tier 1 will use their own body weight for resistance and more repetitions (up to 15). When a patient can do 17 repetitions of a given exercise on their last set, two sessions in a row, then resistance will be increased. For exercise such as wall plank and wall push up exercises, the intensity can be increased by having the body more parallel to the floor.
o Tiers 2-3 will be provided Therabands to increase the resistance of each exercise, where applicable

o As strength builds, resistance and number of sets will be increased and repetitions decreased

o Aerobic training:
o The aerobic exercise intensity will be determined at the baseline, in-person visit by calculating 40% to 60% of heart rate reserve (HRR) from measured resting heart rate (RHR) and estimated maximum heart rate [HRR= (208-0.7*age-RHR x 40%) to (208-0.7*age-RHR x 60%)]. In order to ensure accuracy, patients will be asked to abstain from caffeine for at least 1 hour prior to these measurements.
o Patients will perform their walking sessions unsupervised at a maximum RPE of 13/20 on the BORG RPE scale However,
o In-person, supervised aerobic exercise sessions (treadmill walking) will be scheduled during CAREPRO visits in order to adjust the intensity based on the patient's rate of perceived exertion (Modified Borg Scale), to ensure the patient is always working between 40% to 60% of HRR, as measured by pulse oximetry.

o Stretching exercises:
o Stretching will target the large muscle groups of the upper and lower body used in resistance training
o Stretching will be performed at the end of each supervised, remote exercise session.
o Calves, glutes, hamstrings, quadriceps, chest, bicep and tricep muscles will be stretched.
o Flexibility exercises will be repeated 2 times with each exercise held for 10 to 30 seconds.

• Occupational therapist: provide strategies to reduce fatigue, brain fog and anxiety
o E.g., sleep hygiene, cognitive exercises, deep breathing

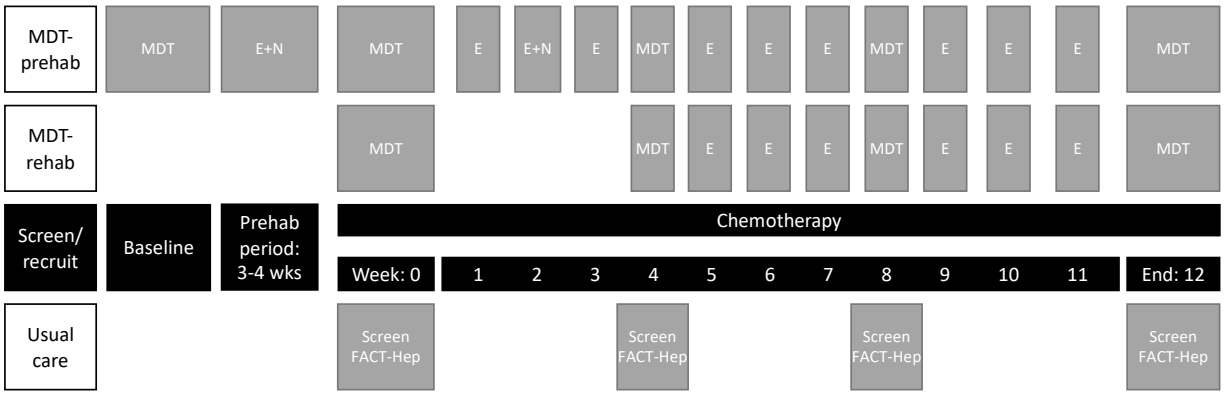
Usual care group:

As part of UC at the MUHC, patients with PaC receive nutritional counselling. Patients also have the support of an oncology pivot nurse. Specialized symptom management may be offered through referral to the MUHC cancer pain clinic, or supportive care clinic. However, patients are rarely followed by a physiotherapist/occupational therapist/kinesiologist. All of these services are offered based on individual need, at different times within the disease trajectory, with each professional working outside of a MDT. The UC group will be offered to receive MDT (referral to CAREPRO) 12 weeks after the start of chemotherapy (at the end of the study).

