Evaluating the role of exercise as a management strategy to counteract the burden of cancer cachexia

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EVALUATING THE ROLE OF EXERCISE AS A MANAGEMENT STRATEGY TO COUNTERACT THE BURDEN OF CANCER CACHEXIA

by

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Statement of Authorship and Sources

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis. All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

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Publications Arising from Thesis

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Bland KA, Cormie P, Michael N, Trevaskis M, Moore M, Weil J, Martin P, van Loon LJC, Zopf EM. Adherence Rates and Tolerability to a Supervised Virtual Exercise Intervention for Patients with Cancer Cachexia. Asia Pac J Clin Oncol. 2021;17:181. E-Poster presentation at the Clinical Oncology Society of Australia Annual Meeting, Melbourne, VIC. Nov 16, 2021.

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List of Abbreviations

6MWT: 6-minute walk test

AKPS: Australia-modified Karnofsky Performance Status

BMI: body mass index

CI: confidence interval

COVID-19: coronavirus

CRP: C-reactive protein

DXA: dual-energy X-ray absorptiometry

ECOG: Eastern Cooperative Oncology Group

EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Scale Quality of Life Questionnaire

EORTC-QLQ-C15-PAL: European Organization for Research and Treatment of Cancer Scale Quality of Life Questionnaire Core 15 Palliative

EPA: Eicosapentaenoic acid

ESAS: Edmonton Symptom Assessment Scale

FAACT: Functional Assessment of Anorexia/Cachexia Therapy

FACT-F: Functional Assessment of Cancer Therapy-Fatigue

FACT-G: Functional Assessment of Cancer Therapy-General

GLMM: generalised linear mixed model

HADS: Hospital Anxiety and Depression Scale

HR: Hazard ratio

1L-1β: interleukin-1β

IL-6: interleukin-6

IL-8: interleukin-8

INF-γ: interferon-γ

KPS: Karnofsky performance status

LBM: lean body mass

MD: mean difference

NSCLC: non-small cell lung cancer

OR: odds ratio

PG-SGA: Patient Generated Subjective Global Assessment

PG-SGA-SF: Patient Generated Subjective Global Assessment Short Form

QOL: quality of life

RCT: randomised controlled trial

REE: resting energy expenditure

RPE: rating of perceived exertion

SD: standard deviation

SF-36: Medical Outcomes Short Form

SMI: skeletal muscle index

TNF-α: tumour-necrosis factor-α

TOI: trial outcome index

VO_2peak: peak oxygen consumption

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Abstract

Cancer cachexia is a multifactorial syndrome characterised by progressive, involuntary body weight loss and skeletal muscle wasting. Cachexia disproportionately affects patients with advanced or incurable cancers and significantly contributes to cancer morbidity and mortality. The physical and psychosocial burden of cancer cachexia is extensive and includes reductions in physical function, a greater number of and more severe cancer symptoms, increased patient-reported distress (i.e., anxiety and depression), and lower overall quality of life (QOL). Despite the burden of cancer cachexia, no universal therapies exist for its treatment and management. Moreover, supportive care options for cancer cachexia are limited and understudied. Many patients do not feel their cachexia receives enough attention and particularly in its early stages, cancer cachexia often goes clinically unnoticed. Exercise is safe, accessible, and inexpensive relative to other pharmaceutical and medical interventions. Exercise also has established health and QOL benefits in people with cancer, although this is principally established among patients with early-stage disease who do not have cachexia. There is both a strong rationale and preliminary evidence in people with more advanced disease to suggest exercise may be an important addition to cancer cachexia management strategies to address unmet patient needs.

The current thesis aims to evaluate the role of exercise as a management strategy to counteract the burden of cancer cachexia in a series of carefully designed studies. The primary findings are: 1) an existing multidisciplinary clinical service for cancer cachexia that prescribes combined medical, pharmaceutical, dietary, and exercise-based support is associated with significant improvements in patient-reported QOL and symptoms, but not clinically-assessed physical function and muscular strength; 2) people with advanced cancer and cachexia perceive exercise as important for their physical and psychosocial health and wellbeing and prefer exercise options with greater support (e.g., professionally supervised and structured exercise) and access (e.g., convenient exercise options) to overcome multifaceted exercise barriers and maximise the potential benefits of exercise; and 3) a virtually supervised exercise intervention delivered using an internet-based videoconference platform is safe and feasible in people with advanced cancer and

cachexia and has benefits on physical function and patient-reported outcomes. Overall, findings from the current thesis help fill critical research gaps on the potential role of exercise for people with advanced cancer and cachexia. The current thesis contributes important new knowledge underscoring that exercise is valued by patients with cancer cachexia and has the potential to be a meaningful intervention. Further, a virtually supervised, structured exercise intervention is feasible in patients with advanced cancer and cachexia and may be a critical new way to provide convenient high-quality exercise-based support to higher risk patients. Altogether, results from the current thesis lay the much-needed groundwork for future high-impact studies in the emerging field of exercise and cancer cachexia research.

1 Introduction

Since the time of Hippocrates, who first described the fatal components of a "wasting syndrome," humans have understood the close association between weight loss, chronic illness, and the risk of morbidity and mortality. Today, disease-related involuntary weight loss and muscle wasting has been termed cachexia, which in Greek stands for kakos, "bad," and hexis, "condition." In adults with cancer, the cachexia syndrome often goes unnoticed and remains a severe, unmet clinical need.[1] Cachexia is prevalent in all cancer types and stages but tends to disproportionately affect people with more advanced or incurable disease.[2-4] The pathogenesis of cancer cachexia is complex and not fully elucidated. However, a loss of appetite (i.e., anorexia), reduced food intake, altered metabolism, including increased energy expenditure, excess catabolism, and inflammation, likely interact to cause cancer cachexia.[5-7] Major adverse effects of cancer cachexia include the ongoing loss of body weight and low skeletal muscle mass, which may increase cancer symptoms (e.g., fatigue and distress) and reduce patient quality of life (QOL),[8-23] decrease physical function,[24-31] increase cancer treatment toxicities,[32-35] and shorten overall survival.[36-45]

The prevention, management, and treatment of cancer cachexia remains challenging from both scientific and clinical perspectives. The multi-dimensional nature of cachexia makes identifying the most salient targets for therapy difficult.[46] No single pharmaceutical agent can effectively treat or reverse cancer cachexia.[47,48] While dietary changes may mitigate body weight loss, promoting skeletal muscle mass and physical function gains through dietary support alone is difficult and often ineffective in patients with or at risk of cancer cachexia.[49-51] Exercise may be an important piece of the puzzle when it comes to cancer cachexia management, specifically to prevent or reverse physical deterioration. When coupled with dietary support and medical interventions as a part of multimodal treatment, exercise may also help maximise intervention effectiveness on patient-reported and clinical outcomes. Current published cancer cachexia treatment guidelines from the American Society of Clinical Oncology and European Society for Medical Oncology both agree on recommendations for select pharmaceutical interventions and dietary counselling.[52,53] However, current recommendations regarding exercise for cancer cachexia management are conflicting simply due to the lack of published data.[52,53]

Decades of evidence supports the incorporation of exercise as an adjunct therapy for people living with and beyond cancer,[54-63] including growing evidence among patients with advanced or incurable disease.[64-66] In addition to improving cancer treatment symptoms and enhancing physical fitness and QOL,[54-63] exercise also holds promise as a strategy to improve cancer treatment completion rates, response and efficacy, and even extend survival.[67,68] Exercise training may seem counterintuitive as an intervention for cachexia, given it is frequently considered as a strategy to promote weight loss. However, exercise, including both resistance and aerobic training, employs several critical physiological adaptations that may mitigate both the drivers and unwanted consequences of cancer cachexia.[69-74] Physical benefits of aerobic and resistance training in people with cancer include improved cardiorespiratory fitness, increased skeletal muscle mass and strength, and ultimately, improved physical function and overall QOL.[54-63] To our knowledge, only one randomised controlled trial (RCT) has investigated the role of exercise in adults with cancer cachexia, but was limited to patients with pancreatic cancer and most participants had early-stage disease.[75] Thus, several critical knowledge gaps regarding the acceptability, feasibility, and efficacy of exercise among people with cancer cachexia, especially those with advanced or incurable disease, exist.

1.1 Thesis Aims and Research Questions

The central aim of the current thesis is to evaluate the role of exercise as a management strategy to counteract the burden of cancer cachexia. The main questions the current thesis aims to address include:

- Is an existing, long-standing multidisciplinary, multimodal clinical service for cancer cachexia that includes pharmaceutical, medical, dietary, and exercise-based support associated with improved patient-reported QOL and physical function?
- What are the perceptions of exercise among people with advanced cancer and cachexia, including key exercise motivators, barriers, and preferences, that may help to inform the feasibility of exercise as a meaningful intervention?

- Is a structured, supervised exercise intervention feasible among people with advanced cancer and cachexia?

1.2 Overview of Thesis Chapters

Chapter 2 of the thesis is a thorough review of the literature on cancer cachexia, including its prevalence and risk factors, the burden of the syndrome, and current treatment approaches. The potential role of exercise as a component of cancer cachexia management strategies is also summarised based on the best available evidence to-date and key research gaps are presented.

Chapters 3 to 5 include a series of three studies including patients with advanced cancer (e.g., unresectable cancer or cancer that has spread to surrounding lymph nodes or tissues or metastatic disease) and an often incurable diagnosis who have cachexia. In study one (Chapter 3), results from an observational retrospective review of medical data from one of the only long-standing multidisciplinary clinical services for cancer cachexia in Australia are presented. The clinical service care team and multimodal treatment plans delivered to patients are comprehensively described, including the specific exercise-based support provided by the service's physiotherapist. The aim of study one is to explore changes over time in patient-reported outcomes, body weight, and physical function among patients who visited the service three times over approximately a three-month period. Study one also describes how an existing clinical service has uniquely integrated exercise-based support as a part of their standard care. Results from study one provide important practice-based evidence to elucidate the role of multidisciplinary, multimodal treatment approaches that include exercise for cancer cachexia. The presented findings also help generate key research questions to inform future studies and identify potential gaps within current cancer cachexia care.

Study two (Chapter 4) is a descriptive qualitative research study that utilises reflexive thematic analysis to understand the perceptions of exercise among patients with advanced cancer and cachexia. Study two was informed by questions arising from study one regarding how to optimise exercise-based support as a component of care for cancer cachexia. The study aimed to generate interview themes to elucidate what exercise means to patients and *how* it should be offered as a component of their care to maximise any potential benefits. In one-on-one interviews, participants described exercise motivators, barriers and preferences that can be used to directly inform future exercise recommendations and intervention design for both clinical and research settings. Findings from study two include patients' attitudes towards and experiences with exercise to help to inform the feasibility of exercise as a meaningful intervention for cancer cachexia.

The third and final study in Chapter 5 is a phase II RCT that aims to determine the feasibility of a structured, virtually supervised exercise intervention in patients with advanced cancer and cachexia. The exercise intervention was designed in line with evidence-based exercise oncology interventions as well as patient-reported exercise preferences identified in study two. Due to COVID-19, the intervention was also transitioned from a supervised in-person setting to a virtually supervised format using an internet-based videoconference platform (i.e., Zoom). It was hypothesised that the exercise intervention would be feasible based on feasibility metrics including, recruitment, retention, follow-up, intervention adherence and tolerance, adverse-events, and patient acceptability. The preliminary efficacy of the intervention on patient-reported outcomes and physical function was also explored. Findings from study three are world-first data summarising the feasibility of a virtually supervised intervention tailored for patients with advanced cancer and cachexia.

To conclude, the final thesis chapter (Chapter 6) is a discussion of the overall body of work. The significance of the studies in Chapters 3 to 5 are described, including critical new contributions to the field. Study strengths and limitations are also presented along with important areas for future research.

2 Background

2.1 Defining Cancer Cachexia

Cancer cachexia is a syndrome driven by a varying combination of tumour, host, and treatment-derived factors that result in a negative energy balance.[6] Reductions in food intake and metabolic changes make cancer cachexia distinct from "starvation" or "malnutrition," which tend to be reversible with the successful provision of dietary support.[46] Historically, cachexia has been challenging to universally define but is invariably presented as a multi-dimensional condition.[76] Various definitions and combinations of criterium have been used to identify patients with cachexia within the published literature.[53] However, an international consensus statement was published in 2011 by Fearon et al. with the aim of providing a clearer cancer cachexia definition and thus, a roadmap from which to develop future research.[7] The 2011 international consensus definition presented cancer cachexia as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without the loss of fat mass) that cannot be fully reversed with conventional nutritional support and leads to progressive functional impairment.[7] Cancer cachexia was also described as a syndrome along a continuum of three phases: pre-cachexia, cachexia, and refractory cachexia (Figure 2.1).

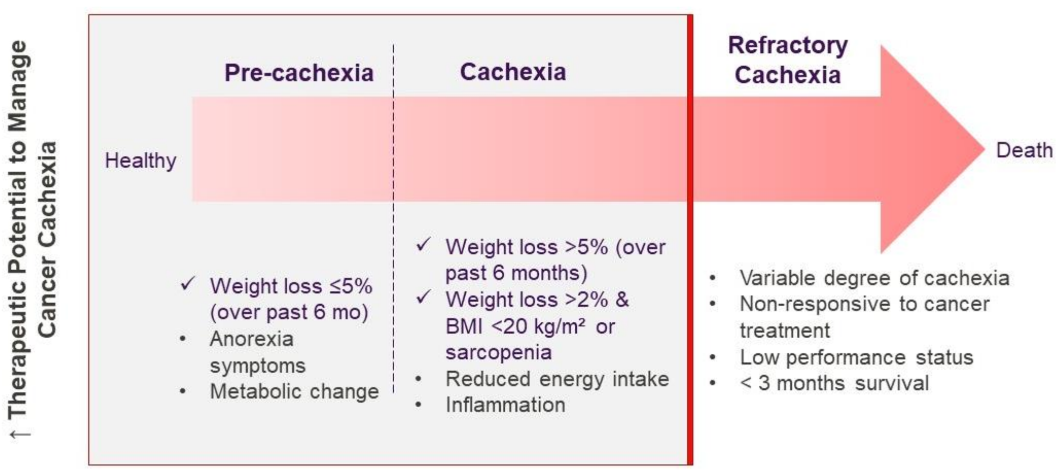

Figure 2.1: Cancer Cachexia Spectrum

Adapted from Fearon, K. et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12, 489-495 (2011).

Within the 2011 international consensus definition, pre-cachexia was defined as the presence of early patient-reported or metabolic signs (e.g., anorexia or insulin resistance) combined with moderate weight loss (≤5% body weight within the past six months).[7,77] Cachexia was defined as weight loss >5% within the past six months, or weight loss >2% with a body mass index (BMI) of <20 kg/m^2 or the presence of sarcopenia (low skeletal muscle mass).[7] Reduced food intake and systemic inflammation were also highlighted as characteristics of cachexia, however, no specific criteria or threshold for these features were provided. Finally, refractory cachexia was described as "clinically obvious" and more common among people moving towards end-of-life who have advanced (pre-terminal) cancer or aggressive cancers that are not responding to therapy. Key features of refractory cachexia include low performance status (World Health Organisation performance status of 3 or 4, capable of limited self-care or disabled, respectively) and a life expectancy of <3 months.[7] Cancer cachexia thus occurs on a continuum and may progress over time; however, not all patients will advance through each phase or to end-stages of the syndrome.[7]

The 2011 international consensus definition by Fearon et al. is primarily based on BMI, body weight loss, and sarcopenia. A seminal study by Blum et al. validated the 2011 international consensus definition and reported a clear distinction between patients with cachexia (using weight loss and BMI criteria only) compared to patients without cachexia (defined as weight change ± 1 kg or weight gain). Among 1070 patients, those with cachexia versus without cachexia had significantly higher levels of inflammation (C-reactive protein (CRP)), reduced food intake, greater loss of appetite, and lower physician-rated performance status (all $P < 0.001$) and significantly shorter survival (139 days versus 269 days, $P < 0.001$).[37] However, in a second analysis, Blum et al. were unable to make distinctions between patients with pre-cachexia (defined as weight loss >1 kg, but <5%) compared to patients with no cachexia, highlighting potential difficulty with identifying patients early within the cachexia continuum based on weight loss alone.[37] Ultimately, weight loss and BMI are important diagnostic features of cancer cachexia and monitoring body weight over time is recommended within clinical assessments.[78] However, when only weight loss is considered, patients with early signs of cachexia who may be experiencing a decrease in appetite or changes in skeletal muscle mass may not be detected.

To aid in the detection of pre-cachexia, body composition assessments to determine skeletal muscle mass may be particularly useful. Cancer cachexia is considered a muscle-wasting syndrome.[7] Low muscle mass (often termed sarcopenia in the oncology literature) is an independent, clinically-relevant feature of cancer cachexia and may initially occur in the absence of significant body weight loss.[79] There are no specific criteria to diagnose pre-cachexia, however, sarcopenia has been defined using the following measures: lumbar skeletal muscle index (SMI) determined with computed tomography (CT) imaging (men <55 cm^2/m^2; women <39 cm^2/m^2), mid upper-arm muscle area by anthropometry (men <32 cm^2; women <18 cm^2), appendicular SMI using dual energy x-ray absorptiometry (DXA) (men <7.26 kg/m^2; women <5.45 kg/m^2), and whole body fat free mass index without bone measured using bioelectrical impedance analysis (men <14.6 kg/m^2; women <11.4 kg/m^2).[80] Importantly, notable limitations of body composition assessments include availability, cost, need for trained personnel, and time, which can make clinical evaluations difficult or impractical.[69]

Since the publication of the 2011 international consensus definition, many clinicians and researchers have discussed the need for more specific criteria to define cancer cachexia to improve the identification of (pre)cachexia and inform the provision of more specific treatment strategies.[1] The presence of weight loss will likely always remain an important clinical sign of cachexia. However, over-reliance on weight loss or BMI alone may make it difficult to discern whether there are alternative causes of weight loss presence, e.g., poor patient eating habits, or may inadvertently rule out patients who may benefit from potential cachexia therapies. Several studies propose adding criteria to better define cachexia, such as signs of altered metabolism, inflammation biomarkers, patient-reported food intake, physical performance, and standardised measurements of body composition.[5,37,40] Prior cachexia definitions by Fearon et al. (2006)[81] and Evans et al. (2008)[82] attempted to capture additional features beyond BMI and weight loss (Table 2.1). However, the current evidence base provides an incomplete picture on the validity of additional assessments, especially markers of altered metabolism, for cancer cachexia. Additional prospective studies are needed to provide important new knowledge to aid in the development and refinement of a cancer cachexia definition, including on 1) the impact of reduced food intake due to anorexia or specific cancer- or treatment-related symptoms, 2) the contribution of metabolic changes, such as altered tumour metabolism, inflammation, and increased proteolysis and lipolysis, and 3) the interactions between obesity, hypogonadism, or age-related changes in anabolism, deconditioning, and comorbidities. Future definitions will likely include a combination of objective and patient-reported measures on top of routine assessments of body weight and BMI. Criteria must strike a balance between scientific specificity and clinical feasibility to adequately identify patients with and at-risk of cancer cachexia. An updated version of the international consensus classification and definition of cancer cachexia is currently underway.[1] Until then, the 2011 international definition remains the best available option to identify patients with cachexia in clinical and research settings.

Table 2.1: Cancer Cachexia Definitions

Fearon et al. 2006 criteria [81]	Evans et al. 2008 criteria [82]	Fearon et al. 2011 criteria[7]
Pre-illness weight loss ≥10% AND Reduced food intake (≤1500 kcal/day) AND Inflammation (CRP ≥10 mg/L)	Weight loss >5% in past 12 months and underlying chronic disease OR BMI <20 AND 3 out of 5 of the below criteria: - Inflammation (CRP >5 mg/L) - Anaemia (Hb <12 g/dL) - Low protein status (albumin <3.2 g/dL) - Fatigue - Anorexia - Decreased muscle strength	Weight loss >5% in past 6 months OR Weight loss >2% in past 6 months AND BMI <20 OR sarcopenia

Abbreviations: BMI: body mass index, CRP: C-reactive protein, Hb: haemoglobin

2.2 Cancer Cachexia Risk Factors and Prevalence

2.2.1 Cancer Type

Cancer is the current leading cause of morbidity and mortality worldwide,[83] and within Australia one in two people will be diagnosed with cancer before the age of 85 years.[84] While cachexia occurs in various chronic diseases, including end-stage heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease, and acquired immune deficiency syndrome, the risk of cachexia in individuals with cancer is exceptionally high.[3,4] Population-based studies estimate that up to 90% of patients with any type of cancer are at risk of developing cachexia, based on definitions adapted from Evans et al.[3,4] However, the reported prevalence of cancer cachexia varies substantially given it is affected by the precise criteria used to define it. In an observational study of 167 cancer patients, for example, 70% of the sample developed cachexia according to the 2011 international consensus definition versus 40% according to the definition by Evans et al.[39]

Despite the criteria applied, certain cancer types are more prominently associated with cachexia.[85] In a landmark study of 3,047 patients, the frequency of weight loss ≥5% prior to cancer diagnosis was highest in patients with pancreatic or gastric cancer (range: 54-66%) and lung cancer (range: 34-36%), and lowest in patients with breast and non-Hodgkin's lymphoma (range: 14-18%).[36] A more recent systematic review on the risk of developing cachexia also found 80-90% of liver, pancreatic, and lung cancer patients may develop cachexia (considered a very high risk group), while 50-70% of head and neck, gastric, and colorectal patients may develop cachexia (considered a high risk group).[85] Other common cancer types were considered middle (endometrial, kidney and renal pelvis, non-Hodgkin lymphoma, urinary) or low-risk groups (thyroid, melanoma, breast, prostate) for cachexia development.[85] Notably, approximately half of all cancer deaths globally (8.2 million people per year) are associated with diseases more closely linked with cachexia, including pancreatic (0.33 million deaths), oesophageal (0.40 million), gastric (0.72 million), lung (1.59 million), hepatic (0.75 million) and colorectal (0.69 million) cancers.[83] Hypothesised reasons underpinning the relationship between cachexia and specific cancer types include the increased likelihood of such cancers being diagnosed at a more advanced stage, possible direct effects of tumours on energy and nutrient intake, digestion and absorption, specific treatment-line characteristics, and overall prognosis.[6]

2.2.2 Cancer Stage

Consistent evidence supports that cachexia is a notable concern among patients with advanced or incurable cancers.[2-4] Hopkinson et al found that over three-quarters of patients with advanced cancer (*n* =

199) reported experiencing weight loss (79%) and/or eating less (76%).[86] Amano et al. reported that among patients with advanced cancer receiving palliative care (*n* = 1702) 70% of all patients had experienced weight loss in the previous month.[87] Cachexia is a concern among certain cancer types, such as gastrointestinal cancers, even in the context of early stages of the disease. However, if primary tumours are localised, cachexia is readily reversible once the tumour is surgically removed or successfully treated.[88] Because complete tumour elimination is more of a challenge in patients with advanced cancer (including cancer that has spread to surrounding tissues or other areas of the body), cachexia is often a more burdensome and long-term problem, potentially lasting until patient death.

Weight loss itself may be an initial sign of advanced cancer and thus, cachexia can often be present prior to a cancer diagnosis. In a 2018 retrospective cohort study of 3,180 patients treated for lung or gastrointestinal cancers, including colorectal, liver, and pancreatic cancer, pre-treatment weight loss >5% over the past six months was identified in 17.6%, 25.8%, 36.6% and 43.3% of stage I, II, III, and IV cancers, respectively.[41] Morel et al. also found that among patients with lung cancer (*n* = 6,595, 80% stages IIIA-IV), over half of all participants had experienced weight loss prior to their initial cancer diagnosis.[89] The prevalence or severity of cachexia, including the loss of skeletal muscle mass, can then also further increase over the course of treatments for advanced cancer. Among 131 patients with advanced gastric cancer, for example, cachexia according to the international consensus definition was prevalent in 53% of patients within the first 12 weeks of starting chemotherapy, but increased to 88% of patients after 48 weeks.[44] Further, in patients with metastatic colorectal cancer, a decline in SMI of 6.1% (95% Confidence Interval (CI): -8.4 to -3.8) was detected using CT-scans following 3-months of chemotherapy.[90] The prevalence of cachexia may become especially high as patients move towards the end of life[91] and this may relate more so to the number of organs impacted by the disease rather than the specific cancer type.[36] Cachexia itself is rarely included in national cancer statistics nor is it listed as the primary cause of death, however, experts predict that the rate of cancer death may in fact be the upper limit for the number of people affected by cancer cachexia.[6]

2.2.3 Other Factors

Other factors, such as older age, sex, the presence of certain comorbidities, and other treatment-related factors are also associated with cancer cachexia. Among 1030 older adults (>70 years) with mixed cancer diagnoses, 534 (51.8%) patients had cachexia according to the international consensus definition.[2] Dunne et al. also reported that among 100 older adults (> 65 years) with cancer, 65% had cachexia.[92] The loss of skeletal muscle mass or presence of low skeletal muscle mass may also be more common among older adults with cancer. In a cohort of patients with lung or gastrointestinal cancer, for example, 68% of those identified as having low skeletal muscle mass were ≥65 years.[93] Progressive involuntary body weight loss and skeletal muscle mass loss among older adults may be explained by a greater number of comorbid conditions, polypharmacy, greater risk of hospitalisation, poorer nutritional intake, physical inactivity and/or the presence of functional limitations.[94-96]

Comorbid conditions, such as cardiac disorders[97] and the presence of cardiopulmonary disease,[9] may be associated with cancer cachexia. Poisson et al. also reported that the prevalence of cancer cachexia tended to be higher among hospitalised patients (62.8%) compared to outpatients (46.1%), higher among patients with poor performance status (68.4%) (Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2) compared to high performance status (ECOG 0-1), in addition to being higher among patients with metastatic cancer (59.1%) relative to localised cancer (46.9%).[2] Weight loss and skeletal muscle mass loss may also be more prevalent in male versus female cancer patients, despite males have higher lean body mass and larger muscular reserves.[37] Among patients with cachexia, the extent of skeletal muscle mass loss is also reportedly larger among men in comparison to women.[40] A leading hypothesis for these sex differences includes hypogonadism and the resultant decrease in circulating testosterone in men with cancer. Hypogonadism can occur in 40-90% of men with advanced cancer, including men who have not yet begun treatment.[98] Lastly, common curative or palliative cancer therapies, including cytotoxic chemotherapy,[90,99-101] androgen deprivation therapy,[102,103] and targeted therapies[104] may contribute to cachexia and skeletal muscle depletion. As a result, several concurrent factors may contribute to both the development and progression of cancer cachexia, including individual patient characteristics, cancer type and stage, and receipt of cancer therapies.

2.3 Impact of Cancer Cachexia

2.3.1 Survival and Cancer Treatment Outcomes

Key features of the cachexia syndrome are consistent prognostic markers of survival in people with cancer, including involuntary body weight loss,[36-44] skeletal muscle mass loss,[105-108] and decreased food intake and markers of elevated inflammation (CRP).[5,42] In a study using population-based data from Canada and Europe (total *n* = 8,160), both increasing percentage weight loss (P < 0.001) and decreasing BMI (P = .010) independently predicted survival across the entire sample.[38] Data were then used to create a grading system to account for high versus low initial BMI in the risk assessment of patients with weight loss. Weight-stable patients with a BMI ≥25 kg/m^2 (grade 0) had the longest survival (20.9 months; 95% CI: 17.9 to 23.9 months) compared to patients with greater weight loss and lower categories of BMI (P < 0.01).[38] Further, in a prospective study of 822 patients with lung cancer, median survival from the beginning of chemotherapy cycle 2 was 13.0, 10.9, and 6.9 months for patients with weight gain, weight loss of <2%, and weight loss ≥2% between cycles 1 and 2, respectively.[43] Multivariate analysis revealed that weight loss ≥2% was associated with reduced overall survival relative to weight gain (hazard ratio (HR): 1.66, 95% CI: 1.33 to 2.07, P < 0.001) and weight loss of <2% (HR: 1.57, 95% CI: 1.27 to 1.95, P < 0.001).[43] Thus, even moderate weight loss greater than 2% that occurs early on in a patient's treatment course may hold prognostic significance. Martin et al. reported that among 12, 253 patients considered at-risk for cancer-associated weight loss, weight loss grades were also significantly associated with shortened survival.[5] The authors also found that moderately and severely reduced patient-reported food intake and elevated CRP were both independently associated with survival (P < 0.001).[5] Findings from Martin et al. illustrate the prognostic significance of key features of cachexia (e.g., food intake) beyond BMI and body weight loss alone.

Several systematic reviews demonstrate a consistent association between low skeletal muscle mass and worse clinical outcomes, including post-operative complications, increased cancer treatment toxicity, decreased treatment tolerance, and lower cancer-specific, disease-free, and overall survival.[105-108] In a systematic review and meta-analysis (*n* = 38 studies) of a total of 7843 patients with metastatic or non-metastatic non-hematologic solid tumours, low SMI was significantly associated with overall survival (HR: 1.44, 95% CI: 1.32 to 1.56), cancer-specific survival (HR: 1.93, 95% CI: 1.38 to 2.70) and disease free-survival (HR: 1.16, 95% CI: 1.00 to 1.30), but not progression free survival (HR: 1.54, 95% CI: 0.90 to 2.64).[105] Over the course of cancer treatment, skeletal muscle can decline and greater losses are associated with an increased risk of reduced overall and progression-free survival.[90,99,100,109] Among patients with stage I–III colorectal cancer (*n* = 1,924), declines in skeletal muscle mass ≥2 standard deviation (SD) or ≥11.4% loss following surgical resection significantly independently predicted increased risk of mortality (HR: 2.15, 95% CI: 1.59 to 2.92).[99] Low skeletal muscle mass is also significantly associated with worse chemotherapy toxicity[32-35] and may impact cancer therapy completion rates and effectiveness, as toxicities tend to result in the need for treatment dose reductions, delays or cancellations. Prado et al. reported that sarcopenia was associated with increased prevalence of capecitabine chemotherapy toxicity, including diarrhea and stomatitis, (HR: 4.1, P = 0.04) and reduced time to tumour progression (62 days, 95% CI: 47.3 to 76.7 versus 105 days, 95% CI: 52.3 to 157.7) in women with metastatic breast.[35] Feliciano et al. found that among patients with nonmetastatic colon cancer (*n* = 2470) severe early chemotherapy discontinuation (<6 cycles of FOLFOX) was significantly associated with shorter survival and noted early discontinuation was most common among patients in the lowest tertial of skeletal muscle mass.[33]

2.3.2 Quality of Life

Cancer cachexia can profoundly impact several facets of patient QOL, including physical and psychosocial dimensions.[21] The association between involuntary loss of body weight and other features of cachexia, such as reduced nutritional status, and worse overall QOL and physical, mental, emotional and social wellbeing are well documented.[8-21] Daly et al. reported that among patients with incurable cancer (*n*

= 1027) weight loss >5% and weight loss >10% were independently associated with lower overall QOL (European Organization for Research and Treatment of Cancer Scale Quality of Life Questionnaire (EORTC-QLQ-C30) (odds ratio (OR): 1.59; 95% CI: 1.01 to 2.51; P = 0.048 and OR: 2.69; 95% CI: 1.63 to 4.42; P < 0.001, respectively).[19] Weight loss was also significantly associated with reduced physical function scores and worse symptoms, including fatigue and appetite loss.[19] De Oliveira et al. found that in a prospective cohort of patients with incurable cancer (*n* = 1039), patients with cancer cachexia according to the international consensus definition and patients with low nutritional status (Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) score of ≥9) were more likely to have lower averages for overall QOL, functioning subscales, and symptom domains (EORTC-QLQ Core 15 Palliative (EORTC-QLQ-C15-PAL) (all P < 0.05).[17]

Reasons underpinning the association between cancer cachexia and lower overall QOL are multidimensional. Muscle wasting and subsequent reductions in muscular strength and physical function may play a specific role in worsening QOL, especially if functional impairment leads to a loss of independence and changes in activities of daily living. In a 2022 systematic review of 14 studies (total *n* = 1375), low skeletal muscle mass was associated with lower health-related QOL scores in people with cancer (mean difference (MD): -0.27, 95% CI: -0.40 to -0.14, P < 0.0001) and poorer physical functioning scores (MD: -0.40, 95% CI: -0.74 to -0.05, P = 0.02).[10] Among adults with incurable cancer (*n* = 237) sarcopenia measured using CT-scans at the level of the third lumbar vertebra was detected in over 50% of participants and was significantly associated with worse overall QOL (Functional Assessment of Cancer Therapy-General (FACT-G)) (P = 0.048) and higher patient-reported depression (Hospital Anxiety and Depression Scale (HADS) (P = 0.005).[23] Among stage IIIB-IV non-small cell lung cancer (NSCLC) patients (*n* = 734), low SMI determined from CT-scans was associated with reduced overall QOL (EORTC-QLQ-C30) (P = 0.001) in men and with lower physical function scores in both sexes (men: P = 0.015; women: P < 0.001).[18] An exception may be among geriatric oncology patients, where an increased prevalence of skeletal muscle mass loss because of the geriatric syndrome and normal aging may potentially mask the prognostic sensitivity of low skeletal muscle mass after a cancer diagnosis. For example, Dunne et al. found that in a study of 100 geriatric oncology patients (mean age: 79.9 years), relative to SMI alone determined using CT-scan analysis, the international consensus definition for cachexia was a stronger predictor of adverse outcomes, including functional impairment (instrumental activities of daily living) and survival (median 1.0 vs 2.1 years, P = 0.011).[92] In general, the presence of low skeletal muscle mass may be a key contributor to declines in physical wellbeing and QOL in patients with cancer cachexia. However, the sensitivity and interpretation of the associations between low skeletal muscle mass and QOL can vary depending on patient characteristics, the body composition assessments employed, and specific classification systems used to quantify skeletal muscle mass.

