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Nutrition, body composition and physical activity in malignant pleural disease: associations with patient outcomes and response to an exercise intervention

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Nutrition, body composition and physical activity in malignant pleural disease: associations with patient outcomes and response to an exercise intervention

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School of Medical and Health Sciences & Exercise Medicine Research Institute
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Abstract

Background: Patients with malignant pleural disease (MPD) have advanced cancer and high symptom burden. Goals of patient care are to optimise health-related quality-of-life (HR-QoL) and participation in daily physical activities. Supportive care interventions such as nutrition and exercise could offer benefit to patients. However, there is a lack of information on the prevalence of low muscle mass (i.e., pre-sarcopenia), malnutrition, inactivity and poor physical functioning in patients with MPD. Additionally, little is known about the factors associated with development of pre-sarcopenia and malnutrition or their associations with patient outcomes.

Purpose: The objectives were to: 1) characterise physical activity levels and their relationship with patient outcomes; 2) compare methodology used to classify pre-sarcopenia; 3) determine the prevalence of pre-sarcopenia and malnutrition and investigate their relationship with activity behaviours and HR-QoL; 3) determine the prevalence of poor physical functioning and nutritional outcomes throughout the two years post-diagnosis; 5) describe body composition changes and investigate their relationship with physical activity and dietary intake; and 6) examine the effects of nutritional status and dietary intake on outcomes of an exercise intervention.

Methods: Three studies in patients with MPD were conducted: a cross-sectional study, a prospective observational study, and an exercise intervention study. Participants in the cross-sectional study (n=46) underwent assessment of physical activity levels (accelerometer). Participants in the observational (n=36) and exercise intervention (n=33) studies underwent assessment of nutritional status (Patient-Generated Subjective Global Assessment), body composition (computed tomography [CT], dual-energy x-ray absorptiometry [DXA]), physical activity levels (accelerometer), physical functioning (Timed Up-and-Go), HR-QoL (Short-Form 36; Functional Assessment of Cancer Therapy [FACT]-General), appetite (FACT-Anorexia Cachexia Scale) and fatigue (FACT-Fatigue). Participants in the intervention study underwent additional tests of physical functioning (Six-Minute Walk Test, chair rise) and muscular strength (1-repetition maximum leg press).

Results: In the cross-sectional study, 89% of participants did not meet physical activity guidelines. There was moderate agreement between CT and DXA for the classification of pre-sarcopenia (κ=0.424; p=0.006). Fifty-four percent of participants were pre-sarcopenic, and 38% were malnourished. Compared to participants with normal muscle mass, pre-sarcopenic participants were more sedentary (p=0.001) and participated in less light activity (p=0.008). Compared to participants who were well-nourished, malnourished participants had poorer HR-QoL (p<0.001). Throughout the two years post-diagnosis, the prevalence of poor physical functioning and low appetite was ≥50%. Participants with muscle loss (56%) became more sedentary (p=0.008), however energy and protein intake did not change (p>0.05). In the exercise intervention, participants with adequate dietary intake (40%) had a significant increase in muscle mass (p=0.004), while participants with inadequate dietary intake (60%) maintained muscle mass (p=0.737). There were no differences between well-nourished and malnourished participants with respect to completion, adherence or tolerance of the intervention (p>0.05).

Conclusion: Overall, there were high rates of pre-sarcopenia, malnutrition, inactivity, and poor physical functioning among participants with MPD. Pre-sarcopenia and malnutrition were associated with negative patient outcomes. Muscle loss was associated with decline in physical activity. The results indicate dietary intake could influence the effects of exercise. Interventions that target both physical activity and dietary intake could be most impactful.

Declaration

I certify that this thesis does not, to the best of my knowledge and belief:

i. Incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;
ii. Contain any material previously published or written by another person except where the due reference is made in text; or
iii. Contain any defamatory material

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Emily Jeffery

PhD candidate

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Research Outputs

Publications

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Jeffery E, Lee YCG, McVeigh J, Straker L, Wooding T, Newton RU, Peddle-McIntyre CJ. Feasibility of objectively measured physical activity and sedentary behavior in patients with malignant pleural effusion. Support Care Cancer, 2017 Oct; 25(10): 3133-3141.

Oral presentations

Jeffery E, Newton RU, Lee YC G, Lyons-Wall P, Nowak A, Peddle-McIntyre C. Relationship between nutritional status, dietary intake and resistance exercise outcomes: results from a pilot study in patients with malignant pleural disease. Dietitians Association of Australia National Conference, Gold Coast, Australia, 14 August 2019.

Jeffery E, Lee YCG, Newton RU, Lyons-Wall P, McVeigh J, Fitzgerald DB, Creaney J, Straker L, Peddle-McIntyre CJ. Malnutrition and sarcopenia in patients with malignant pleural mesothelioma. Clinical Oncology Society of Australia Annual Scientific Meeting, Perth, Australia, 14 November 2018.

Jeffery E, Lee YCG, Newton RU, Lyons-Wall P, McVeigh J, Straker L, Nguyen B, Peddle-McIntyre. Sarcopenia is associated with sedentary behaviour and physical activity in people with malignant pleural mesothelioma. Australian Society of Parenteral and Enteral Nutrition Conference, Gold Coast, Australia, 17 November 2017.

Jeffery E, Newton RU, Lee YCG, Lyons-Wall P, Peddle-McIntyre C. Differences in quality of life, physical functioning and dietary intake amongst malnourished and well-nourished patients with malignant pleural mesothelioma. Dietitians Association of Australia National Conference, Hobart, Australia, 18 May 2017.

Poster presentations

Jeffery E, Newton RU, Lee YCG, Nowak AK, Prado CM, Lyons-Wall P, Schofield C, Peddle-McIntyre CJ. Potential role for a novel body composition analysis technique in patients with malignant pleural mesothelioma. Clinical Oncology Society of Australia Annual Scientific Meeting, Perth, Australia, 13 -15 November 2018.

Jeffery E, Lee YCG, McVeigh J, Newton RU, Straker L, McIntyre C. Actigraphy: an objective measure of physical activity in malignant pleural effusion patients. Thoracic Society Australia New Zealand Annual Scientific Meeting, Perth, Australia, 1 – 6 April 2016.

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Jeffery E. School of Medical and Health Sciences Research Collaboration Travel Grant, Friday Seminar. Edith Cowan University, Perth, Australia, 7 April 2017.

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Abbreviations

1RM	One repetition maximum
ACS	Anorexia Cachexia Scale
ASM	Appendicular skeletal muscle mass
BMI	Body mass index
CRP	C-reactive protein
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
DXA	Dual-energy x-ray absorptiometry
ELISA	Enzyme-linked immunosorbent assay
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General
HR-QoL	Health-related quality of life
IFN-γ	Interferon gamma
IGF-1	Insulin-like growth factor-1
IL-6	Interleukin-6
L3	Third lumbar vertebrae
MPD	Malignant pleural disease
MPE	Malignant pleural effusion
MPM	Malignant pleural mesothelioma
MVPA	Moderate and vigorous physical activity
NSCLC	Non-small cell lung cancer
PG-SGA	Patient-Generated Subjective Global Assessment
SF-36	Short-Form Health Survey
SMI	Skeletal muscle index
TNF-α	Tumour necrosis factor-alpha
VEGF-A	Vascular endothelial growth factor-A
VEGF-C	Vascular endothelial growth factor-C

Glossary of Terms

Aerobic exercise	Exercise in which the body's large muscles move in a rhythmic manner for sustained periods.[1]
Cancer cachexia	A multifactorial syndrome that is defined by an ongoing loss of skeletal muscle mass with or without loss of fat mass.[2]
Chronic disease-related malnutrition with inflammation	A condition that results from the activation of systemic inflammation by an underlying disease such as cancer.[3]
Computed tomography	A method of measuring body composition based on the density of pixels in an image of a person's body tissues.[4]
Dual energy x-ray absorptiometry	A method of measuring body composition based on the amount of energy absorbed when photons pass through a person's body tissues.[4]
Exercise	Bodily movement that is planned, structured and repetitive and undertaken with the purpose of maintaining or improving physical fitness.[5]
Malignant pleural disease	The collective term given to cancers that involve the pleurae.[6]
Malignant pleural effusion	Excessive accumulation of fluid in the pleural cavity attributed to malignancy.[6]
Malignant pleural mesothelioma	A primary pleural cancer primarily attributed to asbestos exposure.[7]
Malnutrition	A state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.[3]
Muscle strength	The amount of force a muscle can produce with a single maximal effort.[8]
Physical activity	Any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels.[5]
Physical function	The capacity of an individual to carry out the physical activities of daily living.[1]
Physical performance	An objectively measured whole body function related with mobility.[8]

Pre-sarcopenia	A term given to the presence of low skeletal muscle mass in the absence of low muscle strength and function.[9]
Resistance exercise	Exercise that causes muscles to work or hold against an applied force or weight.[1]
Sarcopenia	A progressive and generalised skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality.[10]

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Chapter One

1

Introduction

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1.1 Background

Malignant pleural disease (MPD) is the collective term given to cancers that involve the pleurae.[1] MPD currently affects more than 8000 people within Australia and 1 million people across the world each year.[2] MPD includes primary pleural cancers such as malignant pleural mesothelioma (MPM) and secondary pleural cancers or metastatic disease.[1] Globally, 90% of cases of MPD are comprised of patients with metastatic disease, with cancers of the lung and breast most likely to metastasise to the pleurae.[3] In Western Australia approximately 40% of cases of MPD are comprised of patients with MPM.[4]

MPM is a unique cancer in that its aetiology is primarily attributed to asbestos exposure.[5] Asbestos is a group of naturally occurring hydrated mineral silicate fibres[6] that were extensively used in Australia in the manufacturing and construction industries.[7] Historically, people working in mining, manufacturing and construction occupations were more likely to be exposed to asbestos.[8] As these occupations were made up of a predominantly male workforce, there is a higher incidence of MPM among men.[9] Notably, there is a long latency period (mean 44 years)[10] between exposure to asbestos and the development of MPM, therefore the mean age of patients at the time of diagnosis is approximately 70 years.[10]

MPD represents incurable cancer and the 1-year survival rate is less than 25%.[11] However, the median survival of patients with MPD varies considerably depending on the tumour type. Patients with primary lung cancer have the shortest median survival of less than 3 months while patients with MPM have the longest median survival of 12 months.[4] Other factors associated with poorer survival include poor performance status and high inflammatory markers.[4, 11] While patients with MPM have the longest median survival, additional factors associated with poorer survival include the non-epithelioid subtype of disease[12-15], elevated platelet count[12-14] and weight loss.[14, 16]

Patients with MPD typically have a high symptom burden.[17] The majority of patients present with a pleural effusion, which is the excessive accumulation of fluid in the pleural cavity.[1] Fluid in the pleural cavity, which is in excess of 1 litre for most patients with MPM,[18] can cause breathlessness and chest pain.[1] Research in patients with lung cancer indicates that breathlessness is negatively associated with activity levels and quality of life.[19] Therefore, the management of patients with MPD is mainly focused on controlling symptoms in order to optimise physical activity levels and quality of life. While there is substantial data regarding quality of life,[20, 21] there is a notable lack of data measuring physical activity in

this population. Information on the physical activity of patients with MPD is currently limited to self-report of physical functioning as part of quality of life assessment.[22]

Standard management of malignant pleural effusions has changed substantially over time with an increasing focus toward least invasive interventions that will alleviate symptoms, ideally without need for a hospital admission.[23] Current practice for symptomatic patients typically involves insertion of an indwelling pleural catheter to allow for ambulatory drainage of pleural fluid.[23] For patients with MPM, first-line treatment of the disease with cisplatin and pemetrexed chemotherapy can improve symptoms[22] and offers a modest survival benefit.[24]

Malnutrition is defined by a low body weight, weight loss or low muscle mass in combination with reduced dietary intake or inflammation.[25] The potential relationship between malnutrition and patient survival in MPM has been raised in previous research studies.[14, 26] However, an accurate description of the nutritional status of patients with MPM is not available as the amount and timing of weight loss has been poorly described,[13, 27] and there has been no measurement of muscle mass, appetite or dietary intake using validated tools. An existing challenge in the measurement of muscle mass is that there is no consensus on the optimal technique or cut-points for the classification of low muscle mass. There is also evidence that the techniques are not comparable.[28] Therefore, further investigation into the comparability of methods used for the measurement of muscle mass is relevant.

In advanced cancer populations, low muscle mass and weight loss are associated with poorer quality of life[29-36] but no study in this population has examined the association with activity levels. Further, no study in MPM has investigated the relationship between body composition, nutritional status, and quality of life and activity levels. While anecdotally clinicians and patients are concerned about malnutrition and low muscle mass,[37] there is a lack of evidence available to empirically inform development of interventions to address these concerns.

There are multiple factors which contribute to the development of malnutrition and low muscle mass in the cancer context.[38] As MPD indicates advanced cancer, it is plausible that the cancer may indirectly contribute to reduced dietary intake, physical activity and altered metabolism which could lead to the development of malnutrition and low muscle mass.[39] This condition is commonly known as cancer cachexia and it is thought to be at least partly reversible in its early stages.[39] An understanding of the factors associated with

the development of malnutrition and low muscle mass in MPD could lead to more targeted interventions to address these conditions.

Exercise is regarded as a potential strategy to reverse the effects of cancer cachexia.[39] Resistance exercise training is defined as exercise in which muscles work against a force 60% or higher of maximum.[40, 41] Resistance exercise training is well established as promoting gains in muscle mass,[42] and is effective for improving muscle mass in patients with early stage prostate cancer[43] and breast cancer.[44, 45] However, patients with advanced cancer are a distinctly different population. The high symptom burden[46] and high rates of malnutrition[47] among patients with advanced cancer could negatively impact on adherence and tolerance to the intervention. Furthermore, reduced dietary intake could limit muscle gains as amino acids mobilised from muscle are used as an energy source.[48] There is limited body composition data available from resistance exercise intervention studies in advanced cancer populations. Furthermore, no studies have reported on the impact of nutritional factors on exercise outcomes.[49]

1.2 Significance of the research

Patients with MPD face debilitating symptoms and a disease that has no cure. Research aimed at improving daily physical activity and quality of life is imperative for improving clinical care. Results from this study will provide information about the nutritional status and body composition of patients with MPD and their relationship with patient-centred outcomes, which will serve as a rationale for future supportive care interventions.

Effective supportive care interventions are both feasible and target the underlying causes of the problem. Reduced dietary intake, physical activity and altered metabolism have all been implicated in the overall body weight and muscle loss associated with cancer.[39] Therefore, Fearon et al[39] in their review of mechanisms and treatment options for cancer cachexia have recommended the use of multi-modal interventions inclusive of dietary counselling and nutrition support, resistance exercise training and pharmacological agents.[39] A potential problem is that few studies have reported on the feasibility of resistance exercise training in patients with malnutrition. This is a particularly important factor to consider as malnutrition is associated with high symptom burden which could negatively affect adherence to exercise.[50] Additionally, there is no data available on the dietary intake of patients with MPD or the relationship between dietary intake, biochemical markers and nutritional status and body composition. There is paucity of data available to inform the design of supportive care interventions in patients with MPD. Results from this work will

provide information on the feasibility of resistance exercise training in patients with malnutrition and the relationship between changes in body composition and dietary intake and physical activity to guide the development of future supportive care interventions.

1.3 Research purpose

The overall purpose of this research was to describe the physical activity, physical functioning, nutritional status and body composition of patients with MPD. Further, this research sought to evaluate the physical activity and body composition methodology that underpins the research. The objectives were to determine if there was a relationship between physical activity, nutritional status and body composition, and important patient outcomes; describe body composition changes over time and investigate the relationship with physical activity and dietary intake; and examine the effects of nutritional status and dietary intake on outcomes of an exercise intervention.

1.4 Overview of thesis content

Chapter One is an introduction to the thesis. This chapter provides background to the research along with an overview of thesis content. The significance and purpose of the research are also stated.

Chapter Two is a critical review of existing literature related to the measurement of body composition, physical activity and functional status; the prevalence of malnutrition, pre-sarcopenia, physical inactivity and functional impairment in advanced cancer populations; the aetiology and consequences of malnutrition and pre-sarcopenia in advanced cancer populations; the effects of exercise in advanced cancer populations; and the impact of dietary intake on the effects of exercise.

In Chapter Three the results of a cross-sectional study (Study 1) conducted with 46 patients with MPD are presented (**Figure 1.1**). This chapter provides information on adherence to an accelerometer wear protocol, describes objectively measured physical activity and sedentary behaviour and compares these results to physical performance measures used in clinical practice (Manuscript published).[51]

In Chapters Four and Five, data from the baseline assessment of a longitudinal observational study (Study 2) and exercise intervention study (Study 3) conducted in patients with MPM are presented (**Figure 1.1**). In Chapter Four, the measurement of skeletal muscle mass and rates of pre-sarcopenia measured with Dual-Energy X-Ray

Absorptiometry and Computed Tomography is compared. In Chapter Five the rates of malnutrition and pre-sarcopenia are reported and the relationship between nutritional status, body composition and dietary intake, biochemical markers, quality of life and activity levels are reported (Manuscript published).[52]

In Chapters Six and Seven, results from a longitudinal observational study (Study 2) conducted in 36 patients with MPM are presented (**Figure 1.1**). In Chapter Six, the rates of nutritional impairment (high need for nutrition support and poor appetite) and functional impairment (self-reported physical functioning and Timed Up and Go) at different points in the disease course are reported. In Chapter Seven, changes in body composition over time are described and the relationships between energy and protein intake, and physical activity and sedentary behaviour are assessed.

In Chapter Eight, results from an exercise intervention study (Study 3) conducted in 33 patients with MPD are reported (**Figure 1.1**). Adherence to and tolerance of the intervention were compared between malnourished participants and well-nourished participants. Additionally, the relationships between energy and protein intake and outcomes from resistance exercise training, namely body composition and objectively measured physical functioning were assessed.

Chapter Nine is an overall discussion of major findings and conclusions of the collective work with recommendations for future research.

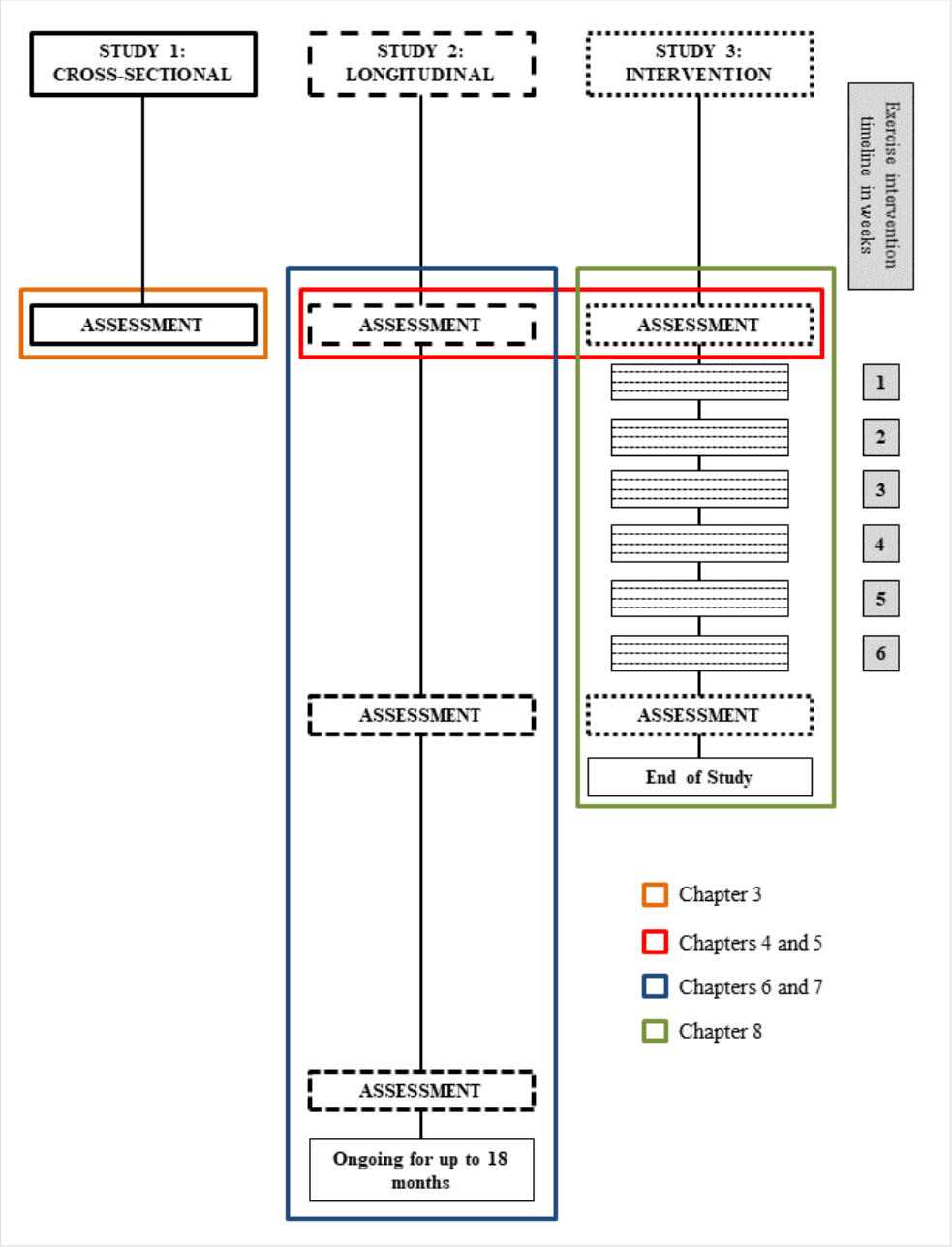

Figure 1.1 Outline of studies

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Chapter Two

2

Literature Review

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2.1 Malignant pleural disease

Malignant pleural disease (MPD) is the collective term for cancers that involve the pleurae, which are two serous membranes that attach to the chest wall and lungs.[1] The small amount of fluid secreted by the pleurae acts as a lubricant to enable the membranes to slide against each other during breathing.[1] MPD comprises both primary pleural cancers and secondary pleural cancers.[2] Primary pleural cancers include malignant pleural mesothelioma (MPM), localised fibrous tumour and pleural liposarcoma.[2] Secondary pleural cancers include metastatic disease, thymoma and lymphoma[2]

2.1.1 Clinical presentation and symptom burden

Most patients with MPD present with a pleural effusion,[2] which is the excessive accumulation of fluid in the pleural cavity.[2] A malignant pleural effusion is a unique fluid that is rich in protein (4 g/100 mL) and tumour secretions such as cytokines.[3] The accumulation of pleural fluid occurs when the volume of fluid that enters the pleural space exceeds the capacity of the lymphatic system to remove the fluid.[2] Approximately 60% of patients with MPD have at least 1 litre of fluid in the pleural space at the time of presentation.[4] A high proportion of patients with a malignant pleural effusion present with symptoms;[5] half of patients report breathlessness, while one-quarter of patients report chest pain at presentation.[2]

2.1.2 Aetiology of malignant pleural effusions

The imbalance between the volume of fluid that enters and is removed from the pleural space occurs when a tumour increases the permeability of the pleural surface; involves the lymphatic system; causes an obstruction which decreases pleural pressure; or involves the pericardium.[2]

2.1.3 Prevalence

Approximately half of all patients with cancer will develop a pleural effusion over the disease course.[6] Currently, 8000 people in Australia and 1 million people worldwide are affected by a malignant pleural effusion each year.[7] The majority of patients with a malignant pleural effusion (90%) have metastatic cancer.[8] Patients with lung and breast cancer represent approximately 55% of all cases of a malignant pleural effusion.[5]

2.1.4 Prognosis

MPD represents advanced cancer, however the median survival of patients with MPD varies according to tumour, biochemical and functional factors.[9] Patients with lung and gastrointestinal cancers have the shortest median survival of less than 3 months while patients with MPM have the longest median survival of approximately 12 months.[10] High pleural lactate dehydrogenase levels, which is indicative of localised inflammation within the pleural cavity,[9] and a high neutrophil to lymphocyte ratio, which is indicative of systemic inflammation, are associated with poorer survival.[9, 11] Poorer performance status is also associated with poorer survival.[9]

2.1.5 Treatment

The management of malignant pleural effusions has changed substantially over time. Early clinical trials for the management of malignant pleural effusions were focused on preventing the reaccumulation of pleural fluid using surgical techniques and sclerosing agents.[12] However, the key goals of patient management have evolved over time to a more patient-centred approach to alleviate symptoms, with the least invasive means and without need for a hospitaladmission.[12] Consequently, recent clinical trials have focused on improving patient-reported outcome measures including breathlessness,[13, 14] chest pain,[14] and quality of life,[13, 14] and reducing the amount of time spent in hospital.[15] Due to the high failure rate of talc pleurodesis (~30%) and the subsequent need for reintervention, many centres now use an indwelling pleural catheter[12] for the management of malignant pleural effusions, which enables ambulatory drainage of pleural fluid and reduces the need for reintervention and time spent in hospital.[15] Existing guidelines on pleural fluid management state that symptoms may also be managed with medication.[16] Where patients are asymptomatic, observation is the recommended approach.[5]