Measures

All screening tests (ESAS-r, aPG-SGA, handgrip dynamometry, 5-time sit-to-stand test) and the FACT-Hep will be taken at recruitment, week 0 (first chemotherapy treatment), week 4, week 8 and week 12. In the MDT groups, all other measures will be taken at baseline, week 4 (intervention mid-point MDT-prehab), week 8 (intervention mid-point MDT-rehab), week 12. Figure 1 outlines the study timeline. Table 1 outlines when each measure is taken for each group.

Figure 1: Study timeline




E: exercise; MDT: multidisciplinary team; N: nutrition

Table 1: Timing of measures for each group

| Measure | Recruitment | Baseline | Week | | | |
|---|---|---|---|---|---|---|
| | | | 0 | 4 | 8 | 12 |
| FACT-Hep | All groups | MDT | All groups | All groups | All groups | All groups |
| ESAS-r | All groups | MDT | All groups | All groups | All groups | All groups |
| aPG-SGA | All groups | MDT | All groups | All groups | All groups | All groups |
| PG-SGA | | MDT | | | | MDT |
| 24-hour recall | | MDT | MDT | MDT | MDT | MDT |
| BFI | | MDT | MDT | MDT | MDT | MDT |
| Handgrip dynamometry | All groups | MDT | All groups | All groups | All groups | All groups |
| 5-time sit-to-stand | All groups | MDT | All groups | All groups | All groups | All groups |
| Timed up-and-go | | MDT | | MDT | MDT | MDT |
| Gait-speed test | | MDT | | MDT | MDT | MDT |
| Weight | UC | MDT | All groups | All groups | All groups | All groups |
| Height | UC | MDT | | | | |
| DXA | | MDT | | MDT | | MDT |
| Blood draw | | MDT | | MDT | | MDT |
| Blood pressure | | MDT-prehab | MDT-rehab | | | |
| Heart rate | | MDT-prehab | MDT-rehab | | | |

Legend: aPG-SGA=abridged patient-generated subjective global assessment; BFI=Brief fatigue inventory; DXA=dual-energy X-ray absorptiometry; ESAS-r=revised Edmonton symptom assessment system; FACT-Hep=Functional assessment of cancer therapy-hepatobiliary (FACT-HEP); MDT=multidisciplinary team (indicates both prehab and rehab, unless otherwise specified); PG-SGA= patient-generated subjective global assessment; UC=usual care

Measures for Primary outcome

To determine change in HRQoL within and between MDT-prehab, MDT-rehab and UC, over time. Change in HRQoL will be assessed utilizing the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire14. In particular, the trial outcome index (TOI) score will be examined. The TOI score encompasses the physical, functional and hepatobiliary symptom subset scores of the FACT-Hep, which are the quality of life components targeted by this intervention. The TOI is commonly used as clinical outcome, as it is reflects changes in physical and functional wellbeing, more effectively than the total FACT-Hep score, which includes social and emotional components15. Social and emotional wellbeing do not

change drastically or quickly, and are not targeted by this intervention. The FACT-Hep questionnaire in patients with metastatic PaC has been deemed a valid and reliable tool in the assessment of HRQoL14.

Measures for Secondary outcomes

Functional and strength measures:
1) Time-up-and-go test to assess mobility, balance and walking ability
2) 5-time sit-to-stand to assess functional lower extremity strength
3) Gait-speed test to assess functional mobility
These measures will be administered based on Canadian Society for Exercise Physiology standards16.

Handgrip dynamometry will be measured using the Jamar hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL). Three measures will be taken from the dominant hand, with the patient seated and arm bent at a 90-degree angle. The highest result will be recorded and compared to cut-offs demonstrating risk of sarcopenia17.

Anthropometric measures such as height and weight will be measured. Height will be taken at baseline. Weight will be measured on a standing scale over the study period. For the UC group, this data will be collected from the electronic medical record (EMR).