An advanced cancer diagnosis alone is also associated with symptoms that present in “clusters” (i.e., three or more symptoms) versus in isolation.[110,111] With cancer cachexia onset and progression, cancer symptom clusters are often more severe and burdensome and may contribute to deteriorating QOL.[8-20] Albeit, the exact type, prevalence, and severity of symptoms may vary depending on several factors, including cancer type, treatment status, and the specific symptom assessment tool used. Blum et al. compared nine symptoms (Edmonton Symptom Assessment Scale (ESAS)-revised) between patients without cachexia ($n = 462$) and with cachexia according to the international consensus definition ($n = 399$) and reported the frequency of all symptoms, except for shortness of breath, depression, and anxiety, were significantly higher in the cachexia group.[37] Zhou et al. also categorised patients with stage III-IV mixed cancer types ($n = 339$) into four groups (no cachexia, pre-cachexia, cachexia, and refractory cachexia based on criteria published by Blum et al.[37]) and found that cachexia stages were associated with worse symptom severity (M.D. Anderson Symptom Inventory) including for pain ($P = 0.005$), fatigue ($P < 0.001$), disturbed sleep ($P < 0.001$), lack of appetite ($P < 0.001$), dry mouth ($P < 0.001$) and vomiting ($P = 0.026$).[8] Percent weight loss also independently correlated with increasing symptom scores (EORTC-QLQ-C30) in a separate study of patients with incurable cancer, including for fatigue, nausea/vomiting, pain, and appetite loss (all $P < 0.001$).[19] Consequently, the physical signs and symptoms of cancer cachexia beyond body weight loss, including burdensome cancer symptoms, may impact one’s own perception of their health, activities of daily living, and in due course, overall QOL.

Cancer cachexia also elicits psychosocial symptoms and emotional distress.[112-115] Sun et al. reported that in addition to lower QOL (EORTC-QLQ-C30), the prevalence of anxiety, depression, severe anxiety, and severe depression (Patient Health Questionnaire-9, Generalized Anxiety Disorder-7) were all higher among patients with cancer cachexia (*n* = 285) compared to patients without cachexia (*n* = 243) (all $P < 0.01$).[13] In a systematic review evaluating the psychosocial effects of cancer cachexia, data from 19 studies indicated that the lack of knowledge of the irreversible nature of cancer cachexia and the psychological impact of unsuccessful attempts to increase body weight were critical adverse reactions.[114] Cross-sectional data also suggests one third of patients with cachexia feel their condition does not receive enough clinical attention, indicating a sizable unmet patient need.[9] Food, eating, and body weight all have symbolic meanings, such as sense of identity, personal control, status, independence, health, and wellbeing.[116] Yuen et al. reported that among 326 people with cancer, being underweight or perceiving oneself as underweight was associated with greater concerns over weight loss and poorer psychosocial wellbeing, personal control, self-esteem, and relationships with others compared to those considered normal weight or overweight/obese.[16]

Patients may also view weight loss and associated symptoms as a sign of disease progression[117] and even imminent death.[118] Eating-related distress is common among advanced cancer patients with cachexia and their family members[119,120] and qualitative evidence highlights that weight and eating-related concerns can disrupt food connections, influencing physical, mental, emotional, and social wellbeing.[121] Body image issues may further exacerbate distress and feelings of self-consciousness, and may be a barrier to social engagement and lead to social isolation.[117] Body image dissatisfaction, evaluated using a body image scale, was significantly correlated with weight loss ($r = 0.31$, $P = 0.006$), anxiety (HADS, $r = 0.37$, $P < 0.001$), depression (HADS, $r = 0.46$, $P < 0.001$), as well as symptoms (ESAS), including pain ($r = 0.25$, $P = 0.026$), fatigue ($r = 0.28$, $P = 0.014$), and wellbeing ($r = 0.29$, $P = 0.011$) in patients with advanced cancer.[122] Consequently, the psychosocial and emotional burden of cachexia may influence several domains of patient wellbeing and QOL.

2.3.3 Physical Function

Progressive functional impairment has been highlighted as a distinguishing feature of cancer cachexia.[7] Broadly, physical deconditioning is a cornerstone of cancer survivorship.[123] Numerous physiological systems, from cardiopulmonary, neurological to musculoskeletal, suffer from the adverse effects of cancer treatment and disease progression.[124] In the event of one system becoming compromised, other systems may attempt to compensate and subsequently, deteriorate. Over time, the sequela may lead to impaired physical function, subsequent reductions in QOL, and an increased risk of adverse effects, such as premature death.

Physical inactivity following a cancer diagnosis and during cancer treatment may have a special contribution to physical deconditioning and is also associated with reduced survival across several cancer types.[125] Physical activity levels are frequently low prior to cancer diagnosis and low physical activity is a known risk factor for several cancer types.[125] Physical activity may then decrease further following diagnosis and never return to pre-diagnosis levels, even among people with early-stage cancer.[126,127] Knowlton et al. found that in a cross-sectional analysis (*n* = 640) only 44% of all cancer survivors and 34% of patients living with advanced disease met current physical activity guidelines.[128] Further, over 70% of patients with advanced disease and 47% of cancer survivors reported decreasing physical activity post-diagnosis.[128] Among people with the cancer cachexia syndrome and often a more advanced or aggressive cancer diagnosis, changes in physical activity and the extent of physical deconditioning may exceed those typically observed in patients with cancer who do not have cachexia.[30] Available evidence suggests that people with cancer cachexia experience reductions in not only patient-reported physical function (typically assessed via QOL instruments as previously discussed in section 2.3.2) but also physician-rated performance status,[36,37] and objectively measured physical function[24-30] relative to people who do not have cachexia.

Characterisation of functional impairments among people with cancer is most often completed using performance status measures (e.g., ECOG or Karnofsky Performance Status (KPS)), given their prognostic significance.[129-131] Body weight loss and low skeletal muscle mass are associated with more pronounced reductions in performance status among people with cancer.[132,133] Dewys et al. reported that decreasing body weight significantly correlated with decreasing performance status evaluated using the ECOG.[36] Blum et al. also found performance status (KPS) was significantly different between patients without cachexia (n = 462) and cachexia (n = 1,399) (74.5, 95% CI: 73.1 to 76.0 versus 68.3, 95% CI: 66.7 to 70.0, $P < 0.001$).[37] Performance status measures are simple, easy, and validated tools and are an important part of characterising function in oncology.[129-131] In addition to their potential ability to predict patient survival, performance status also predicts patient-reported QOL among patients with incurable cancer.[19] Notable limitations of using performance status measures, however, include relying on physician subjectivity, risking under or over-estimating performance status, and dealing with some inconsistency in predicting survival.[134,135] As a result, coupling measures of performance status with additional patient-reported or objective assessments of physical function can paint a clearer picture of the nature and extent of functional impairment that may occur with cachexia.

Studies that have objectively characterised physical function and muscular strength in people with cancer cachexia are more limited; although frequently suggest notable physical deconditioning relative to people with cancer without cachexia.[24-29] In a study of 503 patients with mixed cancers, Schwarz et al. found that cachexia according to the international consensus definition was present in 26% of patients and was significantly associated with reduced physical performance on a cycle ergometer (absolute: 83 versus 108 Watts; relative performance: 1.34 versus 1.53 Watts/kg, both $P < 0.01$).[24] Stene et al. performed a secondary analysis from a feasibility RCT among 46 patients with stage III-IV NSCLC or inoperable pancreatic cancer and found relative to those with pre-cachexia or no cachexia, those with cachexia experienced physical function declines over the six week study period (KPS: -3.8 points, $P = 0.03$; self-reported physical function (EORTC-QLQ-C30): -8.8 points, $P = 0.027$; handgrip strength: -2.6 kg, $P = 0.026$).[28] A small number of other studies have reported significantly reduced aerobic capacity in patients with cancer cachexia, evaluated using a symptom limiting incremental exercise test.[30,136,137] However, none of the studies made comparisons to patients with cancer without cachexia and used healthy adults or patients without cancer as controls.[30,136,137] Evidence suggests reductions in physical fitness and function are common among patients with cancer cachexia, although more data is needed to comprehensively capture the extent of this physical deconditioning and potential longitudinal changes.

Preliminary evidence suggests a loss of skeletal muscle mass may be a key driving factor of physical deconditioning and precede subsequent declines in objectively measured physical function.[25,31] Anderson et al. found that patients with cachexia (*n* = 28) had lower skeletal muscle cross-sectional area and SMI assessed using CT-scans and lower DXA appendicular lean mass compared to patients without cachexia (*n* = 28) and non-cancer patients (*n* = 19).[31] Both CT and DXA body composition variables were significantly associated with physical function and strength endpoints, including stair climb power (Watts) and chest press strength (kg) (both $P \leq 0.01$).[31] Naito et al. also reported that among patients with advanced NSCLC (*n* = 30), skeletal muscle depletion (lumbar SMI, cm^2/m^2) during chemotherapy was significantly associated with reduced handgrip strength (β: 0.3 ± 0.1, P = 0.0127) and reduced walking distance (β: 8.8 ± 2.4, P = 0.0005).[26]

The implications of physical deconditioning with cancer cachexia are wide-ranging and may influence participation in activities of daily living, patient-reported distress, risk of disability, and thus, several domains of QOL.[22,138,139] Functional impairments have also emerged as predictors of overall survival in people with cancer.[139-146] Addressing functional impairments is an important focus for cachexia intervention strategies and is a highlighted treatment-goal across current cachexia guidelines.[52,53] However, physical function assessments are wide-ranging and are designed to capture various features of physical fitness, mobility, and strength. Certain measures may better translate to improvements in QOL or have greater prognostic sensitivity compared to others. Klepin et al. found that in patients with metastatic cancer, faster 20 meter usual walking speed was significantly associated with overall survival (HR: 0.89, 95% CI: 0.79 to 0.99), but handgrip strength was not.[146] The authors postulated that handgrip strength pre-cancer diagnosis versus post-diagnosis may be a more sensitive prognostic marker; or that handgrip strength may not be appropriate for predicting outcomes over shorter periods of time.[146] The preservation or improvement of physical function in people with cancer cachexia is an important research and clinical focus. However, more information on the most clinically relevant and patient-centred functional outcomes for a cancer cachexia population is needed.

2.4 Cancer Cachexia Mechanisms and Pathophysiology

Mechanisms underpinning cancer cachexia are not a central focus of the current thesis. However, major contributors are summarised. Briefly, cancer and its treatment can immensely disrupt the homeostasis of energy balance. A negative energy balance arising from both diminished food intake and disrupted metabolism, relating to a pro-inflammatory catabolic state, may contribute to the development of cancer cachexia.[147,148] While both food intake and inflammation-mediated metabolic change are considered hallmarks of the cachexia syndrome, the relative contribution of each appears to still be an important topic of clinical and scientific debate.[46] Figure 2.2 summarises key mechanisms underpinning cachexia development and the subsequent burden the syndrome imposes on patients.

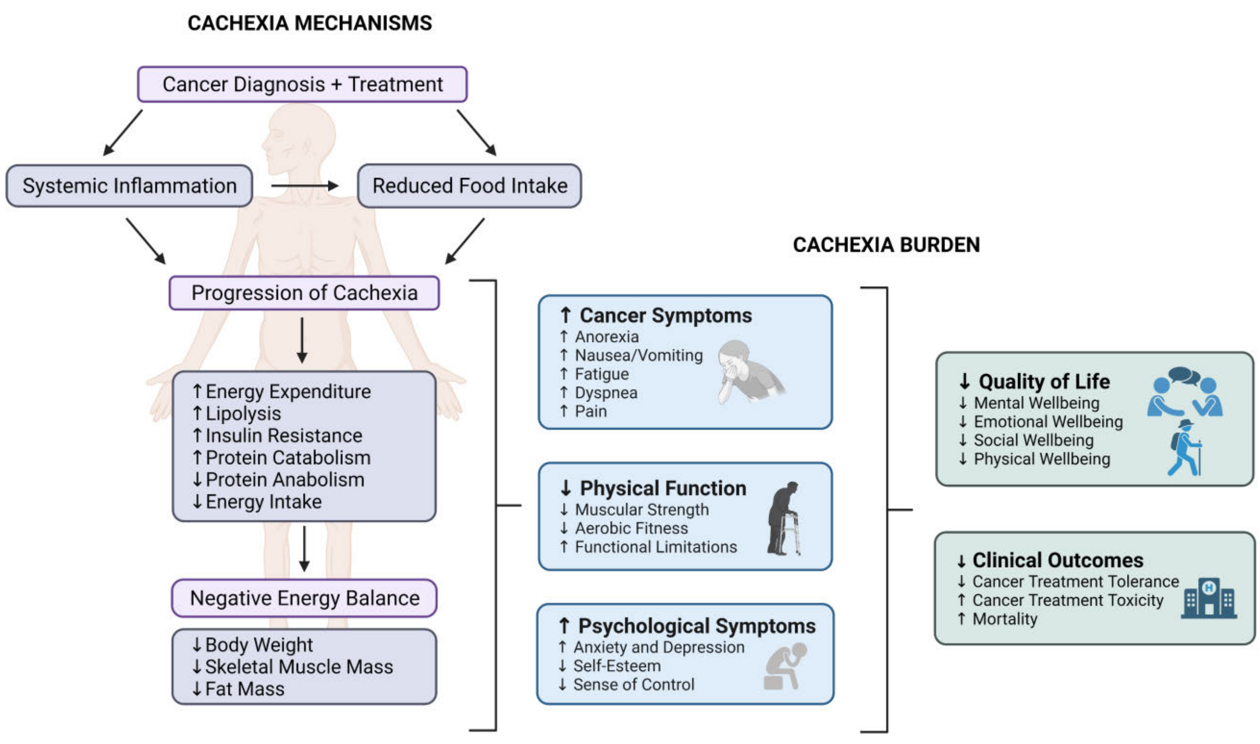

Figure 2.2: Cancer Cachexia Mechanisms of Action and Burden of Syndrome

2.4.1 Inflammation

A relationship between chronic inflammation and cancer is frequently reported. Inflammatory cells promote tumour development by creating favourable environments for tumour growth, facilitating genomic instability, and promoting angiogenesis.[149] When inflammation is present, many physiological changes can occur, a process described as the "acute phase response." During the acute phase response, in both acute and chronic inflammatory settings, immune cells activate intracellular signalling polypeptides, called cytokines. Interleukin-6 (IL-6), interleukin-1β (1L-1β), tumour necrosis factor-α (TNF-α), interferon-γ (INF-γ), transforming growth factor β and interleukin-8 (IL-8) are examples of cytokines that stimulate acute-phase proteins, including CRP. A pro-inflammatory state is hypothesised as being one of the leading underlying causes of cancer cachexia.[46] In a pro-inflammatory state, catabolism and hypermetabolism, elevated protein breakdown and hypoalbuminemia are often observed and contribute to reduced survival.[46,150,151] CRP is commonly used as a proxy of inflammation and is associated with loss of body weight[5,152] and is a relatively consistent prognostic marker within the cachexia literature.[153-161] Serum albumin, to identify hypoalbuminemia, is also frequently used in combination with CRP to quantify inflammation (modified Glasgow Prognostic Scores) and is associated with patient outcomes.[162]

Cytokines may be produced by both the tumour and host-tissues, including skeletal muscle and adipose tissues, and can trigger increased muscle protein breakdown, the loss of skeletal muscle, a negative nitrogen balance, increased adipose tissue lipolysis, and subsequently, cachexia.[163] The source and relevance of individual cytokines involved in cancer cachexia is not entirely clear, possibly due in part to the redundant nature of cytokine networks.[164] TNF-α administration in humans has been shown to result in increased acute-phase protein synthesis, elevated resting energy expenditure (REE), lipolysis, proteolysis, and anorexia.[165,166] In a study of 63 patients with pancreatic cancer, higher levels of serum TNF-α levels correlated with lower BMI, haematocrit, haemoglobin, and poor patient nutritional-protein status.[167] Similar reports exist in patients with prostate cancer [168-170] and hepatocellular carcinoma.[171] However, TNF-α levels may more strongly relate to disease stage, as a reflection of tumour size, relative to weight loss.[164] Mouse models of cancer cachexia have also shown that overexpression of circulating IL-6 leads to skeletal muscle and adipose tissue depletion.[172] In humans, increased serum IL-6 levels also correlate with weight loss, sarcopenia, and decreased survival in individuals with cancer.[170,173-176] Serum IL-1β has also been related to weight loss and sarcopenia in advanced cancer patients.[176] Alternately, in one study of patients with terminal cancer, serum levels of TNF-α, IL-6, and IL-1 did not significantly correlate with weight loss or anorexia symptoms.[177] Overall, systemic inflammation is prevalent among people with cancer and may be a critical component of cachexia development. However, the complete contribution of pro-inflammatory cytokines in cancer cachexia pathophysiology is still a developing area of research.

2.4.2 Anorexia and Reduced Food Intake

Anorexia and reduced food intake are predominant contributors to involuntary weight loss in cancer cachexia. In an observational study of 438 patients with solid tumours (any stage) pre-treatment, the prevalence of patient-reported anorexia ranged from 40% to 65% depending on the outcome measure used.[178] Anorexia identified using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score, self-assessment of appetite, and the Visual Analog Scale, all significantly correlated with body weight loss.[178] Another analysis of aggregated data from Canadian and European research studies (total $n = 12{,}253$ patients) in patients at risk of cancer-associated weight loss found severe weights loss (i.e., ≥15% over six months) was more likely if patient-reported food intake was moderately (OR: 6.28, 95% CI: 5.28 to 7.47) or severely reduced (OR: 18.98, 95% CI: 15.30 to 23.56).[5] Reduced food intake was also significantly associated with overall survival ($P < 0.0001$). Of note, CRP was identified as a significant independent prognostic marker for weight loss severity and survival, but the association was more modest in comparison to food intake.[5] The relevance of reduced food intake may therefore outweigh detectable changes in inflammatory markers.

Nutritional deficiencies related to decreased food intake, notably decreased total energy and protein intake, can also exacerbate body weight and skeletal muscle mass loss.[179,180] Patients with head and neck cancer with lower daily protein and energy intake levels (defined as <75% of recommended intake), for example, lost an average of 3.7 kg of fat free mass along with significant reductions in fat mass and total body weight over the course of radiotherapy with or without chemotherapy (mean duration: 43.5 ± 5.6 days).[180] Skeletal muscle mass maintenance and growth is regulated by muscle-protein synthesis and muscle-protein breakdown rates.[181] This muscle protein turnover process requires adequate energy and protein intake so that muscle-protein breakdown does not exceed synthesis. Low levels of energy and protein intake, also referred to as protein-energy malnutrition, can diminish muscle protein synthesis and promote body weight loss and muscle wasting.

Causes of reduced food intake remain complex and relate to both tumour and treatment-specific factors that influence appetite and the ability to eat and digest food.[182-188] A leading hypothesis is that pro-inflammatory cytokines, particularly IL-1, but also TNF-α, vistafin, and INF-γ may supress appetite by inhibiting the orexigenic neuropeptide Y/agouti-related peptide neurons and supressing the inhibition of the anorexigenic proopiomelanocortin/cocaine- and amphetamine-regulated transcript neurons within the hypothalamus.[189] Patients with lung cancer with anorexia have been shown to have lower hypothalamic activity compared to patients without anorexia.[190] Neural pathways within the hypothalamus may be influenced by a number of other factors, including lactate and cannabinoids,[191] and hormones, such as leptin and ghrelin.[192] Pro-inflammatory cytokines may, for example, increase plasma leptin concentrations via adipose stimulation, signalling the hypothalamus to suppress appetite and increase energy expenditure.[163] Certain tumour characteristics and select cancer therapies can also impact food intake and digestion by triggering nutritional impact symptoms, such as anorexia, early satiety, nausea, vomiting, diarrhoea, and constipation, or interfering with nutrient absorption.[185,186] Reductions in food intake may also be related to treatment-related damage to taste and smell receptors (dysgeusia), which can persist after treatment completion and lead to long-lasting changes in taste and smell.[187] Chemosensory alterations have also been correlated to 20-25% fewer calories per day (~430 kcal/day) and greater weight loss (-3.3 to -6.1 kg, $P = 0.0018$) compared to patients with no alterations.[193] Cancer symptoms beyond nutritional impact symptoms (e.g., pain, fatigue) and psychological distress can also significantly impact appetite and eating habits and are related to reductions in food intake.[188]

2.4.3 Skeletal Muscle Protein Synthesis and Breakdown

In healthy adults, skeletal muscle mass remains relatively constant because protein synthesis and breakdown are balanced in the absence of stimuli, such as increased protein ingestion and exercise. With cancer cachexia, increases in whole body protein turn-over are observed and lead to the ongoing loss of skeletal muscle mass.[194] Skeletal muscle protein breakdown is brought on via various proteolytic pathways and is frequently accompanied by diminished protein synthesis with cachexia.[194] There are three central protein degradation pathways: 1) the lysosomal system, 2) cytosolic calcium-activated system, and 3) the ubiquitin-proteasome pathway. All three degradation pathways have been implicated to some extent in muscle wasting in individuals with cancer.[72] However, the ubiquitin-proteasome pathway is especially critical, as most cellular proteins are degraded this way.[72] Both animal and human cancer cachexia studies have identified the ubiquitin-proteasome pathway as a key player in myofibrillar protein degradation, including among patients with weight loss >10%.[194] In a study of gastric cancer patients (n = 20) with weight loss of >6%, levels of ubiquitin mRNA were ~50% higher relative to controls with benign abdominal disease ($P < 0.01$).[195] A pro-inflammatory state may stimulate protein degradation pathways, including the specific actions of TNF-α and IL-6.[72] When TNF-α binds to its receptor site, the ubiquitin ligase, TNF receptor associated factor, is activated.[196] IL-6 and TNF-α also upregulate ubiquitin enzymes that are induced at the onset and progression of muscle wasting.[197]

On top of exaggerated protein breakdown, decreased protein synthesis is also present in cachexia, creating a double-edged sword. Insulin resistance may be a predominant culprit of poor protein synthesis in patients with cancer cachexia.[198] Insulin is a central hormone that drives muscle proteolysis. When blood glucose levels rise following a meal, insulin is secreted from the β-cells of the pancreas to decrease circulating glucose and stimulate protein synthesis via the secretion of insulin-like growth factor (IGF-1).[198] IGF-1, an anabolic growth factor, stimulates protein synthesis and the proliferation of satellite cells, and suppresses protein breakdown. In a cross-sectional observational study by Jasani et al glucose tolerance was significantly impacted in patients with cachexia versus patients without cachexia ($t = 4.23$, $P < 0.01$).[199] Jasani et al. also reported virtually identical glucose tolerance in cancer patients without cachexia and healthy age-matched controls, signifying glucose intolerance may relate to cachexia development.[199] A blunted glucose response to insulin has also been reported in cachectic tumour-bearing mice, along with the induction of muscle proteolysis and autophagy.[200] Decreased insulin sensitivity with cachexia may be linked to the pro-inflammatory cytokine, TNF-α, along with other elements of a maladaptive inflammatory state.[201] Chronic inflammation may lead to the inhibition of the tyrosine phosphorylase activity of the insulin receptor, resulting in impaired insulin stimulated glucose uptake.

Physical activity is a potent stimulus for protein synthesis and in the case of cachexia, sedentary behaviour may further compromise metabolic homeostasis and result in skeletal muscle mass loss. Physical activity includes any movement involving skeletal muscles and can be categorised into different subgroups, such as recreational or leisure-time activity (performed for enjoyment, pleasure etc.) or occupational activity (performed at work).[202] Physical activity may be performed at varying durations and intensities, including light (e.g., housework), moderate (e.g., brisk walking) and vigorous (e.g., running).[202] Research exploring changes in physical activity as a mechanism explaining cancer cachexia is needed. However, physical inactivity may exacerbate catabolism and decrease muscle sensitivity to anabolic signals, which can directly result in muscle wasting and poorer health outcomes.[71] Fouladiun et al. reported that weight loss >10% in patients with cancer (n = 53) inversely related to physical activity levels, evaluated as the number of accelerations per minute (coefficient: -8.7, $P < 0.0006$).[30] Physical activity was also independently correlated with lower CRP (coefficient: -1.4, $P < 0.04$).[30] Even in healthy adults, 28 days of bed rest has been shown to result in a significant reduction in strength (28.4 ± 4.4%, $P < 0.01$), lower limb skeletal muscle mass (1.4 ± 0.1 kg, $P < 0.01$) and protein synthesis (fractional synthesis rate, day 1: 0.08 ± 0.004%, day 2: 0.05 ± 0.007%/hr $P = 0.02$).[203] In total, altered metabolism may be compounded by reduced physical activity or prolonged periods of bed rest or sedentary time to perpetuate body weight and skeletal muscle mass loss via reduced protein synthesis.

2.4.4 Elevated Energy Expenditure

In some cases, metabolic alterations may promote body weight loss even in the presence of normal food intake or at least, beyond what might be expected with decreased food intake alone.[46] Abnormalities in lipid, carbohydrate, and protein metabolism among people with cachexia may reduce the efficiency of energy metabolism and elevate REE.[148] In a cross-sectional study, Jouinot et al. identified hypermetabolism in over half of their patient sample (total n = 277, 76% with metastatic cancer), defined as the ratio of measured REE to predicted REE >110%, and abnormal metabolism significantly predicted cancer treatment toxicity (OR: 2.37, 95% CI:1.13 to 4.94).[204] Patients with hypermetabolism may be more likely to experience >5% body weight loss, a negative energy balance, and shortened survival, even if mean daily energy intake is similar to normometabolic or hypometabolic patients.[151] In a study of patients with mixed cancer types (n = 297), those with the most severe weight loss (n = 126) had the highest REE (24.0 ± 3.9 $kcal \cdot kg^{-1} \cdot day^{-1}$) relative to patients without weight loss (n = 85, 22.5 ± 3.5 $kcal \cdot kg^{-1} \cdot day^{-1}$, P = 0.02).[205] However, food intake in absolute amounts did not differ between hyper or normo-metabolic patients. In fact, energy intake per kilogram of body weight tended to be higher in weight-losing patients (28 ± 12 $kcal \cdot kg^{-1} \cdot day^{-1}$) compared to weight-stable patients (24 ± 8 $kcal \cdot kg^{-1} \cdot day^{-1}$, P = 0.052).[205] Thus, the disconnect between energy intake to energy expenditure may create an energy deficit and contribute to cachexia manifestation.

Primary causes of hypermetabolism are complex, although may relate to an elevated adrenergic state or systemic inflammation.[170,206] Pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α, and the subsequent acute phase-response may act as mediators of metabolic change.[164,207] REE is reportedly higher in pancreatic cancer patients (n = 21) with an acute-phase response (CRP > 10 mg/L), compared to those without such a response (85.5 ± 10.0 vs. 64.3 ± 3.0 kcal·kg body cell $mass^{-1}$, P < 0.04).[206] Altered metabolism may also occur because the tumour itself disrupts the balance between muscle protein synthesis to breakdown rates. Tumour protein synthesis rates may exceed muscle protein synthesis and disrupt whole-body protein metabolism[208] or the tumour may influence basal and postprandial muscle protein synthesis rates, increasing muscle protein breakdown.[209] Energy and substrate usage of tumours may also contribute to increased energy cost of some cancers, however, separating the body's energy demand from the cancer itself is difficult. Human tumours can have elevated glucose uptake and an increased rate of glycolysis/lactate production that may persist even in the presence of oxygen (Warburg effect).[210] The energy cost of tumours has been estimated to range greatly (100-1400 kcal/day).[211] Tumours in patients with cachexia have been reported to consume approximately 10-25% of energy derived from glucose within the body.[211] Other sources of elevated REE include the increased mass of visceral organs (e.g., the liver), which is prevalent in metastatic disease cases.[212] In patients with metastatic colorectal cancer (n = 34), increases in both visceral and tumour mass during the last three months of life resulted in a ~17,700 kcal increase in REE.[212] The increased energy demand of metabolically active organs can promote peripheral and fat store mobilisation from skeletal muscle and adipose tissue and lead to involuntary body weight loss.

2.5 Cancer Cachexia Treatment and Management

Cachexia treatment goals will vary based on individual patient factors, including estimated survival, but typically should include managing cancer symptoms, preserving or improving patient QOL and physical function, increasing cancer treatment tolerability, and prolonging survival. Modifying body composition alone in the absence of improved patient-reported, functional, or clinical outcomes is not in patients' best interest. Indeed, body composition is not a recommended primary endpoint for clinical studies testing the efficacy of cachexia interventions and may not be useful beyond proof-of-concept studies.[1] Cachexia intervention strategies should also be delivered as early as possible, and during active adjuvant or palliative cancer therapy, as opposed to waiting until patients are refractory or less responsive to anti-cancer therapies.[7] More research is needed to establish effective evidence-based management for cancer cachexia. To-date, several studies have evaluated the potential for various dietary or pharmaceutical interventions to address cancer cachexia and its adverse effects. However, no intervention has been found to successfully prevent or reverse cancer cachexia. Dietary interventions and select pharmaceuticals may produce modest changes in body weight, QOL, and symptoms, but providing evidence-based recommendations remains a challenge due to inconsistent results across studies, the heterogeneity of study designs, and the need to balance interventions with potential risk of adverse effects (specifically with pharmaceuticals).[52,53] Hereafter, current cancer cachexia treatment recommendations, key limitations of the available evidence, and important knowledge gaps are summarised.

2.5.1 Pharmaceutical Agents

Alterations of major cachexia outcomes has not been possible with the use of pharmaceuticals alone.[46] Presently, only two classes of pharmaceutical agents have evidence to support their use for anorexia (corticosteroids and progestins) and are currently recommended for the management of cancer cachexia.[52,53] Studies evaluating corticosteroids (e.g., dexamethasone) have shown benefits, including increased appetite and wellbeing, although effects only last a few weeks.[213] However, corticosteroids have not been found to increase body weight or survival[213] and long-term corticosteroid use can lead to skeletal muscle mass loss, insulin resistance, and an increased risk of infections.[214] Medroxyprogesterone acetate and megestrol acetate are derivatives of the hormone progesterone (progestins) and have a history of being prescribed as first-line agents for anorexia and cachexia.[47] Ruiz Garcia et al. performed a Cochrane review summarising 23 RCTs and found that megestrol acetate was associated with significant improvements in appetite and body weight, although benefits on patient QOL and physical function were inconsistent.[215] Notable adverse effects of progestins include increased risk of thromboembolic events, oedema, breakthrough bleeding, hyperglycaemia, hypertension, and Cushing's syndrome.[47] Currow et al. conducted an RCT comparing 480 mg of megestrol versus 4 mg of dexamethasone versus placebo for 4 weeks (n = 190 patients with advanced cancer) and reported no differences in anorexia symptoms or body weight between groups[216] Over 90% of participants also experienced adverse events, including altered mood and insomnia.[216] Thus, while progestins and corticosteroids can be prescribed to potentially increase appetite and body weight, the risk of adverse effects must be considered and may impact the frequency of their clinical use.

Other pharmaceuticals have also been evaluated for the management of cancer cachexia, however, most evidence remains insufficient for widespread use in clinical practice. Anamorelin is a ghrelin receptor agonist and has been rigorously tested. Data from two RCTs (ROMANA I and II) in a total of 979 people with advanced NSCLC with cachexia demonstrated improvements with anamorelin in body weight, lean body mass, and patient-reported QOL, but not handgrip strength.[217] While data from the ROMANA RCTs were reviewed by the US Food and Drug Administration, approval for anamorelin was not received and approval has also not been granted in Europe.[52,53] Olanzapine is an antipsychotic drug that is associated with weight gain in clinical use. Navari et al. found combined megestrol acetate and olanzapine versus megestrol acetate alone was superior in terms of improvements in body weight and appetite in 80 patients with advanced gastrointestinal cancer or lung cancer with appetite loss and >5% body weight loss.[218] Olanzapine also significantly reduced non-chemotherapy-induced nausea in an RCT of 30 patients with advanced cancer compared with placebo.[219] European cancer cachexia guidelines state olanzapine can be considered for treating chronic nausea in people with advanced cancer,[53] however, American recommendations do not include use of olanzapine due to the paucity of evidence.[52] Additional pharmaceutical interventions, including nonsteroidal anti-inflammatory drugs, cannabinoids, prokinetics (e.g., metoclopramides and domperidone), androgens, and thalidomide, have also been tested for the management of cancer cachexia but the strength of the available evidence remains low.[47,48] Overall, determining appropriate pharmaceutical treatment and management options for cancer cachexia is a complex task. Given the multi-dimensional nature of cachexia, reversal of specific elements using pharmaceuticals can likely only make a minor contribution to the entire syndrome.[46] Most clinical RCTs to-date have also been restricted to late-stage cancer cachexia patients and whether treatment effects are greater in earlier stages of cancer cachexia is unknown. Unwanted side effects and added monetary cost also make pharmaceutical interventions a less than ideal treatment strategy. As a result, pharmaceuticals likely need to be prescribed concurrent to other therapies to achieve the best clinical outcomes for patients with cancer cachexia.

2.5.2 Dietary Interventions

American and European cancer cachexia guidelines currently recommend clinicians refer patients with advanced cancer and a loss of appetite and/or involuntary body weight loss for dietary counselling with a registered dietitian.[52,53] However, the strength of evidence supporting the recommendation remains low and is based on the potential benefits of dietary support outweighing risks.[220] Dietary counselling may include advice and recommendations about food and eating habits as well as the provision of oral nutritional supplements.[49,50] In a 2020 systematic review of 12 studies delivering dietary interventions to patients with incurable cancer, significant benefits of dietary counselling and/or oral nutritional supplements (e.g., energy and protein dense supplements) were reported across studies for body weight (*n* = 6 studies), QOL (*n* = 8 studies), nutritional intake (*n* = 6 studies), and nutritional status (*n* = 3 studies), although effect sizes were small and not all studies were RCTs.[50] Early dietary intervention may be particularly important to maintain nutritional status among patients as they navigate treatment. Van der Werf et al. reported that among patients with metastatic colorectal cancer (*n* = 107) randomisation to individualised dietary counselling delivered at the start of the first chemotherapy cycle had a positive effect on body weight (effect size 1.7, P = 0.045), but not handgrip strength (effect size -1.0, P = 0.289), patient-reported QOL (effect size 2.2, P = 0.617), and physical functioning (effect size 0.7, P = 0.860) relative to usual care.[51] Notably, there was also a significant improvement in overall survival with dietary counselling versus usual care (21.7 versus 16.0 months, log rank P = 0.046).[51] Dietary counselling and the provision of oral nutritional supplements may play an important role in increasing energy and protein intake, managing body weight loss, improving patient QOL and potentially, modifying clinical outcomes in patients with or at-risk of developing cancer cachexia. However, more research is needed to unveil the timing, type, and duration of dietary interventions across diverse patient samples to improve knowledge on this topic and refine current recommendations.