2.2 Malignant pleural mesothelioma

MPM represents 90% of primary pleural cancers[8] and develops from the mesothelial surfaces of the pleurae.[17] There are four histological subtypes of MPM: epithelioid, sarcomatoid, desmoplastic and biphasic, which contains both epithelioid and sarcomatoid components.[17] The most common of the histological subtypes is epithelioid, which is present in 60% of cases.[18]

2.2.1 Aetiology

Most cases of malignant pleural mesothelioma (MPM) can be attributed to asbestos exposure.[19] The association between MPM and asbestos was first described in 1960.[20] Asbestos is defined as a group of naturally occurring hydrated mineral silicate fibres.[17] The proposed mechanisms for development of MPM from asbestos exposure include pleural irritation, interference with mitosis, generation of toxic oxygen radicals and persistent kinase-mediated signalling.[19] People exposed to brown and blue asbestos are more likely than those exposed to white asbestos to develop MPM although the reason is unknown.[21]

2.2.2 Patient characteristics

In Australia, asbestos was mined, manufactured into building products and used in construction from the 1950s. A total ban on the use of any type of asbestos was not introduced in Australia until 2003.[22] Historically, people working in mining, manufacturing and construction occupations were more likely to be exposed to asbestos.[23] As these occupations were made up of a predominantly male workforce there is a higher incidence of MPM among men.[24] While concerns around MPM originally centred on those workers who were responsible for mining asbestos and manufacturing asbestos products, the 'new wave' of MPM could be attributable to those who have had short term or low-level exposure to asbestos through home maintenance or renovation.[22]

Data from New South Wales indicates there is typically a long latency period between exposure to asbestos and development of MPM[19] with a mean latency period of 44 years,[25] and a mean age at diagnosis of 70 years.[25]

2.2.3 Clinical presentation and symptom burden

Patients with MPM often have a high symptom burden. Between 60-80% of patients with MPM have breathlessness and chest pain at presentation.[19, 26] Breathlessness in MPM is related to the presence of a malignant pleural effusion or the restriction of lung movement by the tumour.[27] Chest pain is usually a consequence of the invasion of tumour to the chest wall or rib involvement and is therefore more prevalent amongst those with advanced stage disease.[27] Other commonly reported symptoms at diagnosis are the constitutional symptoms of fatigue and weight loss.[19] Between 20-50% of patients with MPM report weight loss at the time of diagnosis, although the amount, composition (muscle vs. fat loss), and timing of weight loss has been poorly described.[28, 29]

2.2.4 Prevalence

Australia has the highest incidence of MPM per capita in the world with 30 cases per million people and rates of disease are expected to peak between 2014 and 2021.[17, 30] These high rates of MPM are reflected in studies of patients with MPD. Patients with MPM are usually less than 10% of an MPD cohort, however in Western Australia patients with MPM comprise almost 40% of an MPD cohort.[9]

2.2.5 Prognosis

MPM is a universally incurable cancer.[19] Unlike other advanced cancers, MPM is predominantly a localised disease and the reason for death remains largely unknown.[31] In the largest post-mortem study published, including 318 patients from Western Australia, a precise cause of death could be determined in only 20% of cases. Notably, patients with an unknown cause of death had significantly lower body mass index (BMI) than those with an identified cause of death (18.8 ± 4.3 vs. 21.0 ± 4.7; p=0.034), and the authors proposed that nutritional status or body composition could be associated with the cause of death in patients with MPM.[31]

Patients diagnosed with MPM have a median survival of 12 months[32] with the one-year survival rate reported as 41% and the three year survival as 12%.[33] In the largest prospective study investigating prognostic factors in MPM (n=8740) the presence of non-epithelioid histological sub-type of the disease and poor performance status were associated with poorer survival.[33]

The most recent prognostic model for MPM was published in 2016.[32] The study, which included patients with newly diagnosed MPM (n=482) identified individual clinical characteristics associated with survival and defined four risk groups based on a combination of clinical characteristics.[32] The individual clinical characteristics associated with poorer survival were non-epithelioid histological subtype, weight loss, performance status ≥2 and altered blood parameters (haemoglobin ≤121 g/L and albumin ≤43 g/L).[32] Regarding the risk groups, those with a combination of no weight loss and haemoglobin ≥153 g/L and albumin ≥43 g/L had the longest median survival (34.0 [IQR 22.9 – 47.0] months),[32] while those with a combination of weight loss, performance status 0-1 and the sarcomatoid histological sub-type of MPM had the shortest median survival (7.5 [IQR 3.3 – 10.9] months).[32]

2.2.6 Treatment options

Treatments are usually provided to MPM patients with palliative intent. Chemotherapy, with pemetrexed and cisplatin is the only first-line treatment available.[34] In a phase III randomised study of patients with MPM (n=456), patients who received pemetrexed and cisplatin in combination had a greater median survival time compared with those who received cisplatin alone (12.1 vs. 9.3 months; p=0.020);[35] and greater response rates to treatment compared with the single agent (41.3% vs. 16.7%; p<0.001).[35]

Radical surgical resection, which involves en bloc resection of the parietal pleura, pericardium, diaphragm, lung and visceral pleura has been shown to be detrimental to patients with MPM.[36] In a randomised controlled trial (n=50) the reported hazard ratio for overall survival was 2.75 (1.21 – 6.26; p=0.016) between those who underwent surgery and those who did not.[36] Median survival for the surgery group was 14.4 (5.3 – 18.7) months vs 19.4 (13.4 to time not yet reached) months in the non-surgery group.

Research trials are currently investigating the effects of immunotherapy in patients with MPM. While there are some promising results from phase I and phase II trials, results of phase III trials are needed to determine if and how immunotherapy should be integrated into standard care for patients with MPM.[37]

There are several treatment options available for symptom management. Radiotherapy for localised pain can improve pain temporarily in approximately half of patients.[16] Pleural fluid management should be considered to manage breathlessness in patients with a pleural effusion.

2.3 Measurement of physical function, physical performance and physical activity

2.3.1 Physical function

Physical function is defined as a person's ability to complete the physical activities of daily living and is a reflection of a person's physical fitness and their usual physical activity level.[38] In clinical practice, performance status measures are commonly used to describe a person's level of physical function.

The most commonly used performance status measures in cancer are the Eastern Cooperative Oncology Group (ECOG) performance status[39] and the Karnofsky Performance Status (KPS).[40] The ECOG performance status scale consist of six levels

from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead) **(Table 2.1)**.[39] The Karnofsky performance status scale consists of eleven levels, which decrease by ten points at each level, from 100 (normal no complaints; no evidence of disease) to 0 (dead).[40]

Table 2.1 Eastern Cooperative Oncology Group Performance Status Scale[39]

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up to and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; total confined to bed or chair
5	Dead

Assessment of performance status is an important part of clinical care in cancer patients, including those with MPD. There is a strong relationship between performance status and prognosis in patients with advanced cancer[41] and MPD,[34] therefore performance status ratings are used to determine a person's suitability for treatment and predict treatment tolerability.[34]

Although performance status scales are simple to administer,[42] assessment is subjective and could inaccurately assess a person's actual functioning.[42] This is highlighted in research that has compared patient and physician ratings of performance status;[41] patients rated their performance status worse than physicians, which suggests that patient and physician ratings of performance status differ. Additionally, performance status categories are broad, and where a response to an intervention is expected to be small, performance status scales may not detect this small, but meaningful change in a person's activity. Therefore alternative measures are required provide a more accurate and objective assessment of physical function.

2.3.2 Physical performance tests

Physical performance tests objectively measure a person's functional capacity. Suboptimal physical performance may be present before a person's usual daily activities are affected,[43] and could predict a decline in activities of daily living.[44] As these tests

assess the integrative capacity of skeletal muscle in a functional setting they have greater clinical utility than muscle function tests, such as handgrip strength, that measure only strength and power of individual muscles.[43]

Several studies have reported on the relationship between physical performance and patient outcomes. In a recent systematic review, the authors concluded that poorer physical performance was associated with reduced survival in patients with cancer.[45] Physical performance tests can predict patient outcomes better than performance status.[46] In a study of 62 patients with non-small cell lung cancer, better physical performance test results were associated with an increased likelihood of completing more cycles of chemotherapy and decreased adverse effects of treatment.[46] Notably, no relationship was observed between ECOG performance status and treatment outcomes.[46] These result indicate that physical performance tests are associated with important patient outcomes.

Commonly used physical performance tests are described in **Table 2.2.** Physical performance tests are typically low-cost and easy to administer. Currently, there is no information on the physical performance of patients with MPD.

Table 2.2 Commonly used physical performance tests[43]

Test	Purpose	Description	Time to complete
Short-distance walk test (i.e., 4 m walk)	Measures gait speed	The time taken to walk the required distance is recorded with a stopwatch.	2 min
Long-distance walk tests (i.e., 400 m walk)	Measures gait speed	The time taken to walk the required distance is recorded with a stop watch	15 min
Chair rise test	Measures lower body power, balance and endurance	The time taken to stand from a chair and sit down five times.	1-2 min
Timed Up and Go test	Measures gait and dynamic balance	The time taken to rise from an armed chair, walk 8-feet, turn and walk back to the same chair and sit back down again	2-3 min
Short Performance Physical Battery	Measures standing balance, gait speed and lower body strength	Includes three physical performance tests: standing balance, a short-distance walk test and chair rise test.	10 min

2.3.3 Physical activity questionnaires

Caspersen et al[47] defined physical activity as movement of the body that is generated by skeletal muscles and leads to an increase in energy expenditure. Physical activity is most commonly assessed with a self-report physical activity questionnaire. Questionnaires are inexpensive and relatively low burden, which is often advantageous, particularly for large population based studies. The Godin Shepherd Leisure-Time Physical Activity Questionnaire (GSLTPAQ) is frequently used in cancer research to assess physical activity.[48] Participants completing the GSLTPAQ are asked to recall how many times in a week they participate in mild, moderate and strenuous physical activity for 15 minutes or more.[49] The International Physical Activity (IPAQ) and Global Physical Activity (GPAQ) questionnaires have also been used in cancer research.[50]

Self-report physical activity questionnaires can appropriately classify patients as sufficiently active or inactive relative to physical activity guidelines.[50, 51] However, participants tend to overestimate the time spent in moderate and vigorous physical activity (MVPA), for example brisk walking, vacuuming, running, swimming, and underestimate their time spent as sedentary such as sitting or lying down.[50, 52, 53] Factors that affect the level of accuracy include education level, sex, and age[52] as well as activity level.[54] Therefore, physical activity monitors may offer more accurate information about a person's individual activity levels.

2.3.4 Physical activity monitors

Physical activity monitors objectively measure a person's activity levels. Physical activity monitors are small and portable to facilitate continuous monitoring of activity behaviours. The current available physical activity monitors are pedometers, accelerometers and multi-sensor systems.[55] Pedometers only measure step counts. Accelerometers assess and quantify a range of movements associated with activity including sedentary time, light activity, such as shopping or walking around the home, and MVPA.[56] Multi-sensor systems measure the amount and intensity of physical activity alongside a physiological measure such as heart rate or body temperature. Therefore, accelerometers and multi-sensor systems provide more comprehensive information about activity behaviours compared with pedometers.

Accelerometers are reliable and valid when compared with the doubly-labelled water method of determining energy expenditure.[55, 57] Despite their validity, there are several factors that need to be considered in research using accelerometers. Accelerometers collect

continuous data and convert physical activity behaviours into a digital signal. Data are compressed, filtered and analysed using algorithms to generate physical activity outputs. These activity end points include measures of the amount of activity, for example time spent in light activity, and total number of steps, and patterns of activity such as bouts of light activity, and breaks in sedentary time).

Decisions made regarding accelerometry measurement and processing can affect accelerometry outcomes. Accelerometers can differ in their placement on the body and how they collect data.[56] Additionally researchers can choose how to process data by making choices around physical activity cut-points and non-wear time.[56] These factors can impact on reproducibility and comparability of the physical activity outputs produced.[56]

2.4 Physical activity levels in cancer populations

In recent years there has been a growth in research examining physical activity in cancer populations.[56] Existing research indicates patients with lung cancer are less physically active than healthy adults.[58, 59] Several studies have evaluated activity levels in lung cancer patients with early stage disease. In a study of patients following curative intent treatment for early stage non-small cell lung cancer, participants with non-small cell lung cancer (n=20), compared with healthy controls, spent a greater proportion of their waking hours in prolonged bouts (≥30 min) of sedentary behaviour (42 [30-58]% vs. 49 [42-65]%; p=0.048) and lesser proportion of waking hours light intensity physical activity (26 ± 8% vs. 21 ± 9%; p=0.04).[58] In another study of patients with stage I-IIIB non-small cell lung cancer (n=50), the participants with lung cancer, compared with age and gender matched controls, took significantly fewer steps per day (8483 ± 558 vs. 6120 ± 579; p<0.01);[59] and fewer participants with lung cancer met recommendations of 150 minutes of MVPA per week (71% vs. 40%; p=0.01).[59] Therefore, even in lung cancer patients with early stage disease, the majority were inactive.

Few studies have reported on the activity levels of patients with advanced cancer, and no study has included patients with MPD. In one study of patients with advanced lung cancer (n=84), participants took, on average, 4246 ± 2983 steps per day and spent 19.7 ± 2.1 of all hours per day as sitting or lying down.[60] Similarly in another study that included patients with early and advanced stage lung cancer (n=124),[61] participants completed on average, 4596 ± 2106 steps per day and spent 9.8 ± 1.6 of their waking hours per day as sedentary; only 23% of participants met recommendations of 150 minutes MVPA per week.[61] In a study of patients with brain metastases (n=31), the average step count was lower, at 2784 ±

2278 steps per day.[62] By comparison in Australia, an average healthy adult accumulates 7400 steps per day.[63] These data indicate that patients with advanced cancer have particularly low activity levels. However, research is needed to understand the physical activity levels of patients with MPD, and how this relates to important clinical outcomes.

2.5 Physical performance and muscle strength in cancer populations

Research indicates that patients with lung cancer have poorer physical performance and muscle strength compared with healthy adults.[59, 64] In a study of patients with early stage lung cancer (n=50) the average Six-Minute Walk Distance was 84% of the predicted value for healthy adults,[59] and handgrip strength and quadriceps strength were lower among participants with lung cancer.[59] In another study of patients with lung cancer (n=39), including a high proportion with advanced stage disease, the average Six-Minute Walk Distance was 76% of the predicted value for healthy adults;[64] and the majority of participants had upper and lower extremity strength that was 20% below the healthy reference population.[64]

A number of studies have also reported on the physical performance and strength of older adults with cancer.[44, 65-67] In a study of breast cancer survivors aged >65 years (n=40), the average chair stand time, handgrip strength and Short Performance Physical Battery score were lower than for healthy controls,[65] while in another study of patients with early stage breast cancer aged >65 years (n=123), 20% of participants had a slow 4-m walk speed, 31% had a suboptimal Short Performance Physical Battery score and 57% had a low handgrip strength. In two larger studies of older adults with cancer (n=389 and n=354),[66, 67] with approximately half who had advanced stage disease, a suboptimal Short Performance Physical Battery score was recorded for 71% and 78% of participants, respectively. Overall, these findings suggest that physical performance and strength are commonly impaired in people with cancer. Two of these studies[65, 67] also reported a higher symptom burden was associated with poorer physical performance. While the high symptom burden associated with MPD indicates patients could be vulnerable to physical performance limitations, research is needed to understand the extent of the issue of functional impairment in MPD.

2.6 Measurement of body composition

Body composition refers to the relative amounts of muscle, fat and bone within the body.[68] The evaluation of muscle and fat, in particular, is integral for the diagnosis of a

range of conditions relevant to cancer populations. There are multiple methods available for assessing body composition and knowledge of how these techniques measure body composition is essential for understanding their potential research application.

2.6.1 Levels of body composition

The science that underpins current body composition assessment methodology has been explained in a five-level model of human body composition published in 1992.[69] The model depicts human body composition as atomic, molecular, cellular tissue and whole body levels **(Figure 2.1)**.[69]

The atomic level, describes the elements which are the building blocks of human body composition.[69] Ninety-eight percent of the human body is made up of six atomic elements.[69] Oxygen is the most abundant element in the human body, followed by carbon, hydrogen, nitrogen, calcium and phosphorous.[69]

The molecular level divides body composition into six compartments; water, lipids, protein, carbohydrates, bone minerals and soft tissue minerals.[69] Water is the most predominant molecule, comprising 60% of the human body.[69] Fats, the term given to the body's triglyceride stores, are the largest source of lipid in the body.[69] Non-fat lipids, for example phospholipids, which play an important structural role in the body are present in much smaller proportion.[69] Protein includes the nitrogen containing compounds found in the body.[69] Carbohydrates, mainly stored as glycogen, minimally contribute to body composition.[69] The predominant minerals found in the body are calcium and phosphorous, which make up bone.[69]

The cellular level, divides body composition into cell mass, extracellular fluids and extracellular solids.[69] Cell mass refers to the components found within a cell, including water, protein and minerals.[69] Extracellular fluid is predominantly water referred to as plasma (intravascular space) or interstitial fluid (extravascular space).[69] Bone minerals, collagen and elastic fibres make up the majority of extracellular solids.[69]

The tissue level is comprised of skeletal muscle, adipose tissue, bone, visceral organs, the heart and brain.[69] At this level, the measurement of tissues, for example, adipose tissue, includes both the fat (triacylglycerol) as well as the protein, minerals and water that make up the tissue.[69] Analysis of adipose tissue at this level can be further categorised as subcutaneous, visceral or interstitial.[69]

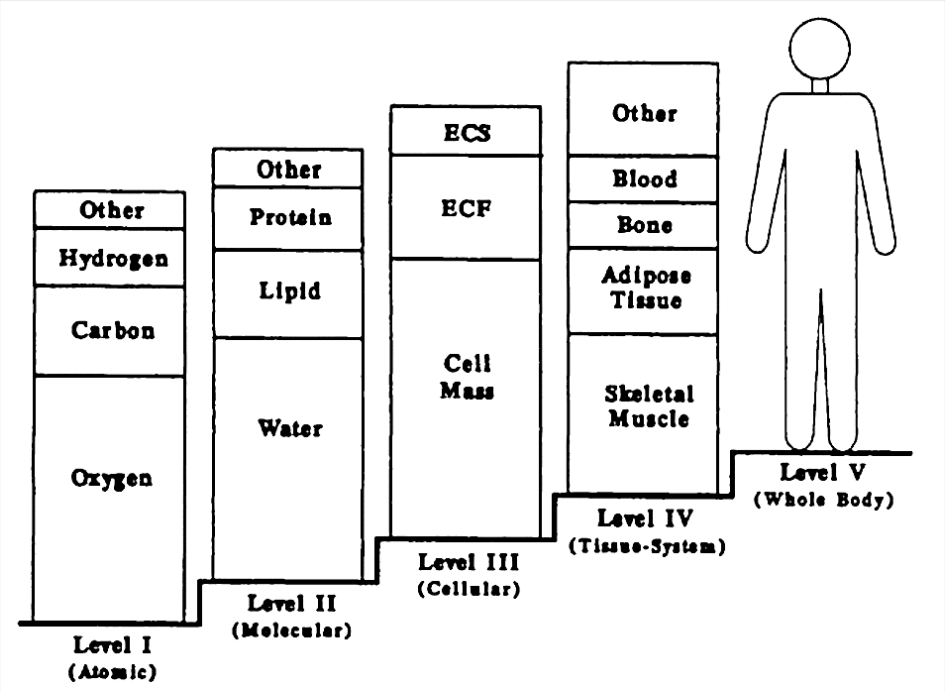

Figure 2.1 The five levels of human body composition. Source: Wang et al. 1992

2.6.2 Methods for body composition assessment

Methods for body composition assessment can be combined into five categories. These categories are anthropometry, total body water, major body elements, impedance and imaging.[70] Imaging is considered to be the most valid method for body composition assessment.[71] Imaging methods are comprised of computed tomography (CT), magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DXA) and ultrasound.[70] CT and DXA are the most commonly used methods for body composition assessment and therefore, are described in more detail in the following sections.

Computed Tomography

CT evaluates body composition at the tissue level and identifies bone, skeletal muscle, visceral organs and adipose tissue **(Figure 2.2**).[70] Participants undergoing CT are exposed to x-rays. The x-ray attenuation through tissues is detected by a computer software program and cross-sectional images are reconstructed.[72] The pixels that make up the image have a known attenuation relative to air and water and this is signalled by the Hounsfield Units allocated to it.[72] The body tissues have their own specific Hounsfield Unit ranges and these are used for body composition analysis.[72] The total number of pixels in the given surface area are summed to give the cross-sectional tissue area (cm^2).[70]

CT is a valid and reliable method for whole-body and regional measurement of body composition.[72] An advantage of CT is its capability to measure body composition at the tissue level, meaning it can examine individual muscle groups and intramuscular adipose tissue.[70] However, the precision of the CT method may be affected by the phase of the CT scan and the use of contrast during the scan.[73, 74] Whole-body CT imaging is associated with a high radiation dose and cost.[70]

CT scans that are typically used for patient care can be re-purposed to examine body composition.[75] This has the potential to reduce radiation exposure, research costs and participant burden. When re-purposed CT scans are used in research, skeletal muscle and adipose tissue are measured from a single cross-sectional image at the third lumbar vertebrae.[76] Abdominal skeletal muscle is strongly correlated with whole body skeletal muscle in healthy adults[77] and in patients with lung and gastrointestinal cancer.[76] Although, prediction equations used to provide an estimate of whole-body skeletal muscle mass may be inaccurate.[78]

Dual Energy X-Ray Absorptiometry

DXA evaluates body composition at the molecular level and therefore measures bone mineral mass, lean soft tissue and fat mass **(Figure 2.2**).[70] Participants that undergo a DXA scan are exposed to low-dose x-rays. All DXA machines have an x-ray source and a detector. The x-ray beams have two different photon-energy levels (low and high).[79] When the photons pass through an absorber (i.e., a person's body tissues; person), the amount of energy absorbed (i.e., how much the photons are scattered; attenuated) can be measured by a detector.[79] The overall attenuation is expressed as a ratio (R) of the absorption (attenuation) for the lower energy photon to absorption of the higher energy photon.[79] Each atomic element in the body has a characteristic R value/ratio, and the R values of molecules (calculated from elemental composition) and various body composition components (i.e., bone mineral, protein) have been calculated.[79]

DXA assumes that humans consist of three components that are distinguishable by their x-ray attenuation properties: fat, bone mineral and lean soft tissue.[79] Bone is separated out from fat and lean soft tissue because bone has a much higher R value.[79] Tissues are quantified from the assumed component R values, image processing methods and soft tissue distribution models.[79]

DXA is considered to be a valid and reliable method for body composition assessment.[72] Additionally, DXA involves a relatively low radiation dose and is quick to

complete.[70] Although, the precision of the DXA method may be affected by differences in machine software or the machine itself, patient positioning and hydration.[80] An additional limitation of DXA is that measured lean soft tissue includes skeletal muscle, organs, fibrous and connective tissue and there is no way to assess whole-body skeletal muscle separately.[81]

DXA has the capacity for regional body composition analysis. This means the arms and legs can be segmented from the trunk, enabling measurement of appendicular lean soft tissue, which is predominantly skeletal muscle.[70] Existing research indicates that appendicular lean soft tissue is highly correlated with whole-body skeletal muscle.[82, 83] Therefore, DXA can be used for research where skeletal muscle is an outcome of interest.