Body composition will be measured using dual energy X-ray absorptiometry (DXA). Of particular interest is change in lean body mass (LBM) over time. LBM in the arms and legs will be isolated from a full-body DXA scan, and used to calculate the appendicular skeletal muscle mass index (ASMI) for each patient, using the following equation:
ASMI = [LBM arms (kg) + LBM legs (kg)]/height2(m)

Nutritional status will be assessed by a registered dietitian in the MDT groups using the Patient-Generated Subjective Global Assessment (PG-SGA). The PG-SGA is a validated tool to determine the presence and severity of malnutrition in patients with cancer18.

Assessment of food intake will be performed using a 24h-recall administered by a registered dietitian. Overall energy and protein intake, as well as macronutrient distribution (e.g., amount of carbohydrates, fats, proteins, and fibre at each meal) will be calculated using the Food Processor SQL® Nutrition Analysis software (ESHA Research, Salem, OR).

Laboratory tests will include: 1) A complete blood count (CBC) to assess the presence of anemia, neutropenia, 2) eGFR and creatinine to assess renal function, 3) albumin and 4) C-reactive protein to assess inflammatory status.

Blood pressure will be recorded using a sphygmomanometer.

Heart rate, both resting and during activity, will be monitored and recorded, at each in-person exercise session using a pulse oximeter.

Descriptive information including sex, age, ethnicity, level of education, past medical history and medications will be recorded at recruitment.

Cancer diagnosis including stage, site of metastasis (if applicable), location of the tumour, as well as chemotherapy regimen and any other procedures undergone due to cancer treatment will be recorded from the EMR at recruitment.

Process measures will include patient recruitment and retention. Additionally, adherence to the treatment will be assessed weekly in both MDT groups during an exercise session; the frequency and duration of aerobic activity, the use of PERT, the use of medications prescribed to manage symptoms and the application of occupational therapy advice will be recorded. Both groups will also be asked to report any fatigue, difficulty eating, inability to perform their usual activities, and whether chemotherapy side-effects made them feel ill in the previous week. Additionally, they will be asked to rate their quality of life on a scale of 0-10 (0=best quality of life, 10=worst quality of life).

Intervention timing will be recorded as follows: 1) time from diagnosis to first chemotherapy (all groups), 2) time from diagnosis to start of MDT-prehab/rehab, 3) time from first chemotherapy to start of MDT-prehab/rehab. Additionally, any consultations in the UC group to manage symptoms (e.g., nutrition, supportive care, physiotherapy, etc..) will be noted from the EMR.

Cancer outcomes including whether patients received surgery after neoadjuvant treatment, time to progression, chemotherapy changes and time to death will be recorded.

Subjective Assessments

The Revised Edmonton Symptom Assessment System (ESAS-r)19 is currently used at the MUHC Cedars Cancer Centre to assist in the assessment of pain, tiredness, nausea, depression, anxiety, drowsiness, lack of appetite, wellbeing, and shortness of breath. Each symptom is rated from 0 to 10 on a numerical scale based on severity, with 0 indicating that the symptom is absent and 10 that it is the worst possible severity.

The abridged PG-SGA (aPG-SGA) questionnaire will assess reported body weight changes, altered food intake, nutrition impact symptoms and ECOG-PS. A score of ≥9 determines a risk of malnutrition requiring care from a MDT.

The brief fatigue inventory (BFI)20 assesses the level of fatigue and its impact on activities of daily living. The test has 9 questions: three questions are designed to assess the patient's fatigue during the immediate waking hours and 6 questions address how fatigue has interfered in the patient's life over the previous 24 hours. Each question uses a scale rating from "0" (no fatigue) to "10" (unimaginable fatigue).
Benefits associated with the study

Improvement in HRQoL is the primary objective of this study. Participants may or may not personally benefit from this study, as the effect of an early MDT intervention on HRQoL in this

population is unknown. However, study results will contribute to the advancement of scientific knowledge in patients with PaC receiving palliative chemotherapy.

Risks associated with the study

The risk of experiencing a cardiac event during the exercise intervention is minimal. Some musculoskeletal soreness may be expected in patients naïve to resistance exercise.

Side effects from the use of the whey protein supplement are uncommon, and only experienced with high doses. Occasionally, abdominal cramps and bloating can occur. This is usually corrected by increasing fluid intake or discontinuing the product.