Increasing energy and protein intake is a critical and intuitive treatment strategy for cancer cachexia management. However, unlike many forms of weight loss, including anorexia nervosa, cachexia is not often solely dependent on reduced energy intake or poor eating habits.[194] Patients with cancer cachexia and their carers may themselves recognise the problem of weight loss and subsequently, attempt to increase energy consumption.[221] Schwarz et al. found that patients with cancer cachexia took in more meals per day and sometimes had higher energy intake compared to patients with cancer without cachexia.[24] In healthy humans, increasing energy and protein intake stimulates muscle protein synthesis and evidence suggests patients with incurable cancer have similar exploitable anabolic potential.[222] Yet, the extent of such anabolic potential has not been confirmed and it may not hold true for all patients with cancer cachexia who are in a catabolic state. The reduced protein synthetic response to energy intake in cachexia has been termed 'anabolic resistance.'[222] For this reason, stand-alone conventional dietary counselling, with or without the use of oral nutritional supplements, is critical but only one piece of the puzzle when it comes to cancer cachexia management.

Several studies have also investigated the role of specific nutritional supplements to manage involuntary weight loss and other health outcomes in people with cancer. Eicosapentaenoic acid (EPA), an omega-3 fatty acid found in some fish, has both anti-inflammatory and anti-catabolic properties and may benefit people with cancer cachexia.[223] Large clinical trials have failed to show a clear effect of EPA on body weight or lean body mass in people with cancer, likely due to differences in intervention timing/delivery, contamination of control groups, and indirect assessments of skeletal muscle mass.[224-226] However, more recent studies have shown a positive effect of EPA or fish oil (EPA and docosahexaenoic acid) on skeletal muscle mass loss in patients with head and neck cancer,[227] and oesophageal cancer,[228] as well as skeletal muscle mass and treatment efficacy in advanced lung cancer,[229] although sample sizes were small in all studies. Specifically, Murphy et al. found that among 31 patients with NSCLC, fish oil supplementation (four 1-g capsules per day) for the duration of chemotherapy (~10 weeks) increased or maintained skeletal muscle mass in 69% of participants.[229] The largest gains in skeletal muscle mass correlated with increased plasma EPA concentrations ($r^2 = 0.55$, $P = 0.01$).[229] Systematic review and meta-analysis results also indicated that high-protein oral nutritional supplements enriched with omega–3 fatty acids tended to be more likely to improve body weight, attenuate lean body mass loss, and improve select domains of QOL among patients receiving chemotherapy relative to dietary interventions that did not contain omega–3 fatty acids.[49]

Other supplement options to promote increases in lean body mass include anti-oxidants, amino acids, and lactoferrin.[230] Amino acid supplementation may increase muscle protein anabolism,[222] although data from RCTs are limited and present findings are mixed. One RCT in people with cancer with ≥5%

weight loss demonstrated that amino acid supplementation (beta-hydroxyl beta-methyl butyrate, glutamine and arginine) significantly increased lean body mass (1.1 ± 0.7 kg) compared to placebo controls (-1.3 ± 0.8 kg, P = 0.02).[231] Yet, in a phase III RCT of patients with advanced cancer (*n* = 400) with up to 10% weight loss, those randomised to beta-hydroxyl beta-methyl butyrate, glutamine, and arginine for eight weeks did not have significantly different lean body mass relative to placebo controls.[232] Thus, more research is needed to confirm the effect of amino acid supplementation in patients with cancer cachexia before incorporation into current clinical management. Preliminary evidence to support nutritional supplements is promising and supplements remain a relatively low risk intervention that may help address nutritional deficits in patients with cancer cachexia. However, conflicting study results to-date suggest cachexia interventions cannot rely on nutritional supplementation alone and no nutritional supplements are currently recommended for standard treatment of cancer cachexia.[52,53]

2.5.3 Exercise

Hundreds of RCTs have confirmed the positive effects of exercise among people living with and beyond cancer.[54-62] It is now globally accepted that exercise should be included a standard adjunct therapy during cancer care.[233-237] Exercise interventions delivered during active cancer treatments have a low risk of adverse events and have been shown to preserve cardiorespiratory fitness, physical functioning, and muscular strength, improve QOL and fatigue, and reduce anxiety and depression.[54-62] Regular, repeated bouts of aerobic and resistance exercise training stimulate a range of physiological adaptations that may help address several adverse effects of cancer cachexia, with the most notable being physical deterioration. Aerobic exercise is typically exercise carried out in a continuous manner and involves high repetition and low resistance demands during skeletal muscle contraction (e.g., running, cycling); typically prescribed as a percentage of maximum workload, oxygen consumption, or heart rate at intensities ranging from low to vigorous.[238] Resistance or strength training involves weight-loaded exercise performed in short bursts in a series of sets and repetitions at a prescribed intensity that is often a percentage of maximal strength (e.g., lifting weights using dumbbells or weight machines).[238] Among the general population and cancer survivors, the most well-established benefit of aerobic exercise is a marked improvement in peak aerobic capacity (VO_2peak),[55,238] while resistance exercise can significantly increase skeletal muscle mass and strength.[58,63] The effects of aerobic and resistance exercise, however, are not black and white. Both exercise modalities may elicit unique and overlapping effects, including at a molecular, functional, and psychosocial level, to counteract cancer cachexia progression and reduce the overall burden of the syndrome.[69-71]

Empirical evidence from human studies exploring the role of exercise to manage the burden of cancer cachexia is scarce. Grande et al. published a Cochrane review in 2021 and reported that no exercise RCTs specifically included patients with cancer cachexia according to the international consensus definition.[239] The review, however, included four RCTs that reported that at least 50% of the enrolled patients had cachexia; two studies in head and neck, one study in lung and pancreas, and one study of mixed cancer types. No conclusions could be made regarding exercise safety, feasibility, or efficacy based on the reported findings and very low quality of evidence.[239] Since the publication of the Cochrane review, to our knowledge, only one exercise RCT by Kamel et al. enrolled patients with cachexia according to the international consensus definition.[75] Participants with stage I-IV pancreatic cancer (n = 40) were randomised to the three-month supervised, in-person resistance training intervention had improved physical function, including as measured by a faster 400m walk test (MD: -7.3 seconds, 95% CI: -12.17 to -2.4, P = 0.005) and chair rise test (5 times) (MD: -0.92 seconds, 95% CI: -1.33 to -0.51, P = 0.001) relative to the control group.[75] Upper limb, lower limb, and appendicular skeletal muscle mass also significantly increased relative to control with the exercise intervention (all $P < 0.001$), as did muscular strength measured using peak torque of knee extensors, elbow flexors, and elbow extensors ($P \leq 0.01$).[75] Kamel et al. provide important preliminary information on the potential for exercise to help people with cancer cachexia. However, more data on the safety, feasibility, and efficacy of exercise on physical fitness, patient-reported, and clinical outcomes particularly in advanced cancer populations with cachexia is needed.

2.5.3.1 Exercise for Advanced Cancer

The majority of exercise oncology research to-date has focused on patients with early-stage disease. While RCTs remain somewhat heterogenous, and findings are mixed, emerging evidence suggests exercise is safe and feasible in patients with advanced or incurable cancer and may produce important physical health and psychosocial benefits (Table 2.2). Survey evidence suggests that patients with lung cancer (n = 600, 60% with advanced stage cancer) report that their top issues when it comes to individualising their care are: QOL, maintaining independence, ability to perform normal activities, ability to sleep, and not being fatigued.[240] Thus, exercise has the potential to directly address some of the key issues that affect patients with an advanced cancer diagnosis. Oldervoll et al. reported that among patients with advanced cancer (n = 163), a supervised exercise intervention delivered two days/week led to significant improvements in objectively measured physical function, including the shuttle walk test (marker of functional capacity) (P = 0.01), 30s sit-to-stand test (P = 0.05), handgrip strength (P = 0.001), and maximal step length (to assess balance) (P = 0.04).[241] Patients randomised to the exercise intervention also significantly increased their body weight (MD: 1.3 kg, 95% CI: 0.3 to 2.3, P = 0.01), while those randomised to usual care lost weight.[241] Other exercise RCTs in patients with advanced cancer have demonstrated significant improvements in patient-reported outcomes including QOL,[242,243] fatigue,[244,245] physical function/wellbeing,[243,244,246-248] social function and wellbeing[244,249] and anxiety and depression.[249]

Findings from exercise RCTs in advanced cancer cannot simply be extrapolated to people with both advanced cancer and cachexia. Yet, the current evidence base on exercise in advanced cancer helps to build a rationale for further research on the role of exercise in a cancer cachexia population to address key adverse effects of the syndrome. Main considerations include that relative to people with advanced cancer who do not have cachexia, people with cancer cachexia may experience worse physical deterioration, have a greater number of or more severe cancer symptoms, and subsequently, have lower QOL. On one hand, differences in physical health and wellbeing implies that people with cancer cachexia have more to gain from receiving exercise-based support. Nadler et al. conducted a systematic review and meta-analysis of 16 exercise RCTs in a metastatic cancer setting and reported that patients with more severe physical deconditioning and worse QOL at baseline tended to benefit the most from exercise.[65] Similar results were found in a meta-analysis by Buffart et al. of 34 exercise RCTs among people with cancer where exercise produced the largest effects on physical function and fatigue among patients with more severe symptoms at baseline.[62] Alternatively, patients with worse baseline physical fitness and function may be less likely to take part in exercise interventions or have greater challenges adhering to an exercise intervention and request dropout. Scott et al. reported that among women with metastatic breast cancer (*n* = 65), 9 of the 33 women randomised to the supervised exercise intervention requested dropout due to either disease progression (*n* = 3), pain (*n* = 2), or a non-health related reason (e.g., low motivation) (*n* = 4).[250] Moreover, only 14 of the 33 women randomised to the supervised exercise intervention were able to adhere to the prescribed exercise. Women who were more likely to adhere to the prescribed exercise targets had higher physical fitness prior to starting the intervention, as measured by baseline cardiopulmonary exercise testing.[250] Low performance status or physical fitness, worse QOL, and higher anxiety and depression have also been shown to predict dropout from supervised exercise interventions among RCTs in people with advanced cancer.[241,249] As such, appropriate methods to support patients with advanced cancer to engage in exercise are urgently needed.

2.5.3.2 Factors to Facilitate Exercise Feasibility

Exercise interventions that are delivered in structured, supervised, in-person settings have been shown to produce effects on QOL and physical function that are twice as large compared to unsupervised or self-directed home-based interventions.[62] Possible reasons for greater effects include enhanced adherence to the exercise prescription, access to better equipment, more challenging exercise targets (e.g., exercise intensity), and the benefits of having added attention and hands-on feedback from an exercise professional. However, home-based exercise interventions are often a more feasible exercise option for many patients. Among patients with more advanced disease, preferences for home-based exercise exist,[251] potentially due to fewer exercise barriers, including travel, time and cost. Notable challenges of home-based exercise, however, include restricted access to exercise equipment, limited space for exercise, potential safety concerns exercising alone, and difficulty monitoring patient exercise adherence to ensure exercise targets are met. However, home-based exercise interventions have still been shown to be beneficial. Edbrooke et al., for example, found patients with advanced lung cancer randomised to an 8-week home-based exercise intervention did not experience significant changes in physical function or patient-reported outcomes post-intervention (9-weeks), but did report significantly higher QOL (Functional Assessment of Cancer Therapy–Lung) (MD: 13.0, 95% CI: 3.9 to 22.1, P = 0.005) and lower symptom severity (MD Anderson Symptom Inventory–Lung Cancer) (MD: -2.2 95% CI: -3.6 to -0.9, P = 0.001) at six months relative to usual care.[252]

Providing a higher level of home-based intervention support is one way to potentially increase the efficacy of such interventions in an advanced cancer population. The home-based intervention in the RCT conducted by Edbrooke et al. included three home visits with a physiotherapist as well as weekly telephone calls to review the exercise among participants and provide advice on symptom management.[252] Utilising technology is an increasingly attractive option to provide patients with a higher level of exercise support for home-based exercise interventions. Telehealth, telemedicine, or telerehabilitation are general terms used in the context of delivering home or distance-based interventions via information and communication technologies to assess, educate, monitor and/or deliver exercise or other healthcare interventions.[253] Telehealth has had more limited use for exercise delivery in an advanced cancer setting. However, one landmark study by Cheville et al. randomised 516 patients with advanced cancer to either a control arm, telerehabilitation arm, or telerehabilitation with pharmaceutical pain management for six months.[243] Telerehabilitation included aerobic and resistance exercise delivered telephonically by exercise specialists, with electronic monitoring and the ability for participants to request calls with exercise specialists as needed. Relative to the control arm, telerehabilitation resulted in significantly improved physical function (AM-PAC basic mobility computer adaptive test) (MD: 1.3, 95% CI: 0.08 to 2.35, P = 0.03), pain interference (Brief Pain Inventory) (MD: -0.4, 95% CI: -0.78 to -0.09, P = 0.01) and average pain intensity (MD: -0.4, 95% CI: -0.78 to -0.07, P = 0.02).[243] Hospitalisation outcomes were also explored and mean lengths of hospital stay were 7.4 days (control arm), 3.5 days (telerehabilitation arm) and 5.0 days (telerehabilitation with pain management arm). Length of stay was significantly shorter in the telerehabilitation arm compared to the control arm (P = 0.01).[243]

Following the onset of the coronavirus (COVID-19) pandemic, interest in using telehealth to improve home-based exercise intervention delivery within oncology grew.[254] Most published examples of home-based exercise interventions incorporating telehealth in oncology settings prescribe "unsupervised" or "self-directed" exercise. In a review summarising "pre-pandemic" home-based exercise interventions for people with cancer, technology was often used among studies for physical activity self-monitoring, such as via physical activity (*n* = 66 studies) or heart rate monitors (*n* = 29 studies).[255] Other studies (*n* = 33 studies) used videos to provide specific exercise instructions, typically in the form of DVDs, online websites, or smartphone applications.[255] A major adaptation within exercise oncology that occurred following the COVID-19 pandemic was the implementation "virtually supervised" exercise. That is, exercise delivered using internet-based videoconference platforms (e.g., Zoom, FaceTime, Skype, WhatsApp), so that exercise professionals can remotely deliver exercise sessions and monitor participants in real-time from home. Virtually supervised exercise is a safer alternative to in-person exercise settings for immunocompromised people, such as people with cancer, where risk of COVID-19 exposure is more of a concern. Gonzalo-Encabo et al. recently reviewed published examples of virtually supervised home-based exercise interventions in oncology and identified seven studies (all published 2020 or later).[256] Most studies were not originally designed for assessing virtual exercise and were frequently analysed in subgroups of participants.[256] Findings suggest, however, that virtually supervised exercise is generally feasible, well-accepted, and associated with preliminary benefits among people living with and beyond cancer.[256] More information on the role of technology in the delivery of exercise to people with cancer is still needed, including factors that may facilitate or act as barriers to uptake and effectiveness. Regardless, telehealth appears to be a new and important option to possibly improve the quality of home-based exercise interventions.

There is a rationale based on the existing exercise oncology literature to delve into the feasibility and potential benefits of exercise as a management strategy for people with advanced cancer and cachexia. Yet, exercise interventions can range dramatically (i.e., from general exercise advice and self-guided physical activity to tightly controlled, structured, supervised interventions) depending on individual patient needs and preferences, and available resources. There is no one size fits all approach and patients with cancer cachexia may have distinct attitudes towards, or experiences with, exercise. Qualitative evidence among people with advanced or incurable cancer illustrates that patients view exercise as important,[251,257-259] however, this is not well established in patients with advanced cancer and cachexia. Moreover, there may be additional complex exercise motivators and barriers in patients with advanced cancer and cachexia that should be considered to tailor exercise recommendations and design appropriate exercise interventions. Among patients with metastatic cancer (n = 131), for example, feeling weakened from one's tumour therapy, physical symptoms, and fatigue hinder physical activity participation.[260] In addition, patients with higher motivation are 5.6 times more likely to be physically active and motivation has been shown to be predicted by fatigue, depression, knowledge about physical activity and QOL, physical activity before diagnosis, and interest in an exercise program.[260] Mikkelsen et al. also found that among older adults with advanced cancer (n = 25 interviews) "comorbidities and external circumstances prevent physical activity" and participants also described how "fatigue overshadows life.[258]" Such information helps build our understanding of potential exercise motivators, barriers, and preferences in an advanced cancer population. However, the experiences of people with both advanced cancer and cachexia are likely unique. Generating greater information on the perceptions of exercise among patients with advanced cancer and cachexia is thus a critical preliminary step to elucidate the feasibility of exercise as a meaningful intervention. The current lack of knowledge on patients' perceptions of exercise restricts the ability to provide exercise-based support with the greatest potential to engage patients and address patient needs.

2.5.4 Multidisciplinary, Multimodal Treatment

Given cancer cachexia is a multidimensional condition, many clinicians and scientists advocate for a multimodal treatment approach. The pathophysiology of cancer cachexia remains complex and is likely due to various contributions of mechanisms that require different treatment strategies.[46] Multimodal treatment is considered any therapy that combines one or more treatment. Goals of multimodal treatment for cancer cachexia may involve addressing poor nutritional intake, changes in physical activity and function, targeting factors directly associated with cachexia pathophysiology (e.g., inflammation), and relieving psychosocial distress. Exercise-based support may be a critical component of multimodal interventions for cachexia, although several questions remain regarding how exercise should be prescribed and what level of exercise-support is needed to ensure exercise is feasible, tolerable, and beneficial. In theory, exercise may help optimise outcomes in people with cancer cachexia when combined with dietary counselling and/or supplementation, pharmaceutical agents, and even psychological or spiritual interventions.

There is a paucity of evidence supporting the use of multimodal treatment with exercise for cancer cachexia. However, preliminary evidence in people with advanced cancer suggests exercise may be an important component of multimodal interventions (Table 2.3). Solheim et al. examined home-based aerobic and resistance exercise, plus EPA supplementation, anti-inflammatory medication (celecoxib), and nutritional counselling, for six weeks in 46 patients with advanced lung and pancreatic cancer undergoing chemotherapy (MENAC pilot RCT).[261] The intervention was deemed safe and feasible and resulted in significantly improved body weight over time (MD: 0.91 ± 2.47 kg) compared to controls (MD: -2.12 ± 2.50 kg, $P < 0.001$).[261] No group differences in skeletal muscle mass (CT-scans), six-minute walk test (6MWT), physical activity levels (accelerometer), handgrip strength, or CRP were observed, although the study was not powered to determine the efficacy of these outcomes. A phase III RCT of the MENAC intervention is now underway to establish efficacy.[262] More recently, Mikkelsen et al. evaluated the effects of a 12-week multimodal intervention with a strong focus on exercise in older adults with advanced cancer undergoing chemotherapy.[263] The multimodal intervention included twice weekly supervised aerobic and resistance exercise training, plus a high-energy high-protein oral nutritional supplement to consume post-exercise, and nurse-led counselling for symptom management. Relative to usual care, there was a significant between group difference favouring the multimodal intervention for physical function, including the 30s sit-to-stand test (MD: 2.4 ± 0.6 reps, $P < 0.0001$), 6MWT (41.4 ± 16.2 $P = 0.002$), and handgrip strength (MD: 2.4 ± 1.0, $P = 0.029$).[263] There were also significant differences between groups favouring the intervention for lean body mass (MD: 0.9 ± 0.4 kg, $P = 0.033$), physical activity (daily step count, MD:

2529 ± 567 steps, $P < 0.0001$), QOL (EORTC-QLQ-C30, MD: 13.3 ± 5.3 points, $P = 0.020$) and anxiety (MD: -1.8 ± 0.7 points, $P = 0.033$) and depression (MD: -2.2 ± 0.6 points, $P = 0.004$).[263] Thus, multimodal interventions with structured, supervised exercise interventions may have a significant positive effect on multiple patient reported and physical health outcomes among higher risk patient groups, including older adults with advanced cancer actively undergoing cancer therapy.

Data from RCTs on the feasibility and efficacy of multimodal interventions is beginning to emerge but remains particularly scarce in a cancer cachexia setting. However, there are a select number of long-standing multidisciplinary clinical services for cancer cachexia that exist worldwide.[264] One example includes the Cancer Appetite and Rehabilitation (CARE) clinic at the Joan Karnell Cancer Centre at Pennsylvania Hospital in the United States that was started in 2007.[265] The CARE clinic includes a physician, nurses, dietitian, physiotherapist, swallowing therapist, patient navigator, and program assistant.[265] Nurses in particular, play an important role conversing with patients and their carer to provide education, information, and create patient-centred goals. The University of Texas M.D. Anderson Cancer Centre also has a cachexia clinic offered as a part of its supportive care services, where patients receive dietary counselling from a dietitian, standard exercise recommendations, and opportunities to enrol in RCTs of pharmaceutical interventions for cachexia (e.g., thalidomide, mirtazapine).[150,266] In a retrospective chart review of the M.D. Anderson Cancer Centre cachexia clinic of 151 patients, appetite improved among patients (ESAS) (median 7/10 versus 5/10, $P < 0.001$) and 34% of patients gained weight at follow-up (median 5.6 kg).[266] One of the first and currently longest-standing multidisciplinary care services for cachexia operates out of the McGill Cancer Nutrition Rehabilitation Program clinic at the Jewish General Hospital in Canada,[267,268] which has also been expanded to a second site located at the McGill University Health Centre. Within the McGill team are a physician, nurse, dietitian, and physiotherapist. The team evaluate patients every six weeks and devises multidisciplinary care plans, including diet, exercise (with the potential to complete exercise twice weekly in-person at the hospital), and pharmaceuticals for symptom control. Evaluations of the McGill program suggest it is associated with a maintenance of body weight and significant improvements in patient nutritional status, QOL, and physical function.[268-271]

Long-standing multidisciplinary clinical services for cancer cachexia are few and far between globally. As such, publishing data from current clinical services can advance our understanding of feasible and beneficial cachexia care strategies, including the potential role of exercise. Analyses of existing clinical services have shaped our knowledge on the clinical presentation of patients with cancer cachexia, informed the role of multidisciplinary, multimodal treatment strategies, and helped to identify gaps within care. From an exercise-standpoint, evaluations of clinical services provide insight into how exercise is currently delivered to patients with cancer cachexia and help to generate hypotheses on the possible effects of exercise on key patient outcomes. In an analysis from the McGill Cancer Nutrition Rehabilitation Program, Parmar et al. found that patients who experienced improvements in physical function at follow-up (6MWT distance by >40 m) had substantially greater improvements in QOL compared with patients who had little change or deterioration in their 6MWT (e.g., change in FAACT total score: 15.1 ± 15.5 versus 2.6 ± 20.4, $P < 0.001$), suggesting the potential importance of exercise as part of their multidisciplinary care plan to improve QOL.[269] Consequently, utilising data from existing clinical services can provide critical practice-based evidence from which to learn from to develop critical research questions, inform more robust research studies, and develop current recommendations for cancer cachexia care.

2.6 Summary of Literature Review

Cancer cachexia is a complex syndrome that can impose a significant burden on people with advanced cancer. Adequate management and supportive care for cancer cachexia remain critical unmet patient needs. Most patients with cancer cachexia do not receive adequate attention for their syndrome and if they do, it is often not until their cachexia has entered a refractory stage. Exercise has the potential to be an important adjunct therapy to support people living with advanced cancer and cachexia. From both a physical and psychosocial perspective, exercise may help to manage the burden of cancer cachexia and ultimately, address key cachexia therapeutic goals, including preserving QOL and physical function. The current paucity of evidence supporting the delivery of exercise to people with cancer cachexia and advanced stage disease makes it challenging to develop and provide any recommendations regarding exercise to this unique and higher-risk patient group. There is an urgent need to further our understanding on the role of exercise among patients with advanced cancer and cachexia, including as part of multidisciplinary, multimodal treatment strategies. Several questions remain regarding how exercise interventions should be designed to optimise the effect of exercise on key patient outcomes. The studies presented in the following chapters of the current thesis set out to make critical first steps towards understanding the acceptability, feasibility, and potential efficacy of exercise in patients with advanced cancer and cachexia and how exercise-based support may best serve patients.

Table 2.2: Randomised Controlled Trials Delivering Exercise to People with Advanced Cancer or Cancer Cachexia

Author	Population	Cachexia Assessed	Exercise Intervention	Exercise Prescription	Findings*
Brown et al. 2022[272]	Metastatic gastrointestinal cancer undergoing chemotherapy (n = 20)	No	Supervised exercise 1 day/week Home-based exercise 12 weeks total	AET: 150 min/week (combined supervised and home-based) RET: 3 x 10 reps, lower body exercises using ankle weights Balance training	↑ Physical Activity Levels ↔ Handgrip Strength ↔ SPPB ↔ Gait Speed ↔ QOL
Cheung et al. 2021[273]	Stage IIIB-IV NSCLC during treatments (n = 30)	No	Supervised exercise 2 days/week 12 weeks total	AET: Walking, cycling, 50-60% HRR RET: 1 x 10 reps, 60% 1RM, 4 exercises	↑ 30s Sit-To-Stand (Pre-Post) ↑ Timed Up and Go (Pre-Post) ↔ Sleep Quality ↔ Anxiety/Depression ↔ 6MWT ↔ 1-Leg Standing ↔ Physical Activity Levels ↔ Circadian Rhythms
Evans et al. 2021[274]	Metastatic prostate cancer (n = 40)	No	Web-based exercise 2-3 days/week Telehealth consultations (Week 1 and 4) 8-weeks total	AET: 16-40 min, OMNI RPE 6-7/10 RET: 2-3 x 8-12 reps, elastic bands, OMNI RPE 6-7/10	↑ Physical Activity Levels ↑ 400m Walk (Subgroup) ↑ Upper Body Strength (Subgroup) ↔ QOL ↔ Fatigue ↔ Anxiety/Depression ↔ Sleep Quality ↔ Tug (Subgroup) ↔ Chair Rise Test (Subgroup) ↔ Lower Body Strength (Subgroup)
Kamel et al. 2020[239]	Stage I-IV pancreatic cancer during and post-chemotherapy who met the criteria for cancer cachexia[a] (n = 40)	Yes Cachexia[a] prevalence: 100%	Supervised exercise 2 days/week 12 weeks total	RET: Week 1-4: 1-2 x 20 reps, 5 exercises Week 5-12: 3 x 8-12 reps, 60-80% 1RM, 8 exercises, 60 min	↑ 400m Walk Test ↑ 6m Usual Walk Test ↑ Chair Rise Test ↑ Muscular Strength ↑ Lean Body Mass

Poort et al. 2020[275]	Mixed cancers undergoing palliative treatment (n = 88)	No	Supervised exercise 2 days/week 12 weeks total	AET: cycle, intervals, 4 min (60-80% HRR) x 3 min (35-50% HRR), 35 min total RET: 3 x 8-12 reps, 60-80% 1RM, 7 exercises	↔ Fatigue ↔ QOL
Quist et al. 2020[249]	Stage IIIB-IV NSCLC or extensive disease small-cell lung carcinoma undergoing chemotherapy (n = 218)	No	Supervised exercise 2 days/week 12 weeks total	AET: Cycling Warm-up: 60-80% HRmax, 10 min; Intervals: 70-90% HRmax, 10-15 min RET: 3 x 5-8 reps, 70-90% 1RM, 4 exercises	↑ Muscular Strength ↑ Social Wellbeing ↓Anxiety/Depression ↔ VO_2peak ↔ 6MWD ↔ QOL ↔ FEV1
Cheville et al. 2019[243]	Stage IIIC-IV solid or hematologic cancers (n = 516)	No	Tele-exercise +/- pain management 5-7 days/week 6 months total	AET: Walking, step count set by participants RET: 5 exercises, 10-15 reps	↑ Physical Function ↑ QOL ↓ Pain ↓ Length Of Hospital Stay
Edbrooke et al. 2019[252]	Inoperable NSCLC undergoing mixed treatments (n = 92)	No	Home-based exercise with three home visits and 2x/ week phone calls 2 days/week Symptom management advice provided by nurse 8 weeks total	AET: Walking, 10 min (minimum), Borg Dyspnoea Scale "4" RET: 2-3 x 8-10 reps, 80% of 10RM, 5 body weight exercises	↑ QOL ↓ Symptom Severity ↔ 6MWD ↔ Physical Activity Levels ↔ Symptom Distress ↔ Anxiety/Depression
Egegaard et al. 2019[276]	Stage IIIA-IV NSCLC undergoing chemoradiotherapy (n = 13)	No	Supervised exercise 5 days/week 7 weeks total	AET: Cycling, intervals 5×30s at 80–95% peak power output, continuous 80% peak power output, 20 min	↔ Pulmonary Function ↔ VO_2peak ↔ Incremental Peak Power Output ↔ 6MWD ↔ Blood Pressure ↔ HR maximum or HR resting ↔ QOL ↔ Anxiety/Depression ↔ Physical Activity Levels

Rutkowska et al. 2019[277]	Stage IIIB-IV NSCLC during treatment (n = 30)	No	Supervised exercise 5 days/week 4 weeks total	AET: Cycling, 30-80% peak work rate, 20-30 min RET: 40-70% 1RM	↑ Timed Up and Go ↑ 6MWT (Pre-Post) ↑ Chair Stand Test (Pre-Post) ↑ Arm Curl Test (Pre-Post) ↑ FEV1, FVC, FEV1/FVC (Pre-Post) ↓ Dyspnoea (Pre-Post) ↔ Sit And Reach ↔ Back Scratch
Yee et al. 2019[244]	Stage IV breast cancer during and post-treatment (n = 14)	No	Supervised exercise 2 days/week Home-based exercise 5 days/week 8 weeks total	Supervised: AET: Brisk walk, Borg RPE: 11-13, 10-15 min RET: 2 sets x 10-12 reps, 6-7/10 on Adult OMNI Perceived Exertion, Scale7 exercises, 30-40 min Home-based: AET: Brisk walk, Borg RPE: 11-13, 10-15 min	↓ Fatigue ↑ Physical Function ↑ Role Function ↑ Social Function ↑ VO_2max ↑ 6MWT
Scott et al. 2018[250]	Stage IV breast cancer during and post-treatment (n = 65)	No	Supervised exercise 3 days/week 12 weeks total	AET: Treadmill walking, 55-80% VO_2max, 20-45 min	↓ QOL ↓ Social Wellbeing ↔ VO_2peak ↔ 6MWT ↔ 30s Sit-To-Stand ↔ Timed Up and Go ↔ Fatigue ↔ Pain ↔ Sleep Quality ↔ Physical Functioning
Zimmer et al. 2018[246]	Metastatic colorectal cancer undergoing mixed treatments (n = 30)	No	Supervised exercise 2 days/week 8 weeks total	AET: Cross-trainer, cycling, walking Borg RPE: 12-13 RET: 2 x 8-12 reps, 60-80% h1RM, 5 exercises Balance and coordination practice	↑ Trial Outcome Index ↑ Physical Wellbeing ↑ Functional Wellbeing ↑ Advanced Static Balance ↑ Muscular Strength ↓ Neuropathic Symptoms ↔ QOL ↔ Static or Dynamic Balance ↔ 6MWT

Galvao et al. 2018[247]	Metastatic prostate cancer undergoing mixed treatments (n = 57)	No	Supervised exercise 3 days/week 12 weeks total	AET: Walking, cycling, elliptical, 60-85% HR_{max}, 20-30 min RET: 3 x 10-12 reps, 10-12 RM, 6 exercises	↑ Physical Function ↑ Muscular Strength ↔ Timed Up and Go ↔ 6m Walk Test ↔ 400m Walk Test ↔ Lean Body Mass ↔ Fat Mass ↔ Fatigue
Dhillon et al. 2017	Stage III-IV lung cancer completed ≥ chemoradiotherapy (n = 112)	No	Supervised exercise 1 day/week Home-based exercise 8 weeks total	Supervised AET: Walking, cycling, 30-45 min Home-based exercise: guided by behaviour support sessions	↑ Physical Activity Levels ↔ 6MWT ↔ Handgrip Strength ↔ Fatigue ↔ QOL ↔ ADL ↔ Anxiety/Depression ↔ Cognitive Symptoms ↔ Sleep Quality ↔ Dyspnoea ↔ Pulmonary Function ↔ Glasgow Prognostic Score ↔ Cytokine Levels ↔ Insulin Growth Factor
Schuler et al. 2017[278]	Mixed cancers during or post curative and palliative treatment (n = 70)	No	Home-based exercise +/- physical therapy treatments 3 days/week 12 weeks total	AET: Walking, cycling, or running, RPE ≥13, 20-30 min RET: 20-30 min, RPE ≥13, 5 exercises	↓ Mental Fatigue (Pre-Post) ↑ Albumin (Pre-Post) ↔ General Fatigue ↔ Physical Fatigue ↔ Reduced Activity or Motivation ↔ 6MWT
Tsianakis et al. 2017	Advanced or metastatic mixed cancers during and post-treatment (n = 42)	No	Home-based exercise 4 days/week 12 weeks total	AET: Walking, 30 min	↔ QOL ↔ Fatigue ↔ Anxiety/Depression ↔ Physical Activity Levels ↔ Mood ↔ Exercise Self-Efficacy ↔ Performance Status