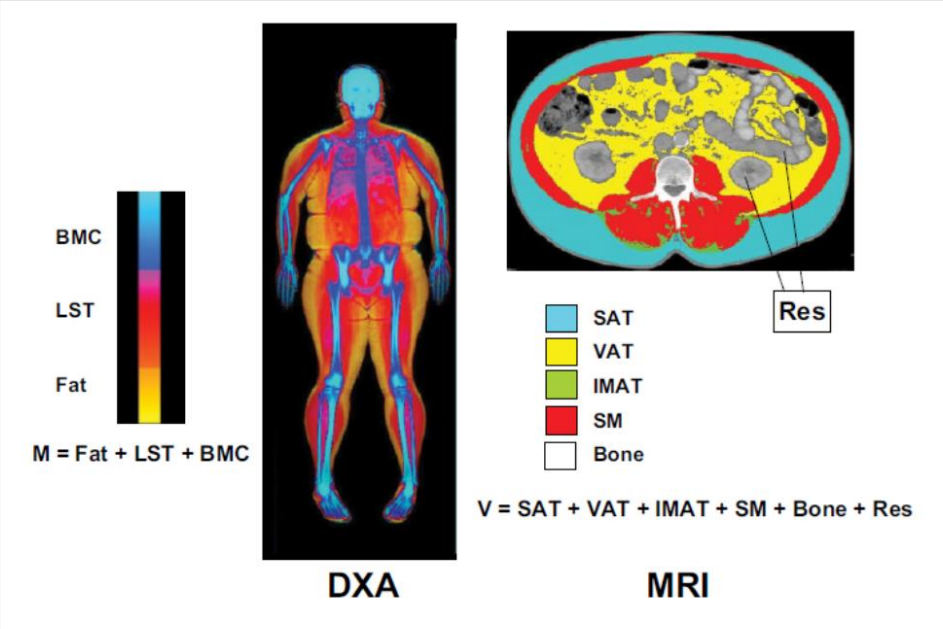

Figure 2.2 Components of body composition measured by dual energy x-ray absorptiometry and magnetic resonance imaging or computed tomography. Source: Prado et al. 2014.

2.7 Malnutrition

Malnutrition is a term used to describe weight loss and the associated reduction in muscle and fat mass.[84] Malnutrition can result from inadequate nutrient intake, impaired nutrient absorption, impaired nutrient utilisation, or a combination of these factors.[84] The development of malnutrition and subsequent loss of skeletal muscle is of concern due to its important role within the body. Skeletal muscle is primarily known for its role in physical movement therefore, the loss of skeletal muscle mass could negatively impact on locomotion and activities of daily living.[85] Skeletal muscle also has an important role in body metabolism and is the reservoir from which amino acids can be supplied to other

organs for the synthesis of new body proteins.[86] Consequently, reduced skeletal muscle mass could impact on the body's ability to prevent and respond to illness.

2.7.1 Diagnosis of malnutrition

Multiple diagnostic criteria have been developed for malnutrition.[87-89] In 2012, an expert group from the European Society for Parenteral and Enteral Nutrition (ESPEN) convened to produce a consensus statement on diagnostic criteria for malnutrition.[87] The recommendations from the ESPEN expert group were that malnutrition could be defined by either 1) BMI of <18.5 kg/m^2 or 2) unintentional weight loss of >10% over any time period; or unintentional weight loss of >5% over a 3 month time period in combination with several factors including: a BMI <20 kg/m^2 if aged <70 years; or a BMI <22 kg/m^2 if aged ≥70 years; or muscle mass of <17 kg for men and <15 kg for women.[87] Therefore, earlier diagnostic criteria for malnutrition focused on the physical characteristics associated with the condition.

The clinical nutrition community has recommended that the aetiology of malnutrition is identified within the diagnosis.[90] In 2017, an ESPEN working group published a list of clinical nutrition terminology that recognised aetiology-based diagnosis of malnutrition. The ESPEN working group recommended the use of 'disease-related malnutrition' to describe situations where underlying disease has caused a reduction in nutrient intake, absorption or utilisation[84] and the use of 'disease-related malnutrition with inflammation' is used where malnutrition exists in the context of a disease that results in underlying inflammation.[84]

Updated diagnostic criteria for malnutrition were required to reflect the aetiology-based diagnosis. In 2016, members of the Global Leadership Initiative on Malnutrition (GLIM) convened to produce an updated consensus on the diagnostic criteria for malnutrition.[88] The recommendations were that malnutrition should be defined by both the physical characteristics, known as phenotypic factors, and aetiologic factors associated with the condition.[88] According to the GLIM criteria, a diagnosis of malnutrition requires the presence of either low BMI, weight loss or reduced muscle mass plus evidence of reduced nutrient intake, absorption or utilisation or the presence of inflammation.[88]

Of several nutrition assessment tools which include the phenotypic and aetiologic factors of malnutrition,[88] the Patient-Generated Subjective Global Assessment (PG-SGA) has been validated for use in patients with cancer.[91] The PG-SGA includes a patient-generated component where weight history, food intake, symptoms and function are assessed, and involves a professional component where muscle and fat stores are visually

inspected and disease and metabolic factors are assessed.[92] Completion of the PG-SGA results in a score as well as a global rating of nutritional status.[92]

While existing research indicates that weight loss is common in patients with MPD at diagnosis,[28, 29] the amount and timing of weight loss is seldom described and there has been no assessment of associated changes in muscle mass, dietary intake or inflammation using validated tools. Therefore, a more comprehensive evaluation of nutritional status and body composition is needed to determine the extent of malnutrition over the disease course in patients with MPD.

2.8 Cancer cachexia

Cancer cachexia is an example of 'disease-related malnutrition with inflammation' and is characterised by the preferential loss of muscle mass but can be accompanied by fat loss.[93] Three stages of cancer cachexia have been defined.[94] Pre-cachexia is the term given to the first stage of the syndrome, while cachexia is the second stage and refractory cachexia is the final stage.[94] Pre-cachexia is characterised by weight loss of ≤5% in combination with a poor appetite and metabolic changes.[94] Cachexia is defined as weight loss of >5% in 6 months; or weight loss >2% in 6 months in combination with a BMI of <20 kg/m^2 or clinically low levels of muscle mass.[94] These physical characteristics of cancer cachexia are often accompanied by reduced dietary intake and systemic inflammation.[94] Refractory cachexia is characterised by weight loss in the context of a poor performance status and expected survival of less than 3 months.[94]

2.8.1 Mechanisms of cancer cachexia

In healthy adults, there is a balance between muscle protein synthesis and degradation which helps to preserve muscle mass.[86] For muscle loss to occur, there must be a decrease in muscle protein synthesis, an increase in muscle protein degradation or a combination of both.[95] Muscle protein synthesis is affected by dietary protein intake, especially the essential amino acid leucine, as well as exercise and anabolic hormones.[96] Muscle protein degradation can be affected by inflammation.[86] Although the mechanisms are unclear, cancer cachexia is influenced by a combination of both reduced dietary intake and altered metabolism.[93]

Reduced dietary intake

Studies in patients with advanced cancer have reported that individual dietary intake varies substantially[97] and a proportion of patients do not meet energy and protein requirements.[97, 98] In a study of patients with advanced lung or gastrointestinal cancer (n=51), energy intake ranged from 14 – 55 kcal/kg/day and protein intake from 0.6 – 2.2 g/kg/day,[97] and 27% of participants did not achieve an energy intake of ≥25 kcal/kg/day, while 43% did not achieve a protein intake of ≥1.0 g/kg/day.[97] In another study of patients with advanced lung or gastrointestinal cancer (n=84), 27% of participants did not achieve an energy intake of ≥30 kcal/kg/day, 1% did not achieve a protein intake of ≥1.0 g/kg/day and 33% did not achieve an energy intake of ≥30 kcal/kg/day or protein intake of ≥1.0 g/kg/day.[98] These results indicate that inadequate energy intake, in particular, is common in patients with advanced cancer.

A number of factors are thought to be responsible for the reduced dietary intake frequently observed in patients with advanced cancer. In particular, pro-inflammatory cytokines and hormonal changes are thought to result in a lack of appetite. A recent review article on the pathophysiology of cancer cachexia suggests inflammatory cytokines can mimic the hormone leptin, which is responsible for reducing appetite.[95] At the same time, hormones that stimulate appetite such as ghrelin and neuropeptide Y are suppressed.[95] The resultant lack of appetite can lead to a reduction in dietary intake.

There are no data to confirm a causal relationship between lack of appetite and reduced dietary intake, however, there is a reported association between appetite and energy intake. In a study of patients with breast cancer who underwent chemotherapy (n=114), each point decrease in appetite was associated with a 26.5 kcal (95% CI 14.4 – 38.5) decrease in energy intake.[99] Research in patients with advanced cancer (n=143) found that those self-reporting a lack of appetite had significantly lower energy intake compared to those reporting a normal appetite (1515 ± 544 vs. 1149 ± 580 kcal/day; $p<0.001$).[100] These results indicate that a poor appetite is associated with lower energy intake, which if unresolved could lead to the development of cancer cachexia.

Beyond lack of appetite, cancer and its treatment can cause additional symptoms that negatively impact on dietary intake. For example, in the study of patients with breast cancer who underwent chemotherapy, compared to healthy controls participants with breast cancer reported poorer taste when measured with the Appetite, Hunger feelings and Sensory Perception questionnaire (30.9 ± 0.71 vs. 22 ± 0.57; $p<0.05$). Additionally, each

point decrease in taste was associated with a 16.4 kcal (95% CI 7.0 – 25.8) decrease in energy intake.[99] In a study of patients with advanced pancreatic cancer (n=39) who were followed prospectively every 4 weeks until the end of life,[101] moderate to severe pain at rest (≥4 on Edmonton Symptom Assessment Scale) was associated with significantly lower energy intake compared with low pain at rest at study inclusion and at three, monthly follow up assessments. Other symptoms including oral dryness, nausea and fatigue were also associated with a lower energy intake.[101]

The difference in energy intake between weight losing and weight stable patients with cancer has been investigated in several studies. In a large study of patients with mixed cancer diagnoses (n=297), where weight loss was defined as >5% body weight, there were no significant differences in energy intake between weight stable and weight losing participants.[102] Weight losing participants consumed 28 ± 12 kcal/kg/day compared with weight stable patients who consumed 24 ± 8 kcal/kg/day (p=0.052). A similar result was observed in a study of patients with advanced pancreatic cancer (n=20) where cachexia was defined as >5% weight loss within 6 months or >2% weight loss in those with a BMI <20 kg/m^2.[103] Participants with cachexia consumed 22.1 [14.3 – 33.9] kcal/kg/day compared with participants who were non-cachectic who consumed 28.9 [8.6 – 79.7] kcal/kg/day (p=0.09).[103] These results indicate that energy intake is not significantly different between those with and without weight loss. These findings may be attributable to variable energy requirements between individuals related to differences in age, sex and lean mass.[104] However, these result could also indicate that factors beyond reduced food intake are likely to be involved in the development of cancer cachexia.

Altered metabolism

Pro-inflammatory cytokines and hormones could play a key role in the altered metabolism of cancer cachexia. There are multiple components to the altered metabolism seen in cancer cachexia including hypercatabolism, hypermetabolism and hypoanabolism. Regarding hypercatabolism, tumour necrosis factor α (TNFα) and interleukin-6 (IL-6) promote insulin resistance that decreases protein synthesis and stimulate the ubiquitin-proteasome pathway that leads to protein catabolism.[105] Adipose tissue is lost as a result of increased lipolysis which occurs due to the tumour-induced lipid mobilising factor. [105]

Several studies have evaluated differences in cytokines or biomarkers between weight losing and weight stable patients with cancer. Although findings are inconsisent[106-108] IL-6 is the most commonly studied of the cytokines, with the most consistent results.[109-111]

Several studies have reported that serum IL-6 concentrations are higher in weight losing compared with weight stable patients.[109-111] Additionally, albumin concentrations are lower and C-reactive protein (CRP) concentrations are higher in cancer patients with weight loss and low muscle mass.[112-116]

Low concentrations of anabolic hormones such as testosterone could contribute to the loss of skeletal muscle in patients with cancer. Testosterone concentrations can be lowered by increasing age, cancer treatment,[117] inflammation,[117] and opioid medications used to treat pain.[117] Consequently, low testosterone concentrations are common among patients with cancer, affecting between 40 and 90% of patients.[117] Two studies in patients with advanced cancer have previously examined the relationship between testosterone levels and weight loss,[118, 119] and both studies reported that there was an inverse correlation between testosterone concentrations and weight loss.[118, 119]

Hypermetabolism, which is an increase in resting energy expenditure, could also play a role in the onset and progression of cancer cachexia. When energy expenditure is increased, amino acids are released from skeletal muscle for energy production resulting in an overall loss of skeletal muscle.[85] The tumour, hepatomegaly and liver metastases, and activation of brown adipose tissue may contribute to an increase in resting energy expenditure.[120] Conversely, some patients with cancer may have a lower total energy expenditure due to low physical activity levels and reduced food intake.[120] Hypermetabolism affects approximately 40% of patients with advanced lung cancer.[121, 122] Despite the theoretical relationship between hypermetabolism and weight loss, research indicates that weight loss does not differ between hyper- and normo-metabolic patients.[102] Overall, these results highlight that more research is needed to fully understand the relationship between metabolism and weight loss in patients with cancer, including those with MPD.

2.8.2 Treatment of cancer cachexia

Cancer cachexia could also be partly reversed by addressing inadequate dietary intake before the refractory stage of cachexia is reached.[93] Where weight loss is present, the American Society of Clinical Oncology (ASCO) guidelines for the management of cancer cachexia recommend referral to a dietitian for dietary counselling on a high-energy, high-protein diet.[123] Energy and protein intakes of 25 – 30 kcal/kg/day and 1.0 – 1.5 g/kg/day are considered appropriate targets.[124]

Exercise has been proposed as another potential treatment for cancer cachexia. As resistance exercise training is associated with muscle hypertrophy,[125] this type of

intervention could help to negate muscle loss associated with cancer cachexia. There are currently a lack of exercise interventions in patients with cancer cachexia,[123] therefore there is insufficient evidence to make a recommendation of the role of exercise in the management of cancer cachexia.[123]

Cancer cachexia cannot be fully reversed without also addressing the underlying metabolic alterations.[94] Early clinical trials suggest that ghrelin analogues, selective androgen receptor modulators, anti-inflammatory agents and cannabinoids are promising pharmacological treatments for cancer cachexia.[126] However, there is insufficient evidence to recommend any of the studied pharmacological treatments for cancer cachexia, and no treatments are clinically available.[123]

Multi-modal interventions that include a combination of nutrition support, exercise training and pharmacologic agents could have an important role in the management of cancer cachexia. Fearon et al[93] has proposed that multi-modal interventions may be more effective than single interventions as they address the multiple factors that contribute to cancer cachexia. However, information on the relationship between nutritional status, body composition and dietary intake, physical activity and inflammation are needed to establish the potential for multi-modal interventions in patients with MPD.

2.9 Prevalence of malnutrition in cancer populations

Approximately one-quarter of patients with cancer have malnutrition.[127] However, the prevalence varies according to the cancer population, stage of disease and type of cancer treatment received.[127] Research from Australia indicates that upper gastrointestinal, head and neck and lung cancer populations have the highest prevalence of malnutrition.[127] Additionally, those who have metastatic disease or are receiving chemotherapy or combined chemo-radiation are more likely to have malnutrition.[127]

There is a lack of information on the prevalence of malnutrition in patients with MPM, as patients with MPM have historically been included in studies of patients with lung cancer.[128] Several studies have evaluated the prevalence of malnutrition in advanced lung cancer populations.[107, 129-137] The studies range in size from 25 – 1219 participants and the majority of studies assessed nutritional status using the PG-SGA[130, 132-134] or SGA,[129, 131, 138] although other studies used the Mini-Nutritional Assessment (MNA),[107] Malnutrition Universal Screening Tool,[135] or GLIM criteria.[137] Notably, there was a large range in the prevalence of malnutrition of between 24 – 100% of participants **(Table 2.3)**. This large range in the prevalence of malnutrition is likely related to the different criteria used to

assess nutritional status. The lowest prevalence of malnutrition was observed where the MNA or GLIM criteria were used, while the highest prevalence of malnutrition were observed where a PG-SGA score of 2-8 was considered indicative of moderate malnutrition. A PG-SGA score of two can be reached if a person is older than 65 years and has a diagnosis of cancer, therefore this cut-point can result in a false positive diagnosis of malnutrition. Regardless of these differences in assessment methods, these results highlight that malnutrition is common in patients with advanced lung cancer. However, as advanced lung cancer is distinctly different from MPM, research is needed on the prevalence of malnutrition specifically in patients with MPM.

Several studies have also evaluated weight changes over time in patients with advanced cancer. In a study of patients with unresectable pancreatic cancer (n=20), participants were assessed for a median duration of 27 weeks.[139] The median BMI at diagnosis was 20.7 kg/m^2 and BMI just before death was lower at 17.7 kg/m^2, which represented a median weight loss of 5 kg over the course of the disease.[139] This result indicated that weight loss could be progressive over the disease course in patients with advanced cancer.

Further studies have indicated that weight loss occurs only in a proportion of patients during any given time period. In a large prospective observational study of patients with incurable cancer (n=544) patient-reported weight loss was graded from 0 to 4 based on percentage weight loss and BMI.[140] While the majority of participants did not change weight loss grade in 3 months, between 19 and 39% of patients progressed to a more advanced grade within 3 months[140] and between 4 and 13% improved weight loss grade.[140] A similar result was reported from a multi-institutional prospective, observational study in patients with non-small cell lung cancer (n=406) where the incidence rate of ≥5% weight loss was reported at four time points over the disease course.[141] At 3, 6, 9 and 12 months the incidence rate of ≥5% weight loss ranged between 0.248 and 0.288. Therefore, within any 3-month period approximately 30% of participants experienced greater than 5% weight loss.[141] These results indicate that in some advanced cancer populations there is a risk of weight loss across the disease course. However, research is needed to understand the extent of the issue of malnutrition across the disease course specifically in patients with MPM.

Table 2.3 Prevalence of malnutrition in advanced cancer populations

Study	Cancer population	Study design, sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence of malnutrition
Antoun, 2019[142]	Metastatic colorectal cancer	Prospective, n=76	Mean age 61 years, 50% men	Prior to chemotherapy	>5% weight loss or >10% weight loss	49% with >5% weight loss 26% with >10% weight loss
Araujo dos Santos, 2015[143]	All cancer groups (27% prostate, 22% breast, 9% lung). 49% with metastatic disease	Cross-sectional, n=96	Mean age 71 years, 50% men	No specified time point	PG-SGA global rating of B or C	44% malnourished
Arrieta, 2010[129]	Advanced non-small cell lung cancer	Prospective, cross-sectional, n=100	Median age 59 years, 53% men	Prior to chemotherapy	SGA global rating of B or C	51% malnourished (34% moderately malnourished, 17% severely malnourished)
Barata, 2017[130]	Advanced lung cancer	Cross-sectional, n=37	Mean age 67, 84% men	While awaiting medical consultation or treatment	PG-SGA global rating of B or C	81% malnourished (73% moderately malnourished, 8% severely malnourished)
Bozzetti, 2009[144]	All cancer types (42% colorectal, 18% head and neck, 16% stomach, 12% lung); 42% stage IV disease	Prospective, cross-sectional study, n=1000	Median age 64 years, men-to-women ratio 1.8	No specified time point	NRS score ≥3 and weight loss >10%	40% malnourished
Cehreli, 2019[131]	Advanced lung cancer	Prospective, n=25	Mean age 63 years, 16% men	Newly diagnosed, prior to chemotherapy	SGA global rating of B or C	80% malnourished (48% moderately malnourished, 32% severely malnourished)

Study	Cancer population	Study design, sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence of malnutrition
Chabowski, 2018[145]	Lung cancer; 40% with metastatic disease	Cross-sectional, n=257	Mean age 63 years, 55% men	No specified time point	MNA score ≤11	23% malnourished
Dong, 2020[132]	Advanced lung cancer	Prospective, n=59	36% aged ≥65 years, 70% men	No specified time point	PG-SGA score 2-8 is moderate malnutrition; and ≥9 is severe malnutrition	100% malnourished (25% moderately malnourished, 75% severely malnourished)
Ge, 2019[133]	Advanced lung cancer	Prospective, n=495	61% aged >60 years, 71% men	Newly diagnosed	PG-SGA score ≥9 indicates need for symptom management and/or nutrition support	25% with need for symptom management and/or nutrition support
Gioulbasanis, 2011[107]	Metastatic lung cancer	Cross-sectional, n=115	Median age 66 years, 88% men	Newly-diagnosed, prior to chemotherapy treatment	MNA score ≤11	25% malnourished
Kiss, 2014[146]	Lung cancer; 25% with advanced disease	Retrospective, n=96	Median age 67 years, 64% men	First or second week of radiotherapy	PG-SGA global rating of B or C	15% malnourished (15% mildly to moderately malnourished, 0% severely malnourished)
Koom, 2012[147]	Head and neck, lung and gastrointestinal cancer (lung 27%); included palliative treatment intent	Prospective, n=1,000	Mean age 59 years, men to women ratio 7:3	Assessed 3 weeks after the initiation of radiation therapy.	SGA global rating of B or C	40% malnourished (35% moderately malnourished, 5% severely malnourished)

Study	Cancer population	Study design, sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence of malnutrition
Li, 2018[148]	All cancer sites (lung 20%); 45% metastatic cancer	Cross-sectional, n=1138	Mean age 61 years, 58% men	No specified time	>5% weight loss in 6 months or BMI <20 and >2% weight loss	41% malnourished
Lin, 2019[134]	Advanced lung cancer	Prospective, n=465	Mean age 60 years, 52% men	Prior to chemotherapy	PG-SGA global rating of B or C	77% malnourished (66% moderately malnourished, 11% severely malnourished)
Mohan, 2017[135]	Advanced non-small cell lung cancer	Prospective, n=148	Mean age 57 years, 87% men	Not specified	MUST score ≥2 indicates a need for treatment of malnutrition	64.9% with a score ≥2
Montoya, 2010[149]	All cancer groups receiving chemotherapy (lung cancer 23%); 55% stage IV disease	Cross-sectional, n=88	Mean age 56 years, 36% men	During chemotherapy	SGA global rating of B or C	48% malnourished (43% moderately malnourished, 5% severely malnourished)
Muscaritoli, 2017[150]	All cancer groups lung cancer 16%); 48% metastatic	Prospective, observational study, n=1,952	Mean age 63 years, 48% men	First medical oncology visit	MNA score ≤11	9% malnourished
Percival, 2013[151]	Thoracic cancer (0.4% mesothelioma); 74% palliative treatment intent	Prospective, n=243	Mean age 70 years, 57% men	No time specified	BMI <18.5 kg/m^2, >10% weight loss, or BMI <20 kg/m^2 and >5% weight loss	35% malnourished (20% of patients with mesothelioma malnourished)

Study	Cancer population	Study design, sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence of malnutrition
Platek, 2011[152]	All cancer groups (lung cancer 39%); 40% metastatic disease	Retrospective study, n=227	Mean age, 56% men	During hospital admission	ICD-9 codes documented by physician Dietitian assessment that patient "compromised" BMI of <18.5 kg/m^2	9% malnourished using ICD-9 codes 26% malnourished using dietitian assessment 9% malnourished using BMI
Sanchez-Lara, 2012[136]	Advanced non-small cell lung cancer	Cross-sectional, n=119	Mean age 62 years, 46% men	Newly diagnosed prior to chemotherapy	SGA global rating of B or C	60% malnourished (33% moderately malnourished, 27% severely malnourished)
Segura, 2005[153]	All cancer groups (lung cancer 23%); 56% locally advanced or metastatic cancer	Retrospective, cross-sectional study, n=781	Median age 62 years, 64% men	All treatment phases included	PG-SGA global rating of B or C	52% malnourished (40.4% moderately malnourished, 11.8% severely malnourished)
Wie, 2010[154]	All cancer groups (lung cancer 20%); 60.5% stage III or IV cancer	Prospective, cross-sectional study, n=8895	Mean age 55 years, 56% men	During hospital admission	BMI <18.5 kg/m^2, albumin <2.8 g/dL, total lymphocyte count <1200 cells/mm^3 and nothing per oral intake	61% malnourished (36.5% high risk of malnutrition, 24.8% at moderate risk of malnutrition).
Yin, 2020[137]	Lung cancer, 40% with stage IV disease	Prospective, n=1219	Mean age 59 years, 67% men	During hospital admission	GLIM criteria with calf circumference and body weight standardised handgrip strength to assess reduced muscle mass	24% malnourished

2.10 Relationship between malnutrition and patient-related health outcomes

2.10.1 Quality of life

The relationship between malnutrition, defined by percent weight loss, and quality of life in cancer populations has been reported in multiple studies.[155] No data are available on the relationship between malnutrition and quality of life in patients with MPM, however some data is available from patients with lung cancer.[136, 156] One large study in patients with non-small cell lung cancer (n=531) with predominantly advanced stage disease, compared the relationship between the different stages of cachexia, and quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[157] The study reported that the functional, role and social domains of quality of life decreased with advancing cachexia stage.[157] Additionally, in a cross-sectional study of patients with newly diagnosed advanced lung cancer (n=119), participants with malnutrition had significantly lower physical functioning and role functioning scores on the EORTC QLQ-C30 compared with well-nourished participants.[136] In another cross-sectional study which included patients with all stages of lung cancer (n=180), global quality of life on the EORTC QLQ-C30 as well as all of the questionnaire domains, including physical, role, emotional, cognitive and social, were significantly lower in patients with malnutrition compared to well-nourished participants.[156] These results highlight a relationship between malnutrition and poorer quality of life, particularly for domains related to physical and functional aspects of life, however it is not known if this relationship exists in patients with MPM.