Sample Size

A medium to large effect size (Cohen's d=0.77) is estimated, based on changes in FACT-Hep TOI over 3 cycles of chemotherapy, in patients with PaC14. In order to ensure adequate power for this study, a conservative medium effect size will be used to calculate sample size for a repeated measures ANOVA (Cohen's f=0.25). At a power of 90% and an alpha of 0.05, a total of 33 patients will need to be recruited. Considering the advanced nature of disease in these patients, we predict a dropout rate of 40% (failure to complete the 12-week assessment). This is slightly greater than the 29% who dropped out of a prehabilitation program undertaken by our group in patients with PaC awaiting surgery. Therefore, the recruitment of 48 patients (16 per group) will be required to adequately power this study.

Statistics

All statistical analyses will be performed using SAS version 9.4 (Cary, NC). Students' t-test or the Wilcoxon-Mann-Whitney test (for nonparametric data) will be used to assess differences between groups at baseline. Differences in categorical variables will be examined using the chi-square test or Fisher's exact test. For the primary outcome, a repeated measures ANOVA will be performed to examine the interaction between time and treatment group on change in FACT-Hep TOI. Covariates to be explored for best fit in the model will include sex, age, chemotherapy regimen and disease severity (locally advanced versus metastatic). A minimal important difference (MID) of 8-9 points has been reported for the FACT-Hep and of 7-8 points for the FACT-Hep TOI21. As such, we will use the chi-square test to assess differences between groups in the frequency of achieving the MID. We will also explore relationships between changes in symptom burden (ESAS-r), nutritional status (aPG-SGA), fatigue (BFI), weight, body composition (DXA), functional/strength tests and FACT-Hep TOI by calculating Pearson or Spearman (for non-parametric data) correlation coefficients. Bivariate/multivariate regression analyses will be performed to further explore relationships between symptom burden (ESAS-r), nutritional status (aPG-SGA), fatigue (BFI), weight, body composition (DXA), functional/strength tests and FACT-Hep TOI. Intention-to-treat analyses will be performed to account for missing data or patient withdrawal.

Feasibility and time line

Every month, at least 10 patients with metastatic PaC are referred to the HPB surgery clinic at the MUHC. Assuming a recruitment rate of 21%, as seen in a recent study by our team in patients with PaC awaiting surgery, we can assume recruitment of 2 patients per month. Therefore, we would need 24 months to recruit 48 patients.

Significance

Interventions that offer meaningful outcomes for patients should be prioritized and pursued in those undergoing palliative cancer treatments22. While the management of physical wellbeing is one of the tenets of supportive care in cancer, it is unclear how this translates to changes in HRQoL. The proposed MDT-prehab and MDT-rehab intervention may help patients undergoing palliative chemotherapy for PaC achieve good control over cancer symptoms, allowing for the maintenance of physical strength, function and nutritional status, thus enhancing HRQoL. If the MDT interventions are successful, it would then be of interest to consider early MDT referral as UC in all patients with PaC.

Financial support

Popi Kasvis has received the following fellowships from Concordia University to support her doctoral studies: The J.W McConnell Memorial Doctoral Fellowship-Faculty of Arts and Sciences, the Concordia University Graduate Fellowship-Faculty of Arts and Sciences.

Confidentiality

The information collected for the purpose of this study will be kept strictly confidential. All data collected on paper (e.g., informed consent, data collection sheet, questionnaires, nutrition database, etc…) will be kept together in a study file which will be stored in a locked cabinet located at the McGill Nutrition and Performance Laboratory. On days when patients are seen in person at the hospital, the data collected will be brought directly to the laboratory by the researcher and added to the patients stored data file. The laptop where data are entered, and USB key with a backup of the data, are located in a locked cabinet. Data will be kept for seven years after the study closure. All staff have signed a confidentiality agreement.

Ethical considerations

This study will be conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2 (2018).

Dissemination of results

The findings of this study will be presented at relevant conferences, and in academic journals. Additionally, our results will be shared within the MUHC (e.g., oncology grand rounds) and partners across the Rossy Cancer Network (e.g. Rossy Cancer Network annual retreat).

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