Vanderbyl et al. 2017[279]	Stage III-IV NSCLC (n = 12) or GI cancer (n = 12)	No	Supervised exercise 2 days/week Home-based exercise 5 days/week 6 weeks total	Supervised: AET: 60-70% HR_{max} RET: NR Home-based: Walking, 60 min	↑ 6MWT ↓ Feelings of Weakness ↔ Anxiety/Depression ↔ Other Cancer Symptoms ↔ QOL ↔ Simmunds Functional Assessment (Additional Outcomes)
Ligibel et al. 2016[280]	Stage IV breast cancer undergoing mixed treatments (n = 101)	No	Home-based exercise 16 weeks total	AET: 150 minutes/week, "moderate-intensity"	↔ QOL ↔ Aerobic Fitness (Bruce Ramp Time) ↔ Fatigue ↔ Physical Activity Levels
Henke et al. 2014[248]	Stage IIIA-IV NSCLC undergoing inpatient chemotherapy (n = 46)	No	Supervised exercise 7 days/week 3 chemotherapy cycles total	AET: Walking, 55-70% HRmax, 6 min (5 days/week) RET: 3 x 10 reps, 50% max capacity, resistance bands (7 days/week)	↑ 6MWT ↑ Staircase Walking ↑ Physical Functioning ↑ Cognitive Functioning
Cheville et al. 2013[245]	Stage IV lung (n = 34) and colorectal cancer (n = 32)	No	Home-based exercise 4 days/week 8 weeks total	AET: Walking, ~3.5 mets, 20 min RET: 5 exercises, 10-15 reps	↑ AM-PAC Mobility ↑ Sleep Quality ↓ Fatigue
Cormie et al. 2013[281]	Metastatic prostate cancer (n = 20)	No	Supervised 2 days/week Home-based exercise 12 weeks total	Supervised: AET: "low level" exercise, 15 min RET: 2-4 x 8-12 RM, 8 exercises Home-based: AET: moderate-intensity, 150 min/week	↑ Muscular Strength ↑ 400m Walk ↑ 6m Walk ↑ Physical Activity Levels ↑ Lean Body Mass ↔ Fat Mass ↔ Fatigue ↔ QOL ↔ Psychological Distress
Hwang et al. 2012[282]	Stage IIIA-IV NSCLC undergoing targeted therapy (n = 22)	No	Supervised exercise 3 days/week 8 weeks total	AET: Treadmill or cycling, intervals 2-5 min 80% VO_2peak or Borg RPE 15-17), active recovery 60% VO_2peak or Borg RPE 11-13), 30-40 min total	↑ VO_2peak (Pre-Post) ↓ Dyspnoea (Pre-Post) ↓ Fatigue (Pre-Post) ↔ Muscular Strength ↔ QOL ↔ Muscle Oxygenation ↔ Insulin Resistance ↔ CRP

Oldervoll et al. 2011[241]	Mixed incurable and metastatic cancer (n = 163)	No	Supervised exercise 2 days/week 8 weeks total	Circuit training, 40 min, 6 exercises (body weight, bands machines)	↑ Body Weight ↑ Chair Stand Test ↑ Handgrip Strength ↑ Max Step Length ↑ Shuttle Walk Test ↔ Fatigue

[a]Weight loss >5% previous 6 months or >2% and BMI <20 kg/m^2 *significant between group differences, ↑ statistically significant increase, ↓ statistically significant decrease, ↔ no statistically significant difference;

Abbreviations: 6MWT: 6 minute walk test, AET: aerobic exercise training, ADL: activities of daily living, AM-PAC: Ambulatory Post Acute Care Daily Activities Short Form, CSA: cross-sectional area, CRP: C-reactive protein, handgrip strength: handgrip strength, HR: heart rate, NR: not reported, NSCLC: non-small cell lung cancer, QOL: quality of life, RET: resistance exercise training, RPE: rating of perceived exertion, RM: repetition maximum, SPPB: Short Physical Performance Battery, VO_2peak: peak oxygen consumption

Table 2.3: Randomised Controlled Trials Delivering Multimodal Interventions with Dietary and Exercise Support to People with Advanced Cancer

Author	Population	Cachexia Assessed	Multimodal Intervention	Exercise Component	Findings*
Mikkelsen et al. 2021[263]	Stages III/IV pancreatic cancer (n = 36), biliary tract cancer (n = 9) or NSCLC (n = 39) undergoing palliative treatment	No	Supervised exercise 2 days/week Protein drink or bar (200-330 calories, 12-18 g protein) post-exercise Nurse-led counselling 12 weeks total	AET: cycling or relay games, “light” intensity, 15 min RET: 2-3 x 10-15 RM, 7 exercises, 35 min	↑ 30s Sit-to-Stand ↑ 6MWT ↑ Handgrip Strength ↑ Lean Body Mass ↑ Daily Step Count ↑ QOL ↓ Anxiety/Depression
Storck et al. 2021[283]	Locally advanced or metastatic mixed cancers (n = 52)	No	Supervised exercise 2 days/week Home-based exercise 1 day/week Leucine-rich protein supplement (13 g protein, 5055 mg leucine) 2x/day on exercise days Dietary counselling 12 weeks total	Supervised: AET: Treadmill, cycling, Borg Scale 4-6/10 RET: 3 x 10-15 reps, strength circuit Home-based: RET: Elastic bands AER: Walking, cycling, 30 min	↑ Handgrip Strength ↔ SPPB ↔ 60s Sit-to-stand ↔ Timed Up and Go ↔ Body Composition ↔ Fatigue ↔ QOL ↔ Dietary Intake
Solheim et al. 2017[261]	Stage III/IV NSCLC or inoperable pancreatic cancer (n = 46)	Yes[a] Cachexia prevalence: NR Weight loss (%) over previous 6 months: 5.7 (range: 0.6–13.3)	Home-based exercise 2-3 days/week Oral nutritional supplement with EPA (2g/day) Dietary counselling NSAIDS (200 mg/day, Celecoxib) 6 weeks total	AET: 30 min, type NR RET: 20 min, 6 exercises with free weights & body weights	↑ Body Weight ↔ Muscle Mass ↔ handgrip strength ↔ Physical Activity Levels ↔ 6MWT ↔ Nutritional Status/Intake ↔ Fatigue ↔ CRP

Uster et al. 2017[284]	Metastatic or locally advanced tumours, gastrointestinal (n = 38) or lung (n = 20)	No	Supervised exercise 2 days/week Protein supplement (18-20 g) provided after each training session Dietary counselling 12 weeks total	AET: Cycle, 10 min warm-up RET: 2 x 10 reps, 60-80% of 1RM, 6 machines Balance: 4 exercises (single leg/standing)	↑ Protein & Energy Intake ↔ QOL ↔ Body Weight ↔ Body Composition ↔ Physical Function ↔ Medical Outcomes

[a]Weight loss % in previous 6 months reported *significant between group differences, ↑ statistically significant increase, ↓ statistically significant decrease, ↔ no statistically significant difference;

Abbreviations: 6MWT: 6-minute walk test, AET: aerobic exercise training, CRP: C-reactive protein, handgrip strength: handgrip strength, HR: heart rate, NR: not reported, NSCLC: non-small cell lung cancer, QOL: quality of life, RET: resistance exercise training, RM: repetition maximum, SPPB: Short Physical Performance Battery

3 Evaluation of a Multidisciplinary Clinical Service for Cancer Cachexia: A Retrospective Observational Review

3.1 Preamble

The last chapter summarised that cancer cachexia is a prevalent and burdensome syndrome among patients with advanced cancer with limited treatment options. A key argument is that multidisciplinary, multimodal care for cancer cachexia that includes exercise-based support may help improve patient outcomes. However, current available evidence supporting the delivery of multimodal treatment approaches with exercise specifically for cancer cachexia is scarce. An important step in developing our understanding of the role of multimodal treatment with exercise-based support includes taking advantage of available routine medical data from existing multidisciplinary clinical services that have been serving patients with cancer cachexia over several years.

In the first study of this thesis and current chapter, an evaluation of one of the only long-standing multidisciplinary clinical services for cancer cachexia in Australia was performed. The study design was a retrospective observational review of routinely available medical data from the Barwon Health Cachexia and Nutritional Support Service. The study aimed to evaluate changes in QOL and symptom burden and explore changes in patient body weight and clinically assessed physical function and muscular strength over time among patients who attended the multidisciplinary clinical service. A detailed description of the multidisciplinary clinical service care team is also provided, along with the nature and goals of the service, to illustrate the importance of each healthcare provider within the team. The clinical service description also highlights how exercise-based support has been uniquely integrated into multimodal treatment plans and as a standard component of cancer cachexia care.

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3.2 Publication: Quality of life and symptom burden improve in patients attending a multidisciplinary clinical service for cancer cachexia: a retrospective observational review.

[redacted]

3.3 Chapter Conclusion

Findings from study one elucidate the potential strengths and weakness of an operating multidisciplinary clinical service for cancer cachexia in Australia and help identify topics for future research investigations to improve cancer cachexia care, including on the relative importance of exercise-based support as a part of multimodal treatment plans. Overall, the Barwon Health Cachexia and Nutritional Support service was associated with improved patient reported QOL and symptoms, but not changes in clinically assessed physical function and muscular strength. The exercise component of the clinical service included physical activity advice and a home-based resistance exercise program. It is possible that relative to further declines in physical function, patients experienced a maintenance or stabilisation in function. It is equally possible that the exercise component of the multimodal care plan was not robust enough to elicit the exercise training response needed to modify physical function (i.e., total exercise volume was not high enough to increase muscular strength). Participants may have also not adhered to their prescribed exercise, due to a lack of motivation to self-direct exercise, for example.

Information generated from study one supports the clinical use of multidisciplinary, multimodal treatment approaches for cancer cachexia. However, specific to the exercise component of the multimodal treatment plans, questions remain regarding how to optimally prescribe exercise-based support to promote exercise feasibility (e.g., patient adherence) and efficacy on desired outcomes, such as physical function. Consequently, gathering more information regarding what patients themselves feel would be most beneficial and tolerable in terms of exercise-based support is an important next step. Study two in the following chapter aims to explore the perceptions of exercise specifically among patients with advanced cancer and cachexia to address this research gap.

4 Perceptions of Exercise in Patients with Advanced Cancer and Cachexia: A Descriptive Qualitative Study

4.1 Preamble

There is no one-size-fits all approach to exercise recommendations and intervention design for people with cancer. Various exercise interventions with established safety, feasibility, and efficacy in people with cancer who do not have cachexia, may not be suitable or equally as effective among patients with advanced cancer and cachexia. Findings from study one (Chapter 3) suggest there may be room for improvement beyond unsupervised home-based exercise advice to modify physical function in patients with advanced cancer and cachexia. However, prior to designing or altering any exercise intervention approach, it is useful to collect more information on both patients' perceptions of exercise, including their exercise preferences. Information on patients' thoughts towards and experiences with exercise is vital to inform both *if* and *how* exercise can be delivered to maximise feasibility and effectiveness.

In the second study of this thesis and current chapter, a diverse group of patients with advanced cancer and cachexia, according to the international consensus definition, were interviewed about their perceptions of exercise. The qualitative study design aimed to comprehensively capture what patients believe about exercise, including any potential benefits or harms associated with exercise, factors that motivate them to exercise, and barriers to exercise engagement. Participants were also interviewed about their exercise preferences, including exercise settings and types. Increasing our understanding of patients' perceptions of exercise may help clarify the feasibility of implementing exercise for cancer cachexia and promote the design of patient-centred exercise intervention approaches and recommendations.

This chapter has been published as: Bland KA, Krishnasamy M, Parr EB, Mulder S, Martin P, van Loon LJC, Cormie P, Michael N & Zopf EM. "I want to get myself as fit as I can and not die just yet" – Perceptions of Exercise in People with Advanced Cancer and Cachexia: A Qualitative Study. BMC Palliative Care. 2022;21(1):75. Supplementary files from this publication can be found in the Appendices.

4.2 Publication: "I want to get myself as fit as I can and not die just yet" – Perceptions of Exercise in People with Advanced Cancer and Cachexia: A Qualitative Study

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RESEARCH

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"I want to get myself as fit as I can and not die just yet" – Perceptions of exercise in people with advanced cancer and cachexia: a qualitative study

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Abstract

Cachexia is a prevalent muscle wasting syndrome among people with advanced cancer that profoundly impacts patient quality of life (QoL) and physical function. Exercise can improve QoL, physical function, and overall health in people with cancer and may be an important addition to treatment approaches for cancer cachexia. Greater understanding of patients' perception of exercise can help elucidate the feasibility of implementing exercise interventions for cancer cachexia and facilitate the design of patient-centered interventions. We aimed to describe the perception of exercise in patients with advanced cancer and cachexia, and capture exercise motivators, barriers, and preferences, to inform the feasibility of exercise interventions. Individual interviews ($n = 20$) with patients with locally advanced or metastatic cancer with cachexia were conducted and analyzed using reflexive thematic analysis. Main themes from interviews were: 1) Life is disrupted by cancer and cachexia; 2) Exercise offers hope; 3) Exercise barriers are multifaceted; and 4) Exercise access and support are important. Participants reported that their cancer and cachexia had intensely altered their lives, including ability to exercise. Exercise was perceived as important and participants described a hope for exercise to improve their health and wellbeing. Yet, several complex exercise barriers, such as burdensome cancer symptoms and the overwhelming impact of the COVID-19 pandemic, hindered exercise participation and prevented participants from fully realizing the perceived benefits of exercise. Factors believed to improve exercise engagement and overcome exercise barriers included increased exercise support (e.g., professional supervision) and accessibility (e.g., convenient locations). Patient-reported exercise barriers and preferences can inform the design of exercise interventions, particularly within future research studies aiming to establish exercise feasibility and efficacy in people with advanced cancer and cachexia.

Keywords: Advanced cancer, Palliative care, Cancer cachexia, Exercise, Physical activity, Barriers, Motivators, Preferences, Qualitative interviews, COVID-19 pandemic, Thematic analysis

Introduction

Cancer cachexia is a multifactorial syndrome characterized by the ongoing loss of muscle mass, with or without the loss of fat mass, that cannot be reversed with conventional nutritional support alone and leads to progressive functional impairment [1]. Cachexia is prevalent in all cancer types, but tends to disproportionately affect

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people with more advanced or incurable disease [2, 3]. Prominent adverse effects of cancer cachexia include increased mortality [4–6], greater treatment toxicity [7, 8], declines in physical function [9, 10], and reduced overall quality of life (QoL) [11–13]. Despite the significant burden cancer cachexia places on both patients and their carers [14, 15], cachexia remains both challenging to clinically identify and treat.

A multimodal intervention strategy that includes pharmaceuticals, dietary support, and structured exercise training may hold the greatest potential to support patients with cancer cachexia, although evidence remains limited [16, 17]. Specific to both aerobic and resistance exercise training, benefits include the possibility for exercise to address the underlying causes of cancer cachexia and the associated adverse effects. On one hand, exercise may help counteract disrupted metabolism, for example, due to chronic inflammation, causing cancer-related weight loss or muscle wasting [18, 19]. Equally, exercise might prevent declines in skeletal muscle mass [20] and manage cancer symptoms, increase physical function, and improve overall QoL [21, 22]. There is evidence that aerobic and resistance exercise training (typically delivered in a structured, supervised setting) is beneficial among people with advanced cancer [23], including older adults with advanced cancer undergoing treatment [24]. Preliminary evidence from a recent randomized controlled trial in 40 patients with pancreatic cancer and cachexia also found a three month, supervised resistance training intervention may improve muscle strength and lean body mass [25]. However, more information on the feasibility and efficacy of exercise as either a standalone or as part of a multimodal strategy for the management of cancer cachexia, including among patients with advanced or incurable disease, is needed.

A critical first step in establishing the feasibility of exercise for patients with advanced cancer and cachexia includes exploring patients' openness and willingness to exercise. Adverse effects of cancer cachexia, including a loss of appetite, reduced food intake, and involuntary body weight loss [26, 27] may exacerbate cancer symptoms and reduce physical function and strength [28–30]. Thus, the burden of both an advanced or incurable cancer diagnosis coupled with the experience of living with cachexia may reduce exercise motivation and tolerability relative to other people with cancer. Several qualitative studies report that people with advanced cancer experience complex barriers to exercise, including cancer-specific (e.g., cancer-related fatigue), psychosocial (e.g., low confidence or mood), and environmental factors (e.g., weather) [31–35]. Despite these reported challenges, patients with advanced cancer still express interest in exercise and view exercise positively [31–34, 36]. To our knowledge, perceptions of exercise in those with advanced disease who have cancer cachexia have not been specifically investigated. Understanding patients' experiences with and interest in exercise is key to establishing the feasibility of implementing exercise as a meaningful intervention for cancer cachexia. The current descriptive qualitative study aimed to explore the perceptions of exercise among patients living with advanced cancer and cachexia and capture perceived exercise motivators, barriers, and preferences.

Materials and methods

Study design

We conducted a descriptive qualitative study using individual, semi-structured interviews. Reflexive thematic analysis was applied to the data to understand perceptions of exercise among people with advanced cancer and cachexia. Quantitative data on participant demographics and medical characteristics, cachexia and nutritional status, and current physical activity levels were collected to provide context and to aid the transferability of the study's qualitative findings. The reporting of this study is in accordance with the Standards for Reporting Qualitative Research (SRQR) checklist [37].

Participants

Eligible participants were adults (≥ 18 years) with metastatic or locally advanced cancer (e.g., unresectable cancer or a larger tumor that has spread to nearby lymph nodes or tissues) with cachexia (i.e., involuntary body weight loss > 5% over the previous six months; or weight loss > 2% and body mass index (BMI) < 20 kg/m^2) [1]. Participants were excluded if they had an expected survival of < 3 months, were receiving parenteral nutrition or enteral nutrition via a feeding tube, were less than four weeks post-surgery, had full-time reliance on a mobility aid (e.g., wheelchair) for all day-to-day activities, or were unable to communicate in English. Patients were recruited via convenience sampling. Patients were referred to the study by a member of their cancer care team, including palliative care physician or medical oncologist, from St. Vincent's Hospital Melbourne, Cabrini Health, and Barwon Health in Victoria, Australia or learned about the study via word-of-mouth from community-based clinicians. A target sample size of 20 participants was deemed sufficient to support data adequacy in terms of the number and variety of participant experiences that would be collected. Informed consent was obtained from all participants. Participants were interviewed between July 2020 and April 2021 and thus, following the commencement of the coronavirus (COVID-19) pandemic and often during periods of public health restrictions in Victoria, Australia.

Data collection

A single 30-min one-on-one semi-structured interview was conducted over the phone or via a videoconference call. All participants completed the interviews from home in a private space. Interviews were conducted by a cisgender woman, doctoral research student, and exercise physiologist (KB), with prior graduate-level training in qualitative research methods. No interviewees had previously worked with the interviewer in an exercise setting. Participants did, however, have an awareness of the interviewer's professional and research experience in exercise oncology. The interview guide was informed by prior research and the clinical expertise of study team members (KB, MK, and EZ). Interview follow-up questions and prompts were employed to facilitate discussion and elicit more detailed responses. The interview guide was pilot tested with a non-study team member with relevant clinical and research experience and revised, accordingly. During the interview, participants were asked to discuss their experiences and perceptions of physical activity, including both incidental physical activity (e.g., occupational, household) and planned, structured and repetitive physical activity for the purpose of maintaining physical fitness, i.e. exercise [38]. Discussions aimed to capture participants' overall current physical capabilities, including any changes in physical function since being diagnosed with cancer, as well as their tolerance for and interest in exercise, specifically. The final interview guide is provided is Table 1.

Participant demographics were collected using a researcher-generated questionnaire, along with relevant medical information, including current cancer diagnosis, stage and treatment. The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) was administered to characterize nutritional status. The PG-SGA collects patient body weight, food intake, nutritional impact symptoms (e.g., nausea, vomiting, lack of appetite), functional capacity, metabolic demands, and includes a physical assessment [39]. The short form version of the PG-SGA has been validated in oncology outpatients [40, 41] and forgoes the disease/condition, metabolic demands, and physical assessment components, so that it may be completed entirely by the patient. Total point scores for the PG-SGA SF were calculated to determine malnutrition severity [40]. A modified-version of the Godin Shepard Leisure Time Questionnaire was used to collect patient-reported physical activity levels, including the number of times they completed mild, moderate, and strenuous aerobic exercise and any resistance exercise training within a typical 7-day period [42]. A Leisure Score Index was calculated for aerobic exercise (frequency of mild $\times$ 3, frequency of moderate $\times$ 5, and frequency of strenuous $\times$ 9); where an index $\geq$ 24 was classified as being "sufficiently active," an index of 14–23 as "moderately active," and an index $<$ 14 as "insufficiently active" [42].

Table 1 Interview Guide

Main Questions and Prompts
1. Do you currently do any type of exercise or physical activity? • If yes, please describe the type of activity. a) structured exercise (e.g., gym), b) other leisure-based (e.g., sports), c) household-based (e.g., gardening), d) transportation (e.g., walking to train) and e) occupational • If no, please describe why. a) no previous exercise or activity, b) lack of interest in exercise, c) exercise not enjoyable, d) don't see point of exercise, and/or d) injury or illness related
2. Has your cancer diagnosis or cancer treatments affected your daily level of activity or ability to move? • Please describe any changes. a) type of change and b) when change occurred
3. Is it important for you to be able to be physically active? • a) perceived benefits, b) perceived harms and c) what does being physically active mean for you (physically, mentally, emotionally, socially)? • If unable to be physically active, what does this mean for you (physically, mentally, emotionally, socially)?
4. What (if anything) makes it difficult for you to stay physically active or to exercise in your current situation? • a) cancer symptoms, b) motivation, c) safety, d) other injuries or illnesses, d) logistics (e.g., travel) and e) COVID
5. Is there anything that does- or might motivate you to be physically active or exercise? • a) advice or information about exercise, b) perceived benefits of exercise, b) certain types of exercise, c) people to exercise with, d) structured program or professional supervision, and e) access
6. Has anyone spoken with you about being active or engaging in exercise following your cancer diagnosis? • If yes, who and what did you speak about? a) reasons provided to exercise or b) advice not to exercise or concerns • If no, would you have wanted to speak with somebody about exercise? Please describe.
7. I am interested in hearing your thoughts about what exercise you might prefer. • a) setting (e.g., outdoors, fitness centers, home), b) type (e.g., walking, strength training, yoga) and c) time (e.g., duration, time of day) • Do you prefer exercising on your own or with others? If with others, who and why?
8. Any other areas/things you'd like to mention or discuss?

Data analysis

Descriptive statistics were used to summarize questionnaire data. Quantitative data are presented as totals and percentages or mean ± standard deviation (SD). Given the current study aimed to investigate an under researched construct, qualitative data analysis and interpretation of the interviews was performed using inductive, reflexive thematic analysis by the first author (KB), as described by Braun and Clarke [43, 44]. Reflexive thematic analysis was chosen because of its flexibility and potential to offer rich and complex understandings. A social constructionist approach underpinned the analysis, where meaning and experience are understood to be socially produced [43]. Thus, the thematic analysis took place at the latent level and involved interpretative work. We sought to acknowledge and consider underlying ideas, assumptions, and meanings that shaped what was articulated in the data. All interviews were audiotaped, de-identified and transcribed verbatim. Interview transcripts were cross-checked with audio files and verified for accuracy. Initially, interviews were read and re-read for data familiarization. Two transcripts were also read and reviewed by a blinded study team member (SM). Prior to coding, overarching concepts were mapped out and relevant notes were written down and discussed (KB and SM). An initial coding framework was developed (KB and SM) to allow for systematic coding of data, but not with the intention of pre-defining themes (Supplementary File). Initial coding of the entire data set took place using NVIVO software (version 12, QSR International Pty Ltd) [45] and initial codes were then sorted into meaningful groups for interpretive analysis. Candidate themes were developed and an initial thematic map was created. Any experiences that stood apart from the developing themes were explored further to ensure an accurate representation was provided and themes illustrated data complexity, including any contradictions within the data. Themes were then reviewed and, as appropriate, further refined to ensure data within each theme meaningfully aligned. Subthemes (i.e., themes within themes) were identified to provide further structure and to illustrate a hierarchy of meaning within the data. Theme names, final descriptions, and the allocation of quotes were questioned and critiqued for credibility and trustworthiness by the entire study team over multiple rounds until themes were deemed to provide an accurate representation of the data.

Researcher reflexivity and rigour

The subjectivity of the first author researcher (KB) was considered a resource during both data collection and analysis [46]. Subjectivity guided decision-making during interviews and informed the flow of questioning and prompts, and the nature and type of verbal response elicited to the often sensitive topics discussed. Participants were listened to with empathy, compassion, and curiosity. Throughout the thematic analysis, interview data were actively interpreted and not merely described, with both researcher and participant subjectivity recognized throughout. The researcher acknowledged, for example, that interviews were conducted in a familiar and comfortable setting to encourage participants to speak more freely about their experiences. Throughout data analysis, the researcher actively reflected on how her experience and knowledge may influence both participant responses and data interpretation, allowing her to identify contradictions within individual participant interviews. Both familiar and new concepts and ideas were identified, noted, and reflected upon during the analysis to allow for a full and complete interpretation of the data.

Results

Participant characteristics

Twenty-two patients were invited to be interviewed. One patient declined and another did not take part due to cancer symptoms. Thus, 20 patients were interviewed. Participant characteristics are presented in Table 2. Participants (mean age: 61 ± 13 years) had diverse cancer types. Most patients had metastatic disease and 90% of patients were diagnosed with incurable cancer. Two-thirds of participants were considered critically malnourished (PG-SGA SF scores ≥ 9). Patient-reported physical activity levels indicated that four participants (20%) were sufficiently active (score index: ≥ 24), two participants (10%) were moderately active (score index: 14–23) and 14 participants (70%) were insufficiently active (score index < 14).

Interview themes

Reflexive thematic analysis of interview data resulted in the generation of four main themes, each with a series of subthemes (Fig. 1). The first theme, "Life is disrupted by cancer and cachexia," relates to the extent to which participants felt their cancer diagnosis and cachexia influenced several facets of life, reflecting on changes in physical wellbeing, independence, and activities of daily living, decreased social participation, and reduced mental and emotional wellbeing. The second theme, "Exercise offers hope," encapsulates how exercise was perceived as a potential tool to overcome the adversity participants were experiencing because of their cancer and cachexia. The third theme, "Exercise barriers are multifaceted," captures the myriad of exercise barriers preventing participants from fully realizing their believed benefits that exercise held, including barriers directly relating to or exacerbated by their cancer. "Exercise access and support

Table 2 Participant Characteristics

Demographics	
Age (years) (mean ± SD)	61 ± 13
Sex (n (%))	
Female	14 (70%)
Male	6 (30%)
Marital Status (n (%))	
Single	3 (15%)
Married/Committed Relationship	14 (70%)
Divorced/Separated/Widowed	3 (15%)
Employment Status (n (%))	
Retired	11 (55%)
Employed	5 (25%)
Unemployed/Other	4 (20%)
Education (n (%))	
Highschool Diploma or Less	4 (20%)
Bachelor's Degree/Diploma	12 (60%)
Higher than a Bachelor's Degree	3 (15%)
Prefer not to Answer	1 (5%)
Medical Characteristics	
Disease Stage (n (%))	
Metastatic	16 (80%)
Locally Advanced	4 (20%)
Tumor Type (n (%))	
Gastrointestinal	4 (20%)
Breast	3 (15%)
Lung	2 (10%)
Gynecological	2 (10%)
Sarcoma	2 (10%)
Hematological	2 (10%)
Other	5 (25%)
Current Treatment (n (%))	
Chemotherapy	8 (40%)
Immunotherapy	5 (25%)
Hormonal/Targeted Therapy	3 (15%)
Not Undergoing Treatment	4 (20%)
Cachexia and Nutritional Status	
Anthropometrics (mean ± SD)	
Body Weight (kg)	60.0 ± 8.3
Body Mass Index (kg/m^2)	21.5 ± 2.4
Six-month Weight Loss (%)	6.0 ± 2.5
Patient-Generated Subjective Global Assessment Short Form[a]	
Score 2–8 (n (%))	7 (35%)
Score ≥ 9 (n (%))	13 (65%)
Total Score (mean ± SD)	10 ± 5
Physical Activity Levels	
Godin-Shephard Leisure-Time Physical Activity Questionnaire Leisure Score Index (mean ± SD)	
Mild	20.3 ± 17.1
Moderate	8.8 ± 13.1
Strenuous	3.1 ± 10.4
$\text{Overall}_{\text{moderate+strenuous}}$	11.9 ± 18.6
Resistance Exercise (mean ± SD)	
Minutes per week	16.3 ± 27.4

Table 2 (continued)

[a] Patient-Generated Subjective Global Assessment Short Form categories: 0 to 1: no nutritional problems or need of intervention; 2 to 8: patients with increasing nutritional problems who might benefit from but are not in critical need of clinical interventions; and ≥ 9: critical need for improved symptom management and/or nutrition-intervention options

are important" was the fourth and final theme that relates to key factors that participants felt may help to overcome perceived exercise barriers and foster exercise participation in a safe, enjoyable, and more effective way. Themes, subthemes, and representative participant quotes are presented in Table 3 and are described in more detail hereafter.

Theme 1: Life is disrupted by cancer and cachexia

Participants provided diverse descriptions of profound physical, psychological, and social impacts of their cancer diagnosis and the experience of cachexia. Notably, being less physically active or having to give up certain physical activities due to a decline in physical health, was difficult for some participants to discuss and could be a source of distress. Others more openly reminisced about physical activities they previously enjoyed doing either in younger years or prior to being diagnosed. A change in physical condition, coupled with relinquished physical activities, roles, and responsibilities appeared to underpin a change in self-perception and enhance participants' awareness of being ill, creating a new, and often unsettling, normal.

Theme 1.1: Altered sense of self

Participants had an acute awareness of changes in their physical condition and health, which impacted participation in various events or physical activities, including occupational, household, social and exercise-based. The idea that "what we do" is closely linked to "who we are" was apparent. Grappling with a loss of independence and giving up roles and responsibilities, such as looking after grandchildren, were discussed. Some participants were grieving a prior sense of self. One participant (ID #9) described how they had changed "from being a very independent person to someone that relies on others" and accepting this change was an ongoing process. Changes in both physical function and reductions in physical activity, including both incidental physical activity and exercise, had wide-ranging implications. Negative feelings of sadness, frustration, boredom, and guilt were commonly expressed. One participant (ID #3), for example, described feeling guilty about not being able to walk their dog. A change in physical function also had specific social effects for some participants, including for one participant (ID #17) who expressed disappointment in no longer participating in their social walking group because they felt they

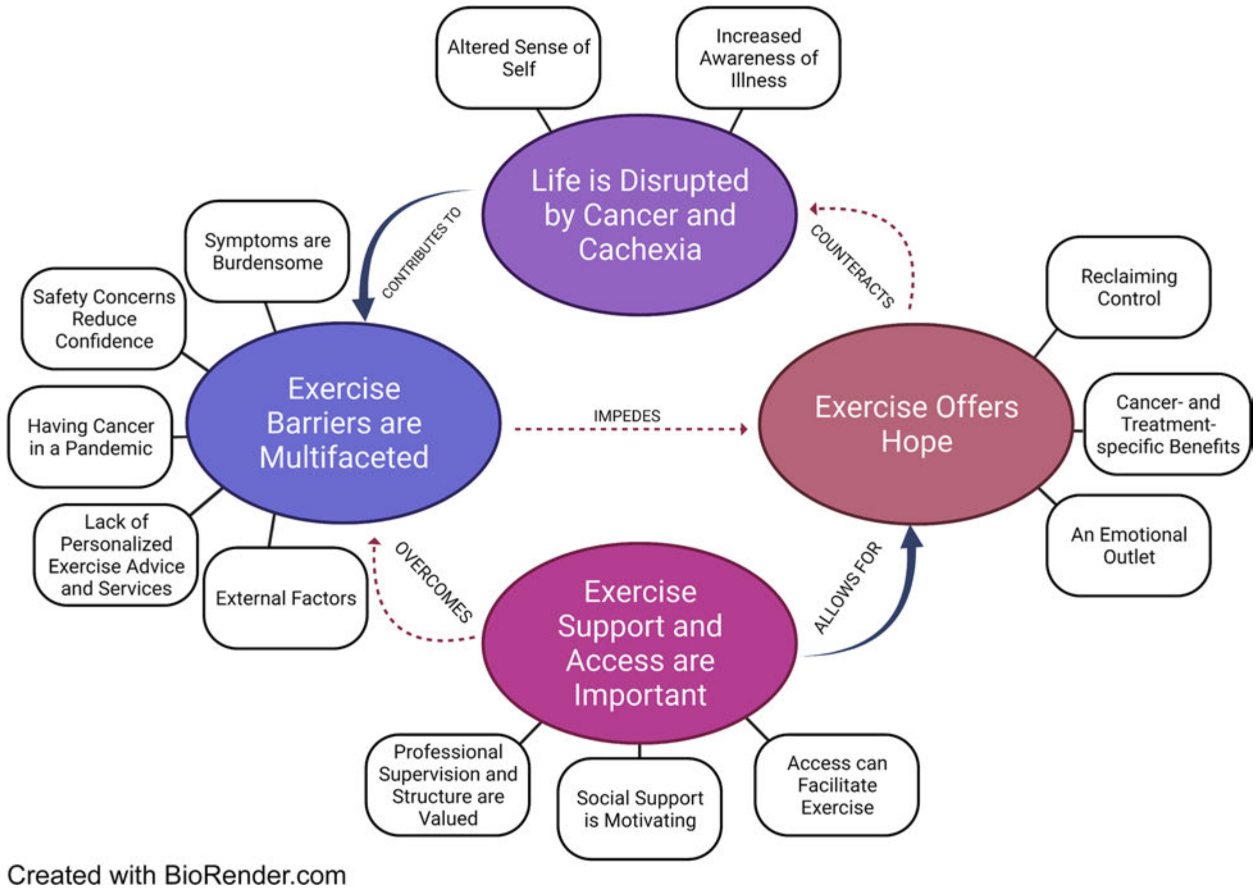

Fig. 1 Thematic Map

couldn't keep up with the group anymore. An exception was one participant (ID #19) who had previously taken part in triathlons and been highly physically active prior to their diagnosis of metastatic cancer. They explained how they didn't miss long bouts of exercise training, simply because they were too tired and in too much pain in their current situation. This participant still had enough physical capacity to go on leisurely walks with friends and highlighted:

> *"I'm just pleased that I'm here and that I can still do what I can do, really." – ID #19.*

Thus, the type and extent of physical function changes and the restrictions they impose may relate to differences in the emotional responses elicited. Physical limitations with greater social repercussions or that impede autonomy may more adversely affect one's sense of self and be particularly challenging to navigate.

Theme 1.2: Increased awareness of illness

The physical signs and symptoms of cachexia were often perceived as a manifestation of having cancer. Many participants commented on looking and feeling different, such as feeling frail or perhaps looking more like "a person with cancer" in a stereotypical sense. An increased awareness of being ill sometimes brought into question whether participants might ever go back to feeling like their normal selves again. Turning points of physical change along the cancer treatment continuum were discussed and coincided with an increased awareness of being ill. Often the increased awareness of their illness coupled with the onset of cachexia. Noticeable body weight loss, physical deconditioning, or exacerbated symptoms could be pinpointed concurrent to undergoing a certain cancer therapy or after being hospitalized, for example. A couple participants (ID #12 and ID #15) had also had previous cancer diagnoses and reflected on how they had "felt better" then and were able to physically do more, including exercise, when their cancer was considered early-stage. These participants had cancer recurrences and reflected on how their current situation felt dramatically different because of their weight loss and symptoms, which were perceived as signs of disease progression.