2.10.2 Physical activity, physical functioning and muscle strength

There is little information available in cancer populations on the relationship between malnutrition and physical activity. However, one study in patients with non-small cell lung cancer (n=531) with predominantly advanced stage disease, compared the relationship between the different stages of cachexia, and self-reported physical activity.[157] The study reported that physical activity decreased with advancing cachexia stage, such that participants who were well nourished participated in a median of 2712 metabolic equivalent minutes of activity per week and participants who were cachexic participated in only 495 metabolic equivalent minutes of activity per week.[157]

Several studies have reported on the relationship between malnutrition and physical functioning and muscle strength. One study of patients with unresectable lung cancer (n=37) assessed nutritional status with the PG-SGA prior to treatment and reported that

those who were malnourished were more likely to have a handgrip strength in a lower percentile compared with those who were not malnourished (p=0.026). Additionally, in a study of patients with colorectal cancer (n=67)[158] where nutritional status was assessed prior to surgery, those who were malnourished, defined as weight loss >10%, had significantly lower handgrip strength compared to those who were well-nourished, defined as weight loss <10% (19.4 vs. 27.3 kg; p=0.013). Regarding measures of physical functioning, a cross-sectional study conducted amongst older adults with cancer (n=185) reported that compared to participants without weight loss, participants with unintentional weight loss (weight loss >3 kg) had significantly lower handgrip strength (p=0.040) but there was no difference in walking speed (p=0.172).[159] The available data indicates that malnutrition could be associated with poorer physical activity and muscle strength. In patients with MPM one of the goals of care is to improve daily physical activities so an understanding of the factors that could impact on daily physical activities will help to inform future research and could impact on clinical practice.

2.11 Sarcopenia

The term sarcopenia was first defined in 1988,[160] and is used to describe the presence of low skeletal muscle mass and the resulting impairment of physical function.[161] More recently, sarcopenia has been defined as a skeletal muscle disorder that is progressive and generalised in nature and is associated with a range of negative outcomes.[162] Sarcopenia was originally used to describe the age-related loss of skeletal muscle mass, however it is now accepted that loss of skeletal muscle mass can be a consequence of inactivity, inadequate dietary intake, disease or a combination of these factors.[161]

2.11.1 Diagnosis of sarcopenia

The first consensus statement on the diagnosis of sarcopenia was published by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010.[161] The working group identified three stages of sarcopenia: pre-sarcopenia, sarcopenia and severe sarcopenia.[161] Pre-sarcopenia was defined as the presence of low skeletal muscle mass, while sarcopenia was defined as the presence of low skeletal muscle mass with either low muscle strength or function and severe sarcopenia was defined as low skeletal muscle mass with both low strength and function.[161]

An updated consensus statement on the diagnosis of sarcopenia was published by EWGSOP in 2019.[162] The updated statement does not refer to pre-sarcopenia and rather

provides an alternative algorithm to facilitate the diagnosis of sarcopenia in clinical practice.[162] The working group recommended that assessment of sarcopenia begins with an evaluation of muscle strength, and only if this measurement is low, is evaluation of muscle mass or muscle quality performed.[162] Although the EWGSOP criteria are commonly used to define sarcopenia, it is acknowledged that multiple definitions of sarcopenia exist, and there remains no international consensus on diagnostic criteria for sarcopenia in older adults.

There is currently no consensus on the optimal body composition assessment method for the measurement of muscle in patients with cancer. CT and DXA are both considered appropriate for the measurement of muscle,[162] although each has limitations as outlined in section 2.6.2. To determine if muscle mass is indicative of low or normal muscle mass a cut-point is applied. Multiple cut-points are available for both CT and DXA **(Table 2.4**). CT cut-points have been established from values that were associated with mortality,[163, 164] however it is not known if these values correspond with other clinical outcomes such as physical function. DXA cut-points have been established from values that were more than 2 standard deviations below a reference population of healthy young adults[165, 166] or the lowest 20% of values of a population of older adults,[167, 168] and are associated with functional impairment in older adults.[169] There is limited information on the comparability of CT and DXA cut-points, however results from one study in advanced lung and gastrointestinal cancer indicate only moderate agreement between methods for the classification of low muscle mass.[78] Further comparison of CT and DXA and their cut-points are needed to investigate the impact of methodological decisions on research findings.

Table 2.4 Published cut-points for the classification of low muscle mass

Study	n/sex/age	Reference population	Cut-point method	Cut-point value
Computed tomography				
Prado et al. 2008[163]	250; 54% men; 35-88 years	Cancers of the respiratory or gastrointestinal tract	Optimal stratification, cut-off values associated with mortality	<52.4 cm^2/m^2 for men <38.5 cm^2/m^2 for women
Martin et al. 2013[164]	1473; 56% men; 64.7 ± 11.2 years for men, and 64.8 ± 11.5 years for women	Cancers of the respiratory or gastrointestinal tract	Optimal stratification; cut off values associated with mortality	<43 cm^2/m^2 for men with BMI ≤24.9 kg/m^2; <53 cm^2/m^2 for men with BMI>24.9 kg/m^2 <41 cm^2/m^2 for women
Dual energy x-ray absorptiometry				
Baumgartner et al. 1998[165]	808; 53% men; 73.6 ± 5.8 years for men and 73.7 ± 6.1 years for women	Healthy young adults	2 SD below mean of healthy young adults	<7.26 kg/m^2 for men <5.45 kg/m^2 for women
Newman et al. 2003[167]	2984; 48% men; 70-79 years	Older adults	Sex-specific lowest 20% of the distribution index	<7.23 kg/m^2 for men <5.67 kg/m^2 for women
Delmonico et al. 2007[168]	2976; 48% men; 70-79 years	Older adults	Sex-specific lowest 20% of the distribution index	<7.25 kg/m^2 for men <5.67 kg/m^2 for women
Gould et al. 2014[166]	2371; 60% men; 20-93 years	Healthy young adults	2 SD below mean of healthy young adults	<6.94 kg/m^2 for men <5.30 kg/m^2 for women

2.11.2 Aetiology of low muscle mass

Age

As people age, and particularly from the fifth decade of life, muscle mass declines.[170] In a review which included five longitudinal studies ranging in duration from 5 – 12 years, the authors reported that median yearly muscle loss in participants with a mean age of 75 years ranged from -0.024% to 1.3%,[171] the decline in strength was disproportionate to muscle mass; and that strength deteriorated at a greater rate than muscle mass. Notably, changes in muscle mass and strength differed according to the sex of participants. Compared to women, men experienced a greater decline in muscle mass (0.64 – 0.70% vs. 0.8 – 0.98%) and strength (2.5-3.0% vs. 3.0 – 4.0%).[171] These findings indicate that while muscle loss and functional decline occur in both men and women, men are more severely impacted.

As a result of this gradual decline in muscle mass, the prevalence of low muscle mass increases with older age. In the New Mexico Elder Health Survey study of older adults (n=426), the authors reported the prevalence of sarcopenia in Caucasian adults of different age brackets, where sarcopenia was defined as muscle mass >2 standard deviations below healthy adults.[165] Sarcopenia was present in 13.5% of Caucasian men aged <70 years and 23.1% of women aged <70 years; and in 52.6% of men aged ≥80 years and 43.2% of women aged ≥80 years.[165] In another study, the authors reported the prevalence of sarcopenia in healthy older adults (n=4504), where class II sarcopenia was defined as muscle mass >2 standard deviations below healthy adults. The prevalence of sarcopenia was low and remained consistent across age brackets.[169] Class II sarcopenia was present in only 6% of men aged and 9% of women aged 60-69 years; and in 7% of men and 11% of women aged 70-79 years and ≥80 years.[169] These results indicate that the prevalence of low muscle mass increases with advancing age, although rates of low muscle mass vary by gender and between populations.

The mechanisms responsible for the decline in muscle mass and function are unknown, although several physiological changes that occur with older age could be involved. These include an increase in the proportion of muscle fibres to a single motor unit, fatty infiltration of the muscle, neural changes and hormonal changes such as anabolic resistance, and inflammatory changes.[172]

Physical activity

Individuals with higher physical activity levels are reported to have a lower risk of developing low muscle mass. Steffl et al[173] conducted a systematic review and meta-analysis[173] of observational studies to evaluate the risk of low skeletal muscle mass among adults aged older than 40 years (n=4605) according to their physical activity level and reported that the odds ratio was 0.45 (95% CI 0.37 – 0.55) for those with the highest physical activity level. This finding indicates that adequate physical activity could be protective against the development of low skeletal muscle mass in older adults. However, there is little information on the relationship between physical activity and changes in skeletal muscle in patients with cancer. This information could be used to guide the development of supportive care interventions aimed at preserving skeletal muscle mass.

Dietary intake

Higher protein intakes are associated with greater skeletal muscle mass and less loss of skeletal muscle mass over time. In a cohort study of older adults (n=740),[174] participants who did not meet the recommended daily intake (RDI) for protein, of 64 – 81 g/day for men and 46 – 57 g/day for women depending on the age group, had lower levels of appendicular lean mass at baseline after adjusting for confounding factors (mean difference -0.81, [95% CI -1.54 - -0.08] kg; p=0.03). In the Health, Aging and Body Composition study[175] where older adults aged between 70 and 79 years (n=2732) were followed for three years, total protein intake was inversely associated with change in total lean mass and appendicular skeletal muscle mass after adjusting for confounding factors. Specifically, higher protein intake was associated with less muscle loss. Additionally, participants with the highest protein intake of 1.2 g/kg/day lost 43% less total lean mass and 39% less appendicular lean mass than those with the lowest protein intake of 0.8 g/kg/day ($p<0.01$). This indicates that adequate protein intake is protective against muscle loss and that the level of adequate protein intake is higher in older adults compared to young adults. As with physical activity, there is a lack of information on the relationship between dietary intake and changes in skeletal muscle in patients with cancer, which is critical for the development of supportive care interventions.

2.11.3 Prevalence and factors contributing to low muscle mass in cancer populations

The overall prevalence of low muscle mass in patients with cancer is reported to be 40%.[176] In a review paper, Ryan et al[177] summarised the prevalence of low muscle mass according to cancer diagnosis, and reported the median prevalence of low muscle mass ranged between 38 – 70%, although there was a large prevalence range within each diagnosis. There is little information on the prevalence of low muscle mass in patients with MPD, however a systematic review and meta-analysis has reported the overall prevalence of low muscle mass in patients with lung cancer was 45%.[178] Five of the studies included in this publication were specifically in advanced lung cancer **(Table 2.5)**.[179-183] Other studies have also reported on the prevalence of low muscle mass in advanced lung cancer.[184, 185] The studies ranged in size from 33 – 441 participants and the majority of studies used CT[180-185] to measure muscle mass with only one study using DXA.[179] There was a large range in the prevalence of low muscle mass of between 38 – 71% of participants. This large range in prevalence of low muscle mass could be related to the different cut-points used to assess muscle mass between studies. Regardless, these results indicate high rates of low muscle mass among patients with advanced lung cancer. This suggests that low muscle mass may also be common among patients with MPD, however currently there is a lack of body composition data specific to patients with MPD to investigate this hypothesis.

There is limited data available on characteristics associated with low muscle mass in patients with cancer, however the prevalence of low muscle mass in men, at 25%, is almost double that of women, at 13%.[176] While chemotherapy is thought to contribute to muscle loss in patients with cancer, due to its proteolytic effect on muscle,[186] existing research indicates that muscle loss can occur regardless of cancer treatment.[183, 187] In a study of patients with advanced lung cancer (n=222) who received a placebo in phase III trials, and were therefore not receiving active treatment, 53% of participants lost skeletal muscle over the trial period.[187] In another study of patients with lung cancer (n=35) who were receiving cancer treatment,[183] 54% of participants lost skeletal muscle over the treatment period, and 46% of participants maintained skeletal muscle.[183] These findings indicate that muscle loss may be related to factors beyond cancer treatment.

Progressive or advanced disease is a factor associated with muscle loss over time. Conceptually, this make sense as the tumour is assumed to be responsible for the catabolism associated with cancer cachexia.[93] In a large study of patients with advanced

cancer (n=368),[188] skeletal muscle loss was greater and occurred more rapidly within 1 month of death compared with skeletal muscle loss that occurred more than 9 months from death (cross-sectional muscle area -20.4 ± 13.4 cm^2 vs. -13.6 ± 5.5 cm^2; $p<0.003$),[188] and the chance of skeletal muscle loss within 90 days of death was increased (OR 2.67 [95% CI 1.45 – 4.94]; p=0.002).[188] These results could indicate that an increased rate and amount muscle loss are indicative of the end of life. Prospective evaluation of body composition in patients with MPM is needed to provide knowledge of the body composition changes that occur over time and the factors associated with these changes. This could lead to the development of targeted interventions to prevent or manage losses.

Table 2.5 Prevalence of low muscle mass in advanced cancer populations

Study	Cancer group	Study design/ sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence low muscle mass
Antoun, 2019[142]	Metastatic colorectal cancer	Prospective, n=76	Mean age 61 years, 50% men	Prior to chemotherapy	CT SMI at L3 <43 cm^2/m^2 for men if BMI <25 kg/m^2 and <53 cm^2/m^2 if BMI >25 kg/m^2, and <41 cm^2/m^2 for women	53%
Baracos, 2010[184]	Advanced non-small cell lung cancer	Prospective, n=441	Mean age 67 years for men and 65 years for women; 52% men	New patient assessments referred for treatment	CT SMI at L3 <55.4 cm^2/m^2 for men and <38.9 cm^2/m^2 for women	47%
Chambard, 2018[179]	Non-small cell lung cancer with bone metastasis	Prospective, n=64	Mean age 52 years, 75% men	Time of first bone metastasis	DXA ASM <7.26 kg/m^2 for men and >5.45 kg/m^2 for women	47%
Daly, 2018[189]	Foregut cancer (61% gastro-oesophageal, 39% hepato pancreato-biliary); 51% with stage IV disease	Prospective, n=225	Mean age 66 years, 67% men	Prior to chemotherapy	CT SMI at L3 <43 cm^2/m^2 for men if BMI <25 kg/m^2 and <53 cm^2/m^2 if BMI ≥25 kg/m^2, and <41 cm2/m2 in women	40%
Kakinuma, 2018[185]	Advanced non-small cell lung cancer	Retrospective, n=65	Mean age 66 years, 62% men	Prior to chemotherapy or molecular targeted therapy	CT SMI at L3 <49 cm^2/m^2 for men and 31cm^2/m^2 for women	40%

Study	Cancer group	Study design/ sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence low muscle mass
Kim, 2015[190]	Small cell lung cancer; 68% extensive disease	Retrospective, n=149	Mean age 69 years, 85% men	Newly diagnosed	CT SMI at L3 <49 cm^2/m^2 for men and 31cm^2/m^2 for women	53%
Kim, 2018[191]	Lung cancer; 72% with advanced disease	Retrospective, n=778	Mean age 68 years, 73% men	Newly diagnosed	CT SMI at L3 of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	48%
Kimura, 2015[180]	Advanced non-small cell lung cancer	Retrospective, n=134	Median age 66 years, 60% men	Newly diagnosed	CT SMI at L3 of <41 cm^2/m^2 for men and <38 cm^2/m^2 for women	38%
Kiss, 2018[192]	Non-small cell lung cancer; 44% with stage IIIB disease	Retrospective (secondary analysis), n=41	Mean age 66 years, 71% men	Prior to radiotherapy	<43cm^2 for men if BMI <24.9 kg/m^2 and <53 cm^2 in men if BMI >25 kg/m^2, and <41cm^2 for women,	61%
Nipp, 2018[193]	Incurable lung or non-colorectal gastrointestinal cancer (57% lung cancer)	Prospective, n=237	Mean age 64 years, 54% men	Within 8 weeks of diagnosis; no prior therapy for metastatic disease	CT SMI at L3 of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	55%
Onishi, 2019[194]	Unresectable advanced oesophageal cancer	Prospective, n=176	Mean age 65 years; 85% men	Prior to treatment	CT SMI at L3 of <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women	57%
Prado, 2008[163]	Respiratory and colorectal cancer (43% lung cancer); 34% stage IV disease	Prospective, n=250	Mean age 64 years, 54% men	New patient assessments	CT SMI at L3 of <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women	15%

Study	Cancer group	Study design/ sample size	Study population (age, % men)	Timing of observation	Assessment criteria	Prevalence low muscle mass
Prado, 2013[195]	Advanced non-small cell lung or colorectal cancer	Retrospective (secondary analysis); n=28	Mean age 65 years, 68% men	No particular time point described.	DXA ASMI <7.26 kg/m^2 for men and <5.45 kg/m^2 for women	36%
Rier, 2018[196]	All cancer groups (haematological and solid cancers); 45% stage IV disease	Prospective cohort, n=131	Median age 72 years, 56% men	Prior to, during and after chemotherapy	CT SMI at L3 <43 cm^2/m^2 for men if BMI <25 kg/m^2 and <53 cm^2/m^2 if BMI ≥25 kg/m^2, and <41 cm^2/m^2 for women	48%
Rossi, 2018[181]	Advanced non-small cell lung cancer	Retrospective, n=33	Mean age 66 years, 18% men	Prior to treatment with Gefinitib	CT SMI at L3 <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	61%
Sheean, 2019[197]	Metastatic breast cancer (oestrogen receptor positive)	Prospective, n=41	Median age 62 years, 0% men	Currently undergoing treatment	CT SMI at L3 <41 cm^2/m^2	34%
Srdic, 2016[182]	Advanced non-small cell lung cancer	Prospective, n=55	Median age 64 years, 67% men	Prior to chemotherapy	CT SMI at L3 <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	47%
Stene, 2015[183]	Advanced non-small cell lung cancer	Prospective, n=35	Mean age 67 years, 52% men	Prior to chemotherapy	CT SMI at L3 of <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women	71%

2.12 Relationship between low muscle mass and patient-related health outcomes

2.12.1 Quality of life

A small number of studies have reported on the relationship between low muscle mass and quality of life in cancer populations.[193, 198] In a large study in chemotherapy naïve patients with advanced lung cancer (n=734)[198] the authors reported an association between skeletal muscle mass and global quality of life among men, where men with lower skeletal muscle mass had significantly poorer scores on the EORTC QLQ-C30. Notably, the researchers identified a cut-point for both men and women below which quality of life scores began to deteriorate, while above the cut-point quality of life scores were stable.[198] In a retrospective, study of patients with newly diagnosed advanced cancer (n=237), low skeletal muscle mass, was associated with lower scores on the Functional Assessment of Cancer Therapy – General (FACT-G) quality of life assessment after adjusting for age, sex, marital status, education and cancer type (p=0.048).[193] These data indicates that low skeletal muscle mass could be associated with poorer quality of life in patients with advanced cancer, however it is not known if this relationship exists in MPM.

2.12.2 Physical activity, physical functioning and muscle strength

There is a lack of information on the relationship between low muscle mass and physical activity in patients with cancer, however a small number of studies have reported on the relationship between low muscle mass, physical functioning and strength. In a study of older adults with cancer (n=131), including 45% with stage IV disease, participants underwent evaluation of muscle mass via CT and completed five functional tests; the five times sit to stand test (FTSTS); handgrip strength; steep ramp test; walking speed and Timed Up and Go.[199] There was a significant association between muscle mass and FTSTS, handgrip strength and the steep ramp test, but not walking speed or Timed Up and Go;[199] and participants with low muscle mass in combination with slow walking speed or low handgrip strength (n=10) had greater limitations in their activities of daily living following chemotherapy.[199] In a study of overweight patients with advanced cancer (n=28),[195] participants completed handgrip strength testing and a two-minute walk test. Compared to those with normal muscle mass, mean handgrip strength was lower among participants with low skeletal muscle mass;[195] no differences were observed in two-minute walk test results between groups. Similar findings were reported in a prospective study of older adults with advanced lung cancer (n=30) undergoing chemotherapy.[200] Participants in this study

underwent handgrip strength measurements and completed an incremental shuttle walking test at study enrolment, 6 and 12 weeks;[200] a significant linear association was found between changes in skeletal muscle index and changes in handgrip strength, however no differences were observed with regard to the walk test.[200] These preliminary data indicate a relationship between muscle mass and handgrip strength, however handgrip strength may not reflect overall strength or function.[201] Physical activity data and physical performance tests, especially muscle strength-dependent tests such as the chair rise and Timed Up and Go,[43] are therefore needed to evaluate the relationship between low muscle mass and physical functioning in patients with MPM.

2.13 Effects of exercise on physical function and body composition

Exercise is distinct from physical activity in that it is planned, structured and repetitive; and undertaken with the purpose of maintaining or improving physical fitness.[47] The two principal modes of exercise are resistance and aerobic exercise training. The American College of Sports Medicine has defined resistance exercise training as exercise in which muscles work against a force 60% or higher of maximum,[38, 202] while aerobic exercise training has been defined as exercise in which the large muscles of the body move in a rhythmic manner over a period of time.[38]

Considerable research has examined the impact of exercise interventions on patients with cancer[203] and more recently the impact of exercise has been examined in patients with advanced cancer. When the first systematic review article of exercise interventions in patients with advanced cancer was published in 2009[204] only three were randomised controlled trials were identified. Several review articles of exercise interventions in patients with advanced cancer have since been published[205-208] and 15 randomised controlled trials have now been identified.[206]

2.13.1 Physical functioning

Physical functioning is commonly reported as an outcome measure in exercise intervention studies in patients with advanced cancer.[208] Outcome measures include a combination of self-report questionnaires, physical performance tests and muscle strength tests.[208] The physical performance tests included were the Six Minute Walk Test, 400 m walk, 6 m walk, chair stand, timed up and go and Self Physical Performance Battery.[208] Results showed that 87% of the studies that assessed physical function reported a significant improvement in at least one physical functioning measure following the exercise intervention.[208]

A Cochrane review has recently investigated the effects of exercise training specifically in patients with advanced lung cancer.[209] Regarding the outcome measures, three randomised trials included six-minute walk test (n=59) and three randomised trials included self-reported physical functioning (n=73).[209] The findings were that exercise participants had a significantly greater improvement in six-minute walk distance when compared with the control participants.[209] However, there was no difference between groups for self-reported physical functioning.[209]

In another randomised trial in advanced lung cancer (n=218),[210] patients participated in a 12 week supervised aerobic and resistance exercise intervention or received usual care and completed measurements of muscle strength and a six-minute walk test. Participants in the intervention group had significantly greater strength at the end of the intervention, when compared with the control group.[210] However, there was no difference between groups for six-minute walk distance.[210]

In a randomised trial of women with metastatic breast cancer (n=14), women participated in a supervised resistance exercise and unsupervised walking intervention or received usual care.[211] Participants completed a measurement of leg strength and a six-minute walk test. While adherence to the supervised resistance exercise was high, there were no differences between the intervention and control group for leg strength or six-minute walk distance.[211] Overall, exercise interventions appear to have a positive effect on physical functioning outcomes in advanced cancer populations.

2.13.2 Body composition

There has been substantial research on the effects of exercise interventions on body composition outcomes in patients with prostate and breast cancer. A meta-analysis which included seven prostate cancer studies,[212] concluded that whole body lean mass increased significantly following resistance exercise interventions. The estimated improvement in whole body lean mass was 1 kg (95% CI [0.15 – 1.84]; p=0.028). Two randomised controlled trials in prostate cancer have been published since this meta-analysis. The first was a study of the effect of aerobic and resistance exercise training in men treated with androgen deprivation therapy.[213] The findings were that, compared with the control group the intervention group gained significantly more lean mass (mean difference 0.8 kg; p=0.015).[213] The second study, was an investigation of the effects of aerobic, resistance and flexibility training in men with advanced prostate cancer and bone metastases.[214] In

contrast, there were no differences between the control and intervention group with regard to the change in lean mass (mean difference 0.3 kg; p=0.584).

Randomised controlled trials conducted in patients with breast cancer also indicate that resistance exercise interventions have a positive impact on lean mass.[215, 216, 217, 218] In a study of patients with breast cancer undergoing chemotherapy, resistance exercise training was compared with aerobic exercise and usual care.[215] Compared with the usual care group the resistance exercise group gained significantly more lean mass (mean difference 0.32 kg/m^2; p=0.017), however there were no differences between the aerobic and resistance exercise intervention groups (mean difference 0.18 kg/m^2; p=0.35).[215] This indicates that there is evidence that exercise training improves lean mass in patients with prostate and breast cancer.

There is currently limited data on the effects of exercise training on body composition outcomes in advanced cancer populations. Of the review articles on exercise interventions in patients with advanced cancer, only one reported on body composition outcomes.[208] In this review, nine randomised controlled trials were identified that assessed body composition.[208] Of these, only four used non-anthropometric measures for body composition assessment; three used DXA and one used plethysmography. The four studies were conducted in patients with prostate cancer, lymphoma and myeloma. All exercise interventions were of 3-months duration, but differed in the level of supervision and type of exercise. The findings were that exercise training significantly improved lean mass in all four studies. Notably, none of these studies included patients with MPD or other thoracic cancers. As patients with thoracic cancers have a particularly high disease burden, it may be more difficult to achieve improvements in lean mass with exercise training in these cancer populations.

2.14 Effects of dietary intake on exercise efficacy

One concern around exercise training in advanced cancer populations is the potential impact of inadequate dietary intake on exercise outcomes. Approximately one-quarter of patients with advanced cancer have inadequate energy intake.[97, 98] During periods of inadequate energy intake amino acids from the diet or skeletal muscle may be used as an energy source rather than for muscle protein synthesis,[219] which may result in a reduced physical functioning and body composition response to exercise. However, there is a lack of published research on the relationship between dietary intake and response to exercise interventions in cancer populations.

Although there is a lack of information on the relationship between dietary intake and exercise outcomes in cancer populations, there are a small number of studies in healthy older adult populations. A recent systematic review and meta-analysis reported on randomised controlled trials that compared the effects of dietary protein on body composition outcomes in healthy older adults.[220] Only three of the studies had compared dietary protein intakes and body composition outcomes following resistance exercise training.[221-223] Overall, findings indicated that participants with protein intakes greater than the Recommended Daily Allowance (RDA) of 0.8 g/kg/day had significant improvements in lean mass while participants who had protein intakes consistent with the RDA had no change in lean mass.[220] These findings indicate that higher than usual protein intakes may be required to produce improvements in lean mass in older adults participating in resistance exercise training.

Contrasting results were reported in a randomised controlled trial of postmenopausal women (n=23) who participated in a 10-week resistance exercise intervention.[224] All participants in the study were given individualised dietary plans with the same calories as their usual diet, however the intervention group consumed 1.2 g/kg/day of protein and the control group consumed 0.8 g/kg/day of protein.[224] Both the intervention and control groups had a significant improvement in lean mass.[224] Therefore, higher protein intake in excess of the RDA did not result in greater improvements in lean mass.

One study has explored the effects of protein intake on body composition and physical functioning outcomes in older women living in retirement villages.[225] The women, aged 60 – 90 years, participated in a 4-month progressive resistance exercise intervention.[225] The intervention group had two 80 g servings of cooked lean red meat per day, while the control group had cooked rice or pasta as the alternative.[225] There were no significant differences between the intervention and control groups with regard to energy intake but protein intake was significantly higher in the intervention group.[225] Compared with the control group, the intervention group had a greater improvement in lean mass and muscle strength. However, both groups had similar improvements in the physical performance tests.[225] This indicates that while adequate protein intake may be important for optimising muscle mass, improvements in physical performance could be independent of dietary intake.

There is limited information on the relationship between energy intake and outcomes of exercise training. However, one study in adults aged 56 – 80 years (n=12) has reported on the relationship between energy intake and body composition outcomes following a 12-week resistance exercise intervention.[223] Energy expenditure increased as a result of

increased resting metabolic rate and exercise, and the mean energy intake required for weight maintenance increased by approximately 15%.[223] These results indicate that during exercise training participants may need greater amounts of energy to achieve muscle gains and maintain a stable weight. This finding is particularly relevant for development of exercise interventions for patients with advanced cancer, as participants may have difficulty increasing their energy intake to meet the metabolic demands of exercise. As weight maintenance is an important clinical goal it is imperative that this outcome is not disrupted with exercise training. Research is needed to clarify the relationship between dietary intake and exercise outcomes in advanced cancer populations, which will help to inform the design of future exercise interventions.

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Chapter Three

3

Feasibility of Objectively Measured Physical Activity and Sedentary Behaviour in Patients with Malignant Pleural Effusion

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ORIGINAL ARTICLE

Feasibility of objectively measured physical activity and sedentary behavior in patients with malignant pleural effusion

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Abstract

Purpose: Malignant pleural effusion (MPE) affects 1 million people worldwide annually and can significantly impair physical activity. Accelerometry is a validated method of objectively assessing physical activity. The purpose of this study was to determine the compliance in patients with MPE to accelerometry and describe their activity.

Methods: Patients with MPE wore an Actigraph GT3X accelerometer over a 7-day continuous wear protocol. Compliance was measured as the percent of patients who had ≥4 valid days (i.e., 8-hour/day of waking wear-time). Eastern Cooperative Oncology Group performance status was documented the day of actigraphy initialization.

Results: Forty-six patients with MPE received accelerometers; 44 (95.7%) returned their device. No complications were reported on their use. Forty subjects (90.9%) had ≥4 valid days of wear-time. Patients spent most of their waking hours sedentary [mean 11.0 (SD 1.95) hours], with limited participation in moderate and vigorous physical activity [mean 9.5 (SD 14.16) minutes]. Compared to patients with better performance status (n=32), patients with poorer performance status (n=11) spent significantly more hours/day sedentary [mean difference 2.1 (CI 0.86-3.32); p=0.001], as did those who survived <3 months (n=5) compared to >12 months (n=27) [mean difference 2.6 (CI 0.49-4.77); p=0.013).

Conclusion: Accelerometry was applied successfully in patients with MPE with high compliance and no adverse events. This is the first reported objectively measured physical activity in patients with MPE and revealed high sedentary behavior and low physical activity. The data reflected patient performance status and discriminated between survival groups. Accelerometry can provide a useful measure for future interventional studies in patients with MPE.

3.1 Introduction

Malignant pleural effusions (MPE) are estimated to develop in 200,000 people in the United States each year.[1] The development of an MPE can be a consequence of metastatic spread of any cancer, but more commonly lung, breast and gynecological cancers or from primary pleural neoplasms (e.g., mesothelioma).[2] The presence of MPE represents incurable disease and median survival ranges from 3 to 12 months from first presentation.[2] Breathlessness is a common and debilitating symptom reported by this patient group and interventions are aimed at managing symptoms for optimal quality of life.[3]

Breathlessness and other symptoms that result from MPE are likely to limit a person's ability to be physically active. In patients with lung cancer, breathlessness and fatigue appear to be associated with lower physical activity levels.[4, 5] Preliminary research suggests that patients with advanced cancer spend the majority of their time sedentary, with Lowe et al[6] reporting that patients with brain metastases spend an average of 20.2 hours per day supine or sitting, and none met physical activity guidelines of 150 minutes per week of moderate to vigorous physical activity (MVPA). In patients with breast, colorectal, lung and ovarian cancer, those that are more physically active report better quality of life.[7-12] However, activity levels in patients with MPE remain unknown. Considering this clinical population has a poor prognosis, high symptom burden, and often undergoes invasive medical treatments (e.g., indwelling pleural catheter, chemotherapy).[3] data regarding physical activity and sedentary behavior in patients with MPE is needed.

Performance status rating is routinely used in cancer populations to assess patient suitability for interventions[13] and is a reliable predictor of survival in patients with MPE.[2] The Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status scales are the most commonly used measures of performance status in this population.[14, 15] These ratings are largely based on the ability of patients to engage in their usual activities of daily living, including physical activity.[14, 15] However, as performance status ratings are subjective and broad, they may fail to detect small but meaningful changes in physical activity levels. Accelerometers, which objectively measure physical activity and sedentary behavior, may be more sensitive to these modest changes and could be more reliable. However, it remains to be seen if accelerometry derived objective measures of physical activity and sedentary time can differentiate between patients by performance status category or categorized survival groups.

The primary aim of this study was to determine if patients with malignant pleural effusion (MPE) were compliant with accelerometry designed to measure physical activity and sedentary behavior. Second, we aimed to describe the physical activity and sedentary behavior of patients with MPE. We also aimed investigate the relationship between physician ratings of physical performance status, survival and accelerometer measured physical activity and sedentary behavior.

3.2 Methods

3.2.1 Participants

This study was approved by the Sir Charles Gairdner Group Human Research Ethics Committee (Quality Improvement No: 11149). From December 2014, patients with MPE at this center were asked by their physician to wear an accelerometer as part of clinical care. Patients were included in this study if they had a confirmed diagnosis of MPE and had worn an accelerometer between December 2014 and April 2016.

3.2.2 Measures

Demographic and medical variables

Patient's medical records were reviewed for baseline demographic data, cancer diagnosis, performance status, pleural effusion characteristics and comorbidities. iSOFT Clinical Manager was used to access date of death. Survival was calculated as the time between accelerometer initialization and date of death. Patients were then categorized into groups <3 months, 3-12 months or >12 months based on their survival. Chest radiographs completed within one week of accelerometer wear were characterized and graded on a scale of 0 to 5 according to established criteria.[16] Specifically, a grade 1 effusion represented blunting of the costophrenic angle, grade 2 is more than blunting of the costophrenic angle but less than 25% of the hemithorax occupied by pleural fluid, grade 3 occupying 25-50% of the hemithorax, grade 4 occupying 50-75% of the hemithorax and grade 5 occupying >75% of the hemithorax.[16]

Accelerometer compliance

Compliance with actigraphy protocol was assessed by the number and percentage of patients who wore the actigraph for 4 or more valid wear days.[17]

Physical activity and sedentary behavior

Patients were instructed to wear the accelerometer (Actigraph GT3X+; Actigraph, Pensacola, FL, USA) on their hip continuously (24hr/day) for 7 days and record any non-wear time in a diary provided for the 7-day period.

Accelerometers were programmed to record raw data at a frequency of 30Hz. Data were later reduced to vertical axis movement counts per 60-second epoch. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA). Waking wear time was determined by visual inspection of the ActiGraph file by a trained rater and an automated algorithm.[18] A valid day was defined as 8-hours (hr) of waking wear time.[19] Accelerometers with at least one valid day of data were analyzed.

Common cut off points were used to classify sedentary time as <100 counts/minute (cpm), light activity as 100-1952 cpm and MVPA as >1952 cpm.[20, 21] Bouts of sedentary time and physical activity were classified as <5 min, 5 to <10 min, 10 to <20 min, 20 to <30 min, 30 to <60 min and ≥ 60 min. Prolonged sedentary time was defined as time spent in sedentary bouts of ≥20 and ≥30 minutes. Step counts were processed as uncensored (Low Frequency Extension turned on) and censored (36% adjustment for overestimation).[22] We used commonly reported targets of ≥150 minutes moderate intensity activity/week and ≥7,000 accelerometer measured steps/day to assess adherence to physical activity recommendations.[23] All variables were calculated per day and then averaged across all valid days for each patient. Data from returned Actigraph GT3X devices were analyzed and the results filed in the patient's medical record. For the current study, the information on physical activity and sedentary behavior was accessed from medical records retrospectively.

Performance status

Physicians' recorded physical performance status was assigned according to the ECOG rating classification.[14] An ECOG rating of 0 is assigned to a person who is fully active and able to carry on all pre-disease performance without restriction, a rating of 1 is given when a person is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, a rating of 2 is assigned to a person who is ambulatory and capable of all self-care but unable to carry out any work activities and are up and about more than 50% of waking hours, a rating of 3 is assigned to a person capable of only limited self-care and confined to bed or chair more than 50% of waking hours, a rating of 4 is given when a person is completely disabled and cannot carry out any

self-care and is totally confined to bed or chair.[14] Physician rated performance status was recorded on the same day that accelerometers were initialized and accessed from medical records retrospectively. Patients were grouped as either good performance status (I.e., ECOG 0-1) or poor performance status (I.e., ECOG ≥2), as these are common cut-points used in decision making for treatment and clinical trials.

3.2.3 Statistical analyses

Patients with at least one valid day of data were included in the analysis. Statistical analyses were conducted using SPSS (version 23, IBM Corporation, Somers, NY, USA). Data were expressed as mean (SD) unless otherwise stated. Demographic and medical data were analyzed using descriptive statistics. Patients were grouped according to ECOG status (i.e., 0-1 and ≥2) and physical activity and sedentary behavior were analyzed using descriptive statistics. Two-tailed independent t tests were used to test for differences between the mean physical activity and sedentary time for ECOG groups 0-1 and ≥2. One-way ANOVA was used to test for differences between the mean physical activity and sedentary time for survival groups <3 months, 3-12 months and >12 months. Where the data were not normally distributed, the Mann-Whitney and Kruskal Wallis tests were applied and the median and inter-quartile range (IQR) is reported. An alpha of 0.05 was used to determine statistical significance. Figures were created using GraphPad Prism (version 7, GraphPad Software, La Jolla, California, USA).

3.3 Results

3.3.1 Participant characteristics

Actigraph GT3X accelerometers were given to 46 patients with MPE [72% male; mean age 69 (SD 8.2)]. Thirty-three patients (71.7%) had an ECOG performance status rating of 0 to 1, seven patients (15.2%) had an ECOG rating of 2 and six patients (13.0%) were given an ECOG rating of 3. Twenty-nine patients (63.0%) survived more than 12 months from the date of accelerometer initialization, eleven patients (23.9%) survived 3-12 months, six (13.0%) survived less than three months. Demographic and medical characteristics of patients are reported in **Table 3.1**. Approximately two-thirds (65.2%) of patients had a diagnosis of mesothelioma. Most (70%) of the patients had a mild to moderate sized effusion occupying up to 50% of the hemithorax (i.e., grade 2 or 3 on chest radiograph).

3.3.2 Accelerometer compliance

Forty-four accelerometers (95.7%) were returned and one accelerometer did not meet the minimum requirements for analysis. Of the two accelerometers that were not returned, one patient died shortly after the 7-day wear time was completed and the patient's family did not return the accelerometer, the second patient reported they lost the device. Of the forty-three accelerometers analysed, forty (93.0%) were returned with four or more valid days. The number of valid days and average wear time obtained from returned accelerometers is presented in **Table 3.2**.

3.3.3 Physical Activity and sedentary behavior

Patients in this study averaged 15.3 (SD 1.69) hours of waking wear time per day. On average patients spent 11.0 (SD 1.95) hours sedentary and participated in 4.2 (SD 1.65) hours of light activity and 9.5 (SD 14.16) minutes of MVPA per day, which was equivalent to 71.6%, 27.4% and 1.0% of their waking hours, respectively. Five (10.9%) patients completed ≥150 minutes of MVPA over the seven-day period. More than a third (37.1%) of all sedentary time was spent in bouts of 30 minutes or more, equivalent to 4.1 (SD 2.10) hours per day. On average patients took 8817 (SD 4838) uncensored or 5643 (SD 3096) censored steps per day. Fifteen (34.9%) patients achieved the target of ≥7000 censored steps per day.

3.3.4 Physical activity and sedentary behavior according to performance status and survival groups

Patient physical activity level according to performance status is reported in **Table 3.3**. The two performance status groups had equivalent wear time however, patients with good performance status spent significantly less time as sedentary compared to those with poor performance status [10.4 (SD 1.67) hr/day vs. 12.5 (SD 1.94) hr/day; p=0.001]. Light activity in patients with good performance status was on average 1.5 hours higher than for the poor performance status group [4.6 (SD 1.65) hr/day vs. 3.1 (SD 1.04) hr/day; p=0.06]. Patients with good performance status took more than double the median number of steps compared with patients of poor performance status [6721 (IQR 4150 - 9193) vs. 3126 (IQR 1035 - 3845); p<0.001; **Figure 3.1**].

Wear time and patient physical activity according to survival groups is reported in **Table 3.4**. Patients with a survival of >12 months and 3-12 months spent significantly less time sedentary compared to those who survived <3 months [10.8 (SD 2.09) hr/day and 10.6 (SD 1.51) hr/day vs. 13.3 (SD 2.62) hr/day; p=0.013 and p=0.044 respectively;

Figure 3.2]. Those patients who survived >12 months participated in almost 2 hours more light activity per day than those who survived <3 months [4.5 (SD 1.48) vs. 2.6 (SD 1.45) hr/day; p=0.044; **Figure 3.2**]. The median number of steps taken by patients with a survival of >12 months was 1.5 times the steps recorded by those with 3-12 months survival and more than double the steps taken by those with <3 months survival. However, this result was not statistically significant [6340 (IQR 3728-9224) vs. 4114 (IQR 1753-6632) vs. 3216 (IQR 1831-5830); p=0.106; **Figure 3.1**].

Patients with good performance status had two fewer bouts of prolonged sedentary time of ≥20 minutes compared with patients of poor performance status [7.5 (SD 2.26) vs. 9.4 (SD 2.14); p=0.019]. Performance status groups did not differ significantly in the number of prolonged bouts of sedentary time ≥30 minutes [4.2 (SD 1.81) vs. 5.0 (SD 1.78; p=0.177].

Patients with good and poor performance status participated in a similar number of bouts of light activity for short periods of <5 minutes [71.7 (SD 14.06) vs. 72.4; (SD 10.81); p=0.871]. These short bouts of light activity were the most common form of light activity in both performance status groups. Patients with good performance status spent 50.9% (SD 14.23) of total light activity in short bouts compared to 69.0% (SD 16.48) for those with poor performance status (p=0.001). Patients with good performance status completed almost five additional bouts of light activity of between 5 and 10 minutes [11.7 (SD 4.41) vs. 6.9 (SD 4.52); p=0.004]. Light activity according to performance status accumulated in bouts of 5 minutes or more is presented in **Figure 3.3**.

Table 3.1 Demographic and medical characteristics of patients

		Eastern Cooperative Oncology Group performance status	
	Total (n=46) *n (%)*	**Good (n=33)** *n (%)*	**Poor (n=13)** *n (%)*
Age (years)	68.5 (SD=7.85)	69.2 (SD=7.16)	66.7 (SD=9.46)
Gender (%)			
Male	33 (71.7)	22 (66.7)	11 (84.6)
Female	13 (28.3)	11 (33.3)	2 (15.4)
Body mass index (kg/m^2) (n=43)	26.7 (SD=4.82)	27.2 (SD=3.73)	25.3 (SD=7.19)
Cancer diagnosis (%)			
Mesothelioma	30 (65.2)	24 (72.7)	6 (46.1)
Lung Cancer	11 (23.9)	6 (18.2)	5 (38.5)
Other	5 (10.9)	3 (9.1)	2 (15.5)
Pleural effusion (%) (n=37)			
Effusion grade (0-5)			
0	0 (0)	0 (0)	0 (0)
1	8 (21.6)	4 (15.4)	4 (36.4)
2	14 (37.8)	12 (46.2)	2 (18.2)
3	12 (32.4)	7 (26.9)	5 (45.4)
4	3 (8.1)	3 (11.5)	0
5	0 (0)	0 (0)	0
Bilateral effusions	3 (8.1)	2 (6.1)	1 (9.1)
Loculation	13 (35.1)	11 (33.3)	2 (18.2)
Catheter	19 (51.4)	12 (36.4)	7 (63.6)
Comorbidities (%)			
COPD	5 (10.9)	3 (9.1)	2 (15.4)
Asthma	4 (8.7)	4 (12.1)	0 (0)
IHD	5 (10.9)	4 (12.1)	1 (7.7)
Diabetes	2 (4.3)	2 (6.1)	0 (0)
OA	6 (13.0)	5 (15.2)	1 (7.7)
Depression	2 (4.3)	1 (3.0)	1 (7.7)

COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic Heart Disease, OA: Osteoarthritis

Table 3.2 Number and mean valid days of accelerometry data.

		Eastern Cooperative Oncology Group performance status	
	Total (n=46) *n (%)*	**Good (n=33)** *n (%)*	**Poor (n=13)** *n (%)*
Number of valid days (%)			
7	16 (36.4)	13 (40.63)	3 (27.27)
6	17 (38.6)	13 (40.63)	4 (36.36)
5	4 (9.1)	3 (9.38)	1 (9.09)
4	3 (6.8)	3 (9.38)	0 (0)
3	3 (6.8)	0 (0)	3 (27.27)
2	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)
0	1 (2.3)	0 (0)	0 (0)
Mean valid days	**5.9 (SD=1.18)**	**6.12 (SD=0.94)**	**5.36 (SD=1.63)**

Table 3.3 Comparison of physical activity levels and sedentary time according to Eastern Cooperative Oncology Group performance status group

	Eastern Cooperative Oncology Group performance status group				
	Good (n=32)	**Poor (n=11)**	**Mean difference (95% CI)**	**Test statistic**	**P value**
Waking wear time (hr/day)	15.3 (SD 1.13)	15.6 (SD 1.99)	-0.40 (-1.38, -0.59)	t = -0.81	0.421
Sedentary time (% waking wear time)	68.6 (SD 10.20)	80.1 (SD 6.32)	-11.46 (18.09; -4.82)	t = -3.49	0.010
Light activity (% waking wear time)	30.1 (SD 10.08)	19.7 (SD 6.24)	10.34 (3.78; 16.90)	t = 3.18	0.003
MVPA (% waking wear time), median	0.9 (IQR 0.32 – 1.43)	0.1 (IQR 0.05 – 0.25)		z = -3.67	<0.001
Prolonged sedentary time ≥30 min bouts (hr/day), median	3.4 (IQR 2.09 – 4.78)	4.5 (IQR 2.97 – 6.97)		z = -1.56	0.119
Meeting MVPA guidelines ≥150 mins/wk, n (%)	5 (15.63)	0 (0.00)			

Table 3.4 Comparison of physical activity levels and sedentary time according to survival group.