Table 3 Main Themes and Subthemes

Themes and Subthemes	Representative Quotes
1. Life is Disrupted by Cancer and Cachexia	
1.1 Altered Sense of Self	I used to do everything. It's affected my thinking, my memory. I'm always tired. I was, I was always busy, busy, busy and now, I don't know how I can feel as if the day's gone and I've done nothing. It's slowed me down. I can't go, I don't go to the shops, not just because of the COVID. But before COVID, I couldn't go to the shops on my own. My husband drives me everywhere. So, I've stopped driving. Yes. So it's just changed from being a very independent person to someone that relies on others. – ID #9
	I don't feel as healthy, if I'm not exercising. So, I have a bit of a thing that I want to be doing something every day. And on the days when I'm feeling sick from the treatment, I find it psychologically frustrating as well as physically frustrating to not be able to…even go for a walk or have the strength to do anything like that. So, exercise has been part of my daily routine for a very long time. So I think it's…the change of lifestyle as much as how your body feels for not doing exercise. – ID #11
1.2 Increased Awareness of Illness	Well, it's hard to gauge, you know, where the disease starts and stops. You know, where it's just constant and symptoms. – ID #3
	It's like, it's like a bit of a black spot, you know… you can't do something that you want to do. And you know what the feelings are when you're able to do a particular exercise for a particular period of time, you know how you're gonna feel. But I just know that my system at themoment just wouldn't handle what I would do. Mentally, I think it wears on you and…then you keep saying to yourself, "Well, I wonder whether I'm ever gonna go back to what I had?" – ID #4
2. Exercise Offers Hope	
2.1 Reclaiming Control	I want to do stuff. I want to get myself as fit as I can and…not die just yet. – ID #10
	I'd like to maintain at least my level of activity that I have now. I don't want it to deteriorate anymore. I would like… for as long as I can. I realize that I only, I can do this for a certain length of time. But I want to try and keep going as long as I can. – ID #7
2.2 Cancer and Treatment-specific Benefits	I think it's important just to kind of keep your physical health at a point, at a good point where you can actually deal with side effects. So, I mean… immunotherapy is my first…treatment that I've experienced. So, I haven't done chemo. I haven't done any other ones. So, my, in my mind, it's like… I want to prepare myself for possible change in treatment, different side effects. I mean, your body, medication and your body sometimes is just unpredictable. So, my, my idea is just more to prepare myself, but also feel like I'm contributing to my own health. – ID #2
	No, I think it's totally important to have exercise because it's getting all the chemo around you, your cells and your body through, through your blood. And but also, it's not wasting your muscles away. And, and, and especially my bone density, density and my, and all my bones need strengthening…so it's really important. – ID #19
2.3 An Emotional Outlet	So getting out there and doing a bit of exercise takes your mind off, off your diagnosis as well. And if it makes you feel better, well, naturally, your body's gonna start feeling better as well, you know? – ID #14
	Well, well, [exercise], it lifts my mood. It, it levels me out. It levels things out. It makes me clearer. I can think clearer. – ID #1
3. Exercise Barriers are Multifaceted	
3.1 Symptoms are Burdensome	For a while there, it was sort of difficult, just because of not having muscle mass and just also at the moment, because of the breathing. It's a bit of an issue because breathing isn't as good as it used to be. So, I'm aware of my breathing and then I get sort of, if I exert myself really quickly, I can't breathe. – ID #8
	You know you tell yourself, I want to go for that walk. But you certainly cannot actually get yourself out of bed. It's the strangest feeling…kind of, it's just weird. Sort of, it's sort of almost…something to do with your will to get up and do it. You can't will yourself. I don't know if it's because of the tiredness because it messes with all the things in your body, and your brain. I don't know, I don't know what it is, but it's weird. – ID #20
3.2 Safety Concerns Reduce Confidence	I'm just worried that I'll be damaging the spine. That's the only thing, I think. Whether I'll get another crushed vertebrae… because I don't know why. – ID #16
	The exercise, I sometimes get a bit paranoid about whether it's the stiffness that I'm getting, because I'm not using [those] muscles…Yeah, so that's where I've got to sort of weigh out whether it is pain from building my muscles up again or whether it's pain from the fractures or, you know, my bones. I suppose I am a bit, bit worried, conscious of all that, because they're the, the tumors are in all my bones. – ID #19

Table 3 (continued)

Themes and Subthemes	Representative Quotes
3.3 Having Cancer in a Pandemic	Because of the COVID, I haven't been anywhere. I haven't been out. – ID #7
	Um, I don't think this, this lockdown thing helps at the moment, you know, because you can't see anybody, you can't really go. You know, I would, you know, my daughter would come and take me and she'd make me go for walks and things like that. – ID #6
3.4 Lack of Personalized Exercise Advice and Services	I think they may have responded to a question I asked about, "Is [exercise] okay?" But it has never been offered as a strategy to use to alleviate some of the symptoms I've experienced. – ID #11
	I think one of the frustrations I've been having is that these programs or physiotherapy, or going to the gym… there's no structure or continuity to them. I can't really track so much my progress or create milestones. There's no one really accompanying my physical rehabilitation. It's all just there's some exercise here, some exercise there, and you know, wish for the best sort of thing. – ID #13
3.5 External Factors	And having a one-on-one, like having a personal trainer, I would say financially because I don't work, and I don't have a pension. So, you know, it's just money out of your own savings, really. – ID #9
4. Exercise Access and Support are Important	
4.1 Professional Supervision and Structure are Valued	Oh, I know that [exercise] would be something that would be beneficial. And I've often thought, geez, maybe I would exercise if I could just do it one-on-one with someone. And if like, they could help me build myself up slowly, rather than…every time you see people exercising, [they're] just like going at 100 miles an hour and it's like, well, that's not…what I could manage. Anyway, I would need someone who could slowly help me get to a better point. – ID #8
	"Well, [an exercise] program motivates me, a specific program." – ID #1
4.2 Social Support is Motivating	I'm probably more motivated with the people around me doing it as well. Whereas, if I'm on my own, you don't need to do it. – ID #6
4.3 Access to Facilitate Exercise	But if you're going through chemo, traveling is a big thing. You want things nearby…It's got to be accessible because if you 're sick and you sleep half of the day, your only window is say, the afternoon. What are you going to do? You want to maximize the time you have to feel that… you have achieved something for the day as well. – ID #20

"So, I was still able to do normal things back then. This one... hit me a lot harder with the weight, I guess. Because with the liver, it's always different when it comes with the liver." – ID #15

The increase in cancer symptoms could be a constant or prominent reminder of one's deteriorating health. One participant discussed noticing their skeletal muscle mass declining and how this seemed to correlate with feeling more fatigued and breathless. The change in symptom burden increased their awareness of being ill. They said:

"It wasn't that long ago that I was asymptomatic and now, I'm symptomatic. So, you know, it does… sort of make you think…there is something going on inside me…you feel different... you're more conscious of the fact that…you are ill." – ID #18

Theme 2: Exercise offers hope

Regardless of each participant's current individual level of physical activity, exercise was commonly perceived as beneficial for one's health and wellbeing. For participants who were currently exercising, exercise participation was associated with feelings of accomplishment and pride. For participants who were less physically active, there was a divide between people who felt they were simply "not up to it" and those who were open to exercising more because they believed exercise was something they could do to help themselves. Indeed, exercise was often perceived as a possible antidote to some of the disruption or turmoil in participants' lives that had been caused by their cancer. Taking part in exercise, or even perhaps the act of discussing exercise, kindled a level of hope.

Theme 2.1: Reclaiming control

Some participants discussed utilizing exercise as a current or potential tool to reclaim control in their lives. Exercise was perceived as something participants could do to actively contribute to their physical and psychological health in a time when their health could largely feel beyond control.

"For me, [exercise is] really important to have some control over my life." – ID #11.

Interestingly, for one participant who described never regularly exercising prior to their cancer (ID #2), they now believed exercise to be part of their "survival mode." Their diagnosis was described as a "life-changing moment" and presented them with an opportunity to reflect on what they could do for themselves to take back some control over their health. From a psychological perspective, participating in exercise could be empowering. One participant (ID #5) described how exercise was their "personal stand" against their diagnosis and a way to reclaim control over their psychological wellbeing.

> *"I don't want to think the cancer is beating me." – ID #5*

From a physical standpoint, exercise often presented as a positive opportunity for goal setting, including sustaining one's physical function or capacity to live life more meaningfully by being able to still "do stuff." While cancer and its treatment could strip away one's strength, for example, exercise was a perceived strategy to try to regain what had been lost or prevent further physical deconditioning. Further, for participants who were maintaining a higher level of physical activity, they saw staying physically active or exercising as a personal responsibility.

> *"If you don't do it, you lose it." – ID #19*

Theme 2.2: Cancer- and treatment-specific benefits

The prospect of exercise acting as a supportive care strategy to better manage one's cancer diagnosis was often a source of motivation. Particularly among participants who were maintaining some level of physical activity, exercise was identified as a strategy to alleviate common cancer symptoms. A few participants made comments about how exercise, often walking outside, could improve symptoms, such as fatigue, nausea, and appetite loss. While less tangible, a handful of other participants also discussed their hope for exercise to improve their treatment tolerance, treatment efficacy and even their prognosis.

> *"I think [exercise], well, I'm hoping, it's going to help you improve, get better results for your tests. I know mine's incurable…but it might extend time." – ID #9*

Most participants were not familiar with the term cachexia or elements of the syndrome. Yet, several commonly described their belief that exercise may address some of the adverse effects of their cachexia, including regaining muscular strength. No participants expressed significant concerns about exercise exacerbating weight loss. Some mentioned that exercise was once a strategy to lose weight prior to their cachexia and reflected on how their exercise goals had shifted towards maintaining strength and physical function and away from losing weight. One participant (ID #18) highlighted their hope for exercise, including resistance exercise training, to help manage or reverse their weight loss. In a few cases, the physical health, cancer, and treatment-specific benefits of exercise were reinforced by healthcare providers through discussions or direct referrals to cancer exercise professionals, including exercise physiologists or physical therapists. Medical advice to exercise and encouragement from healthcare providers could be a source of motivation for some participants.

> *"The surgeon who originally diagnosed me, he said, 'Get to a gym right now and start building your muscle strength.' So, I did." – ID #12*

Theme 2.3: An emotional outlet

Exercise was viewed as a tactic to relieve psychological distress and improve mental and emotional wellbeing. Some of the positive mental benefits of exercise that were described included exercise's ability to help participants maintain a positive outlook or as one participant phrased (ID #15), "it puts you in a better place." Similarly, another participant (ID #14) described how sitting around and doing nothing at home could make them "dwell on the situation a bit more." A common talking point included how one's diagnosis, and the underlying uncertainty for the future, had the potential to make participants feel like a "victim" or "down in the dumps." Exercise was thus seen as an important way to overcome negative feelings by improving one's train of thought or allowing participants to feel more like their "normal selves."

> *"I think [exercise] gives you more confidence in yourself." – ID #12*

Spending time exercising outside, with others, or simply away from home was also believed to reduce the feeling of being confined by one's cancer or could act as a positive distraction. Exercise was perceived as a positive opportunity to reflect and gain perspective.

> *"[Exercise can be] a really good…mental break from home…and then you see…there's a bigger world out there than…what you're going through." – ID #2*

Theme 3: Exercise barriers are multifaceted

Each participant described struggling with multiple, complex exercise barriers that directly related to or were often exacerbated by their current cancer diagnosis. Challenges and frustrations with not feeling well enough to exercise, despite wanting to exercise or acknowledging the importance of exercise, were expressed. Multifaceted exercise barriers prevented participants from experiencing the full extent of the physical and psychosocial benefits that they perceived exercise could offer. Exercise barriers appeared to hinder the frequency, type, duration, and intensity of exercise as well as apparent exercise self-efficacy.

Theme 3.1: Symptoms are burdensome

Cancer and treatment-related symptoms were wide-ranging, debilitating, and common across all participants. Most participants dealt with several concurrent symptoms, such as fatigue, gastrointestinal symptoms, shortness of breath, and pain, that interfered with exercise motivation and perceived physical capacity for exercise.

> *"Well, if you're in one of those troughs of fatigue, then you don't feel like exercising at all." – ID #10*

Many participants discussed having to self-manage their symptoms by reducing their exercise to avoid over-exerting themselves. Some discussed needing to adjust the timing and duration of exercise during periods where symptoms felt worse. While several participants understood that exercise could improve some of their symptoms, many still struggled with motivation to exercise when they were feeling particularly unwell. Further, when participants' awareness of the possible role that exercise could play in symptom management was lower, symptoms appeared to be a larger exercise barrier. In these instances, participants felt they would only be able to start exercising, if their symptoms were to significantly improve. As one participant struggling with fatigue and breathlessness stated:

> *"If my physical situation improves, I will be a bit more active. It's as simple as that." – ID #3*

Theme 3.2: Safety concerns reduce confidence

Several participants raised exercise safety concerns relating to their existing cancer diagnosis or additional comorbidities. Particularly among older participants and one participant with brain cancer, there were balance concerns and a fear of falls. Two participants (ID #9 and ID #16) occasionally used mobility aids (i.e., cane and four-wheeled walker, respectively) outside of the home or for exercise, such as short walks. Specific fears about performing activities around the house (e.g., showering) among those with balance concerns were also discussed and this translated into some fears about performing specific movements while exercising. One participant expressed how a previous fall scared them and reduced their confidence:

> *"I think it scared, the fall, definitely scared me. I didn't realize and then I had a couple of falls, like, in the bathroom…and it scared me." – ID #7*

Other exercise safety concerns included the perceived risk of bone fractures or exacerbated pain with increased bone fragility and the presence of bone metastasis. In addition, participants with greater comorbidities, such as cardiovascular disease or osteoarthritis, also expressed concerns about exercise exacerbating their conditions. Most safety concerns resulted in fear or reduced confidence exercising alone. Moreover, others were hesitant about stepping into traditional fitness centers, where the exercise options may not be tailored to participants' baseline health status and therefore, be potentially unsafe.

> *"I don't think in a lot of cases [fitness centers] are fitting to people who have got different conditions." – ID #4*

Theme 3.3: Having cancer in a pandemic

The COVID-19 pandemic and associated public health restrictions greatly reduced opportunities for exercise. City or state-wide lockdowns often prevented participants from leaving home. For some, this meant current exercise opportunities had been eliminated. One participant (ID #1) discussed how their regular yoga class was cancelled during lockdown and they were not motivated to seek out online classes or services. For others, being forced to spend more time at home decreased physical activity motivation entirely. The pandemic reinforced or normalized sedentary behavior, as staying at home was perceived to be the "right thing to do." Participants also expressed a fear of contracting the COVID-19 virus, particularly given their immunocompromised status. One participant described how the fear of becoming ill with COVID-19 influenced their willingness to visit public spaces, including fitness centers:

> *"It's just COVID's changed everything…I'm just paranoid about going in with people around and [it's] changed my whole mindset of going into a gym." – ID #19*

Theme 3.4: Lack of personalized exercise advice and services

A disappointment towards a lack of personalized or cancer-specific exercise advice and services as a part of their standard care was expressed strongly by a handful of participants. Many also assumed their healthcare providers were aware of their current level of physical activity, without ever having discussed it in detail. Another participant discussed having to take initiative to ask their healthcare provider about exercise services, which did eventually lead to a referral to an exercise physiologist:

> *"Nobody really said anything. It was, it was actually me that brought [exercise] up because I said that I'd lost so much weight and I've lost all my muscle tone." – ID #14*

In other cases, participants reported asking specific questions about exercise but felt discussions with healthcare providers were too brief or generic. The lack of recommendations led to frustration, particularly among participants who were motivated to exercise but were perhaps struggling with a lack of knowledge about what exercise to do and how to do it safely. Participants discussed receiving little feedback or vague statements from their treating healthcare providers, such as "do what you're comfortable with."

> *"You get, you get very little back from them. It's disappointing, to be honest." – ID #10*

Theme 3.5: External factors

Weather, finances, and family responsibilities also interfered with participants' ability to exercise or willingness to seek out exercise services. Notably, symptoms, balance concerns, or functional limitations associated with one's cancer diagnosis or comorbidities could exacerbate the extent to which common external factors interfered with exercise participation. While bad weather may have been an exercise barrier prior to some participants' cancer diagnosis, additional safety concerns associated with exercising outside, such as rain and slippery footpaths, now amplified the extent to which bad weather might restrict their exercise. Furthermore, physical deconditioning also meant that some participants could no longer drive or confidently use public transportation. Thus, the time and effort needed to arrange transportation (e.g., arranging for a carer to drive them somewhere) made attending regular in-person exercise appointments impractical.

> *"I still depend on [my spouse] to take me around to places. So, it's not like I could just get to the gym by my own." – ID #13*

Theme 4: Exercise access and support are important

Exercise preferences differed between participants and were frequently based on past physical activities and experience. Participants often went back and forth between describing their exercise preferences *prior* to their cancer diagnosis and then reflecting on how they were no longer able to do what they previously could. Existing exercise preferences tended to be heavily entwined with confidence in current physical abilities, but also convenience. Many participants described walking as their main form of exercise, as it aligned with their current physical capacity and was accessible. To improve physical activity levels and allow participants to reap greater benefits from exercise, several factors were perceived to help overcome common exercise barriers. Specifically, participants described the importance of engaging in structured exercise programs, receiving supervision from exercise professionals, having social support to stay motivated, and selecting convenient exercise settings.

Theme 4.1: Professional supervision and structure are valued

Access to both professional supervision and programmed or "structured" exercise was perceived as necessary to safely exercise and maintain exercise motivation. Participants discussed the importance of working with an exercise professional who had an awareness of their medical history and could prescribe personalized exercise that felt safe and tolerable. For some participants who felt weak or physically deconditioned, they discussed wanting reassurance from an exercise professional that the exercise would not feel too challenging and strenuous. Other participants felt professional supervision would also help overcome safety concerns, such as concerns regarding musculoskeletal injuries or fractures due to the presence of bone metastasis.

> *"So just I think the concern was that I'm not doing it properly. That's why I probably would want somebody there to say, 'Oh, you know, you should be doing this.'" – ID #16*

Several participants also emphasized the importance of setting an exercise routine to keep them motivated, accountable, and to ultimately, establish behavior change long-term.

> *"I think sometimes when… you're scheduled to turn up type of thing, you can't back out." – ID #10*

Setting a fixed exercise routine or committing to an exercise program with some level of supervision (i.e., fully supervised or partially supervised and partially self-guided) could ease the pressure of having to plan the type and timing of ones' own exercise. Some participants had previously engaged in structured and supervised exercise, including prior to the COVID-19 pandemic or prior to their cancer diagnosis, and reflected on the importance of building exercise into their weekly schedule to facilitate exercise adherence. When COVID-19 resulted in the cancellation of one participant's structured exercise program, they mentioned struggling to start exercising again:

> *"I need to get back into the motivation, like, it's there in my mind…I know that I need to do it. It's just, I think, setting a routine." – ID #15*

Theme 4.2: Social support is motivating

Social networks, including friends and family, were perceived as important sources of exercise motivation. One participant (ID #4), for example, discussed how their spouse was a source of encouragement to go for regular walks. Past or current preferences for group-based exercise or exercise that doubled as a social activity were also discussed. Exercising with others for some participants made exercise inherently more enjoyable. One participant (ID #14) also mentioned that walking with a small group rather than on their own could make exercise feel safer, such as in the event they felt breathless and needed a rest. Social and emotional support and a sense of normalcy were also noted as potentially valuable components of opportunities to exercise alongside other people with cancer. When asked if they would prefer to exercise with friends, family, or in a setting with other people with cancer, one participant said:

> *"Other people who have a similar diagnosis because we probably can be all rubbish together." – ID #7*

Most participants had not been offered the opportunity to take part in a cancer-specific group exercise program but expressed an openness to it and reflected on perceived psychosocial benefits. One benefit was the chance to share an experience with other people facing similar challenges.

Theme 4.3: Improved access to facilitate exercise

Participants preferred convenient exercise options and locations. Strategies to increase access to exercise opportunities, including locating exercise facilities closer to home or offering home-based exercise, were believed to facilitate exercising more regularly. One participant (ID #13) mentioned that exercising at home would "allow me to do it more often." Convenient exercise options were perceived to help overcome common external factors that were barriers to exercise, but also could allow participants to make better use of their time and not waste mental and physical energy traveling. When prompted about exercise support offered via telehealth, several participants expressed that its convenience was a clear asset and could be a way to increase the accessibility of supervised exercise.

> *"Well, if [telehealth] makes [exercise] much more available, then it's, that's the greatest benefit." – ID #1*

However, in-person exercise support was often still predicted to be superior in-terms of being physically assessed by an exercise professional, receiving exercise-related feedback, and having access to exercise equipment and space.

> *"I would always prefer face-to-face, if given a choice." – ID #5*

Discussion

The current study sought to understand the perceptions of exercise in a diverse group of patients living with cancer cachexia and advanced or metastatic disease. Participants richly described the impact of their diagnosis, cancer treatment, and cachexia on their current ability to be physically active, which had broad effects on their lives. Despite commonly reporting reductions in physical activity and function, exercise was still viewed as beneficial and appeared to instill feelings of hope. Challenges planning and completing exercise were common. Each participant described unique barriers to exercise, including the considerable burden of their cancer symptoms. To improve exercise participation, participants highlighted the importance of exercise support and access. Support was discussed in the form of (personalized) professional exercise supervision, structured exercise, and socially, via planned group-based exercise or exercising within social networks. Increasing exercise access (e.g., through more convenient exercise opportunities) was also perceived to facilitate exercise.

Current physical activity levels varied between participants. Several participants expressed a reduction in their physical activity, including exercising less often compared to prior to their diagnosis or not currently being able to exercise at all. Physical activity levels typically decrease and remain low following a cancer diagnosis [47] and are low among people with advanced cancer [48] and cancer cachexia [49]. Among 196 outpatients with cancer cachexia who completed surveys, patients reported low levels of physical activity and low exercise self-efficacy, with beliefs that even moderate intensity exercise may be too difficult [49]. Our findings corroborate these data. We found participants' diagnoses and cachexia disrupted their lives on several dimensions, physically, mentally, emotionally, and socially, including their ability to be physically active. Changes in lifestyle and independence were described by participants, leading to an altered sense of self. Moreover, the confronting physical signs and symptoms of cachexia, including diminishing physical function, were perceived as a manifestation of one's illness. Other studies also report that involuntary weight loss, worsening symptoms, or additional signs of disease progression, are a source of distress among people with cancer [14, 50]. The experience of having advanced cancer and cachexia evidently involves physical health changes, but also psychosocial dimensions, including alterations in sense of self and living with an increased awareness of one's illness.

Exercise was often perceived to ignite hope and was recognized as important for physical health and well-being. Hope is a complex and important construct in palliative cancer care and there is a dynamic relationship between hope and coping [51]. Hope has been presented as traversing from "a faint glimmer or glow" to "a spark, flame, or fire" and can change depending on circumstances, such as bad or good news, or symptom progression [52]. We found exercise, or conversations around exercise, may stimulate hope to overcome the disruption to participants' lives that had been caused by their cancer and to focus on positive events and opportunities for the future. Firstly, exercise was described as a way to reclaim control over one's health. A recent qualitative study in men with metastatic prostate cancer reported similar findings among active participants who associated exercise with re-establishing control, for example, by feeling they were participating in their own care [53]. Multiple participants also discussed the hope for exercise to provide cancer- and treatment-related benefits, including improving cancer treatment effectiveness, alleviating symptoms, and extending survival. Another qualitative study in metastatic lung cancer patients also reported that participants expressed that exercise instilled hope for surviving their cancer [31]. Further, we found exercise acted as an emotional outlet and opportunity to take one's mind off their diagnosis. Often, the psychological benefits of exercise seemed more palpable. Participants could associate immediate feelings of improved mood, for example, with a single bout of exercise rather than perhaps physical changes, which may be slower to experience and require participating in regular exercise over a longer period.

Participants did not express explicit concerns about exercise exacerbating their cachexia (i.e., weight loss). Instead, exercise was viewed as a tool to address various dimensions of the cachexia syndrome, including building skeletal muscle mass and strength, improving appetite, and managing weight loss. A prior qualitative study found that one participant with advanced cancer who had experienced 30 kg of body weight loss held concerns about exercise exacerbating their weight loss [33]. Cachexia is a syndrome spanning from pre-cachexia, to cachexia, and then refractory cachexia [1]. Relative to patients with more extensive weight loss (refractory cachexia), rapid disease progression, and an expected survival < 3 months, participants in the current study had earlier phases of cachexia (average weight loss 6%). Most participants were aware of their muscle mass and weight loss and in some cases, had adjusted their attitudes towards exercise as a weight loss strategy. Instead of exercising to lose weight as they might have done previously, exercise was now perceived as a tool to build strength, sustain physical function, and live life more meaningfully.

Several considerable barriers to exercise were identified in our study. Diverse cancer symptoms, including intense fatigue, influenced perceived exercise capacity and motivation. Cancer symptoms are a well-established exercise barrier among people with advanced cancer [32–36, 48] and in patients with cachexia, symptoms occur in greater numbers and with worse severity [29]. Optimizing the medical management of symptoms and educating patients on the direct role exercise might play in improved symptom management, may stimulate patients' interest in exercise. Palliative patients with cancer cachexia who receive multidisciplinary care, including consultation with a palliative care physician, nurse practitioner, dietitian, and physical therapist, report improvements in cancer symptoms, including fatigue, pain, anorexia, and nausea [54]. Such multimodal treatment approaches may be an important first step to manage symptoms prior to prescribing structured exercise, particularly among inactive patients or those with lower exercise motivation. Exercise safety concerns were also a notable barrier, including concerns relating to balance or falls, bone fractures (with bone metastasis), and exacerbating pre-existing musculoskeletal or other comorbid conditions. Particularly among older adults (≥ 65 years), balance concerns, physical limitations, and managing other comorbid conditions may be more prominent exercise barriers [33]. Individually tailored exercise prescription approaches may therefore need to initially include balance training or low intensity exercise to improve patients' confidence in their physical abilities and overcome safety concerns.

Limited in-depth discussions with healthcare providers about exercise was a source of disappointment and potential reason for lower exercise engagement for some participants. A prior qualitative study of patients with advanced lung cancer also reported that conversations about exercise between patients and their healthcare providers were infrequent or too generic [27]. Our participants reported mixed experiences. When healthcare providers discussed exercise or made referrals to exercise-services, this could be motivating, reinforcing patients' positive beliefs about exercise. When discussions were brief or no direct recommendations were provided, participants sometimes expressed feeling frustrated. Healthcare providers acknowledge that exercise is important for people with advanced cancer, although concerns relating to exercise in patients with bone metastases, including an increased risk of fractures, have been noted [45]. The greater health complexities of an advanced cancer diagnosis may interfere with the nature of conversations that healthcare providers have with their patients about exercise. Current information on healthcare provider attitudes towards exercise for cancer cachexia is also more limited. However, elements of the cachexia syndrome, such as involuntary weight loss, may increase clinical concerns about recommending exercise to this patient group and may underpin differences in exercise recommendations provided to patients with and without cachexia.

Multiple significant external factors appeared to influence current exercise habits. The most notable being the COVID-19 pandemic, which not only directly eliminated exercise opportunities during periods of lockdown, but also introduced health and safety concerns. Systematic review evidence suggests the COVID-19 pandemic and subsequent lockdowns in 2020 were associated with significant reductions in physical activity levels and increased sedentary behaviour worldwide, including among adults living with chronic disease [55]. Moreover, COVID-19 has greatly affected the psychological health of people with cancer, including due to fears around contracting COVID-19 and being immunocompromised [56]. We found that such concerns may impact exercise motivation and preferences long-term, including willingness to visit public exercise facilities. Lastly, other external factors, including weather, travel, and cost, were reported exercise barriers and are well-documented barriers among people with cancer [57]. Ongoing and future exercise recommendations and programming should continue to consider external or logistical factors that influence exercise interest and uptake, most notably the possible lasting effects of the COVID-19 pandemic.

To foster regular exercise participation, participants expressed a desire for greater exercise support and access. Professional exercise supervision with a cancer exercise professional was often desired to ensure exercise was safely prescribed, monitored, and progressed. Preferences for establishing an exercise routine or engaging in structured exercise to increase exercise motivation, accountability, and adherence, were also mentioned. Social support, including in the form of group-based exercise, may also increase exercise motivation and inherently make exercise more enjoyable. Patients with advanced cancer who have engaged in professionally supervised, structured exercise interventions with other people with cancer often report positive experiences [58–62]. Indeed, prior research suggests physical activity or exercise interventions among people with cancer can provide opportunities to build relationships and provides a shared experience that is positive [63]. Our findings support that exercise interventions specifically for people with cancer may offer social benefits, as participants discussed their potential to foster social connectedness and create a sense of normalcy. Many participants also concurrently discussed wanting more convenient exercise options, including home-based exercise. Other studies in palliative cancer settings [36, 64], including one study in cancer cachexia [49] report similar patient preferences for home-based exercise and exercise that is lighter intensity. Leisurely walking was the most common type of exercise that was reported among participants in the current study. Thus, while many reported preferences for more structured, supervised exercise, lower intensity exercise that can be completed at home or close to home may be more feasible and tolerable.

Strengths and limitations

The current qualitative study provides novel findings on the perceptions of exercise among patients with advanced cancer with cachexia. Participants were drawn from real-world clinical settings and our sample was diverse in terms of participant sex, age, cancer type and treatments, and physical activity levels, which increases the breadth of our findings. We did not, however, quantify symptoms or performance status, which may limit the transferability of our findings. We also only included patients who could communicate in English and thus, findings may not extend to non-English speaking patients. Our patient sampling may also be vulnerable to selection bias. Patients, for example, with a greater underlying interest in exercise may have been more willing to participate in an exercise research study. However, only two participants declined to be interviewed and the study sample included a balance of both physically active and inactive participants, suggesting our findings are trustworthy. The low decline rate also suggests that even physically inactive participants were willing to discuss their exercise habits and experiences. A further limitation is that we did not perform repeat interviews due to the potential increased burden on participants' time and vulnerable nature of our sample. However, repeat interviews may have provided a richer understanding of participant perspectives and experiences explored in our study.

Directions for future research and clinical implications

Preliminary findings from our study can be used to inform future research studies on the topic of exercise for people with advanced cancer and cachexia. To broaden our understanding of patient perceptions of exercise, further qualitative research on novel concepts we identified may improve our understanding of patient experiences. An example includes further exploration of the meaning of physical function changes and functional-related goals, particularly among participants with established functional impairment. Moreover, what exercise means among palliative and nonpalliative healthcare providers and what role it may have in supporting patients with cancer cachexia has been underexplored and is an important topic for future research studies. A more precise quantitative characterization of symptom burden, physical fitness and function, muscular strength, and body composition (e.g., skeletal muscle mass) coupled with a qualitative research component in a mixed methods study may also add important new knowledge. This study design could improve our understanding of patient experiences as they relate to key physical health metrics with the potential to be modified with exercise. Our findings suggest there are patients with advanced cancer and cachexia who are open to and willing to participate in supervised and structured exercise interventions. Thus, the next crucial steps include building a stronger evidence base to establish the feasibility and efficacy of supervised and structured exercise as either a stand-alone intervention or as a part of a multimodal approach in patients with advanced cancer and cachexia through randomized controlled trials. From a clinical perspective, we encourage healthcare providers to discuss exercise, including its potential benefits, with palliative patients who may have pre-cachexia or cachexia and consider referral to oncology specific exercise services, if accessible and medically suitable. To foster exercise participation, special attention should be paid to symptom burden and current clinical management, as well as addressing underlying safety concerns associated with any functional limitations or comorbid conditions. Exercise intervention design for clinical settings or in future research studies for patients with advanced cancer and cachexia may wish to consider offering structured, supervised and group-based exercise at convenient locations or at patients' home. Combining unsupervised home-based with supervised exercise, which may include incorporating telehealth, may help balance patient exercise preferences that we identified in the current study.

Conclusions

The aim of this qualitative study was to capture the perceptions of exercise among patients with advanced cancer and cachexia. Our findings suggest an advanced cancer diagnosis and the experience of cachexia intensely disrupt patients' lives, including their ability to be physically active. Despite these challenges, exercise could ignite a level of hope in participants to take back control and better manage their health and wellbeing. Barriers to exercise were multifaceted, but included living with burdensome cancer symptoms and the overwhelming impact of the COVID-19 pandemic on exercise opportunities. To facilitate exercise, participants discussed preferences for professionally supervised and structured exercise, social support, and convenient exercise options. Our study findings can be built upon and explored further in future research to improve and refine exercise recommendations and intervention design for patients with advanced cancer and cachexia.

Supplementary Information

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Additional file 1: Table. Initial Coding Framework.

Authors' contributions

K.A.B., M.K. and E.M.Z. conceived of the study idea. K.A.B. and S.M. carried out the formal analysis. K.A.B. drafted the first version of the manuscript. All authors reviewed and edited the manuscript and approved of the final version.

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Availability of data and materials

A portion of the data is presented in Table 3 and the written text within the Results section. Due to the sensitive nature of the interview transcripts, data are not publicly available. Additional information may be made available upon request by contacting the corresponding author.

Declarations

Ethics approval and consent to participate

The study received ethical approval from the Institutional Review Board (or Ethics Committee) of St Vincent's Hospital Melbourne (HREC 251/18). Informed consent was obtained from all subjects and/or their legal guardian(s). All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

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4.3 Chapter Conclusion

Qualitative findings from study two directly support the importance of exercise for people with advanced cancer and cachexia. Indeed, exercise may help to fill an important treatment gap within current cancer cachexia management given it may help overcome the burden of cachexia on both physical health and psychosocial fronts. Results from study two also include crucial information from which to tailor exercise recommendations and future exercise interventions. Findings suggest many patients do have a desire for greater exercise support in the form of professional supervision to overcome safety concerns and maintain exercise motivation and accountability. Social support was also valued by many participants (e.g., having people to exercise with) and could make exercise inherently more enjoyable. Equally, patients desired convenient exercise options, including exercise close to home or home-based options.