	Survival group			Test statistic	P value
	<3 months (n=5)	**3-12 months (n=11)**	**>12 months (n=27)**		
Waking wear time (hr/day)	15.9 (SD 1.26)	15.0 (SD 1.90)	15.4 (SD 1.16)	F = 0.77	0.470
Sedentary time (% waking wear time)	82.6 (SD 11.27)	72.4 (SD 11.61)	69.2 (SD 8.93)	F = 3.92	0.028
Light activity (% waking wear time)	17.1 (SD 10.76)	27.2 (SD 11.32)	29.4 (SD 8.84)	F = 3.39	0.044
MVPA (% waking wear time), median	0.04 (IQR 0.01-0.72)	0.26 (IQR 0.18-0.57)	0.93 (IQR 0.32-1.69)	Chi square = 8.25	0.016
Prolonged sedentary time ≥30 min bouts (hr/day), median	7.0 (IQR 4.65-9.70)	3.6 (IQR 2.97-4.51)	3.4 (IQR 2.08-4.84)	Chi square = 7.04	0.030
Meeting MVPA guidelines ≥150 mins/wk, n (%)	0 (0.00)	0 (0.00)	5 (18.52)		

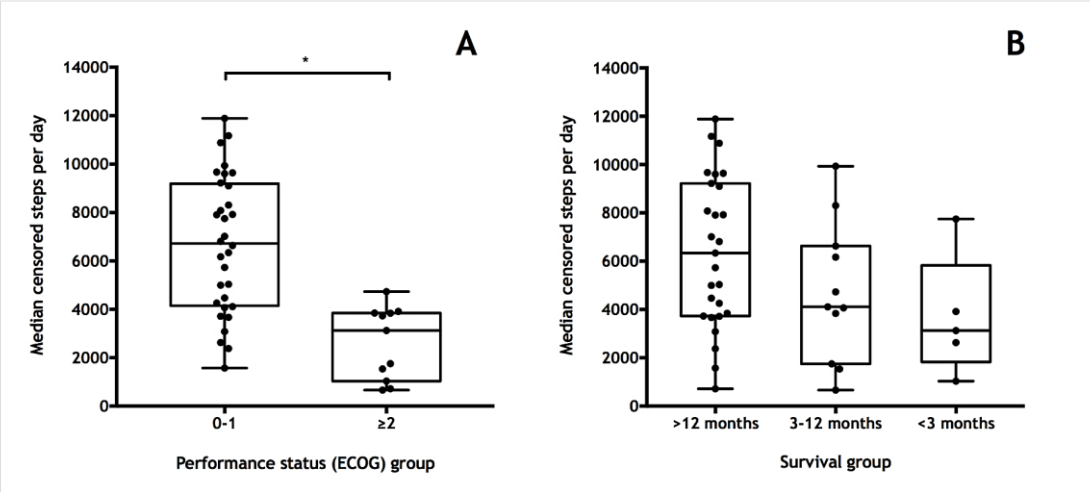

Figure 3.1 **Median censored steps taken per day by patients of A) ECOG performance status 0-1 and ≥2 and B) survival group >12 months, 3-12 months and <3 months. (*) p<0.001**

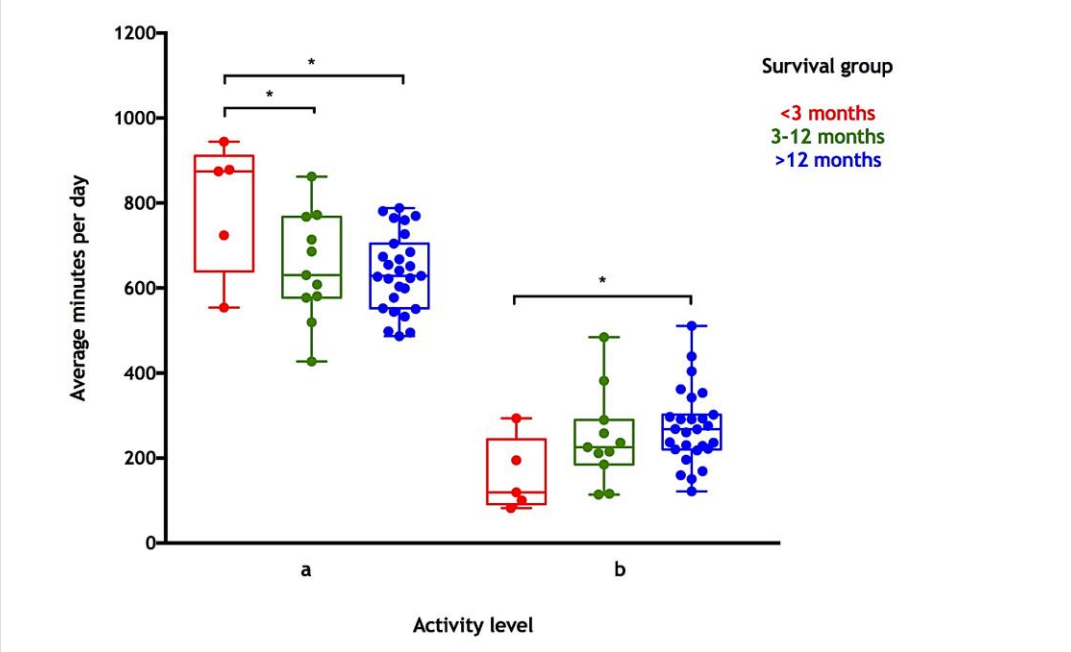

Figure 3.2 **Time spent as sedentary and in light activity according to survival group of <3 months, 3-12 months and >12 months. a) sedentary b) light activity. (*) p<0.05**

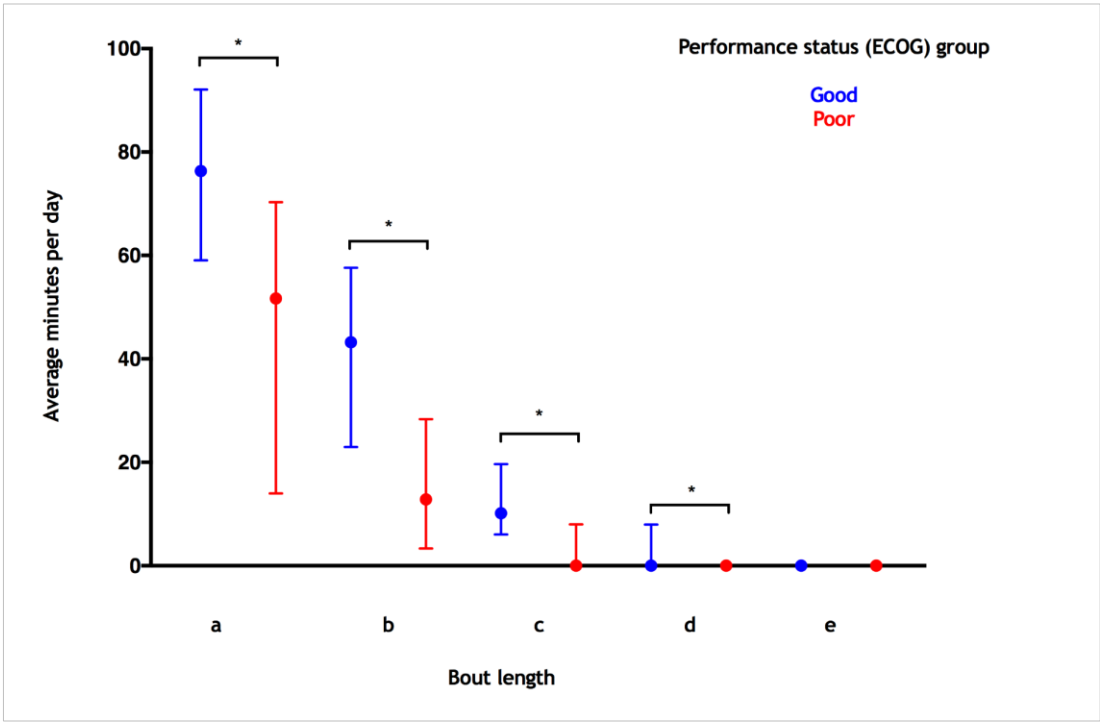

Figure 3.3 **Time spent in light activity according to duration of activity and performance status (ECOG) group. Data are presented as median and IQR. a) 5 to <10 min; p=0.004, b) 10 to <20 min; p=0.004, c) 20 to <30 min; p=0.009, d) 30 to < 60 min; p=0.018, e) ≥60 min; p=0.298. (*) p<0.05**

3.4 Discussion

Our study is the first to report the use of accelerometry in patients with MPE and provides objective measurements of their physical activity and sedentary behavior using a 24-hr wear protocol. Overall, patients with MPE were compliant with accelerometer wear. These patients with MPE were predominantly sedentary and only a small portion met current physical activity recommendations. This research indicates that physical activity in patients with MPE was associated with performance status. Compared to those with a good performance status, patients with poorer performance status were more sedentary and participated in fewer and shorter bouts of physical activity. Patients who survived less than three months were also more sedentary and participated in less physical activity than patients who survived more than twelve months.

Over 90% of patients with MPE provided ≥4 valid days of data from the 7-day recording period. The mean valid accelerometer wear was 5.9 days. These results are consistent with those from a study of 500 women with breast cancer where compliance with a hip-worn accelerometer was 90%[17] and also with those from the National Health and Nutritional Examination Survey study of healthy older adults,[24] where mean valid hip-worn accelerometer wear was 5.8 days. Two studies of cancer survivor populations reported slightly higher mean valid accelerometer wear of 6.6 – 6.8 days.[7, 25] However, these studies used different accelerometer devices, the first used a hip-worn accelerometer[7] and the second used an accelerometer positioned on the anterior mid thigh.[25] Other accelerometry studies in people with cancer have not reported on patient compliance with the accelerometer protocol.[7, 26-28] The high compliance rate in the current study demonstrates that accelerometry is a feasible tool for measuring physical activity and sedentary behavior in patients with MPE.

During the 7-day recording period only one in ten patients in our study met physical activity recommendations and mean MVPA was only 9.5 min/day. Within a cohort with colorectal cancer, patients participated in an average of 28.5 min/day of MVPA as measured by accelerometry, which is almost three times our result.[7] In contrast, in a study of patients with brain metastases, none of the participants registered any activity on their accelerometer that could be considered of moderate or vigorous intensity.[6] The very low activity level of these patients with brain metastases[8] was also reflected in the average step count of 2784 steps/day, which is half of the average steps taken by patients in our study. Two studies of patients with lung cancer reported higher average step counts of 6047[27] and 8863.[26] These large differences in physical activity are likely related to differences in

symptom burden, disease stage and prognosis between cancer groups. Variance in accelerometer wear protocols in relation to the wear time (24 hr vs. waking hours), placement of accelerometer (hip vs. thigh vs. wrist) and the device used amongst studies and processing of step counts as uncensored or censored may also contribute to differences in physical activity results.

Sedentary behavior comprised the bulk of the waking wear time in our study, with patients on average spending 72% percent or 11 hours of their day sedentary. These results were comparable with a sample of twenty patients with lung cancer[26] were sedentary 68% of the time but higher than a cohort of patients with colorectal cancer who spent 61% of their day sedentary.[7] In a prospective study of patients with colorectal cancer who completed a self-reported recreational physical activity questionnaire, the risk of cancer-specific mortality was higher for those who spent ≥6 hr/day sedentary compared to patients who were sedentary for <3 hr/day.[29] However, in healthy adults who were predominantly sedentary, the risk of mortality was reduced through replacing 1hr/day of sedentary time with physical activity of any intensity.[30] Therefore it is reasonable to consider that replacing modest amounts of sedentary behavior with light activity may also be an important consideration in optimizing the health of cancer patients, particularly those with very low levels of physical activity like our current study population.

Our results were that the physical activity of patients with MPE was associated with their performance status and survival group. In this setting, performance status is a strong predictor of survival, and is often used to differentiate between patients well enough to receive treatment and those not.[13] The ability of accelerometry to function in a similar way to performance status suggests the information provided by objective measurement of physical activity may benefit physicians or researchers who need to determine patient suitability for and response to treatment.

In the current study, those patients with good performance status engaged in longer periods of light activity compared to patients with poor performance status. Only one other study to-date has reported on the duration of bouts of light activity. Previous research into patients with lung cancer revealed median percentage of waking wear time in bouts of 10 or more minutes of light activity was 13% compared to 19% in healthy controls ($p=0.025$).[26] As MVPA is very low in these clinical populations, the ability to engage in light activity for longer periods is likely the most suitable indicator of better or improving health. Accelerometry can accurately and reliably determine the duration of bouts of light

activity and this information may be of benefit in interventional studies where increasing physical activity level is the goal.

There are limitations in the current study that should be considered when interpreting the results. A retrospective audit design was used in this study because accelerometers were part of clinical care. However, as a result we have no data on patient factors that may have influenced physical activity and sedentary behavior such as quality of life or symptom burden. Regarding the measurement protocol, as only one 7-day monitoring period was completed for each patient, intra-person reliability of the protocol has not been established in this clinical sample. Further, the sample may have selection bias as patients with MPE were not consecutively asked to wear an accelerometer, rather it was at the discretion of the physician to ask patients to wear an accelerometer and physicians may have avoided asking a patient if they were unwell or in need of another procedure at the time. As not all patients with MPE wore the accelerometers it is plausible that the compliance, physical activity and sedentary behavior of patients in our study could differ to those who did not wear an accelerometer. Additionally, there was a large proportion of patients with mesothelioma in our sample, which is not representative of the worldwide population with MPE. A diagnosis of mesothelioma has a favourable prognosis compared to other primary cancers with MPE[2] and it is probable that this may also impact on physical activity and sedentary behavior.

Despite these limitations, the current study is the first time accelerometer use has been investigated in a population with MPE and it provides a good starting point for further research in this area. A strength of our study is that a 24-hr, 7-day protocol was used to objectively assess physical activity and sedentary behavior in this population. A 24-hr accelerometer protocol has not been used in any previous research in cancer patients rather, all studies have asked participants to wear the accelerometer during waking hours only.[7, 26] However, a 24-hr protocol is thought to maximize waking wear time.[31] Furthermore, the 7-day protocol used in this study is the current best practice for objective measurement of physical activity as it accurately reflects habitual sedentary behaviour.[32]

To better understand the mechanisms contributing to low physical activity levels in the MPE population, future studies should be prospective in nature and include measurements of breathlessness and fatigue amongst others, as these appear to correlate to physical activity levels in other populations.[4, 5] Considering the very low levels of participation in MVPA paired with the high levels of sedentary behavior, the target of interventions to increase physical activity in this population should consider focusing on

increasing light activity and reducing sedentary bouts rather than on the traditional goal of increasing MVPA which may be unachievable for patients with poor performance status. In addition, targeted exercise in particular involving strength training should be considered to slow or reverse deconditioning and functional decline likely to be underlying factors in the low physical activity levels in this population.[33, 34] As this study has demonstrated patients with MPE are compliant with accelerometer wear, future studies can now examine the usefulness of accelerometry in determining suitability for treatment and assessing response to treatment as a patient-centred outcome measure in clinical interventions.

Accelerometry, on a 7-day continuous wear protocol, can be applied successfully in patients with MPE with high compliance and no adverse events. The data obtained reflected patient performance status as assessed with ECOG ratings. The accelerometry results provided, for the first time, quantitative data of the physical activity of patients with MPE and revealed low physical activity and high sedentary behavior in this population. Accelerometry can provide a useful measure for future interventional studies to improve physical activity levels in patients with MPE.

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Chapter Four

4

Agreement between Computed Tomography and Dual Energy X-Ray Absorptiometry for the Classification of Low Muscle Mass in Patients with Malignant Pleural Mesothelioma

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Abstract

Body composition analysis techniques commonly used to classify low muscle mass in cancer populations are used interchangeably, yet there has been little comparison of these methods reported. This study in patients with malignant pleural mesothelioma (MPM) aimed to assess the relationship between muscle measured with computed tomography (CT) and dual-energy x-ray absorptiometry (DXA) and the agreement between cut-points for the classification of low muscle mass. This was a retrospective study of patients with available CT and DXA data collected ≤28 days apart. Skeletal muscle index (SMI; cm2/m2) was measured with CT at the third lumbar vertebrae using sliceOmatic software v.5.0. Appendicular skeletal muscle index (ASMI; kg/m2) was segmented from whole-body DXA. Commonly cited CT and DXA cut-points for low muscle mass were used to assess the agreement between methods. Thirty-seven participants with MPM were included (81% male; median age 67.0 [IQR 62.0-73.0] years). There was a positive correlation between SMI and ASMI ($r=0.679$; $p<0.001$). Percent agreement between CT and DXA cut-points ranged between 54-73%. There was moderate agreement between the CT cut-points from Prado et al and the DXA cut-points from Baumgartner et al ($\kappa=0.424$; $p=0.006$). There was no significant agreement between the other cut-points evaluated ($p>0.05$).

Novelty

- For the first time in patients with MPM, we reported that SMI and ASMI were positively correlated.
- Classification of low muscle mass differs according to the method and cut-point used, and are not universally interchangeable.
- Choice of method needs to be made carefully with consideration of the patient outcome of interest.

4.1 Introduction

In many cancer populations, low muscle mass is associated with poorer outcomes, including decreased survival and greater treatment toxicity.[1] Patients with malignant pleural mesothelioma (MPM) commonly experience weight loss,[2] which is an adverse prognostic indicator.[3] However, few studies have investigated body composition in patients with MPM. As MPM is an incurable cancer, an understanding of the relationship between muscle mass and patient outcomes has the potential to improve clinical practice.

We previously reported difficulty completing dual-energy x-ray absorptiometry (DXA) scans in unwell patients with MPM,[2] which was likely due to the additional burden this placed on them. In contrast, thoracic computed tomography (CT) scans obtained from medical records are performed routinely as part of standard patient care, are more easily accessible to researchers, and do not add to participant burden. Therefore, when available, CT may be a more practical alternative to DXA in patients with MPM. Existing guidelines state that either CT or DXA can be used to identify low muscle mass in patients with cancer,[4] however inherent differences between these methods suggest that they would not produce comparable results, which would hinder our ability to draw conclusions when comparing studies.

CT and DXA are both imaging techniques, one measures skeletal muscle mass, the other lean soft tissue, (i.e., lean mass), which is fundamentally different. Skeletal muscle quantification by CT is possible due to the different radiodensity thresholds (Hounsfield units) of different tissues. The third lumbar vertebrae (L3) is the best correlate of whole body muscle mass, hence used as a single abdominal cross-sectional CT image to provide body composition information.[5] DXA does not measure skeletal muscle. It uses dual-photons to determine lean mass, which is comprised of skeletal muscle, organs and other soft tissue.[6] As skeletal muscle cannot be distinguished from whole body lean mass, appendicular lean mass, which is known to be predominantly skeletal muscle, is segmented from whole body lean mass, and termed appendicular skeletal muscle mass; we will hereby refer to this compartment as “muscle” or appendicular skeletal muscle for consistency in terminology but acknowledge it is actually lean mass, therefore including muscle, water, fibrotic and connective tissue.[6]

To determine whether an individual has low muscle mass, muscle measured with CT and DXA is compared to cut-points, derived from each of these methods. Most commonly used CT cut-points were developed in cancer populations using values associated with

shorter survival,[7, 8] while others were derived from DXA and converted to CT units using a regression equation.[9, 10] Commonly used DXA cut-points were determined in older adults using values that were 2 standard deviations below the mean of a young adult reference population.[11] These cut-points were associated with functional impairment.[12] Therefore, cut-points associated with these body composition assessment methods were derived from different populations, with differing outcomes of interest.

Our previous research suggests that low muscle mass determined with DXA has the potential to predict important clinical outcomes in patients with MPM,[2] however DXA may not be feasible for a sub-group of the population. Information on the comparability of CT and DXA will allow us to understand if these methods categorise patients in the same way, which is important for interpretation and comparability of our research within the literature. Therefore, the aim of this study was to assess the relationship between muscle measured with CT and DXA and compare the agreement between CT and DXA cut-points for the classification of low muscle mass in patients with MPM.

4.2 Materials and methods

4.2.1 Study design and setting

The study was a retrospective, cross-sectional analysis which included a subset of MPM participants from a longitudinal observational study and an exercise intervention study.[9] The studies were approved by the Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255).

4.2.2 Participants

Patients were recruited from a tertiary specialist pleural disease and medical oncology clinic in Western Australia between August 2015 and May 2017. Patient and physician consent was obtained prior to study participation. Participants in the observational and intervention studies with a diagnosis of MPM were screened for eligibility for the current study. Inclusion criteria were completion of a CT and DXA scan within 28 days of each other. Participants were only included in the analysis once, using the first valid set of scans for participants in the observational study or the baseline scans for participants in the intervention study. Those with no CT image available at L3 or of inadequate image quality were excluded.

4.2.3 Measures

Demographic and medical characteristics

Participant's medical records were reviewed for baseline demographic and medical data. Eastern Cooperative Oncology Group performance status was assigned by the physician on the date of assessment.[10]

Anthropometric measures

Weight and height, measured with participants dressed in light clothing with shoes removed, were used to calculate the body mass index (BMI). Participants were classified as underweight, normal weight, overweight or obese based on World Health Organization BMI criteria.[11]

Computed tomography

CT scans performed as part of routine medical care were retrieved from the tertiary specialist imaging system and downloaded in Digital Imaging and Communications in Medicine (DICOM) format. A trained person (EJ) identified a single cross-sectional image at L3 and measured skeletal muscle cross-sectional area (cm^2) using sliceOmatic software v.5.0 (Tomovision, Montreal, QC, Canada). To ensure the reliability of our data, a second independent person (CS) measured skeletal muscle cross-sectional area on all included CT scans. The radiodensity of skeletal muscle was defined as -29 to +150 Hounsfield units[12] and pixels were manually corrected at tissue boundaries. The skeletal muscle index was calculated by dividing the cross-sectional muscle area (cm^2) by the participant's height in m^2. The following cut-points were used to define low muscle mass from CT: 1) Prado et al[7]: <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women, and 2) Martin et al[8]: <43 cm^2/m^2 for men with a BMI ≤24.9 kg/m^2, <53 cm^2/m^2 for men with BMI >24.9 cm^2/m^2 and <41 cm^2/m^2 for all women.

Dual energy x-ray absorptiometry

Whole-body lean mass was measured using whole-body DXA scans (Hologic Discovery A, Hologic Inc., Marlborough, MA, USA). A trained person (EJ) segmented appendicular skeletal muscle from whole-body lean mass at the acromio-humeral and pelvic-femoral joints.[5] Appendicular skeletal muscle mass was then adjusted for height (kg/m2). To define low muscle mass based on this variable, we used appendicular skeletal muscle index cut-points from 1) Baumgartner et al[17]: ≤7.26 kg/m^2 for men and ≤5.45 kg/m^2 for women, and

2) Cruz-Jentoft et al[11]: ≤7.00 kg/m^2 for men and ≤5.50 kg/m^2 for women, which for ease of use, were rounded from cut-points reported by Gould et al[18] of ≤6.94 kg/m^2 for men and ≤5.30 kg/m^2 for women.

4.2.4 Statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (v. 25, IBM Corporation, Somers, NY, USA). Data were expressed as mean ± SD or median [IQR] where the data were not normally distributed. An Intraclass Correlation Coefficient (ICC) was obtained to assess the inter-rater reliability for skeletal muscle index measured at L3. Pearson's correlations were performed to assess the relationship between skeletal muscle index measured at L3 and appendicular skeletal muscle index measured by DXA. Kappa (κ) coefficients were used to assess the agreement between commonly used low muscle mass cut-points on CT and DXA. Receiver Operating Characteristics analysis were used to evaluate the ability of skeletal muscle index to predict low muscle mass on DXA by comparing the sensitivity versus the specificity.

4.3 Results

4.3.1 Participants

Participant characteristics are described in **Table 4.1**. The participants were predominantly male (81%), with the epithelioid subtype of MPM (73%) and all had an ECOG performance status rating of 0 – 1. Participants had a median age of 67.0 [IQR 62.0 – 73.0] years and a mean BMI of 25.9 ± 2.9 kg/m^2.

4.3.2 CT and DXA scans

Of the 40 eligible CT scans, 37 (93%) scans were included in the analysis **(Figure 4.1)**. Two scans (5%) were excluded as there was no image available at L3, while one scan (2%) was excluded as the scan was of inadequate quality to apply the analysis technique. Mean time elapsed between CT and DXA scan was 10.8 ± 8.5 days. Twenty-five scans (68%) were completed within 0 – 14 days of DXA, while 12 scans (32%) were completed within 15 – 28 days from DXA.

4.3.3 Relationship between body composition techniques for measurement of skeletal muscle

A high degree of reliability was found between raters for skeletal muscle index when assessed using the ICC (r=0.992 [95% CI 0.984 – 0.996]; p<0.001). The median skeletal muscle index and appendicular skeletal muscle index of included scans are presented in **Table 4.2**. There was a moderate positive correlation between skeletal muscle index and appendicular skeletal muscle index (r=0.679, p<0.001; **Figure 4.2**).

4.3.4 Agreement between CT and DXA for the classification of low muscle mass using existing cut-points

For each cut-point comparison, the proportion of scans with agreement and disagreement is presented in **Figure 4.3**. Moderate agreement was observed between CT cut-points from Prado et al[7] and DXA cut-points from Baumgartner et al[17] (κ=0.424; p=0.006). There was no significant agreement between the CT cut-points from Martin et al[8] and DXA cut-points from Baumgartner et al[17] (κ=0.132; p=0.419). There was no significant agreement between the CT cut-points from Martin et al[8] and DXA cut-points from Baumgartner et al[17](κ=0.173; p=0.173). There was no significant agreement between the CT cut-points from Prado et al[7] and Martin et al[8] and DXA cut-points supported by Cruz-Jentoft et al[11] (κ=0.173; p=0.173; and κ=0.087; p=0.582, respectively).

4.3.5 Skeletal muscle index for predicting low muscle mass using Dual-Energy X-Ray Absorptiometry as the reference standard

Skeletal muscle index was a fair predictor of low muscle mass in males (n=30) when the DXA cut-point from Baumgartner et al[17] was used as the reference standard (AUC=0.787, 95% CI 0.613 – 0.961; p=0.009). A skeletal muscle index cut-point of 52.9 cm^2/m^2 had a sensitivity of 0.947 and specificity of 0.462 for predicting low muscle mass. Skeletal muscle index was not a significant predictor of low muscle mass in males when the DXA cut-point supported by Cruz-Jentoft et al[11] was used as the reference standard (AUC=0.715, 95% CI 0.529 – 0.901; p=0.059). Skeletal muscle index was not a significant predictor of low muscle mass in females (n=7) when the DXA cut-points from Baumgartner et al[17] and supported by Cruz-Jentoft et al[11] were used as the reference standards (AUC=0.667, 95% CI 0.229 – 1.000; p=0.480 and AUC=0.417, 95% CI 0.000 – 0.886; p=0.724, respectively).