Findings from study two suggest that an exercise intervention that is structured, professionally supervised, convenient and includes social support is desired by patients with cancer cachexia and may hold the greatest potential to promote high exercise adherence and thus, intervention efficacy. Despite expressing an interest and desire for structured, supervised exercise options, the feasibility of this type of exercise intervention among patients with advanced cancer and cachexia is unknown. The next logical step thus includes testing the feasibility of an exercise intervention that accommodates the patient-reported exercise preferences identified in study two through an RCT study design. In the third study of the current thesis and following chapter, the feasibility and preliminary efficacy of a structured, supervised exercise intervention tailored for people with advanced cancer and cachexia is investigated.

5 Feasibility of Virtually Supervised Exercise for People with Advanced Cancer and Cachexia: A Phase II Randomised Controlled Trial

5.1 Preamble

There is a need to evaluate the feasibility of exercise interventions in people with advanced cancer and cachexia that 1) accommodate patient-reported exercise preferences and 2) align with evidence-based interventions in exercise oncology. A notable finding from study two (Chapter 4) is that patients with advanced cancer and cachexia desire greater supervision from exercise professionals to support their exercise training. Thus, establishing the feasibility of supervised exercise interventions in patients with advanced cancer and cachexia is a worthwhile endeavour.

Following the onset of the COVID-19 pandemic, delivering supervised, in-person exercise sessions in a safe and comfortable manner to people with cancer became a challenge. Nation- and state-wide lockdowns in Australia (spanning over 250 days in Victoria, Australia between 2020 and 2021) prohibited the delivering of "non-essential" healthcare in-person, which typically included exercise physiology and physiotherapy services. During the pandemic, virtual supervision (i.e., telehealth) emerged as an important tool to safely deliver supervised exercise by remotely supervising participants using internet-based videoconference platforms as they completed exercise from home.

Study three of the current thesis aimed to evaluate the feasibility and preliminary efficacy of a structured, supervised exercise intervention tailored for people with advanced cancer and cachexia in a phase II RCT. The intervention was originally planned as a structured, supervised and in-person exercise intervention, but was rapidly transitioned to a virtual format using a videoconference platform due to the COVID-19 pandemic. In the third study of the current thesis, the virtual exercise intervention is described in detail to illustrate how technology can be utilised to maintain the rigor and fidelity of supervised in-person exercise while maintaining the safety (i.e., reduced risk of COVID-19 exposure) and convenience of home-based exercise throughout the pandemic. The primary aim of the study was to determine the feasibility of supervised exercise in patients with advanced cancer and cachexia, including exercise intervention adherence and intervention satisfaction. The preliminary efficacy of the exercise intervention on physical function and patient reported QOL was also explored.

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5.2 Introduction

Cachexia is a complex wasting syndrome that is highly prevalent among patients with an advanced cancer diagnosis, especially older adults.[2,7] A variable combination of poor nutritional intake and elevated inflammation arising from tumour, host, and cancer treatment interactions are hypothesised to underpin the involuntary body weight loss and muscle wasting observed in patients with cachexia.[6] The rate and severity of body weight loss, the presence of poor nutritional intake, and elevated inflammation (e.g., C-reactive protein (CRP)) are associated with decreased survival in people with cancer.[5,38] Additional adverse effects of cachexia include reduced physical function,[24-31] psychosocial distress,[112-115] and increased cancer symptom burden and reduced quality of life (QOL).[8-23] Cachexia is currently classified along a continuum of three stages: pre-cachexia, cachexia, and refractory cachexia, with refractory cachexia characterised by low performance status, disease that is not responding to treatment, and a life expectancy of < 3 months.[7] An estimated 50-80% of patients with an advanced cancer diagnosis may develop cachexia,[3,4] yet cachexia is frequently underdiagnosed in its earlier stages in current standard cancer care.[1] If cachexia is identified clinically, it is often in the refractory stage, where patients may be markedly emaciated and approaching end of life.

Effective evidence-based treatment and supportive care options for cancer cachexia remain limited. Dietary advice (with or without the provision of oral nutritional supplements) may help to increase nutritional intake and attenuate weight loss or promote weight (re)gain.[49-51] However, dietary interventions alone cannot reverse cachexia and may be less effective as stand-alone interventions on other relevant outcomes, such as skeletal muscle mass and physical function.[49-51] Pharmaceutical interventions for cancer cachexia have also had limited efficacy[46-48] and as a result, no drug treatment has been approved for use in standard care for cachexia management. The collective lack of effective cancer cachexia screening, identification, and treatment options makes cachexia a sizable unmet need for people with cancer.[1] An understudied, yet possibly crucial, component of cancer cachexia treatment plans includes the provision of high-quality exercise-based support.[69] Recommendations regarding exercise for cancer cachexia are conflicting, principally due to the lack of published clinical trials on this topic.[52,53] However, extensive research on the role of exercise in people living with cancer, including emerging evidence in people with advanced or incurable disease, suggests exercise is a feasible and effective strategy to improve patient QOL, cancer symptoms, and physical fitness and function.[64,242,243,249] Thus, investigating the role of exercise as part of supportive care for people with cancer cachexia is a worthwhile endeavour.

Most randomised controlled trial (RCTs) that have delivered exercise interventions to people with cancer have not specifically screened for cachexia and thus, the safety, feasibility and efficacy of exercise in this unique patient group is largely unknown.[239] However, in a recent qualitative study in patients with advanced cancer and suffering from cachexia, many participants expressed distress over the loss of their physical function and independence, and were interested in receiving exercise support to help improve their physical and psychological health and wellbeing.[285] Participants also expressed a desire for greater exercise access (e.g., convenient exercise options) and support (e.g., professional exercise supervision) to overcome exercise barriers, such as travel, to facilitate exercise participation, and to maintain motivation.[285] Utilising technology, such as internet-based videoconference platforms, to deliver a structured, virtually supervised intervention, that allows participants to exercise from home is a possible strategy to bridge patient preferences for supervised exercise that is convenient to access.[254,256] Since the onset of the COVID-19 pandemic, virtually supervised exercise has become a critical option during a time when in-person and group-based exercise has been more unsafe for immunocompromised patients. The primary aim of the current phase II RCT was to investigate the feasibility of a virtually supervised exercise intervention tailored for people with advanced cancer and cachexia. The preliminary efficacy of the exercise intervention was also explored.

5.3 Methods

5.3.1 Study Design

The Advanced Cancer and Cachexia Exercise Trial (ACE Trial) was a two-arm, phase II feasibility RCT (1:1) comparing exercise (EX) with standard (usual) care (UC) in people with advanced cancer and cachexia. Participants randomised to UC were offered an exercise intervention following the main study period. Ethical approval was obtained from the Human Research Ethics Committee (HREC) of St Vincent's Hospital Melbourne (HREC 251/18). The first participant enrolled on June 21, 2019. The study was suspended between March 16, 2020, and July 5, 2020 due to COVID-19 related government restrictions in Melbourne, Australia (including a nation-wide lockdown). Amendments to the study protocol were made during the study suspension period to comply with government public health restrictions and to minimise participant risk of COVID-19 exposure thereafter. Recruitment reopened and continued between July 6, 2020, and Oct 25, 2021. The study was registered prior to commencement with the Australian New Zealand Clinical Trials Registry and all protocol amendments following the start of the COVID-19 pandemic have been fully reported under the trial registration (ACTRN: 12619000426189).

5.3.2 Setting and Participants

Participant eligibility criteria were adults (≥18 years) with metastatic or locally advanced cancer (e.g., unresectable cancer or cancer that has spread to surrounding lymph nodes or tissues), cachexia according to the 2011 international consensus definition (i.e., involuntary body weight loss >5% over the previous six months; or weight loss >2% and body mass index (BMI) <20 kg/m^2)[7], an Australia-modified Karnofsky Performance Status (AKPS) ≥70, and a BMI <30 kg/m^2. Participants were excluded if they had an expected survival of <3 months, were receiving parenteral nutrition or enteral nutrition via a feeding tube, were less than four weeks post-surgery, had full-time reliance on a mobility aid (e.g., wheelchair) for all day-to-day activities, had a contraindication to exercise as determined by a treating medical physician, or were unable to read and speak English. Patients were recruited via convenience sampling, including word-of-mouth or referral directly from a member of their cancer care team, including medical oncologist, palliative medicine physician, or oncology dietitian, from three sites: St. Vincent's Hospital Melbourne, Cabrini Health, and Barwon Health in Victoria, Australia. All interested and referred patients were screened over the phone to determine eligibility. During the telephone screening, patients were also asked if they had seen a registered dietitian for their involuntary weight loss, appetite symptoms, and/or decreased food intake. Consultation with an oncology dietitian was encouraged to ensure nutritional recommendations (including advice regarding increasing total energy and protein intake) were provided to all participants prior to study enrolment. If participants had not seen a dietitian, referral of patients to an oncology dietitian was facilitated by a study team member via their treating medical physician, if patients approved. All participants provided written informed consent to take part.

5.3.3 Randomisation

Participants were randomised to EX or UC after their baseline assessment using a computer-generated list of random numbers. An independent external researcher generated separate lists with a 1:1 ratio in blocks of 4-6 stratified by sex (male or female) and performance status (AKPS >80 or ≤80). The allocation sequence was concealed from the study personnel that were interacting with participants. Given the nature of the intervention, neither participants nor personnel involved with participant assessments and intervention delivery were blinded.

5.3.4 Interventions

5.3.4.1 Exercise Group

Following the COVID-19 pandemic, the original supervised, in-person exercise intervention was rapidly transitioned to a virtually supervised format. Following COVID-19 related amendments to the study protocol, the EX group was offered an 8-week, virtually supervised home-based exercise intervention delivered via an internet-based videoconference platform (Zoom) in lieu of the in-person intervention. The modified virtually supervised intervention was designed to closely match the original in-person intervention. Remote exercise sessions were offered three days per week in one-on-one or small group-based settings and supervised by exercise physiologists or trained university student volunteers in exercise science or exercise physiology. Session duration was approximately 30-45 minutes and included aerobic and resistance-based training using a combination of body weight exercises and resistance bands provided to participants. Aerobic interval exercise was prescribed as 30 sec of aerobic exercise followed by 30 sec of active recovery for 10 intervals from weeks 1-4 and progressed to 30-45 sec/30-45 sec for 10 intervals by week 5. Resistance training included 5-6 exercises for the major upper and lower body groups starting at 2 sets (10-12 reps) using light to medium resistance bands and progressing to 3 sets (10-12 reps) using medium to heavy resistance bands by approximately week 5. A detailed case example to illustrate the types of exercises prescribed, and the nature of exercise individualisation and progression is provided in Table 5.1. Participant rating of perceived exertion (RPE; Borg Scale 6-20)[286] was collected after both aerobic and resistance exercises to assess intensity and progress the exercise components as individually-tolerable. For both aerobic and resistance exercise, if the reported RPE was ≤12, the exercise sessions were progressed (e.g., light resistance band to medium resistance band). Exercise targets were also adjusted to accommodate anticipated fluctuations in participant symptoms (e.g., fatigue or pain) and other injuries or illnesses. The nature of the adjustments (e.g., reduced exercise intensity or type/number of exercises) were based on participant preference and the judgement of the supervising exercise professional. Participants were also provided with and instructed to consume a protein-dense oral nutritional supplement (Whey Protein Isolate, Bulk Nutrients, Tasmania, Australia) following each exercise session. Servings were approximately 30 g total (~26.5 g of protein) combined with 300-400 mL of water. The total length of the intervention (8-weeks) was determined by balancing 1) the hypothesised amount of exercise training needed to modify physical function[287] with, 2) the tendency for patients with advanced cancer and cachexia to experience rapid physical deterioration and declines in health status,[28] which may lead to request to withdrawal.

5.3.4.2 Usual Care Group

The UC group was a waitlist control group. UC participants were not offered the exercise intervention following their baseline assessment and were told to continue with their usual physical activity. After the main study period (8-weeks), UC participants were offered the same exercise intervention as the EX group.

Table 5.1: Virtual Exercise Intervention Prescription – Case Example 1

Baseline Characteristics:

- Demographics: Female, 70-year-old, married
- Cancer Type, Stage, and Treatment: Incurable multiple myeloma, Revlimid therapy
- Previous Cancer Treatment: Autologous hematopoietic stem cell transplant (1 year ago), chemotherapy
- Areas of Bone Disease: Neck, spine, scapula, pelvis, sternum, and ribs
- Body Weight: 57 kg, 5% weight loss in previous six months
- Physical Activity History: Previously active before diagnosis (attended gym 2-3 days/week)
- Current Activity: Short walks outside usually with cane
- Comorbidities/Complaints: Osteoporosis in hip (pain), dizziness, balance concerns, neuropathy in feet, low blood pressure, previous rib fracture

	Aerobic Exercise			Resistance Exercise		
Week	**Example Exercises**	**Time**	**Intensity**	**Example Exercises**	**Sets + Reps**	**Intensity**
1-2	Chair-based: - Punching - Seated Marching - Arm circles - Sit-to-Stand	30 sec/30sec x 10	RPE ≥ 13	- Partial Squats - Calf Raise - Knee Extension - Chest Press - Seated Row - Bicep Curls/Tricep Ext	2 x 10-12	Lower Body: Body Weight Upper Body: Light (Green) Band
3-4	Chair-based + Standing: - Rowing Arms - Standing Marching - Side steps - Sit-to-stand	30 sec/30sec x 10	RPE ≥ 13	- Squats - Calf Raise - Knee Extension - Chest Press - Seated Row - Bicep Curls/Tricep Ext	2 x 12	Lower Body: Body Weight Upper Body: Medium (Blue) Band
5-6	Standing: - Modified Jumping Jack - Squat and Punching - Side Shuffle	30-45 sec/30-45 sec x 10	RPE ≥ 13	- Squat Variations - Calf Raise - Knee Extension - Wall Push-up - Seated Row - Bicep Curls/Tricep Dips	3 x 10	Lower Body: Body Weight Upper Body: Medium (Blue) Band + Body Weight
7-8	Standing: - Modified Jumping Jack - Boxer Shuffle - Marching and Punching	30-45 sec/30-45 sec x 10	RPE ≥ 13	- Partial Lunge - Squat Variations - Single Leg Calf Raise - Wall Push-up - Seated Row - Bicep Curls/Tricep Dips	3 x 10-12	Lower Body: Body Weight Upper Body: Medium (Blue) Band + Body Weight

5.3.5 Outcome Measures

Outcomes were measured at baseline (week 0) and post-intervention (8-weeks). Assessments of physical health measures, including physical function, body composition, and blood draws, were performed in-person. Participants were provided with the option to complete a modified remote assessment (Zoom) during periods of public health restrictions because of the COVID-19 pandemic or based on participant request due to personal safety concerns regarding COVID-19 exposure or an inability to travel to the testing site.

5.3.5.1 Primary Outcome: Feasibility Metrics

Feasibility was determined via recruitment, retention, follow-up, intervention adherence and tolerance, adverse-events, and acceptability metrics. Study recruitment was determined as the number of patients who agreed to take part in the study out of the total number of eligible patients. Study retention was determined by the proportion of participants who completed the full 8-week intervention and did not request withdrawal. Follow-up was determined by the proportion of participants completing both baseline and post-intervention assessments. Intervention adherence included exercise session attendance (percentage of sessions attended out of total offered) and adherence to aerobic and resistance exercise components (percentage of sessions where aerobic and resistance exercise was completed out of total sessions attended). Tolerance to aerobic and resistance exercise components was assessed via self-report using RPE.[286] Adherence to the protein supplementation was collected via participant self-report on a weekly basis. Adverse events deemed related to the exercise intervention were actively monitored throughout the main study period. Adverse events were tracked by study personnel supervising the exercise intervention, including any events that occurred on non-exercise session days. Adverse events are reported using the Common Terminology Criteria for Adverse Events version 5.0. as either grade 1 (asymptomatic or mild symptoms, clinical or diagnostic observations only and/ or intervention not indicated); grade 2 (moderate, minimal, local or non-invasive intervention required and/or limiting age-appropriate activities of daily living); grade 3 (severe or medically significant but not immediately life-threatening, hospitalisation and/or prolongation of hospitalisation indicated, disabling and limiting self-care activities of daily living); grade 4 (life-threatening consequences and urgent intervention indicated), or; grade 5 (death).

5.3.5.2 Intervention Satisfaction

Participants randomised to EX were asked to report their overall satisfaction with the virtually supervised intervention on 12 items on a 7-point scale (1-not at all to 7-very much). Two additional items asked participants if they would continue exercising after the intervention and if they would recommend the intervention (1-extremely unlikely to 7-extremely likely). One additional item asked if they believed the intervention should be offered as standard care (0-strongly oppose to 4-strongly favour) and one additional item asked how they would rate their overall experience (0-poor to 4-excellent). Four open-ended questions were also included to capture participant thoughts on potential intervention benefits, limitations, and areas for improvement.

5.3.5.3 Demographics, Medical Characteristics, and Nutritional Status

Demographic variables including sex, age, and marital status were collected via self-report. Medical information, such as cancer type and stage, cancer treatments, and body weight were also collected via self-report or extracted from patient medical records where available. The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) was administered to capture participant nutritional status. The PG-SGA summarises patient-reported short and long-term changes in body weight, recent food intake, nutritional impact symptoms (e.g., nausea, vomiting, lack of appetite), functional capacity, metabolic demands, and includes a physical assessment.[288] The PG-SGA SF is a condensed version of the PG-SGA that can be completed entirely by the patient as it does not include the physical assessment or metabolic demands components.[289,290] Total point scores for the PG-SGA SF were calculated to determine malnutrition severity.[289]

5.3.5.4 Quality of Life

Patient-reported QOL, functional wellbeing, and symptoms were evaluated using the Medical Outcomes Short Form (SF-36) and the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaires. The SF-36 is a widely-used measure for health-related QOL and contains 36 items across eight subscales, including physical functioning, health-related role limitations, bodily pain, general health perceptions, vitality, social functioning, emotional-related role limitations, and mental health.[291] Raw scores were transformed to scores ranging from 0 to 100, where higher scores indicate better QOL and functioning. The physical and mental health component summary scores were calculated using factor score weighting of the physical functioning, role physical, bodily pain, general health vitality, social functioning, role emotional, and mental health subscales. The FAACT is a modified version of the Funtional Assessment Cancer Therapy – General questionnaire that has been validated to specifically assess anorexia and cachexia symptoms.[292] The FAACT questionnaire includes five main subscales that use a 5-point Likert scale (0-not at all to 4-very much), including physical wellbeing (score range 0-28), social wellbeing (score range 0-28), emotional wellbeing (score range 0-24), functional wellbeing (score range 0-28) and anorexia-cachexia symptoms (score range 0-48). Additional summary scores are also obtained for the trial outcome index (TOI), composed of physical wellbeing, functional wellbeing, and the anorexia-cachexia subscale score (score range 0-104), the FACT-G total score, composed of the four wellbeing subscale scores (score range 0-108), and the FAACT total score, composed of all five subscale scores (score range 0-156). For all scores, higher values are representative of improved wellbeing, symptoms, and QOL.

5.3.5.5 Fatigue

Cancer-related fatigue was evaluated using the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subsacle.[293] The FACT-F subscale contains 13-items to capture the level of tiredness and fatigue using a 5-point scale (0-not at all to 4-very much). Higher scores correspond to a lower burden of fatigue (score range 0-52).

5.3.5.6 Anxiety and Depression

Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS).[294] Individual subscales to assess anxiety and depression each contain seven items (0-no problems to 3-maximum distress). Total scores range from 0 to 21, where higher scores indicate increased anxiety and depression.

5.3.5.7 Physical Activity Levels

Self-reported physical activity levels were captured using a modified version of the Godin Shepard Leisure Time Questionnaire.[295] Participants reported the frequency (i.e., days/week) where they completed mild, moderate, and strenuous aerobic exercise and any resistance exercise training within a usual 7-day period.[295] An aerobic exercise Leisure Score Index was calculated as frequency of mild exercise × 3, frequency of moderate exercise × 5, and frequency of strenuous exercise × 9.[295]

5.3.5.8 Physical Function

Physical function and strength were assessed using the 30 second (s) sit-to-stand test, handgrip dynamometry, and six-minute walk test (6MWT). The 30s sit-to-stand test evaluates the number of sit-to-stand repetitions performed over 30 seconds and is a reliable and valid measure of leg strength in older adults.[296] Handgrip strength (handgrip strength) was measured as the maximum of three repetitions performed using the Jamar dynamometer on both the dominant and non-dominant sides (Sammons Preston, Bolingbrook, IL, USA). The test was performed with arms flexed at a 90º angle and participants were instructed to maximally squeeze the dynamometer for approximately three seconds for each repetition. The 6MWT calculates the total distance walked during a six-minute period and is an estimate of functional capacity.[297] In the event participants completed remote assessments, only the 30s sit-to-stand test was performed. If the 30s sit-to-stand was assessed virtually at baseline, it was also assessed virtually post-intervention.

5.3.5.9 Body Composition

Dual-energy X-ray absorptiometry scans (DXA; GE Lunar iDXA Pro, encore software Version 16, General Electric, Boston, MA, USA) were performed during in-person assessments to assess total lean body mass (kg) and total body fat percentage. Participants fasted for 12 hours overnight prior to presenting for testing.

5.3.5.10 Biochemistry

A fasted blood draw (5 mL serum vacutainers) was collected at in-person assessments to evaluate levels of CRP as an index of inflammation and serum albumin to detect hypoalbuminemia. Blood samples were left for 30 min at room temperature prior to being spun at 1800 *g* for 10 min at 4 ºC and the resulting serum was stored in aliquots at -80 ºC for later analysis. Analysis of CRP and albumin concentrations were performed on thawed serum samples with a COBAS Integra 400 automated biochemistry analyser (Roche Diagnostics, Switzerland).

5.3.6 Statistical Analysis

Descriptive statistics were used to summarise participant baseline characteristics and feasibility metrics and are presented as mean ± standard deviation (SD), median, or totals and percentages. Exercise intervention adherence is reported for all participants who attended at least one exercise session following their baseline assessment and randomisation. A generalised linear mixed model (GLMM) was selected to explore differences between groups and over time for all patient-reported outcomes (SF-36, FAACT, FACIT-F, HADS and Godin Leisure Time questionnaires) and physical function (30s sit-to-stand). Participant was included as a random effect to account for correlations across time. For these analyses, a relationship link function and distribution that resulted in normality of residuals, or that produced the best model fit, was selected for each outcome. Hypothesised differences between groups and within groups were investigated for significant main or group by time interactions using pairwise corrected contrasts (least significant difference). All GLMM results are reported as mean ± standard error (SE) or mean change (Δ) with 95% Confidence Intervals (CI). As our phase II RCT is intended to inform a more definitive phase III RCT, secondary physical function and patient reported outcomes were also interpreted for their clinical significance based on validated cut points for the 30s sit-to-stand test,[298] the SF-36,[291] and FAACT/FACIT-F.[292,299] Descriptive data are presented for the opt-in DXA scans, bloods biochemistry, and additional functional outcomes performed at in-person assessments, given these outcomes were collected in a subset of participants. Participants offered either the in-person intervention (*n* = 3) or virtually supervised intervention (*n* = 11) were included in the analysis, due to the small sample size. SPSS version 28.0 (IBM, Corporation, Armonk, New York) was used to perform the analyses. Due to the small sample size and multiplicity of testing, all P-values should be interpreted with caution.

5.4 Results

5.4.1 Feasibility Metrics and Study Sample

The flow of patients through the study is depicted in Figure 5.1. A total of 104 patients were referred and screened for eligibility. Out of the 69 eligible patients, 30 (43%) were randomised. Being overwhelmed by the cancer or symptom burden and the time commitment of the study were the two most common reasons for declining to participate. The retention rate was 90%. At the 8-week post-assessment timepoint, 26 of 30 (87%) participants completed questionnaires and 25 of 30 (83%) participants completed the physical health measures either via telehealth or in-person. Optional in-person assessments were completed by 16 participants at baseline (n = 11 EX participants, n = 5 UC participants) and 10 participants post-intervention (n = 6 EX participants, n = 4 UC participants). Of the participants who completed baseline assessments in-person but did not complete the post-intervention assessments in-person, n = 3 withdrew, n = 1 died, n = 1 completed the questionnaire only and n = 1 opted for a telehealth assessment in lieu of an in-person assessment. For the participant who completed the questionnaire only, the telehealth assessment was not performed due to cancer symptoms. Study participants' baseline demographics and clinical characteristics are presented in Table 5.2. Sixteen (53%) participants were female, and the average age was 62 ± 13 years. The most common cancer type was gastrointestinal cancer (43%). Most participants had disease deemed to be incurable (87%), with 70% having confirmed metastatic disease and 30% with locally advanced or unresectable cancer. Mean self-reported six-month weight loss prior to study enrolment was 7.5 ± 2.7 %.

Figure 5.1: Flow through Study

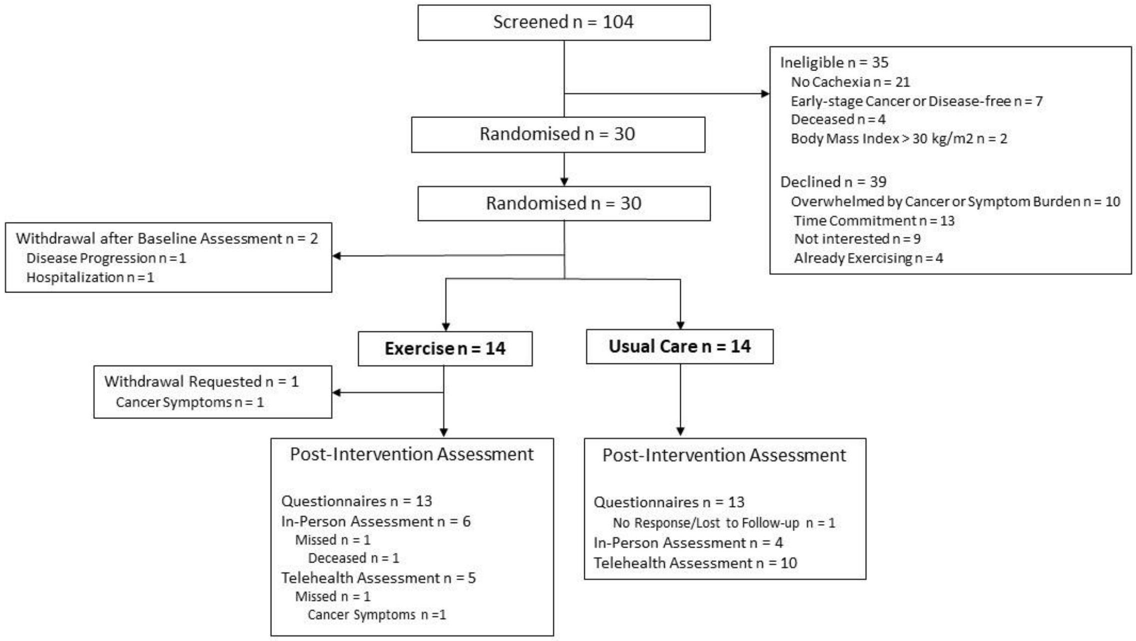


Table 5.2: Participant Baseline Characteristics

Variable	Total (*n* = 30)	Exercise (*n* = 16)	Control (*n* = 14)
Demographics			
Sex (n (%))			
Female	16 (53.3)	7 (43.7)	9 (64.3)
Male	14 (46.7)	9 (56.3)	5 (35.7)
Age (mean ± SD)	62 ± 13	64 ± 13	61 ± 12
Marital Status (n (%))			
Married/Committed Relationship	23 (76.7)	13 (81.3)	10 (71.4)
Widowed	2 (6.7)	1 (6.3)	1 (7.1)
Divorced/Separated	4 (13.3)	2 (12.5)	2 (14.3)
Single	1 (3.3)	0 (0)	1 (7.1)
Education (n (%))			
Highschool Diploma or Below	4 (13.3)	2 (12.5)	2 (14.3)
Vocational Qualification or Diploma	5 (16.7)	3 (18.7)	2 (14.3)
Bachelor's Degree or Above	18 (60.0)	9 (56.3)	9 (64.3)
Unknown/Prefer not to Answer	3 (10.0)	2 (12.5)	1 (7.1)
Employment Status (n (%))			
Paid Employment	9 (30.0)	5 (31.2)	4 (28.6)
Unemployed/Unpaid Leave	4 (13.3)	2 (12.5)	2 (14.3)
Retired	15 (50.0)	7 (43.8)	8 (57.1)
Unknown/Prefer not to Answer	2 (6.7)	2 (12.5)	0 (0)
Clinical Characteristics			
Cancer Type (n (%))			
Gastrointestinal	13 (43.3)	7 (43.8)	6 (42.8)
Lung	3 (10.0)	2 (12.5)	1 (7.1)
Breast	4 (13.3)	3 (18.8)	1 (7.1)
Prostate	2 (6.7)	2 (12.5)	0 (0.0)
Haematological	2 (6.7)	1 (6.2)	1 (7.1)
Gynaecological	2 (6.7)	0 (0)	2 (14.3)
Other	4 (13.3)	1 (6.2)	3 (21.4)
Current Cancer Treatments (n (%))			
Chemotherapy	15 (50.0)	6 (37.5)	9 (64.3)
Immunotherapy	4 (13.3)	2 (33.3)	2 (14.3)
Radiation	2 (6.7)	2 (12.5)	0 (0)
Hormonal or Targeted Therapies	5 (16.7)	3 (33.3)	2 (14.3)
Cancer Stage (n (%))			
Metastatic	21 (70.0)	11 (68.8)	10 (71.4)
Unresectable/Locally Advanced	9 (30.0)	5 (31.2)	4 (28.6)
Presence of Bone Metastasis (n (%))	10 (33.3)	6 (37.5)	4 (28.6)
Cachexia and Nutritional Status (mean ± SD)			
Body Weight (kg)	64.7 ± 11.8	66.0 ± 13.3	63.5 ± 10.3
Body Mass Index (kg/m^2)	22.7 ± 3.3	23.3 ± 3.6	22.0 ± 3.0
Six-month Weight Loss (%)	7.5 ± 2.7	8.1 ± 2.7	6.9 ± 2.5
PG-SGA SF Score	9.3 ± 4.8	9.8 ± 4.4	8.8 ± 5.4
Australia-modified Karnofsky Performance Status			
100	3 (10.0)	1 (6.3)	2 (14.3)
90	12 (40.0)	5 (31.3)	7 (50.0)
80	13 (43.3)	9 (30.0)	4 (28.6)
70	2 (6.7)	1 (6.3)	1 (7.1)

Abbreviations: PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form

5.4.2 Intervention Adherence, Tolerance, and Safety

Sixteen participants were randomised to EX and 14 (88%) commenced the intervention (attended at least one exercise session). Three EX participants enrolled prior to the start of the COVID-19 pandemic and were offered the original in-person exercise intervention. Of these participants, *n* = 2 completed the intervention and *n* = 1 requested withdrawal due to cancer symptoms. For the three participants offered the in-person intervention, attendance was 34 ± 58 %, aerobic exercise adherence was 67 ± 58%, and resistance training adherence was 100%. Exercise tolerability using the Borg RPE scale was 14 ± 1 for both the aerobic exercise and resistance training components (i.e., perceived as ranging between "somewhat hard" and "hard"). For the remaining *n* = 11 who started the virtually supervised intervention, none requested withdrawal. Attendance for the virtually supervised intervention was 82 ± 18%. Of the sessions that were attended, adherence to aerobic exercise was 99 ± 3% and adherence to resistance training was 99 ± 2%. Exercise tolerability was 13 ± 1 for both the aerobic exercise and resistance training components (i.e., perceived as "somewhat hard"). For all participants randomised to the EX group, the protein-dense supplement was consumed 85 ± 26% of the time. Two (14%) participants consumed a modified dose (approximately 50% of the prescribed amount, or half of one standard scoop) for the first half of the intervention to increase tolerability and then consumed the full dose thereafter. Three (21%) participants requested discontinuing the protein-dense supplement within the first four weeks of starting the intervention due to poor tolerability (e.g., nausea). One grade 1 adverse event deemed probably related to the intervention occurred. The adverse event occurred in a participant who reported exacerbated bone pain 2-3 hours following a virtually supervised exercise session. The participant did, however, return to exercise 5 days later with exercise prescription modifications and completed the entire 8-week intervention. No participants requested withdrawal from the study due to adverse events.

5.4.3 Exercise Intervention Satisfaction

Participant satisfaction with the virtually supervised exercise intervention is reported in Table 5.3. Overall, participants felt the intervention met their expectations, was tailored to their needs, and was very beneficial (median: 7, range: 3-7). All participants found the frequency of the intervention, the use of the videoconference platform (Zoom), the types of exercises prescribed, and completing the exercise from home to be acceptable (median: ≥6, range 5-7). Participants reported that the intervention improved both their physical (median: 7, range: 6-7) as well as mental (median: 6, range 3-7) wellbeing. Four participants reported some difficulty consuming the protein (≤3/7), while all other participants found it acceptable (median: 6, range: 1-7). All participants expressed they would continue exercising after the intervention and would be likely to recommend the intervention to other people with cancer (both median: 7, range: 6-7). All participants felt the intervention should be offered as a standard component of cancer care (median: 4, range: 3-4) and rated their overall experience as “very good” or “excellent” (median: 4, range 3-4). Responses to the open-ended questions indicated that overall participants were highly satisfied with the intervention and most reported improvements in physical and mental wellbeing. The convenient format, the individualised exercise prescriptions, and the supervision provided were mentioned most often when participants were asked what they liked best about the intervention. Disappointment in the intervention ending was commonly expressed. Within the open-ended responses, some participants specifically requested for the intervention to be extended in some format, including completing additional follow-up assessments or extending the total duration of the intervention and gradually tapering the weekly frequency of sessions.

Table 5.3: Participant Satisfaction with the Virtually Supervised Exercise Intervention

Intervention Satisfaction Questionnaire Items (Range)	Mean ± SD
1. Did the telehealth exercise program meet your expectations? (1-7)	6.36 ± 1.21
2. Was the telehealth exercise program tailored to your needs? (1-7)	6.64 ± 0.67
3. Was the telehealth exercise program beneficial for you? (1-7)	6.82 ± 0.41
4. Was the frequency of the telehealth exercise sessions (3 per week) acceptable? (1-7)	6.73 ± 0.65
5. Do you believe the telehealth exercise program improved your physical wellbeing? (1-7)	6.91 ± 0.30
6. Do you believe the telehealth exercise program improved your mental wellbeing? (1-7)	5.73 ± 1.42
7. How important was it to you that the telehealth exercise sessions were led by an exercise physiologist? (1-7)	6.64 ± 0.67
8. Did you enjoy exercising at home? (1-7)	6.18 ± 0.87
9. Did you find the telehealth internet platform (Zoom) easy to use? (1-7)	6.82 ± 0.41
10. Did you enjoy completing the band and body weight exercises? (1-7)	6.64 ± 0.67
11. Did you find it acceptable to consume protein after each exercise session? (1-7)	5.0 ± 2.28
12. Will you continue exercising after the exercise program? (1-7)	6.55 ± 0.52
13. Would you recommend the exercise program to other individuals with advanced cancer? (1-7)	6.73 ± 0.47
14. Do you think this telehealth exercise program or other exercise programming should be offered as a standard component of cancer care? (0-4)	3.91 ± 0.30
15. Overall, how would you rate your experience with the telehealth exercise program? (0-4)	3.82 ± 0.41

Open-ended Questions	Most Frequent Reponses	Representative Quotes
16. What, if any, benefits did you receive from participating in the exercise program?	- Improved physical fitness and strength - Something to look forward to - Improved mental wellbeing	"Made me more aware of the importance of exercise and that it can make a difference to my illness." – ID #29
17. Overall, what did you like best about the exercise program?	- Individualisation of exercise - Convenience of remote format - Motivation from exercise physiologists	"[The exercise was] at a pace and intensity that suited me." – ID #20 "Easy to do at home. Easy to access." – ID #13
18. What did you like least about the exercise program?	- Disappointment in program ending	"It was better than I thought. Disappointed the program ended." – ID #11
19. How do you feel we could improve this exercise program in the future?	- Suggestions to extend program length	"Perhaps extend time of program as it has helped me to be stronger again." – ID #18
20. Is there anything else you would like to tell us about the research study?	- Enjoyed participating in the research study - Appreciated encouragement from study staff	"I was very satisfied with the research study. Staff were very professional and encouraging." – ID #28

5.4.4 Secondary Outcomes

Changes in secondary patient-reported outcomes are presented in Table 5.4 and Table 5.5. No statistically significant differences between groups were found for SF-36 outcomes post-intervention (Table 5.4). However, pairwise contrasts revealed a significant within-group improvement in the EX group by the post-intervention timepoint for health-related QOL (general health) (Δ13.1, 95% CI: 5.3 to 20.8, P = 0.001) and bodily pain (Δ16.8, 95% CI: 2.1 to 31.5, P = 0.026). No statistically significant within-group changes were detected for any SF-36 outcomes in the UC group. Within-group changes that met the threshold for clinically meaningful improvements (>3 points) were observed for all SF-36 outcomes in the EX group, except for physical functioning. Only the changes in overall health-related QOL and role emotional subscales met the threshold for a clinically meaningful difference in the UC group.

No statistically significant differences between groups were found for the FAACT outcomes, fatigue, or anxiety and depression (Table 5.5). A statistically significant within-group improvement was found for emotional wellbeing in the EX group by the post-intervention timepoint (Δ1.7, 95% CI: 0.1 to 3.3, P = 0.037). Within-group changes that met the threshold for clinically meaningful improvements were observed in the EX group for the FAACT total score (>7 points) and several additional FAACT outcomes, including anorexia/cachexia symptoms (>3 points) and the FACT-G total score (>4 points). The within-group change in fatigue also met the threshold for a clinically meaningful improvement (>3 points) in the EX group. No statistically significant or clinically meaningful improvements over time were observed for any of the FAACT outcomes or for fatigue in the UC group.

Table 5.4: SF-36 Outcomes

Outcome Measure	Baseline (Mean ± SE)	Post-Intervention (Mean ± SE)	Within Group Change (Mean 95% CI)	Between Group Difference Post-Intervention (Mean 95% CI)	Group*Time Interaction P-value	Main Effect of Time P-value	Main Effect of Group P-value
Physical Functioning							
Exercise	60.3 ± 5.5	60.4 ± 7.3	0.1 (-11.0, 10.8)	5.8 (-15.0, 26.6)	P = 0.732	P = 0.749	P = 0.592
Control	57.1 ± 5.7	54.6 ± 7.4	-2.6 (-13.4, 8.3)				
Role Physical							
Exercise	43.8 ± 5.3	52.0 ± 6.3	8.2 (-5.6, 22.0)	0.8 (-17.1, 18.7)	P = 0.262	P = 0.586	P = 0.483
Control	54.0 ± 5.5	51.2 ± 6.3	-2.9 (-16.7, 11.1)				
Bodily Pain							
Exercise	39.3 ± 5.8	56.1 ± 6.6	**16.8 (2.1, 31.5)***	10.7 (-8.1, 29.5)	**P = 0.035**	P = 0.288	P =0.945
Control	51.0 ± 5.9	45.3 ± 6.6	-5.7 (-20.5, 9.2)				
General Health							
Exercise	28.1 ± 4.4	41.1 ± 5.4	**13.1 (5.3, 20.8)***	0.4 (-15.2, 16.0)	P = 0.078	**P = 0.004**	P = 0.493
Control	37.5 ± 4.6	40.8 ± 5.5	3.3 (-4.5, 11.0)				
Vitality							
Exercise	39.2 ± 4.5	48.5 ± 5.4	9.4 (-0.9, 19.7)	3.7 (-11.7, 19.1)	P = 0.152	P = 0.263	P = 0.802
Control	46.0 ± 4.7	44.8 ± 5.4	-1.2 (-11.5, 9.2)				
Social Functioning							
Exercise	60.0 ± 6.1	64.1 ± 6.7	4.1 (-9.2, 17.4)	4.3 (-14.6, 23.3)	P = 0.802	P = 0.535	P = 0.688
Control	58.0 ± 6.3	59.8 ± 6.7	1.8 (-11.6, 15.1)				
Role Emotional							
Exercise	68.9 ± 6.6	76.8 ± 5.8	7.9 (-4.0, 19.8)	-2.8 (-19.3, 13.7)	P = 0.916	P = 0.083	P = 0.675
Control	72.6 ± 6.8	79.6 ± 5.8	7.0 (-5.0, 19.0)				
Mental Health							
Exercise	69.0 ± 4.3	72.3 ± 4.0	3.3 (-5.1, 11.7)	-3.6 (-14.9, 7.7)	P = 0.566	P = 0.566	P = 0.302
Control	76.1 ± 4.5	75.9 ± 4.0	-0.2 (-8.7, 8.4)				
Physical Health Component							
Exercise	33.4 ± 1.8	37.5 ± 2.6	4.1 (-0.5, 8.7)	3.5 (-3.8, 10.9)	P = 0.070	P = 0.484	P = 0.842
Control	35.8 ± 1.9	34.0 ± 2.6	-1.8 (-6.4, 2.7)				
Mental Health Component							
Exercise	42.6 ± 2.7	46.8 ± 2.4	4.2 (-0.8, 9.1)	-2.1 (-8.7, 4.4)	P = 0.453	P = 0.111	P = 0.504
Control	46.1 ± 2.8	47.6 ± 2.4	1.5 (-3.5, 6.5)				

*Statistically significant improvement over time ($P < 0.05$).

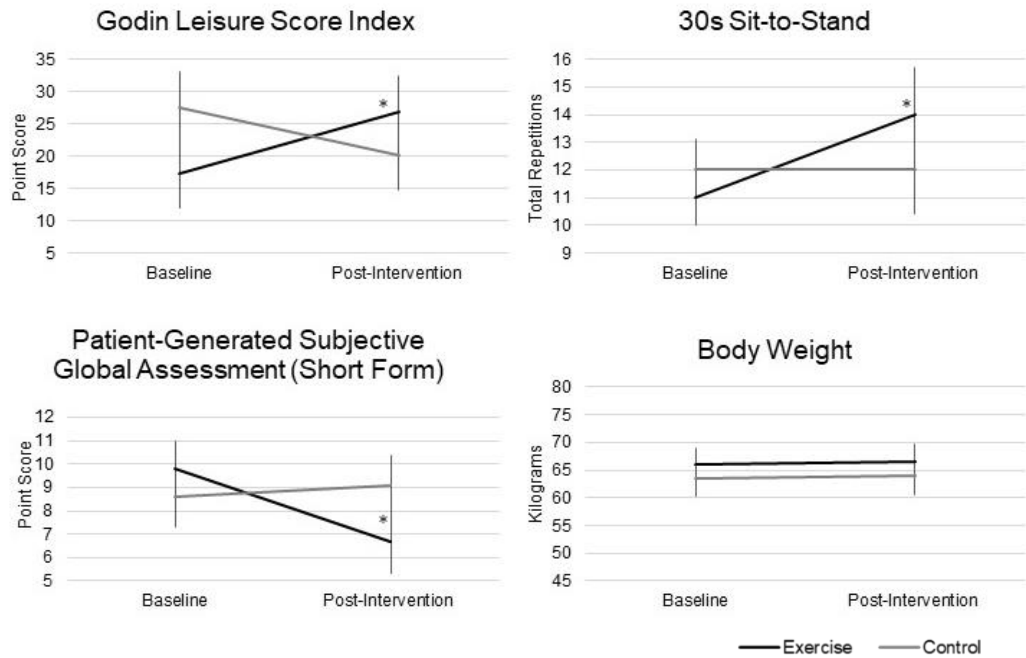
Table 5.5: FAACT, FACIT-F and HADS Outcomes

Outcome Measure	Baseline (Mean ± SE)	Post-Intervention (Mean ± SE)	Within Group Change (Mean 95% CI)	Between Group Difference (Mean 95% CI)	Group*Time Interaction P-value	Main Effect of Time P-value	Main Effect of Group P-value
Physical Wellbeing							
Exercise	18.2 ± 1.1	20.5 ± 1.5	2.2 (-0.5, 5.0)	0.8 (-3.3, 5.0)	P = 0.366	P = 0.157	P = 0.974
Control	19.1 ± 1.1	19.6 ± 1.4	0.5 (-2.2, 3.2)				
Emotional Wellbeing							
Exercise	15.8 ± 1.1	17.5 ± 0.9	**1.7 (0.1, 3.3)***	0.1 (-2.6, 2.7)	P = 0.347	**P = 0.041**	P = 0.735
Control	16.8 ± 1.1	17.4 ± 0.9	0.6 (-0.9, 2.2)				
Functional Wellbeing							
Exercise	13.8 ± 1.1	15.4 ± 1.0	1.6 (-0.4, 3.6)	0.8 (-3.7, 2.0)	P = 0.194	P = 0.352	P = 0.195
Control	16.5 ± 1.2	16.2 ± 1.0	-0.3 (-2.2, 1.7)				
Social Wellbeing							
Exercise	20.0 ± 1.3	20.3 ± 1.2	0.3 (-1.3, 1.8)	-1.9 (-5.4, 1.5)	P = 0.567	P = 0.298	P = 0.345
Control	21.4 ± 1.4	22.2 ± 1.2	0.8 (-0.6, 2.4)				
Trial Outcome Index							
Exercise	63.0 ± 3.3	70.0 ± 3.5	7.0 (-0.3, 14.2)	0.2 (-9.5, 10.0)	P = 0.296	P = 0.094	P = 0.556
Control	67.8 ± 3.4	70.9 ± 3.4	1.6 (-5.5, 8.7)				
FACT-G Total							
Exercise	67.8 ± 3.0	73.6 ± 3.2	5.8 (-0.2, 11.8)	-1.9 (-10.8, 7.0)	P = 0.337	P = 0.075	P = 0.320
Control	73.8 ± 3.2	75.5 ± 3.1	1.7 (-4.1, 7.6)				
Anorexia Cachexia Symptoms							
Exercise	30.6 ± 2.0	34.0 ± 2.1	3.3 (-0.5, 7.0)	0.4 (-5.4, 6.2)	P = 0.479	P = 0.08	P = 0.825
Control	32.2 ± 2.0	33.6 ± 2.0	1.4 (-2.3, 5.1)				
FAACT Total							
Exercise	98.5 ± 4.4	107.4 ± 4.2	8.9 (-0.1, 17.8)	-1.7 (-13.6, 10.1)	P = 0.366	P = 0.059	P = 0.366
Control	105.9 ± 4.6	109.1 ± 4.1	3.2 (-5.6, 12.0)				
Fatigue							
Exercise	30.8 ± 2.1	35.0 ± 2.7	4.2 (-0.5, 8.9)	0.8 (-7.1, 8.6)	P = 0.207	P = 0.217	P = 0.661
Control	34.3 ± 2.2	34.2 ± 2.8	-0.5 (-4.7, 4.6)				
Anxiety							
Exercise	6.0 ± 0.9	5.2 ± 0.9	-0.8 (-1.8, 0.3)	0.6 (-2.0, 3.1)	P = 0.977	**P = 0.044**	P = 0.655
Control	5.4 ± 1.0	4.7 ± 0.9	-0.8 (-1.8, 0.3)				
Depression							
Exercise	6.2 ± 0.9	5.4 ± 0.9	-0.8 (-2.2, 0.7)	-0.6 (-3.2, 2.1)	P = 0.235	P = 0.752	P = 0.971
Control	5.5 ± 0.9	6.0 ± 0.9	0.5 (-1.0, 1.9)				

*Statistically significant improvement over time (P < 0.05).

Results for additional secondary outcomes are shown in Figure 5.2. No significant differences between groups were detected for any secondary outcomes. A statistically significant within-group improvement was detected in the EX group by the post-intervention timepoint for the Godin Leisure Score Index (Δ9.5, 95% CI: 0.6 to 18.4, P = 0.037), 30s sit-to-stand repetitions (Δ3.1, 95% CI: 0.4 to 5.8, P = 0.026), and the PG-SGA SF total score (Δ-3.1, 95% CI: -5.7 to -0.5, P = 0.022). The improvement in the 30s sit-to-stand test among the EX group also met the threshold for a clinically meaningful improvement (>2 repetitions). No statistically significant or clinically meaningful within-group changes were found for the UC group for any of the secondary outcomes (Table 5.6). Body weight remained stable over time in the EX group (Δ0.5, 95% CI: -1.7 to 2.7, P = 0.057) and the UC group (Δ0.4, 95% CI: -1.5 to 2.4, P = 0.057). Subgroup results for the optional functional outcomes, body composition assessment, and blood biochemistry are presented in Table 5.7.

Figure 5.2: Change in Secondary Outcomes: Godin Leisure Score Index, 30s Sit-to-Stand, the Patient-Generated Subjective Global Assessment and Body Weight



Data are presented as mean ± SE. No significant differences between groups.

*Significant change over time in EX participants for (A) Godin Leisure Score Index (P = 0.037), (B) 30s Sit-to-Stand (P = 0.026) and (C) Patient-Generated Subjective Global Assessment (Short Form) (P = 0.022).

Table 5.6: Patient-reported Physical Activity Levels and Physical Function

Outcome Measure	Baseline (Mean ± SE)	Post-Intervention (Mean ± SE)	Within Group Change (Mean 95% CI)	Between Group Difference (Mean 95% CI)	Group*Time Interaction P-value	Main Effect of Time P-value	Main Effect of Group P-value
30s Sit-to-Stand (reps)							
Exercise	10.8 ± 1.0	13.9 ± 1.7	**3.1 (0.4, 6.0)***	2.0 (-2.7, 6.6)	P = 0.058	P = 0.095	P = 0.866
Control	12.1 ± 1.1	12.0 ± 1.6	-0.2 (-2.5, 2.1)				
Godin Leisure Score Index							
Exercise	17.3 ± 5.3	26.8 ± 5.6	**9.5 (0.6, 18.4)***	6.6 (-9.2, 22.3)	**P = 0.009**	P = 0.741	P = 0.793
Control	27.6 ± 5.5	20.2 ± 5.5	-7.4 (-16.0, 1.2)				
Mod-Stren Aerobic Exercise (min/week)							
Exercise	72.0 ± 37.6	132.9 ± 47.5	60.9 (-42.2, 164.0)	73.0 (-59.7, 205.8)	P = 0.101	P = 0.980	P = 0.789
Control	118.9 ± 38.9	59.9 ± 46.0	-59.0 (-159.8, 41.7)				
Resistance Training (min/week)							
Exercise	8.7 ± 13.7	56.4 ± 16.4	**47.8 (5.9, 89.6)***	30.0 (-15.6, 75.6)	P = 0.056	P = 0.200	P = 0.933
Control	36.1 ± 14.1	26.4 ± 15.7	-9.7 (-51.1, 31.8)				

*Statistically significant improvement over time ($P < 0.05$).

Table 5.7: Outcomes from In-Person Assessments (Subgroup Analysis)

Outcome Measure	Baseline (Mean ± SD)	Post-Intervention (Mean ± SD)
6-min Walk Test (m)		
Exercise (n=11)	482.5 ± 114.0	523.4 ± 134.8
Control (n=5)	425.0 ± 101.4	473.3 ± 209.1
Handgrip Strength (kg)		
Exercise (n=11)	29.5 ± 9.3	35.5 ± 9.9
Control (n=5)	26.8 ± 34.4	32.8 ± 3.9
Albumin (g/L)		
Exercise (n = 10)	43.1 ± 4.5	44.3 ± 5.7
Control (n = 4)	46.7 ± 5.0	45.8 ± 4.2
C-reactive Protein (mg/L)		
Exercise (n = 10)	15.8 ± 19.0	4.5 ± 6.5
Control (n= 4)	10.1 ± 9.8	15.2 ± 19.6
Total Body Mass (kg)		
Exercise (n=11)	68.4 ± 14.1	70.2 ± 16.7
Control (n=5)	63.4 ± 13.2	65.0 ± 11.5
Total Lean Body Mass (kg)		
Exercise (n=11)	45.7 ± 9.1	49.1 ± 10.1
Control (n=5)	46.5 ± 10.0	48.5 ± 10.6
Total Bone Mass (kg)		
Exercise (n=11)	28.1 ± 0.9	31.3 ± 0.9
Control (n=5)	24.0 ± 0.5	25.7 ± 0.2
Total Fat Mass (kg)		
Exercise (n=11)	20.0 ± 8.5	19.1 ± 9.4
Control (n=5)	14.7 ± 11.0	16.3 ± 6.1
Total Body Fat (%)		
Exercise (n=11)	29.8 ± 9.5	27.0 ± 9.1
Control (n=5)	23.0 ± 13.5	25.4 ± 9.0

5.5 Discussion

Findings from the current RCT suggest delivering a virtually supervised exercise intervention plus protein supplementation to people with advanced cancer and cachexia is feasible. Our study is unique on a couple of fronts. It is the first, to our knowledge, to evaluate the feasibility of a structured, thrice-weekly exercise training intervention specifically in patients with advanced cancer and cachexia. It also provides preliminary evidence supporting the use of technology to virtually supervise exercise to increase exercise accessibility and convenience among people with advanced cancer. We found both study retention (90%) and adherence to the virtually supervised exercise intervention (>80%) to be excellent. Participants perceived the virtually supervised exercise intervention as tolerable and reported high satisfaction with the intervention format and delivery. Adherence to the protein-dense nutritional supplement was also >80%, although three (20%) participants requested to discontinue the supplementation due to poor tolerability. We did not observe any significant differences between groups in secondary outcomes. However, we did observe significant and clinically meaningful within-group improvements in physical function (30s sit-to-stand repetitions) and patient-reported outcomes, including overall health-related QOL, in the EX group. The observed improvements over time are promising and warrant further investigation.

Exercise can be an important part of supportive cancer care and is recommended for people living with and beyond cancer to positively affect patient-reported QOL, fatigue, and physical fitness (e.g., aerobic fitness and muscular strength).[54,233] While a number of narrative reviews discuss the potential benefits of both aerobic exercise and resistance training for people with cancer cachexia,[70-74] supporting empirical evidence in humans is insufficient. Grande et al. reported in their 2021 systematic review and meta-analysis on exercise for cancer cachexia that no RCTs exclusively enrolled participants who met the criteria for cancer cachexia.[239] Since then, to our knowledge, only one exercise RCT by Kamel et al.[75] has included patients with stage I-IV pancreatic cancer who specifically met the international consensus definition criteria for cachexia (i.e., weight loss >5% over the previous six months).[7] The authors reported that a three-month supervised, in-person resistance exercise training intervention was feasible for pancreatic cancer patients with cachexia and may lead to improvements in lean body mass, muscular strength, and physical function.[75] However, intervention adherence was not reported and most of the included participants had resectable or early-stage cancer and were on average > 1 month post-chemotherapy. Thus, the study's findings pertaining to exercise intervention feasibility and efficacy may not translate to an advanced cancer population with cachexia, where patients may have greater symptom burden and experience greater functional limitations.

The current RCT adds important new knowledge on the feasibility of structured, supervised exercise in patients with cachexia with more advanced or incurable disease. Cachexia is often associated with an advanced cancer diagnosis and occurs in the setting of disease progression.[300] While cachexia exists in patients with early-stage cancer, it is typically reversible once the cancer has successfully been treated.[6] Strategies to support patients living with advanced cancer and cachexia are therefore needed to help manage patient QOL and wellbeing long-term, as they navigate their palliative cancer treatment trajectory and even move towards end-of-life care. Exercise is reportedly safe and feasible in palliative cancer populations.[64,66] However, to our knowledge, the current RCT is one of the first to establish that a virtually supervised exercise intervention is feasible and has the potential to be an important component of supportive advanced cancer care for patients with cachexia.

Conducting exercise RCTs in advanced cancer populations can come with additional challenges, for example, an increased number of patients who may be lost to follow-up due to disease progression. In an RCT of patients with metastatic cancer (*n* = 231), the proportion of patients lost to follow-up was higher among those randomised to a supervised, in-person exercise intervention (35.5%) compared to usual care (22.7%, P = 0.034).[241] Participants with low performance status, lower objectively measured physical function, and decreased patient-reported motivation to exercise were more likely to request withdrawal.[241] In another exercise RCT in patients with advanced, inoperable lung cancer (*n* = 218), 80 patients (36.6%) were lost to follow up.[249] While there were no differences in the number of patients lost to follow-up between those randomised to the supervised, in-person exercise intervention versus usual care, patients were more likely to withdraw if they had lower aerobic capacity, higher depression, and lower QOL.[249]

Patients with advanced cancer experiencing the physical signs and symptoms of cachexia may be more likely to have some of the identified factors associated with exercise dropout among RCTs in patients with advanced cancer, such as reduced physical fitness and function, lower QOL, increased anxiety and depression, and more severe cancer symptoms.[13,17,19] Despite the added challenges experienced by patients with advanced cancer and cachexia, the retention rate in the current RCT (90%) is higher than anticipated and may be for several reasons. The COVID-19 pandemic and associated public health restrictions (e.g., lockdown) resulted in the transition of our original, in-person supervised intervention to a virtually supervised format, which may have increased intervention tolerability and adherence. In an RCT that delivered a home-based exercise intervention with bimonthly telehealth support (with or without pharmaceutical pain medication) to patients with advanced cancer (n = 516), only 3% of participants randomised to the intervention arms requested withdrawal. Thus, there may be important advantages, such as increased convenience, of home-based versus in-person interventions.[243] In the current RCT, participants were also given the option to complete remote study assessments via telehealth appointments at the main study timepoints in lieu of in-person assessments. Remote assessments were offered because of COVID-19 restrictions, but also beyond to accommodate individual participant preferences and safety concerns, such as risk of COVID-19 exposure. The virtually supervised intervention and hybrid approach to participant assessments may have increased the convenience of study participation and ultimately, study feasibility by minimising barriers, such as time, travel, and cost, to attend appointments in-person. Thus, while we originally anticipated the number of patients who would be lost to follow-up to be greater than previous exercise RCTs in patients with advanced cancer who do not have cachexia, various study design features may have resulted in improved retention.

We did note that the top reasons patients declined to participate in the current RCT were feeling overwhelmed by their cancer symptom burden and being unable to make the time commitment. The reasons for declining participation are in line with findings from previous qualitative research that emphasises burdensome cancer symptoms and other external factors (e.g., other commitments) are common exercise barriers in people with cancer cachexia.[285] A less structured exercise prescription approach (e.g., partially supervised) or more gradual exercise frequency progression (i.e., starting at one day per week and increasing to three) may help accommodate patients who are time poor or those with greater symptom burden. Another challenge with delivering structured, supervised exercise interventions can be achieving adequate participant exercise session attendance and adherence to the prescribed intervention components (e.g., exercise duration and intensity) to deliver the intended dose of exercise hypothesised to elicit a training effect. Systematic review evidence of RCTs in people with cancer suggests exercise intervention effectiveness is greater when exercise is delivered in a supervised, in-person training environment,[60-63] as greater intervention support may promote exercise session attendance and adherence to the intervention to improve effectiveness. Home-based interventions (typically unsupervised) may increase participant retention, but tend to produce smaller intervention effects, potentially because participants are left to self-guide their exercise sessions, motivate themselves to exercise regularly, and track their own adherence. Consequently, exercise intervention design must balance what participants may perceive as achievable and tolerable with overall intervention effectiveness.[69] Delivering a home-based intervention to patients with advanced cancer who have cachexia *without* providing adequate interventional support may decrease exercise feasibility and effectiveness. In a phase II feasibility RCT in 46 patients with stage III-IV lung and pancreatic cancer (mean six-month weight loss of approximately 5% at baseline), home-based aerobic and resistance exercise was included as a part of a multimodal intervention.[261] However, only eight (38%) participants randomised to the intervention were able to adhere to >80% of the aerobic and resistance exercise components, highlighting potential adherence challenges with the home-based exercise intervention approach.[261]

Utilising technology to allow exercise professionals to supervise home-based exercise in real-time is a possible tool to improve exercise session attendance and exercise adherence. Technology-mediated interventions may even improve adherence relative to both supervised in-person exercise interventions and unsupervised home-based interventions. Preliminary evidence suggests virtually supervised exercise interventions delivered because of COVID-19 are feasible and effective in people with cancer.[256] In an analysis of data from two RCTs that included survivors of breast and prostate cancer, supervised resistance training interventions were converted to virtual versions (delivered via internet-based videoconference platforms).[301] Feasibility metrics, including retention and intervention adherence, were consistently better for the virtually supervised interventions compared to the in-person version, emphasising significant advantages of this style of exercise intervention design among people with cancer.[301] Notably, in the current RCT, attendance for the virtually supervised intervention was 48% higher than the original in-person intervention. While our sample size is small, adherence challenges with in-person exercise may be an important trend in advanced cancer and cachexia populations to consider in future intervention design. Our participants also reported high satisfaction with the virtually supervised intervention and highlighted that the intervention convenience, access to professional exercise supervision, and individualisation of the exercise prescription components were some of the best features. Given our sample includes a diverse group of higher-risk patients, our intervention adherence results are notably promising and highlight an important direction for exercise intervention design. Incorporating technology to increase the reach of exercise is likely an important consideration for clinical and research interventions to better meet the needs of patients with advanced cancer and cachexia.

In the current RCT, our retention rate, intervention adherence, and participant satisfaction support overall study feasibility. In addition, only one grade 1 adverse event occurred in a participant randomised to the EX group (i.e., patient-reported increase in bone pain) and the participant was able to resume exercising and completed the entire intervention. Our study was not powered to determine intervention efficacy and we did not detect any statistically significantly between-group differences. However, we observed statistically significant and clinically meaningful improvements over time (within-group) in overall health-related QOL, malnutrition severity, and physical function (30s sit-to-stand) in participants randomised to the EX group. We administered two separate questionnaires to provide preliminary data to inform how an advanced cancer and cachexia patient sample compares to the general population (SF-36) and to evaluate cancer and cachexia-specific QOL and symptoms (FAACT). Building on this initial evidence to determine exercise efficacy on key patient-reported and functional outcomes is an important next step for phase III RCTs in people with advanced cancer and cachexia.

We also observed a maintenance in body weight among EX participants over time. A maintenance in body weight is important to highlight, given there may be clinical concerns regarding exercise, particularly aerobic exercise, exacerbating involuntary weight loss. In the current RCT, we ensured participants had seen a dietitian for their weight loss and facilitated referral to a dietitian, if required. Participants were also provided with a protein-dense supplement following each exercise session and we found that most participants were able to consume the supplement (>80% adherence throughout the intervention). Low compliance is often a reported limitation within studies delivering oral nutritional supplements to people with cancer.[49] Our participant tolerance of the supplement was somewhat higher than previous studies. However, we only required participants to consume one serving three days per week following exercise, rather than daily supplementation. In the current RCT, dietetic support and protein supplementation were intended to ensure participants had information about improving energy and protein intake to manage their weight loss and to prevent any nutritional deficits related to exercise. We believe some form of nutritional co-intervention is in the best interest of patients with cancer cachexia and should be considered in exercise studies to offset a negative energy deficit and to facilitate increased muscle protein synthesis to promote skeletal muscle mass and strength gains following exercise.

5.5.1 Limitations

The current RCT has limitations. Participants and assessors were not blinded, although blinding of participants to an exercise intervention is impossible. However, future RCTs could include a stretching or relaxation comparison group to overcome potential issues with various confounders, e.g., increased social support, the provision of health and lifestyle information etc. The RCT design has some risk of contamination of the UC group. However, patient-reported physical activity levels collected among the UC group suggested contamination was minimal and confirmed the difficulty patients with advanced cancer and cachexia have exercising on their own. Furthermore, UC participants were offered the 8-week intervention following the main study period and 13 of the 14 UC participants decided to take part. It is uncertain whether study retention and follow-up would be as high in the current RCT had we not offered patients the opportunity to receive the intervention regardless of their randomisation. We believe our sample size is large enough to inform feasibility, however, it is underpowered to detect intervention efficacy. The small sample size may explain why no between-group differences were observed. Moreover, all within-group changes in secondary outcomes that are reported remain exploratory and should be interpreted cautiously. We also did not include a long-term follow-up assessment. In the future, additional follow-ups can add important information on any potential lasting effects or reversibility of the intervention among participants.

5.6 Conclusions

Our RCT is the first, to our knowledge, to deliver a structured, virtually supervised exercise intervention to people with advanced cancer who suffer from cachexia. Our findings illustrate that patients are willing and able to complete virtually, supervised exercise training and can adhere to and tolerate three aerobic and resistance exercise sessions per week throughout an 8-week intervention period. Participants reported high satisfaction with intervention design and delivery. No significant between-group differences were observed between the EX and UC groups. However, there was a greater number of clinically meaningful improvements in patient-reported outcomes and a larger improvement in the 30s sit-to-stand test among the EX group. Our findings provide important preliminary evidence to support a larger phase III RCT with a focus on exercise interventions for patients with advanced cancer and cachexia.

6 Thesis Summary

The central theme of the current thesis was to investigate the role of exercise as a management strategy for people with cancer cachexia. While the potential role of exercise for cancer cachexia has been the topic of discussion among clinicians and scientists for over a decade,[70-74] current evidence supporting the feasibility and efficacy of exercise-based support tailored for people with cancer cachexia is lacking. Cancer cachexia is a syndrome with high prevalence and high impact, particularly in people with advanced or incurable disease.[2-4] Cachexia has a profound influence on both physical and psychosocial wellbeing in people with advanced cancer and currently remains a significant unmet need for most patients it affects.[1,9] Published guidelines with recommendations for the treatment of cancer cachexia exist, but are principally limited to select short-term use of pharmaceuticals and dietary support with the goal of controlling symptoms, improving appetite, increasing nutritional intake, and promoting weight gain.[52,53] The addition of exercise to cancer cachexia management interventions may aid in targeting additional patient needs, including the improvement of physical function or prevention of functional impairments, which has not been successful with pharmaceutical or dietary interventions alone.[48,49]

Exercise is universally recommended as a component of standard care for the majority of people with cancer,[233-237] as several systematic reviews and meta-analyses of high-quality RCTs have illustrated benefits extending from increased physical function to better cancer symptom control and improved overall QOL.[54,56] However, RCTs to-date that have delivered exercise interventions to people with cancer have largely excluded patients who may have added health complexities, including the cachexia syndrome. As a result, the field of exercise oncology needs to better understand how exercise can be tailored to best support *all* people living with cancer, including more high-risk patient populations. The studies described in the current thesis provide important preliminary information to help fill critical research gaps in the fields of exercise oncology and cancer cachexia research. In the current chapter, study findings, strengths, and limitations from the current thesis are discussed as well as the overall significance of the body of work. The discussion touches on the main themes from the thesis including:

1. The evaluation of a multidisciplinary clinical service for cancer cachexia that includes pharmaceutical, medical, dietary, and exercise-based support.
2. The exploration and description of perceptions of exercise among patients with advanced cancer and cachexia to inform the feasibility of exercise as a meaningful intervention.
3. Establishing the feasibility of virtually supervised exercise that is tailored for people with advanced cancer and cachexia.

6.1 Evaluation of a Multidisciplinary Clinical Service for Cancer Cachexia: A Retrospective Observational Review (Chapter 3)

The first study (Chapter 3) in the current thesis was a retrospective observational review of a novel "real-world" example of a multidisciplinary clinical care service for people with cancer cachexia: The Barwon Health Cachexia and Nutritional Support Service. Multidisciplinary, multimodal care for cancer cachexia is a current research priority, however, empirical data remain limited. The evaluation of existing multidisciplinary clinical services offers an important opportunity to generate practice-based evidence supporting the use of multidisciplinary care and can inform future clinical research to confirm efficacy on this topic. A strength of study one includes the comprehensive description of the Barwon Health Cachexia and Nutritional Support Service multidisciplinary, multimodal approach that includes medical and pharmaceutical management, dietary counselling, and exercise-based support provided by a team of clinicians with expertise in cachexia and palliative care. We found the multidisciplinary clinical service model was associated with significant and clinically meaningful improvements in several domains of QOL and cancer symptoms, including fatigue, pain, appetite loss, and nausea/vomiting. Findings also suggest a maintenance or stabilisation of body weight over time among patients who had mean weight loss > 10% in the six months prior to attending the clinical service. Altogether, the Barwon Health Cachexia and Nutritional Support Service may be an innovative service model in cancer cachexia management, particularly to alleviate burdensome cancer symptoms and improve QOL.