Table 4.1 Participant characteristics, n=37

	n	%
Age, *years*^	67	62.0 – 73.0
Sex, *male*	30	81.0
BMI, $kg/m^{2\#}$	25.9	2.9
ECOG performance status		
0-1	37	100.0
≥2	0	0.0
Histological subtype		
Epithelioid	27	73.0
Sarcomatoid	2	5.4
Biphasic	3	8.1
Unspecified	4	10.8
Unknown	1	2.7
Survival		
<3 months	0	0.0
3 – 12 months	12	32.4
>12 months	25	67.6
Cancer treatment prior to assessment, yes	14	37.8
Type of cancer treatment		
Chemotherapy	8	21.6
Radiotherapy	2	5.4
Chemotherapy and radiotherapy	2	5.4
Chemotherapy, radiotherapy and surgery	2	5.4

^mean, standard deviation; #median, interquartile range; **ECOG –** Eastern Cooperative Oncology Group

Table 4.2 Participant skeletal muscle index and appendicular skeletal muscle index, n=37

	All participants (n=37)		Men (n=30)		Women (n=7)	
	Mean	**SD**	**Mean**	**SD**	**Median**	**IQR**
SMI, cm^2/m^2	46.9	6.5	48.6	5.5	37.9	35.9–43.2
ASMI, kg/m^2	6.8	0.9	7.1	0.7	5.5	5.4–5.9

SMI – skeletal muscle index, **ASM** – appendicular skeletal muscle index

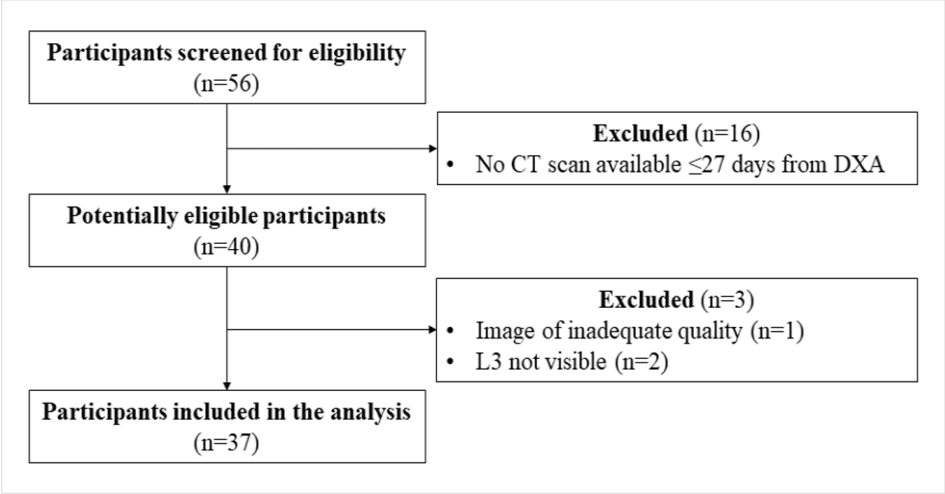


Figure 4.1 Participants included in the retrospective, cross-sectional study

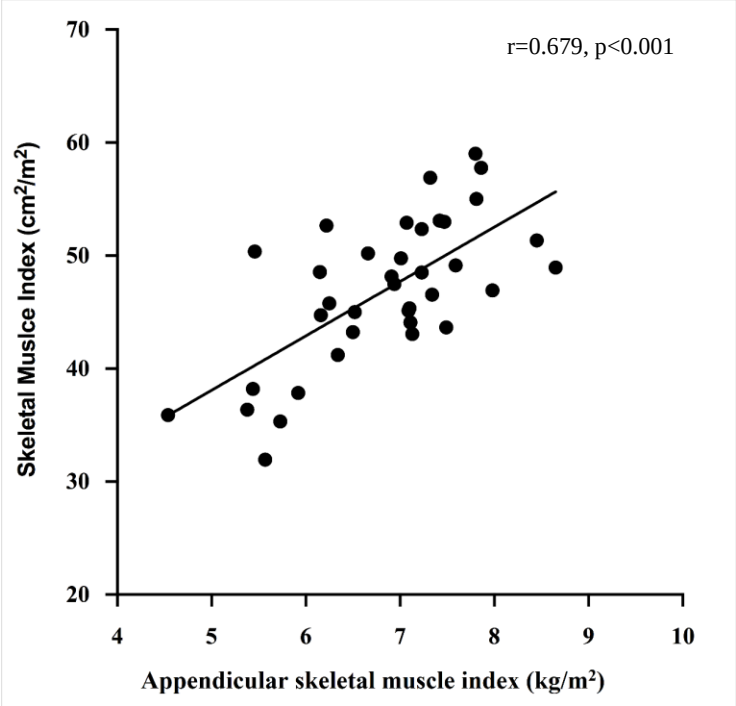
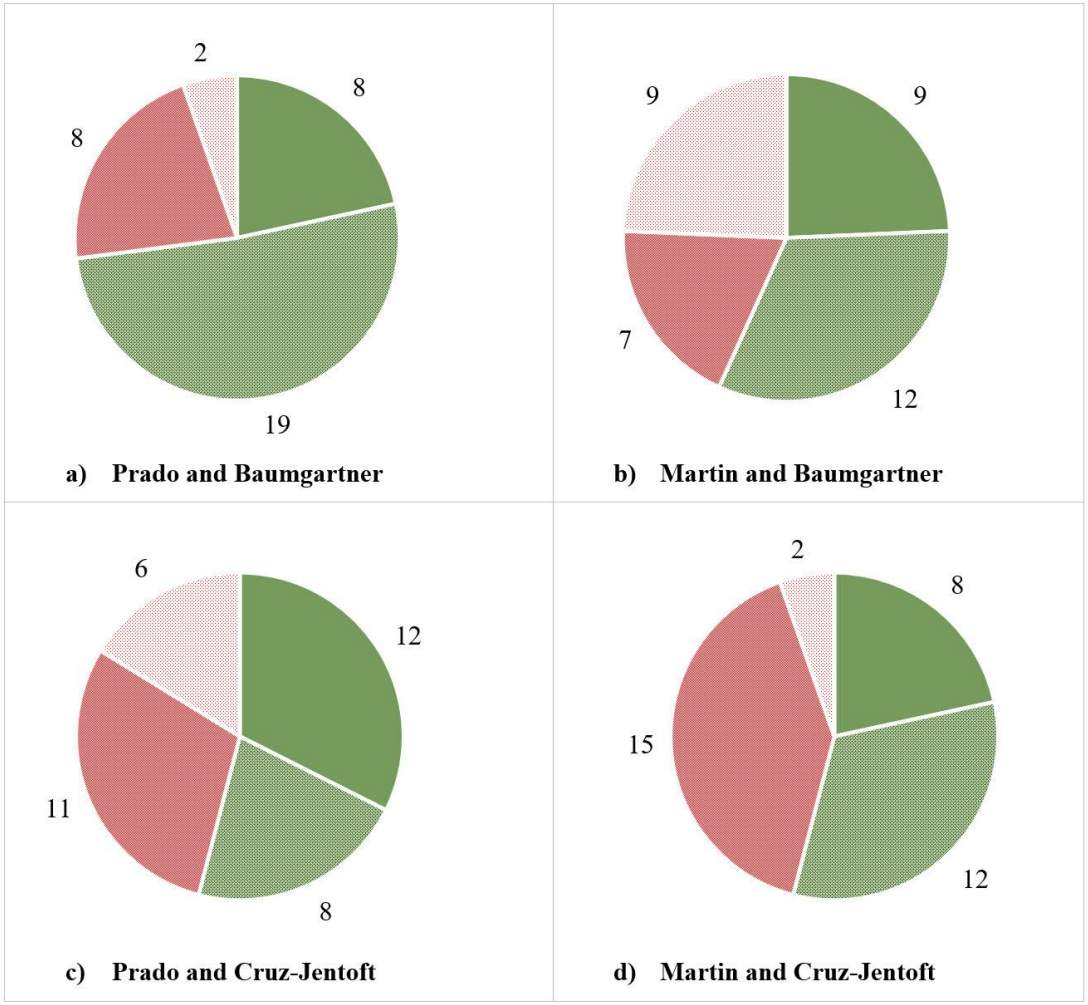


Figure 4.2 Correlation between appendicular skeletal muscle index (ASMI) and skeletal muscle index (SMI) at L3, n=37



CT cut-points:

- Prado[7]: <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women
- Martin[8]: <43 cm^2/m^2 for men with a BMI ≤24.9 kg/m^2, <53 cm^2/m^2 for men with BMI >24.9 cm^2/m^2 and <41 cm^2/m^2 for all women

DXA cut-points:

- Baumgartner[17]: ≤7.26 kg/m^2 for men and ≤5.45 kg/m^2 for women
- Cruz Jentoft[11]: ≤7.00 kg/m^2 for men and ≤5.50 kg/m^2 for women

Figure 4.3 Agreement between CT and DXA cut-points for low muscle mass, n=37

4.4 Discussion

Methods commonly used to assess body composition in cancer populations are inherently different, yet current guidelines do not indicate whether these methods differ in their classification of low muscle mass.[4] There has been little comparison of techniques reported, which make it difficult to come to informed conclusions when comparing studies. In our study we compared muscle measured with CT and DXA and the agreement between cut-points for the classification of low muscle mass in a cohort of patients with MPM. We reported that skeletal muscle index and appendicular skeletal muscle index were positively correlated, but as expected, there was no significant agreement between CT and DXA for the classification of low muscle mass for the majority of cut-points compared.

We found a moderate correlation between skeletal muscle index and appendicular skeletal muscle mass index (r=0.679). In studies of patients with advanced lung and gastrointestinal cancer, the correlation between skeletal muscle index and appendicular skeletal muscle is reported as moderate to strong (ρ=0.704 and r=0.89, respectively).[10, 19] One possible reason for this variability could be the inherent differences between methods. Appendicular skeletal muscle is lean soft tissue and includes muscle, water, fibrotic and connective tissue, therefore individual variability in the proportion of fibrotic and connective tissue in the arms and legs could affect the strength of the relationship between CT and DXA. The proportion of fibrotic and connective tissue present in the lean soft tissue of the arms and legs is greater in older age[20] and with increasing adiposity.[21] Our participants with MPM were heterogeneous with regard to their age (range 42 – 81 years) and BMI category (54% overweight or obese), which may explain the lack of a strong correlation between CT and DXA in our study. Although DXA does not directly measure skeletal muscle, it is an important body composition assessment technique. If research intends to investigate the relationship between body composition and functional outcomes then DXA may preferred over CT as it can estimate the muscle in the arms and legs which are typically responsible for movement. We previously reported that DXA cut-points from Baumgartner et al[17] were associated with poorer physical activity levels and self-reported physical functioning in patients with MPM.[2] It is not known if this relationship exists with skeletal muscle index.

An alternate hypothesis for our finding of a moderate correlation between methods is possible differences in trunk and appendicular loss of skeletal muscle in MPM. Multiple factors could affect the distribution of muscle in patients with MPM. Age is known to

affect skeletal muscle distribution.[22] In a study of healthy older adults, lower body skeletal muscle was lost more rapidly than upper body skeletal muscle.[22] Therefore, it is possible that participants in our study, with a median age of 67 years, could be affected by a similar wasting pattern. One third (n=12) of our participants had received chemotherapy treatment. To our knowledge, no study has reported on regional changes in muscle following chemotherapy, however in a study of patients with prostate cancer receiving androgen deprivation therapy, participants lost a greater percentage of lean mass in the upper limbs compared with the lower limbs.[23] Additionally, MPM is a very localised disease where the bulk of the tumour burden resides in the pleural space and rarely metastasises.[24] This difference, compared to other advanced cancers where tumour burden tends to be more widespread could also impact on wasting patterns. Thus, skeletal muscle distribution could vary between different populations. Further research is needed to determine if there are differences in skeletal muscle distribution between cancer populations, and to understand the implications for body composition research.

There was moderate agreement between CT and DXA cut-points for low muscle mass (κ=0.438) using the CT cut-points from Prado et al[7] and DXA cut-points from Baumgartner et al[17], however there was no significant agreement between CT and DXA for the other cut-points compared. When we used receiver operating characteristics using the Baumgartner cut-point to determine the skeletal muscle index value that had the optimal sensitivity and specificity for detecting low muscle mass in men, it was comparable to the Prado cut-point (52.9 cm^2/m^2 vs. 52.4 cm^2/m^2). These results indicate that in patients with MPM, greater agreement between methods may not be achieved by creating new cut-points. This outcome is not surprising given our finding of a moderate correlation between methods. Researchers should be cognisant that criteria for the classification of low muscle mass are not interchangeable. As there is currently no consensus on diagnostic criteria for the classification of low muscle mass, researchers could consider using continuous variables to evaluate the relationship between muscle and patient outcomes, which would enable comparison between studies.[25]

This study has several limitations. The sample size is small and consists only of patients with MPM and therefore, may not be representative of other cancer populations. There is heterogeneity in our sample with regard to disease status and cancer treatments. Additionally, MPM is substantially more common in men than in women, hence women were underrepresented in this study. This was a retrospective study of CT scans performed as part of routine clinical care and therefore the make and model of CT scanner, slice

thickness and use of contrast enhancement, were not standardised.[26, 27] Changes in muscle could have occurred between the time of CT and DXA scan, although the mean time elapsed between scans was 10.8 days and two thirds of scans were performed on participants >12 months prior to death, a time where reported changes in muscle over time are small.[28] Furthermore, the strong correlation between raters for CT-measured cross-sectional skeletal muscle area indicates that the data is reliable. As this was a retrospective study that utilised CT scans completed as part of routine clinical care, the high inclusion rate of participants (71%) from our longitudinal observational study and exercise intervention study indicates that CT evaluation of body composition is feasible in patients with MPM.

The present study supports the hypothesis that there is a lack of agreement between CT and DXA for the classification of low muscle mass in patients with MPM. Although CT and DXA cannot be used interchangeably, both are relevant body composition assessment methods in cancer research. The decision to use CT or DXA may be dependent on the patient outcome of interest, such as survival or physical functioning, as well as practical considerations. Thoracic CT scans are performed routinely in patients with MPM, and researchers can access scans for retrospective analysis, which can be valuable as prospective research could take many years to complete given the low prevalence of disease and challenges of performing DXA scans in unwell patients with MPM.[2] Considering cut-points for the classification of low muscle mass are subjective, future research in MPM should use continuous data to evaluate the relationship between muscle and patient outcomes.

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Chapter Five

5

Body Composition and Nutritional Status in Malignant Pleural Mesothelioma: Implications for Activity Levels and Quality of Life

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ARTICLE

Protein, malnutrition and wasting disorders

Body composition and nutritional status in malignant pleural mesothelioma: implications for activity levels and quality of life

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Abstract

Background/Objectives: Malignant pleural mesothelioma (MPM) is an incurable cancer and optimizing daily physical activity and quality-of-life are key goals of patient management. Little is known about the prevalence of pre-sarcopenia and malnutrition in MPM or their associations with patient outcomes. This study aimed to determine the prevalence of pre-sarcopenia and malnutrition in MPM and investigate if activity levels and quality-of-life differed according to body composition and nutritional status.

Subjects/Methods: Patients with a diagnosis of MPM were recruited. Pre-sarcopenia was defined as low appendicular skeletal muscle mass (≤7.26 kg/m^2 for men and ≤5.45 kg/m^2 for women), measured by Dual Energy X-Ray Absorptiometry. Malnutrition was defined as a rating of B or C on the Patient-Generated Subjective Global Assessment. Outcome measures included objective activity levels (Actigraph GT3X) and health-related quality-of-life (HRQoL; Functional Assessment of Cancer Therapy General).

Results: Sixty-one people participated (79% male, median age 69 [IQR 62-74] years and median BMI 25.8 [IQR 24.3-28.4] kg/m^2). Fifty-four percent were pre-sarcopenic and 38% were malnourished. Percent of time spent in light activity/day was lower in participants with pre-sarcopenia compared with non-sarcopenic participants (median 25.4 [IQR 19.8–32.1]% vs. 32.3 [27.1–35.6]%; p=0.008). Participants with malnutrition had poorer HRQoL than well-nourished participants (mean 69.0(16.3) vs. 84.4(13.3); p<0.001).

Conclusion: Participants with MPM had high rates of pre-sarcopenia and malnutrition. Pre-sarcopenia was associated with poorer activity levels, whilst malnutrition was associated with poorer quality-of-life. Interventions that aim to address reduced muscle mass and weight loss, should be tested in MPM to assess their impact on patient outcomes.

5.1 Introduction

Malignant pleural mesothelioma (MPM) is an incurable cancer that develops primarily as a result of exposure to asbestos.[1] MPM is distinctly different from advanced lung cancer given the longer median survival of 9 – 12 months,[2] localized nature of the disease [3] and lack of clarity surrounding cause of death.[3] Standard treatment for MPM is chemotherapy, which offers a modest survival benefit.[4, 5] Given the palliative nature of management of MPM, optimizing and maintaining daily physical activity and quality-of-life are primary goals of treatment. As weight loss has been identified as an independent predictor of poor survival in people with MPM,[2] body composition and nutritional status could be integral to optimal supportive care for those with MPM.

While weight loss is commonly noted in MPM, the prevalence of malnutrition has not been reported and no body composition analyses are available. Low muscle mass and malnutrition can exist in people who are not underweight,[6-8] making it challenging for clinicians to identify. If undetected, patients with low muscle mass and malnutrition are unlikely to receive timely treatment to address these conditions.

The implications of low muscle mass and malnutrition on patient-centred outcomes have not been studied in MPM. In patients with advanced cancers, low muscle mass[9, 10] and weight loss, or malnutrition,[11-16] have been associated with poorer quality-of-life. However, none have examined the associations between body composition and nutritional status and daily physical activity. Given that management of MPM is of palliative intent, understanding how modifiable factors, such as muscle mass and nutritional status, influence health-related quality-of-life and patients' ability to take part in daily activities is critical for planning interventions to improve supportive care in MPM.

In cancer populations, reduced muscle mass and malnutrition are conditions with a complicated etiology that could be impacted by dietary intake as well as systemic inflammation.[17] Weight loss can occur in those with adequate energy intakes, suggesting that factors beyond dietary intake influence weight loss.[18] Inflammatory cytokines and many other molecules have been associated with the pathobiology of low muscle mass and malnutrition in cancer patients.[19-24] Knowledge regarding dietary intake and inflammatory profile is therefore essential for guiding the development of interventions to address low muscle mass and malnutrition in MPM.

The primary aim of this study was to determine the prevalence of low muscle mass and malnutrition in patients with MPM. Secondly, we aimed to investigate if there were differences in activity levels, health-related quality-of-life, dietary intake and serum biomarkers according to body composition and nutritional status.

5.2 Materials and methods

5.2.1 Participants

Recruitment took place between August 2015 and May 2017 from a tertiary specialist pleural disease and medical oncology clinic in Western Australia (WA), which has one of the highest incidences of MPM per capita in the world.[25] Patients were eligible if they had cytological or histological confirmation of MPM. Patients were excluded if they were aged <18 years, pregnant or lactating, unable to read and understand English, unable to obtain physician consent, or unable to give informed consent or comply with the protocol.

5.2.2 Study design and setting

The study was a cross-sectional analysis of the baseline data collected from two prospective studies. The studies were 1) a longitudinal observational study of nutritional status and body composition and participants were followed until death or for up to 18 months and 2) a 6-week progressive resistance exercise intervention. Both were pilot studies, designed to provide data for proof of concept and no sample size calculation was performed. The studies were approved by the Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255).

5.2.3 Measures

Demographic and medical variables

Participants' medical records were reviewed for baseline demographic and medical data. Physician-rated Eastern Cooperative Oncology Group (ECOG) performance status[26] was recorded on the date of assessment.

Anthropometric measures

Weight and height, measured with participants dressed in light clothing with shoes removed, were used to calculate the body mass index (BMI). Participants were classified as underweight, normal weight, overweight or obese based on World Health Organization (WHO) BMI criteria.[27]

Body composition

Body composition was assessed using whole body dual-energy x-ray absorptiometry (DXA) scans (Hologic Discovery A, Hologic Inc., Marlborough, MA, USA). Low skeletal

muscle mass was defined as an appendicular skeletal muscle mass/height^2 of ≤7.26 kg/m^2 for males and ≤5.45 kg/m^2 for females.[28] The cut-points for appendicular skeletal muscle mass were set as two standard deviations below the mean of a reference sample of young Caucasian adults, and are associated with physical disability in older adults.[28] Participants with low skeletal muscle mass were categorized as pre-sarcopenic, consistent with the European Working Group on Sarcopenia in Older People diagnosis criteria.[29] Gait speed was not measured in the study and as it is an essential criteria for the classification of sarcopenia and severe sarcopenia, we could not further categorize participants as sarcopenic or severely sarcopenic.[29]

Nutritional status

Nutritional status was assessed using the Patient-Generated Subjective Global Assessment (PG-SGA).[30] Participants were categorized with a global rating of A – well nourished, B – suspected malnutrition/malnutrition or C – severe malnutrition. Malnutrition was defined as a rating of B or C on the PG-SGA. As the PG-SGA categories of B and C both represent participants with malnutrition, the two categories were amalgamated for statistical analysis.

Accelerometer-measured activity levels

Physical activity and sedentary behavior were objectively assessed using the ActiGraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA). Participants were instructed to wear the accelerometer on their hip continuously (24hr/day) for 3 days, to only remove for bathing or swimming and to record any non-wear time in a logbook. Common cut off points were used to classify sedentary time, light activity and moderate and vigorous physical activity (MVPA).[31, 32] Variables were calculated per day and then averaged across all valid days for each participant. Additional accelerometer data collection and analysis methodology is presented in **Supplementary Table 5.3**.

Patient-rated outcomes

Participants completed validated questionnaires to assess cancer specific health-related quality-of-life (HRQoL, Functional Assessment of Cancer Therapy – General; FACT-G),[33] general health-related quality-of-life (Short Form – 36 (SF-36)),[34] appetite (Anorexia Cachexia Scale; ACS)[35] and fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue; FACIT-Fatigue).[36] A score of ≤37 on the ACS indicates poor appetite and a score of ≤34 on the FACIT-fatigue indicates clinically meaningful fatigue.[37, 38]

Dietary intake

Dietary intake was measured prospectively, using an estimated food record over three consecutive days. Written and verbal instructions were provided to participants, explaining how to complete the food record and accurately estimate portion sizes using household measures (e.g. measuring cups and spoons). Returned food records were visually inspected by the researchers and incomplete details were clarified with participants. The food records were then analyzed using Foodworks 8 software (Xyris Software Pty Ltd, Australia). Intake variables were calculated per day and averaged across three days for each participant. Energy and protein intake were expressed as kJ or g per kg of body weight per day. Participants consuming ≥105 kJ/kg/day (1 kcal = 4.186 kJ) or ≥1.0 g/kg/day were classified as meeting energy or protein requirements, respectively.[39] Participant self-reported changes in dietary intake over the previous month were extracted from the PG-SGA.

Serum biomarkers

A blood sample was taken for biomarker analysis. Enzyme linked immunosorbent assay (ELISA) kits was used to measure serum levels of interleukin-6 (IL-6, pg/mL), insulin-like growth factor-1 (IGF-1, ng/mL), ghrelin (ng/mL), leptin (ng/mL), myostatin (ng/mL), adiponectin (mg/L), vascular endothelial growth factors-A (VEGF-A, pg/mL) and C (VEGF-C, ng/mL), tumor necrosis factor-alpha (TNF-α, pg/mL) and interferon-gamma (IFN-γ, pg/mL). ELISA kit manufacturer information is presented in **(**Supplementary Table 5.4**)**. Serum samples of each patient were assayed in duplicates in the same assay. Concentrations of serum CRP (mg/L) and albumin (g/L) measured as part of standard clinical care were obtained from the hospital records.

5.2.4 Statistical analyses

Statistical analyses were conducted using Statistical Package for the Social Sciences (v. 23, IBM Corporation, Somers, NY, USA). Data were expressed as mean (SD) or median [IQR] where the data were not normally distributed. Two-tailed independent t-tests, or the Mann-Whitney test where the data were not normally distributed, were used to test for differences in activity levels, quality-of-life, appetite, fatigue, dietary intake and serum biomarkers between body composition and nutritional status groups. The Chi-Squared test was used to test for associations between body composition and nutritional status and meeting dietary recommendations and self-reported changes in dietary intake. A p-level of <0.05 was considered statistically significant.

5.3 Results

5.3.1 Participants

Sixty-one participants enrolled in the study **(Figure 5.1)**. Participants were predominantly male (79%), with a median age of 69 years, and were enrolled a median 2 months from diagnosis. Forty-three (71%) participants had the epithelioid subtype of MPM and 56 (92%) participants had an ECOG performance status of 0-1. On average patients were overweight (median BMI was 25.8 kg/m^2): no participants were underweight, 41% were in the normal weight range, 44% were overweight and 15% were obese. Demographic and medical characteristics are presented in **Table 5.1**.

5.3.2 Prevalence of pre-sarcopenia and malnutrition

Fifty-three participants completed a DXA scan. Of those, 28 (54%) had pre-sarcopenia. All participants completed the PGSGA, of those 23 (38%) participants were classified as malnourished. Half (54%) of participants with pre-sarcopenia were malnourished. The pre-sarcopenic and malnourished participants are presented according to their BMI category and nutritional status or body composition group in **Figure 5.2**. Differences in characteristics between body composition and nutritional status groups and participants with and without DXA scans are presented in **Supplementary Table 5.5** and **Supplementary Table 5.6**, respectively.