No improvements in physical function (handgrip strength and 30s sit-to-stand test) were observed among patients who attended the Barwon Health Cachexia and Nutritional Support Service. The physical function and strength assessment were limited to only two measures (handgrip strength and 30s sit-to-stand test). A more comprehensive battery of tests may better illustrate potential changes in physical function, although the type and number of assessments selected in a clinical setting must balance clinician time, resources, cost, and level of burden imposed on patients. The exercise component of the multidisciplinary clinical service included physical activity counselling and home-based resistance exercises prescribed by a physiotherapist. However, physical activity levels were not monitored throughout patients' time with the clinical service, so it is impossible to discern whether patients increased their physical activity upon receiving physical activity counselling. Tracking patient physical activity levels via self-report or accelerometers can be challenging due to recall bias, accelerometer adherence issues, and the added clinical cost and resources needed for additional data collection and management. Further, it is also unknown whether patients adhered to their home-based resistance exercise programs. The physiotherapist followed up with patients regarding their exercise at each clinical visit, but exercise adherence was not systematically tracked and patient responses about their home-based programs could be vague and varied.

The optimal exercise dose needed to elicit an effect on physical function and muscular strength in patients with advanced cancer and cachexia is unknown. There are specific principles of exercise training, however, that are considered crucial for resistance exercises to be effective, such as progression (increase exercise volume or intensity gradually over time) and overload (prescribe exercise intensity based on patient's baseline physical fitness).[287] However, prescribing home-based exercise that aligns with established principles of exercise training can be more of a challenge in clinical settings. It is thus somewhat uncertain if the prescribed volume of resistance exercises (sets, repetitions, and weight) within the multidisciplinary clinical service was high enough to elicit a training response.

While clinically assessed physical function and strength did not improve in study one, patient-reported physical function did improve. However, it is hypothesised that patient-reported versus objectively assessed physical function may capture different aspects relating to one's functioning. Patient-reported physical function outcomes are more likely to be influenced by psychosocial factors and symptoms, including pain, adaptive coping, and social and emotional function.[302,303] Alternatively, objective measures may more closely relate to functional capacity and ambulatory activity, which remain different, yet important aspects of physical function that relate to morbidity and mortality.[139-146] Physical function is ultimately more than one's own perception of function and remains multidimensional in nature. Consequently, more work to reveal differences in the meaning and clinical relevance of subjective and objective measures of physical function in an advanced cancer and cachexia population is needed.

To our knowledge, there are a handful of other long-standing existing multidisciplinary clinical services for patients with cancer cachexia that include combined pharmaceutical, dietary, and exercise-based support.[264] A few long-standing services are located at the McGill University Health Centre in Canada,[267-270] and the University of Texas M.D. Anderson Cancer Centre[266] and the Pennsylvania Hosptial[265] in the United States. In Australia, funding was also obtained to offer a short-term service based on the McGill University Health Centre model at the Royal Prince Alfred Hospital at the Sydney Cancer Centre in Australia.[304] Data from these services suggest multidisciplinary clinical services for cancer cachexia are associated with improvements in QOL and symptoms among treated patients, while some also highlighted improvements in physical function.[270,304] Among the clinical services with reported improvements in physical function, a more structured, supervised exercise intervention was delivered. Gagnon et al. reported that at the McGill University Health Centre, semi-weekly in-person exercise sessions with a physiotherapist and a home-based exercise plan that focused on aerobic, resistance and flexibility training were offered to 188 patients who enrolled in the multidisciplinary service for cachexia.[270] The service was associated with improvements in the 6MWT distance (MD: 41 m, 95% CI: 29 to 52 m) and maximal gait speed (MD: 0.15 m/s, 95% CI: 0.09 to 021 m/s). The median number of exercise sessions with the physiotherapist was seven and on average patients attended 82 ± 15% of their scheduled exercise sessions.[270] Providing a higher level of exercise interventional support via routine in-person appointments with the service's physiotherapist may have helped to improve overall exercise adherence among patients and therefore, increased exercise effectiveness.

An important caveat with supervised, in-person exercise includes challenges patients with advanced cancer and cachexia may face with exercise adherence and tolerance, including difficulty traveling to and from exercise facilities. Glare et al. reported that aerobic and resistance exercise training was provided to patients at the Royal Prince Alfred Hospital, Australia as a part of the service's short-term multidisciplinary service for cancer cachexia.[304] Exercise was performed as either a supervised program in the outpatient hospital gym or at home with monthly reviews with the physiotherapist. A total of 58 patients were referred to the service during the nine month study period, however, dropout was high.[304] Only 25 patients (43%) completed their follow-up assessments after two months, with only 10 patients (17%) completing their physiotherapy reassessments.[304] Reasons for dropout included participants losing interest in the service, being too busy, or being too unwell. Adherence to the exercise component of the service was not reported, but the low number of patients completing physiotherapy follow-up assessments relative to other follow-up measures suggests patients may have had specific difficulties committing or adhering to the exercise component of the service.

Altogether, findings reported from study one in Chapter 3 suggest that multidisciplinary, multimodal treatment provided by the Barwon Health Cachexia and Nutritional Support Service is associated with statistically significant and clinically meaningful improvements in patient reported QOL and symptoms. It is possible that providing additional exercise support as a part of multidisciplinary clinical service, perhaps through the option of offering more structured and supervised exercise training, may further optimise multimodal treatment effectiveness on additional outcomes, such as physical function. However, with exercise and any other intervention, there is a need to individually tailor treatment approaches so that the intervention matches the specific needs of each patient. For some patients, unsupervised, self-directed home-based exercise advice may be suitable, while others may benefit from having additional options, including professionally supervised exercise. Overall, the evaluation of the Barwon Health Cachexia and Nutritional Support Service provides preliminary insight into exercise delivery in a real-world setting for patients with advanced cancer cachexia. Data from study one of the current thesis combined with existing information on the role of multidisciplinary care for cancer cachexia helps to build a stronger rationale to investigate multidisciplinary care models that incorporate exercise-based support within future research studies.

6.2 Perceptions of Exercise in Patients with Advanced Cancer and Cachexia: A Qualitative Study (Chapter 4)

The aim of the second study (Chapter 4) in the current thesis was to describe the perception of exercise among patients with advanced cancer and cachexia to inform the feasibility of exercise as a meaningful intervention. Findings from study one (Chapter 3) of the current thesis coupled with systematic review evidence of exercise RCTs in people with cancer[61,62] suggest that patients may benefit from having a wider range of exercise options, beyond physical activity counselling and unsupervised home-based exercise interventions. As a critical first step towards understanding the feasibility of exercise in patients with advanced cancer and cachexia, we interviewed patients to gauge their overall level of interest in and willingness to exercise. Specifically, we aimed to capture patients' perceived exercise motivators, barriers, and preferences to inform patient-centred exercise recommendations and intervention design. To our knowledge, study two includes findings from the first qualitative study to explore the perceptions of exercise in people with advanced cancer with cachexia.

Themes identified within the interview data highlighted that participants' current ability to exercise had declined since their advanced cancer diagnosis and onset of cachexia; for many, this was a source of distress and associated with diminished autonomy. Given the signs and symptoms of cachexia are frequently associated with increased symptom burden, including fatigue,[17,19] and declines in physical function and muscular strength,[27,28] the changes in exercise habits that were described by participants were unsurprising. Importantly, we identified that not being able to engage in exercise or take part in other activities, such as social activities, underpinned alterations in participants' sense of self. The experience of having cachexia was also perceived as a visual manifestation of participants' illness, which could exacerbate psychosocial distress.

Despite the challenges participants faced engaging in regular exercise, our data suggests that participants' still perceived exercise positively. Participants believed exercise offered hope to reclaim control over their health and to improve their physical and psychological wellbeing. These data are some of the first to directly emphasise that people with advanced cancer living with cachexia value exercise. The positive attitudes towards exercise described in study two are in line with other qualitative findings among patients with advanced cancer.[258,259,305] We found exercise may provide patients with hope (e.g., something positive to focus on) and helps them to overcome some of the disruption to their lives caused by both their cancer and cachexia. Hope is an important construct within palliative care and has been defined in several ways. Psychological theories describe hope as a positive motivational state that relates to a belief in oneself to set and meet goals.[306] Hope among people with cancer may thus help guide patients towards achieving goals to enhance QOL, even in the face of threat. Chronic diseases, such as cancer, can generate feelings of hopelessness and fear, which may underpin significant distress and a desire to hasten death.[307] Sustaining hope is associated with more effective coping and improved psychosocial wellbeing following a cancer diagnosis.[308,309] Findings from study two highlight that there may be an important relationship between exercise and hope in an advanced cancer setting and further exploration on this topic is worthwhile. Recognising that patients view exercise positively may help to shift clinical and scientific perspectives regarding the value of exercise and encourage exercise-based support to be considered more seriously as a component of cancer cachexia or palliative care management strategies.

Another important theme identified from interviewing participants was that patients experienced complex barriers, such as burdensome cancer symptoms, that hindered their exercise participation and prevented them from realising their perceived benefits of exercise. Participants described being torn between wanting to exercise, but simply not feeling well enough or motivated enough to do so. Complex exercise barriers are commonly reported among people with advanced cancer,[258-260,305] which is substantiated by our data. Cancer cachexia is a syndrome that imposes a significant physical and psychological burden on patients.[8-20] Thus, it is also plausible that living with the cachexia syndrome on top of an advanced cancer diagnosis may increase the extent and severity to which common exercise barriers hinder exercise participation. Importantly, exercise preferences and factors perceived to diminish reported exercise barriers included greater exercise support in the form of structured exercise, professional supervision, social support, and improved exercise access (convenience). Structured exercise, such as regularly scheduled exercise sessions, supervised by a professional with oncology expertise was perceived to help overcome safety concerns around exercise (e.g., fear of falls) and increase exercise motivation. Participants were also often adamant about wanting the exercise to match their current baseline health and physical fitness status and not overestimate their current abilities. Potential social aspects of exercise (e.g., exercise with friends or in group settings) could also facilitate exercise motivation and enjoyment. Particularly during the COVID-19 pandemic, opportunities for exercise with others may have helped to overcome feelings of social isolation.

Importantly, the preferences for structured and supervised exercise need to be balanced with exercise accessibility. Participants discussed wanting convenient exercise options, such as exercise at facilities close to home or home-based exercise (perhaps with routine check-ups with an exercise professional). Offering a structured, supervised exercise intervention that is, for example, based at one exercise facility, is unlikely to overcome external exercise barriers, such as travel, cost, and time. Thus, strategies to increase the flexibility of how structured and supervised exercise is offered to patients should be considered. A possible and noteworthy solution that was discussed with participants included utilising telehealth to virtually supervise patients while they complete exercise from home.[256] Participants expressed the convenience of telehealth and the benefit of technology being able to "bring exercise to them" rather than participants having to travel somewhere for exercise was a significant benefit.

Findings from study two provide important new information highlighting that exercise is meaningful to patients with advanced cancer and cachexia and that many desire greater exercise support and access as a part of their care. Indeed, many patients with advanced cancer and cachexia viewed exercise positively and perceived exercising as an important strategy to foster hope to improve their physical and psychosocial wellbeing, including physical function. The information generated in study two on patient-reported exercise motivators, barriers, and preferences can also help optimise the provision of exercise-based support for patients with advanced cancer and cachexia to promote uptake, adherence, and effectiveness. It is imperative that exercise interventions with the goal of improving patient QOL and overall health are designed with consumer input to ensure interventions are meaningful and patient needs, and preferences are at the forefront.

6.3 Feasibility of Virtually Supervised Exercise in People with Advanced Cancer and Cachexia: A Phase II Randomised Controlled Trial (Chapter 5)

The third and final study (Chapter 5) builds upon key findings described in the first two studies of the current thesis. Results from study one (Chapter 3) suggest there may be a need to provide additional exercise opportunities beyond physical activity counselling and home-based exercises as a component of multidisciplinary cancer cachexia care to modify patient physical function. Results from study two (Chapter 4) emphasised that patients with advanced cancer and cachexia value exercise and express a desire to receive greater exercise support (e.g., professional supervision) and access (e.g., convenient exercise options) to facilitate their exercise. Thus, in a third study, a phase II RCT was designed to directly evaluate the feasibility of a structured, supervised, but convenient exercise intervention tailored for patients with advanced cancer and cachexia. The study was designed in line with the rationale that supervised exercise interventions are more effective at improving patient outcomes, including physical function, relative to unsupervised, home-based, or self-guided exercise (as prescribed in study one). To our knowledge, the RCT presented in Chapter 5 is the first to directly test the feasibility of a structured, supervised exercise intervention in patients with advanced cancer and cachexia.

In line with our hypothesis, we found that an 8-week supervised exercise intervention was safe and feasible among patients with advanced cancer and cachexia. Recruitment rate was 43%, trial retention rate was 90%, and follow-up was 87%. The format of the exercise intervention attempted to balance key patient exercise preferences. The intervention was novel in that because of unanticipated public health restrictions due to the COVID-19 pandemic, it was converted to a virtually supervised format using an internet-based videoconference platform (Zoom). Adherence to the virtually supervised exercise intervention was high, with exercise session attendance exceeding 80%. Participants also reported that both the aerobic and resistance exercise training was tolerable (RPE $\geq$ 13) and reported high satisfaction with the virtually supervised format of the exercise intervention.

For each participant randomised to the EX group in study three, aerobic and resistance exercise training was completed. Yet, the types of exercises prescribed were individually tailored to accommodate the presence of any functional limitations (such as balance concerns), comorbid conditions, pain, the onset or fluctuations in cancer symptoms or treatment side effects, as well as patient preferences. Consequently, some participants completed most exercises seated in a chair, for example, to overcome pain due to the presence of bone metastasis. Other participants with higher functional status and fewer reported symptoms (e.g., less pain), were able to complete higher intensity exercises, such as aerobic exercises that involved higher impact (e.g., jumping jacks or squat jumps). The goal for each participant was to maintain an RPE ≥13 for each exercise session. The individualisation of the exercise prescription was in line with exercise preferences that were captured study two (Chapter 4) of the current thesis. Exercise individualisation was also commonly reported as an element of the intervention that participants liked best in their open-ended responses in the intervention satisfaction questionnaire. Exercise prescription individualisation may play an important role in increasing patients' confidence and enjoyment while exercising. The individualised nature of the intervention in study three thus may have facilitated intervention tolerability, exercise adherence, and patient-reported intervention satisfaction.

The exercise intervention in study three was also converted to a virtually supervised format to allow participants to exercise from home during the COVID-19 pandemic. The revised intervention still maintained a high-level of supervision, so that all exercises were monitored in real-time by exercise professionals. Incorporating technology to virtually supervise exercise (i.e., telehealth) has notable advantages, including providing a hygienic space for exercise, eliminating the need to wear masks, and removing travel barriers to and from exercise facilities. At the same time, virtual supervision allows patients to still receive professional instruction and monitoring to increase patient accountability to attend sessions, promote adherence to the prescribed exercise targets (e.g., exercise duration and intensity), and to overcome certain safety concerns regarding appropriate exercise form. Telehealth may also have greater clinical applicability given the potential for reduced resources and cost, and improved ability to reach regional patients. Possible challenges of telehealth and virtually supervised exercise, however, include reduced access to higher quality gym-based exercise equipment, limited space at home, inability to fully assess patients, and difficulty monitoring aspects of exercise safety, particularly patient exercise responses (i.e., heart rate, blood pressure etc.) and providing “hands-on” movement-related feedback. An additional notable roadblock to telehealth uptake includes the “digital divide,” whereby structural barriers may limit access to telehealth in places where it may be most needed (e.g., rural areas).[310] Restricted access to internet connectivity and technological devices are important limitations, particularly among individuals of lower socioeconomic status. The digital divide is a social determinant of health and there is a need to fully examine complex factors which may influence successful adoption of telehealth to maximise its impact. Data on the use of virtually supervised exercise interventions in oncology is only beginning to emerge following the increased uptake of telehealth after the onset of the COVID-19 pandemic and thus, information on safety, feasibility, and efficacy is limited.[256] Utilising technology that allows participants and exercise professionals to virtually communicate “face-to-face” may offer important advantages to deliver home-based exercise, however, more data on facilitators and barriers to telehealth exercise service delivery in oncology are needed.

While our RCT was not powered to determine exercise efficacy, the preliminary efficacy of secondary outcomes was explored to inform future research. No significant between group differences in secondary patient-reported or physical function outcomes were found. However, significant within-group changes in EX participants in overall health-related QoL, bodily pain, emotional wellbeing, and malnutrition severity (PG-SGA SF total score) were detected upon completing the exercise intervention ($p < 0.05$). In contrast, but as expected without an intervention, no within-group changes in UC participants were found. We also detected a clinically meaningful and significant within-group change in 30s sit-to-stand repetitions among EX participants (Δ3.1, 95% CI: 0.4 to 6.0), but not among UC participants (Δ-0.2, 95% CI: -2.5 to 2.1). To our knowledge, there are no other RCTs that have specifically delivered a structured, supervised exercise intervention to a mixed advanced cancer population with cachexia. However, systematic review evidence illustrates that the number of RCTs with exercise in mixed advanced cancer populations is growing.[64] While RCT findings remain somewhat inconsistent, RCTs with more than

50 participants, or that have typically included some level of exercise supervision and combined aerobic and resistance training, appear to be more likely to report improvements in physical function outcomes.[241,245,247,248] The current RCT is the first to report improvements in patient-reported outcomes and physical function in patients with advanced cancer and cachexia who take part in a structured, supervised exercise intervention. The combination of including a high level of supervision and concurrent aerobic and resistance training, coupled with the convenience of the intervention, may explain the preliminary benefits of the intervention on secondary patient-reported and physical function outcomes.

Findings from study three demonstrate that a structured and supervised exercise intervention for people with advanced cancer and cachexia is feasible. Novel aspects of the study design include the strict inclusion of advanced cancer patients with cachexia according to international consensus definition.[7] Next, the exercise intervention format itself was unique and is currently understudied within exercise oncology at-large. Virtually supervised interventions hold promise to bridge a key gap between traditional unsupervised, home-based exercise interventions and strict supervised, in-person exercise interventions at designated exercise facilities. The COVID-19 pandemic has undoubtedly induced a shift in how clinicians and researchers consider delivering supervised exercise. Incorporating telehealth is both an exciting and potentially transformative way to deliver high quality exercise-based support in clinical settings. Limitations of home-based exercise will always exist, however, higher risk or more functionally limited patient populations, including people with advanced cancer and cachexia, often experience multifaceted exercise barriers, such as travel, as described in study two (Chapter 4). Thus, home-based exercise may be the *only* option for some patients with complex syndromes, such as cancer cachexia. Utilising technology to improve home-based exercise monitoring likely can only aid in the potential effectiveness of home-based interventions. As a result, findings from study three of the current thesis provide essential foundational evidence to support a larger phase III RCT exploring the efficacy of virtually supervised exercise in patients with advanced cancer and cachexia and to ultimately, move towards implementing exercise as a meaningful intervention for this underserved patient group.

6.4 Strengths and Limitations

An overall strength of the current thesis is the specific focus on the role of exercise in patients with advanced cancer who met the criteria for cancer cachexia according to the 2011 international consensus definition.[7] Specifically, studies two and three (Chapters 4 and 5) include novel data supporting the feasibility of implementing exercise as a meaningful intervention for people with advanced cancer and cachexia. We included diverse participants to increase the generalisability of our findings, including adult men and women with mixed cancer types and treatments, and varying levels of malnutrition severity and baseline performance status. In the RCT presented in Chapter 5, participants were also stratified based on sex and performance status to ensure an equal distribution between the EX and UC groups. The participant cohorts in all three studies captured the range of patients who may be living with both advanced cancer and cachexia and who may benefit from exercise-based support. Additionally, participants were recruited from metropolitan and regional areas in Victoria, Australia for all three studies, which further increases the generalisability of the reported findings. The work described in this thesis includes three different and carefully selected study designs to provide practice-based, qualitative, and quantitative evidence to support the potential for exercise to be included as a part of supportive care for patients with advanced cancer and cachexia. Each study design in the current thesis provided important information and context to inform each subsequent study. Overall, findings help fill important knowledge gaps within exercise oncology and cancer cachexia research and provide critical information from which to develop future studies and inform patient care in clinical practice.

In all three studies, cachexia was principally identified based on patient-reported weight loss over the past six-months and BMI. As it stands, the 2011 international consensus definition published by Fearon et al.[7] is the best available criteria to identify patients with cachexia. However, the definition lacks specificity and this can create challenges within clinical research for cancer cachexia. Cachexia is a complex syndrome. Arguably, reduced food intake and appetite symptoms coupled with increased inflammation are important elements that underpin this syndrome and may be incorporated into a future clinical definition.[5] Fearon et al. acknowledged reduced food intake and inflammation as elements of cachexia in the 2011 international consensus definition, however, no established criteria or thresholds were recommended to better clinically identify or classify patients as having cachexia.[7]

Participants prospectively recruited into studies two and three, were not specifically screened for appetite, food intake, or inflammation and these outcomes were not used as participant inclusion criteria. However, the PG-SGA or PG-SGA SF were used to characterise participant cachexia and nutritional status in all three studies, as these measures include evaluations of appetite symptoms and food intake and have established clinical utility and prognostic significance.[42] We found most, but not all participants reported high symptom burden that impacted appetite and changes in food intake. While we had originally planned to evaluate CRP and albumin in participants recruited into study three, the effects of the COVID-19 pandemic restricted our ability to assess participants in-person throughout much of the study period (2020 to 2021). As a result, the inflammation status of participants included in the current thesis is largely unknown. Opinions regarding appropriate study eligibility criteria for cancer cachexia are wide-ranging, and may include a range of assessments or biomarkers beyond simple measures of food intake and inflammation (e.g., CRP), such as other laboratory assays, radiological images, physical signs, functional status, and patient-reported outcomes.[1] Across the published cancer cachexia scientific literature over the past few decades (and especially prior to the publication of the 2011 international consensus definition), various definitions have been employed to identify patients with or at-risk of cachexia.[53] The use of mixed definitions remain an ongoing and inherent limitation within cancer cachexia research. A revision of the 2011 international consensus definition of cachexia is reportedly underway and will hopefully help streamline future research endeavours as well as inform clinical practice guidelines.[1]

It is also important to point out that there is no consensus on study endpoints that have established clinical meaning for patients with cancer cachexia.[1] To-date, cancer cachexia research studies have included diverse primary and secondary endpoints to assess intervention efficacy, often including patient-reported outcomes, physical function, muscular strength, body composition, and other clinical outcomes, such as cancer treatment tolerability.[48,49] While cachexia is considered a muscle wasting syndrome, regulatory agencies have reported that body composition or specific measures of skeletal muscle mass are not appropriate primary end-points given they do not provide a measure of clinical benefit.[1] However, assessing and monitoring skeletal muscle mass overtime is helpful to establish proof-of-concept for a given intervention and can also provide important context to interpret changes in additional patient-reported and functional outcomes. Study three was originally designed to evaluate total body composition among all participants. As mentioned previously, the COVID-19 restrictions over the course of the study period only allowed for these in-person assessments to take place in a subgroup of participants. Importantly, measuring body composition using DXA scans appeared to be feasible in our participant sample and should be incorporated in future studies with adequate resources, funding, and personnel.

The current thesis emphasises the importance of maintaining physical function. Qualitative data from study two (Chapter 4) highlights that a loss of physical function and strength, decline in independence, and changes in physical activity and activities of daily living, are meaningful to patients. Data also suggest physical function measures may have prognostic significance in people with cancer.[311] Among people with cancer cachexia, improvements in physical function outcomes have also been shown to predict larger increases in overall QoL.[269] However, the clinical relevance of the physical function outcome measures included in the current thesis, including maximal handgrip strength and the 30s sit-to-stand test, has not been established in a cancer cachexia population.[312] It is likely a range of functional measures are needed to fully capture the nature and extent of physical deconditioning that may be present with cancer cachexia. Of note, study three also originally intended to include the 6MWT to capture functional capacity. Again, restrictions imposed by the COVID-19 pandemic limited the number of in-person assessments that could be performed, and thus the number of participants who completed the 6MWT. An important future area of research includes designing clinical studies to prospectively validate potential endpoints for cancer cachexia. For physical function assessments, there is a need confirm minimal clinically important differences to better inform the efficacy of cancer cachexia interventions. More work is needed to elucidate how to best measure physical function and patient-reported outcomes objectively and longitudinally to capture meaningful improvements.

For studies two and three, recruitment rate was relatively high in comparison to other studies in palliative cancer populations. However, the overall number of participants referred into the studies remained low. Particularly for study three, recruitment was open for over two years, with a total of only 104 patients referred and screened for eligibility during that time. Referral to the RCT to provide patients with an opportunity to take part in the supervised exercise intervention was largely dependent on clinicians (e.g., medical oncologist, palliative medicine physicians) to identify potentially eligible and interested patients. In some cases, palliative medicine physicians described that many of their patients were too unwell (e.g., survival < 3 months) and thus, patients were not approached for the study. Further, competing demands for clinicians' valuable time (including throughout the COVID-19 pandemic) coupled with the complex health needs of patients with advanced cancer may have limited the time available for clinician-patient discussions about opportunities for exercise or research study participation.

Strategies to increase referral rate were employed throughout the study, including collaboration with oncology dietitians, which had some success. In the end, 80% of enrolled participants were referred by oncology dietitians and palliative medicine physicians. There is also a longer history of concern over patient involuntary weight loss and nutritional concerns among dietitians and palliative medicine physicians versus other healthcare providers.[80,220] Management of cancer cachexia among healthcare providers is complex and challenging and there are notable differences between palliative and nonpalliative healthcare providers in their care approaches, such as an overreliance on the biomedical model of care among nonpalliative healthcare providers.[313] Moreover, it is possible there may be additional safety concerns among clinicians about exercise potentially exacerbating patient weight loss. Systematic review evidence in people with cancer suggests exercise alone can only produce minor changes in body weight, unless it is also paired with a dietary intervention (e.g., low energy diet).[314] Thus, further education and awareness about how exercise may optimally support patients with cachexia, such as through the maintenance or improvement of physical function and skeletal muscle mass, may be needed. Altogether, with the emergence of new guidelines highlighting the limitations of cancer cachexia care,[52] hopefully improved identification of at-risk patients and the provision of potential treatment and supportive care options will be further supported.

6.5 Significance

Cancer cachexia is increasingly being recognised within oncology as a critical and unmet patient need that can significantly impact patient outcomes and QOL.[52,53] Recently, there has been a call for more research to advance our knowledge on cancer cachexia to improve prevention, screening, timely treatment, and management of this syndrome.[1] The current thesis makes crucial initial steps towards unveiling the possible role of exercise to help manage the burden of cachexia in people with advanced cancer. Although the role of exercise as a part of supportive cancer care is well-studied,[54-62] exercise oncology research has not specifically extended to cancer cachexia populations. Thus, the work in the current thesis, describing the role of exercise among people with advanced cancer contributes to an important new area of interest. In study one (Chapter 3), a rich description of how exercise can be incorporated into multidisciplinary cancer cachexia care is described. In study two (Chapter 4), the first-in-class qualitative evidence is provided to support the feasibility of implementing exercise as a meaningful intervention for people with advanced cancer and cachexia. Lastly, study three (Chapter 5) offers world-first information from a phase II RCT to suggest a structured, virtually supervised exercise intervention is safe and feasible among people with advanced cancer and cachexia and is associated with clinically meaningful improvements in patient-reported outcomes and physical function. Findings from Chapter 5 indicate that telehealth may play a critical role in delivering exercise-based support to higher risk patient populations who may experience additional or more complex exercise barriers. Altogether, the current thesis can help educate healthcare providers on the potential need for exercise to be included in cancer cachexia and palliative care.

RCTs delivering interventions to patients with cancer cachexia (e.g., pharmaceuticals or dietary interventions) have also not typically been able to modify physical function or alternatively, have not included objective measures of physical function.[48,49] Findings from study three in Chapter 5 thus help illustrate important gaps in cancer cachexia care that exercise may address. Indeed, intervention *specificity* is necessary to modify outcomes of interest. In the absence exercise or rehabilitation, and more precisely, direct skeletal muscle contraction, modifying physical function and strength may be particularly challenging for any other interventions. An exception may be if an intervention is able to substantially reduce symptoms (e.g., fatigue), which in turn leads to increased habitual physical activity in patients due to increased energy. But even under the circumstance where symptom improvement may be remarkably immense, physical deconditioning, skeletal muscle weakness, and possibly frailty in the time preceding may have produced functional limitations that are difficult to recover from without direct exercise-based support. As captured in study two (Chapter 4), patients reported that the implications of changes in physical function and strength can be wide-ranging and may impact patient independence, activities of daily living, and overall wellbeing. Exercise-based support is an intuitive intervention to overcome physical function changes, while also facilitating improvements in cancer symptoms and overall QOL. Study three (Chapter 5) demonstrated that structured, supervised exercise-based support is feasible among patients with advanced cancer and cachexia and may be a necessary option to manage functional related concerns. As a result, exercise holds promise as an important co-intervention to round out and even maximise the potential benefits of cancer cachexia treatment plans.

6.6 Conclusion

The current thesis describes a series of carefully designed studies to provide important new knowledge on the role of exercise in people with advanced cancer and cachexia. Key findings from this thesis, include 1) multidisciplinary cancer cachexia care that includes combined medical, pharmaceutical, dietary, and home-based exercise multimodal treatment plans is associated with significant improvements in patient-reported QOL and symptoms, but not clinically-assessed physical function, in palliative cancer patients; 2) people with advanced cancer and cachexia perceive exercise as important and express an interest in receiving greater exercise support (e.g., professionally supervised and structured exercise) and access (e.g., convenient exercise options) to overcome exercise barriers and to maximise the potential psychological and physical benefits of exercise; and 3) a virtually supervised exercise intervention delivered over an internet-based videoconference platform is a safe and feasible way to provide professionally supervised and structured exercise to people with advanced cancer and cachexia. Our results indicate that exercise-based support is desired by patients and can fill a gap in care for cancer cachexia. Overall, the current thesis supports that exercise should play important role as a management strategy to counteract the burden of cancer cachexia.

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7 Appendices

7.1 Additional Publications

7.2 Exercising in isolation? The role of telehealth in exercise oncology during the COVID-19 pandemic and beyond

Bland KA, Bigaran A, Campbell KL, Trevaskis M, Zopf EM. Exercising in isolation? The role of telehealth in exercise oncology during the COVID-19 pandemic and beyond. Phys Ther. 2020; 100(10):1713-1716.

[redacted]

7.3 Publication Copyright Agreements

7.3.1 Quality of life and symptom burden improve in patients attending a multidisciplinary clinical service for cancer cachexia: a retrospective observational review.

Bland KA, Harrison M, Zopf EM, Sousa MS, Currow DC, Ely M, Agar M, Butcher BE, Vaughan V, Dowd A & Martin P. Quality of life and symptom burden improve in patients attending a multidisciplinary clinical service for cancer cachexia: a retrospective observational review. J Pain Symptom Management. 2021;27;62(3): e164-e176.

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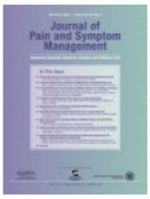

Quality of Life and Symptom Burden Improve in Patients Attending a Multidisciplinary Clinical Service for Cancer Cachexia: A Retrospective Observational Review

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BACK CLOSE WINDOW

7.3.2 "I want to get myself as fit as I can and not die just yet" – Perceptions of Exercise in People with Advanced Cancer and Cachexia: A Qualitative Study

Bland KA, Krishnasamy M, Parr EB, Mulder S, Martin P, van Loon LJC, Cormie P, Michael N & Zopf EM. "I want to get myself as fit as I can and not die just yet" – Perceptions of Exercise in People with Advanced Cancer and Cachexia: A Qualitative Study. BMC Palliative Care. 2022;21(1):75.

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7.3.3 Exercising in isolation? The role of telehealth in exercise oncology during the COVID-19 pandemic and beyond

Bland KA, Bigaran A, Campbell KL, Trevaskis M, Zopf EM. Exercising in isolation? The role of telehealth in exercise oncology during the COVID-19 pandemic and beyond. Phys Ther. 2020; 100(10):1713-1716.

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7.4 Publication Supplemental Materials

7.4.1 Chapter 4

Supplemental materials for:

Bland KA, Krishnasamy M, Parr EB, Mulder S, Martin P, van Loon LJC, Cormie P, Michael N & Zopf EM. “I want to get myself as fit as I can and not die just yet” – Perceptions of Exercise in People with Advanced Cancer and Cachexia: A Qualitative Study. BMC Palliative Care. 2022;21(1):75.

Table 7.1: Initial Coding Framework

Categories and Descriptions	Sub-categories	Codes
Current Exercise and Physical Activity Current exercise and physical activity, including incidental or non-leisure based physical activity and planned, structured exercise.	Non-Leisure Physical Activity	Gardening Household-based (e.g., Cleaning) Other (e.g., Transportation)
	Exercise	Walking Outside Strength Training Other (e.g. Yoga)
Changes in Activity and Function Reported changes in physical function and ability to move since being diagnosed with cancer, including the ability to engage in specific types of physical activity, and the perceived psychosocial impact.	Physical Changes	Relinquished Physical Activities Physical Deconditioning Turning Points of Change in Function
	Psychosocial Impact	Acceptance/Awareness of Illness Negative Emotional Response to Physical Changes Expression of Unmet Clinical Need
Positive Beliefs about Exercise Perceived importance of and benefits associated with physical activity and exercise including, physical, mental, emotional, and social wellbeing.	Physical Aspects	Has Cancer-specific Benefits Improved Physical Health
	Psychosocial Aspects	Positive Mental or Emotional Effects Exercise as a Social Activity
Exercise Motivators Factors perceived to currently support or *potentially increase* exercise and physical activity participation, including intrinsic and extrinsic motivators.	Contribute to Health and Wellbeing	Help with Cancer and Symptoms Improved Mental Wellbeing Get Stronger "Feeling Better"
	Structure and Support	Creating Structure and Routine Community or Social Support Professional Exercise Supervision Discussion with Healthcare Team
Exercise Barriers Factors perceived to currently limit or prevent exercise and physical activity participation.	Since Cancer Diagnosis	Cancer Symptoms (e.g., Fatigue, Nausea) Treatment Schedules Change in Motivation
	Other Health-Related	Other Injuries and Illnesses Concerns with Safety
	Since the Pandemic	COVID-19 Restrictions and Risk

	Logistics/Environmental	Travel Family Responsibilities Finances Weather
Exercise Preferences Thoughts about preferred exercise settings, types and time based on what was considered most enjoyable, interesting, and feasible in each participant's current situation.	Setting	Outdoors Close to or at Home Fitness Centres Telehealth
	Type	Structured Exercise Training Group-based or Classes Walking Individual Exercise Open to Trying New Types
	Time	Duration Time of Day