5.3.3 Differences in activity levels, HRQoL, dietary intake and serum biomarkers according to body composition

Activity levels

Participants with pre-sarcopenia spent a lower proportion of their awake time per day in light activity (median 25.4 [IQR 19.8 – 32.1]% vs. 32.3 [27.1 – 35.6]%; p=0.008) and a higher proportion as sedentary (mean 72.8 (9.3)% vs. 63.5 (9.0)%; p=0.001), compared to non-sarcopenic participants. There was also a significant difference in MVPA time between the two groups (median 0.7 [IQR 0.2 – 2.1]%; vs. 2.9 [0.8 – 4.0]%; p=0.005). Participants with pre-sarcopenia also completed fewer bouts of light activity of 20 to <30 minutes duration (median 0.0 [IQR 0.0 – 0.3] vs. 0.3 [0.0 – 1.0]; p=0.010), 10 to <20 minutes duration (median 1.0 [IQR 0.7 – 2.8] vs. 3.7 [2.3 – 5.7]; p=0.004) and of 5 to <10 minutes duration (median 9.0 [IQR 5.9 – 11.8] vs. 12.7 [11.0 – 15.0]; p=0.002), compared

to non-sarcopenic participants (**Figure 5.3**). The majority of participants (67%) recorded no light activity in bouts ≥30 minutes therefore, statistical analysis was not performed.

HRQoL, fatigue and appetite

Between pre-sarcopenic and non-sarcopenic participants, there were no statistically significant differences in cancer specific HRQoL (mean 78.5 (15.8) vs. 82.2 (14.0); p=0.414), fatigue (median 35.0 [IQR 28.0 – 47.0] vs. 41.0 [IQR 33.5 – 46.5]; p=0.290), or any of the domains for general HRQoL (p≥0.073, **Figure 5.4**). Appetite scores were significantly poorer in pre-sarcopenic participants compared with non-sarcopenic participants (median 37.0 [IQR 29.0 – 42.0] vs. 42.5 [38.8 – 44.3]; p=0.014).

Dietary intake

Pre-sarcopenic and non-sarcopenic participants did not differ significantly in their energy or protein intake (median 125 [IQR 93.2 – 138.2] kJ/kg/day vs. 128 [87.2 – 141.0] kJ/kg/day; p=0.975 and mean 1.4 (0.4) g/kg/day vs. 1.3 (0.5) g/kg/day; p=0.504]). There was no difference between body composition groups with regard to the proportion of participants meeting energy (p=0.606) or protein requirements (p=0.404). The proportion of participants who reported a decrease from their usual intake in the past month did not differ significantly between pre-sarcopenic and non-sarcopenic participants (57.1% vs. 33.3%; p=0.086). Of the twelve participants taking high protein supplements, seven had a DXA scan, of whom 86% (n=6) were pre-sarcopenic.

Serum biomarkers

Differences in serum biomarkers according to body composition group are presented in **Table 5.2**. Among the cytokines analyzed, only IL-6 levels were higher in pre-sarcopenic compared with non-sarcopenic participants (p=0.006). Between pre-sarcopenic and non-sarcopenic participants, there were no differences in levels of myostatin (p=0.085), albumin concentration (p=0.143) or any other measured serum biomarkers.

5.3.4 Differences in activity levels, HRQoL, dietary intake and serum biomarkers according to nutritional status

Activity levels

Malnourished and well-nourished participants did not differ in the proportion of time per day spent in light activity (median 26.6 [IQR 21.2 – 34.8]% vs. 29.7 [24.0 – 34.6]%; p=0.380) or as sedentary (median 72.5 [IQR 65.0 – 78.7]% vs. 68.4 [62.8 – 73.0]%;

p=0.208). There was a significant difference in MVPA between malnourished and well-nourished participants (median 0.6 [IQR 0.2 – 1.3]% vs. 1.6 [0.6 – 3.5]%; p=0.013). There were no significant differences between the two groups for light activity of 20 to <30 minutes, 10 to <20 minutes or 5 to <10 minutes [median 0.0 [IQR 0.0 – 0.7] vs. 0.3 [0.0 – 0.7]; p=0.267, median 1.0 [IQR 0.7 – 3.7] vs. 2.7 [1.3 – 4.3]; p=0.075, median 10.0 [IQR 5.5 – 13.0] vs. 11.3 [8.3 – 13.7]; p=0.189, respectively] (**Figure 5.3**). The majority of participants (72%) recorded no light activity in bouts ≥30 minutes therefore, statistical analysis was not performed.

HRQoL, fatigue and appetite

Compared with well-nourished participants, malnourished participants scored lower for cancer specific HRQoL (mean 69.0 (16.3) vs. 84.4 (13.3); p<0.001) and fatigue (mean 27.4 (12.0) vs. 40.2 (8.9); p<0.001), as well as on all general HRQoL domains (p≤0.041), with the exception of role emotional and mental health (p=0.075 and p=0.124, respectively*;* **Figure 5.4**). Appetite scores were significantly poorer in malnourished participants compared with well-nourished participants (median 29.0 [IQR 19.0 – 36.0] vs. 41.0 [36.8 – 44.3]; p<0.001).

Dietary intake

There was no difference in energy or protein intake between malnourished and well-nourished participants (median 110 [IQR 86.7 – 132.0] kJ/kg/day vs. 128 [93.4 – 140.4] kJ/kg/day; p=0.182 and mean 1.3 (0.4) g/kg/day vs. 1.4 (0.5) g/kg/day; p=0.521) or in the proportion of participants meeting energy (p=0.388) or protein requirements (p=0.814). The proportion of participants who reported a decrease from their usual intake in the past month was significantly higher in malnourished compared with well-nourished participants (91.3% vs. 26.3%; p<0.001). Ninety percent (n=11) of those consuming high energy, high protein nutrition supplements were malnourished.

Serum biomarkers

Differences in serum biomarkers according nutritional status are presented in **Table 5.2**. Among the cytokines, IL-6 and was higher and myostatin was lower for malnourished compared with well-nourished participants (p=0.002 and p=0.032, respectively). Compared with well-nourished participants, malnourished participants had a lower albumin concentration (p=0.004). There were no differences in any other measured serum biomarkers.

Table 5.1 Demographic and medical characteristics of participants, n=61

	n	%
Age, years	69.0^	62.0-74.0^
Gender, male	48	78.7
BMI, kg/m^2	25.8^	24.3-28.4^
BMI category		
Underweight	0	0.0
Normal weight range	25	41.0
Overweight	27	44.3
Obese	9	14.8
Time since diagnosis, months	2.0^	1.0-9.0^
Median survival, months	21^	12.0-30.0^
Histological subtype		
Epithelioid	43	70.5
Sarcomatoid	5	8.2
Desmoplastic	3	4.9
Biphasic	4	6.6
Unspecified	5	8.2
Unknown	1	1.6
ECOG performance status		
0-1	56	91.8
≥2	5	8.2
Received cancer treatment prior to study, yes	21	34.4
Type of treatment received		
Chemotherapy	10	47.6
Radiotherapy	3	14.3
Surgery	1	4.8
Surgery and radiotherapy	1	4.8
Chemotherapy & radiotherapy	3	14.3
Chemotherapy, radiotherapy and surgery	2	9.5
Other	1	4.8
Undergoing cancer treatment at the time of study, yes	9	14.8
Type of ongoing treatment		
Cisplatin and Pemetrexed	1	11.1
Carboplatin and Pemetrexed	4	44.4
Vinorelbine	1	11.1
Clinical trial – AZD4547	1	11.1
Clinical trial – Cisplatin, Pemetrexed and Nintedanib	1	11.1
Clinical trial – Cisplatin, Pemetrexed and Durvalumab	1	11.1

	n	%
Grade of pleural effusion		
0	2	3.3
1	7	11.5
2	21	34.4
3	15	24.6
4	5	8.2
Unknown	11	18.0
Side of pleural effusion, right	41	67.2
Pleural effusion treatment¤		
IPC	23	37.7
ICC	9	14.8
VATS	5	8.2
Therapeutic aspirate	5	8.2
Talc poudrage	2	3.3
Pleurectomy	1	1.6
None	15	24.6
Unknown	1	1.6
Comorbidities		
Hypertension	22	36.1
Hypercholesterolemia	12	19.4
Ischemic heart disease	6	9.7
Atrial fibrillation	3	4.8
Type 2 diabetes	8	12.9
COPD	1	1.6
Osteoarthritis	3	4.8
Hip or knee replacement	3	4.8
Appendicular lean mass, DXA (n=52)		
kg	21.1^	18.0 – 23.0^
kg/m^2	7.0^	6.2 – 7.5^
Body composition group (n=52)		
Non-sarcopenic	24	46.2
Sarcopenic	28	53.8
Self-reported weight loss in 6 months, %	2.6	0.0 – 7.0
Self-reported weight loss in 6 months		
<5%	43	70.5
5-10%	9	14.8
>10%	9	14.8
Nutritional status, PG-SGA		
A – well nourished	38	62.3
B – suspected malnutrition/moderately malnourished	23	37.7
C – severely malnourished	0	0

	n	%
Energy intake (n=56)		
kJ/day	9001	3278
kJ/kg/day	124^	91 – 140^
Protein intake (n=56)		
g/day	103.3	37.6
g/kg/day	1.3	0.5
Energy and protein requirements (n=56)		
Energy requirement met	35	62.5
Protein requirements met	43	76.8
Energy or protein requirements met	43	76.8
Consumed nutritional supplements (n=56)	12	21.4
Poor appetite□ (n=53)	23	43.4
Fatigued▪ (n=52)	21	40.4

^Median, interquartile range; ¤Last treatment prior to date of assessment; □Score ≤37 on Anorexia Cachexia Scale, ▪Score ≤34 on Functional Assessment of Chronic Illness Therapy – Fatigue Scale; BMI – Body mass index; IPC – indwelling pleural catheter; ICC – intercostal catheter; VATS – video-assisted thoracoscopic surgery; ECOG – Eastern Cooperative Oncology Group; COPD – chronic obstructive pulmonary disease; DXA – Dual Energy X-ray Absorptiometry; PG-SGA – Patient-Generated Subjective Global Assessment

Table 5.2 Inflammatory markers and cytokines according to body composition and nutritional status

		Body composition			Nutritional status		
	All participants (n=57)	**Non-sarcopenic (n=23)**	**Pre-sarcopenic (n=27)**	**P value**	**Well-nourished (n=35)**	**Malnourished (n=22)**	**P value**
IL-6, pg/mL	5.3 (2.0-13.5)	2.5 (2.0-7.9)	6.5 (3.1-18.3)	0.006*	2.6 (2.0-7.9)	11.0 (4.7-18.8)	0.002*
IGF-1, ng/mL	9.1 (3.4-15.0)	7.1 (1.6-10.8)	9.9 (5.3-15.0)	0.179	7.1 (2.0-14.0)	11.3 (6.4-17.4)	0.090
Ghrelin, ng/mL	0.38 (0.15-0.75)	0.28 (0.09-0.59)	0.34 (0.14-0.94)	0.255	0.38 (0.09-0.63)	0.39 (0.23-0.88)	0.294
Leptin, ng/mL	5.1 (4.0-7.4)	5.7 (3.9-7.8)	5.2 (4.0-7.2)	0.869	5.1 (4.1-7.0)	5.2 (3.9-8.4)	0.896
Myostatin, ng/mL	1.3 (0.9-1.8)	1.7 (1.0-1.9)	1.2 (0.8-1.8)	0.085	1.6 (1.1-1.9)	1.1 (0.7-1.8)	0.032*
Adiponectin, mg/L	3.5 (1.9-6.3)	3.2 (0.9-4.6)	4.0 (2.3-6.5)	0.127	3.3 (2.5-5.7)	3.8 (0.0-6.6)	0.935
VEGF-A, pg/mL	0.29 (0.13-0.57)	0.27 (0.13-0.46)	0.30 (0.13-0.64)	0.704	0.33 (0.13-0.59)	0.21 (0.13-0.53)	0.768
VEGF-C, ng/mL	22.7 (16.0-26.7)	23.1 (20.4-31.6)	22.7 (15.4-23.9)	0.216	23.1 (17.0-28.0)	18.5 (13.2-23.9)	0.127
Albumin, g/L (n=55)	40.0 (37.0 – 42.0)	40.0 (38.0-43.0)	39.5 (36.0-41.0)	0.167	40.0 (38.5-42.0)	37.0 (34.8-41.0)	0.005*
CRP, mg/L (n=46)	19.5 (6.5-70.3)	13.0 (2.1-49.0)	27.0 (7.1-98.0)	0.122	19.0 (3.2-60.5)	35.0 (6.7-84.0)	0.516

Data is presented as median (interquartile range); *p<0.05; IL-6 – Interleukin-6; IGF-1 – Insulin-like Growth Factor-1; VEGF – Vascular Endothelial Growth Factor
TNF-α and IFN-γ levels were undetectable in 89.7% (n=52) and 74.1% (n=43) of samples, respectively, and statistical analyses were not performed.

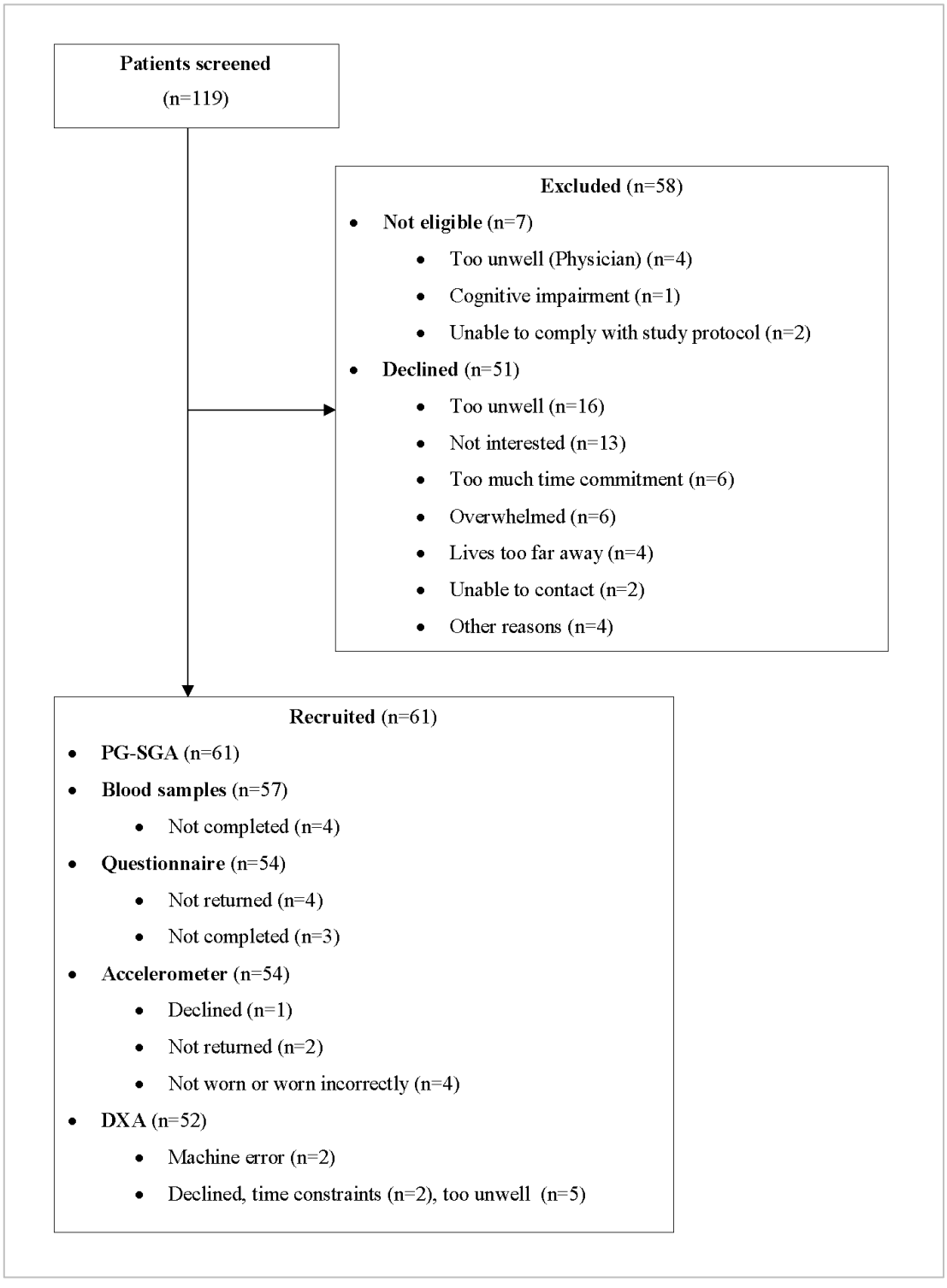

Figure 5.1 Recruitment of participants to the study

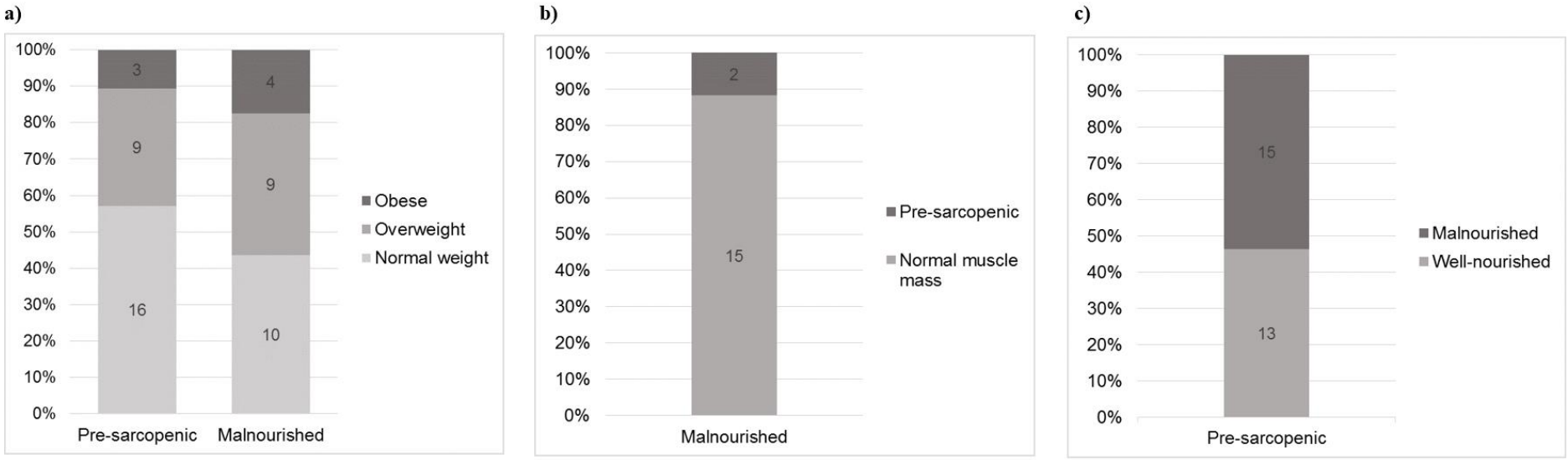

Figure 5.2 Pre-sarcopenic and malnourished participants. a) Pre-sarcopenic and malnourished participants according to BMI category (n=23 and n=28, respectively), b) pre-sarcopenic participants according to nutritional status (n=28), and c) malnourished participants according to body composition group (n=17)

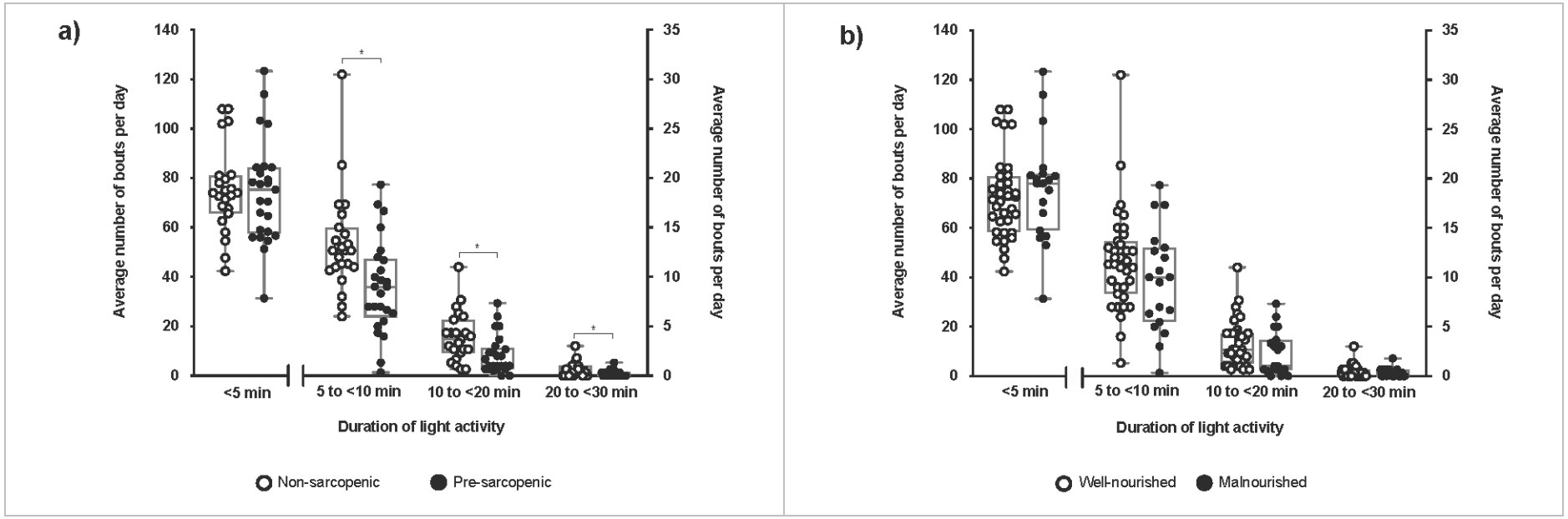

Figure 5.3 Differences in the number of bouts of light activity according to a) body composition (n=48) and b) nutritional status (n=54),*p<0.05

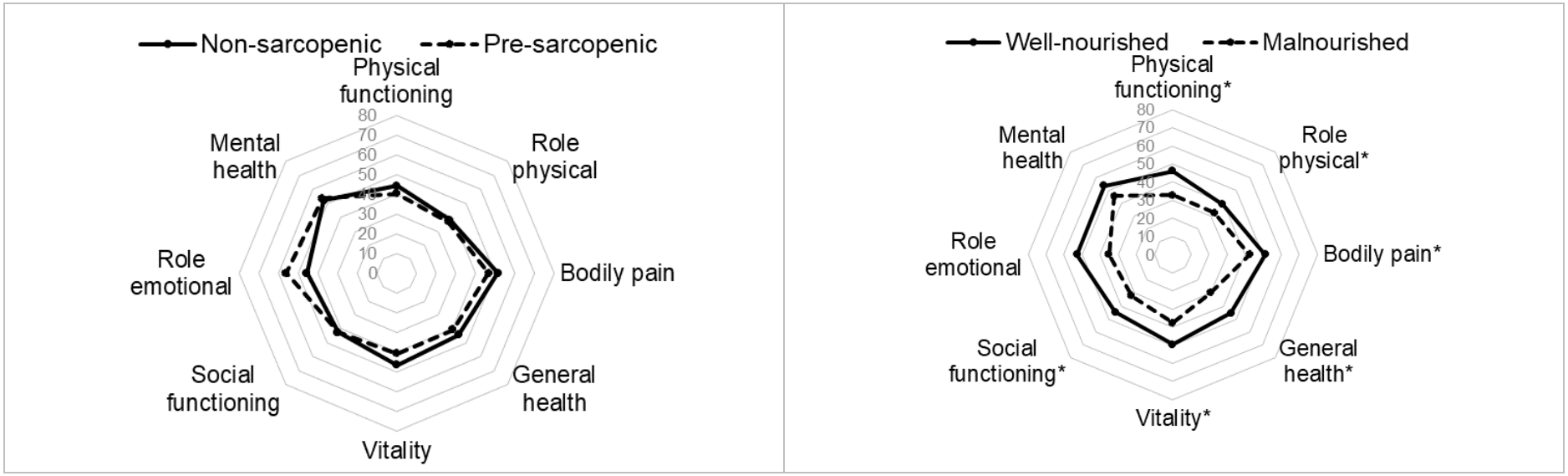

Figure 5.4 Median scores for the general health-related quality of life domains according to a) body composition (n=46) and b) nutritional status (n=54), *p<0.05

5.4 Discussion

Our study found high rates of pre-sarcopenia (54%) and malnutrition (38%). Compared to data from healthy older adults, we report a much higher prevalence of these conditions in MPM.[40, 41] This result is particularly striking because none of the participants were underweight, the large majority had a good performance status and were early in their diagnosis. Consistent with population trends, a high proportion of cancer patients are overweight or obese.[42] In our study, two thirds of participants were overweight or obese and had similar rates of pre-sarcopenia and malnutrition compared with those in the normal weight category. Studies in other cancer populations have reported reduced muscle mass[6] and malnutrition[7, 8] across all weight categories and in those with good performance status.[43] These results highlight that pre-sarcopenia and malnutrition are common in MPM patients where clinicians might not expect, for example, newly diagnosed, overweight and obese patients of a good performance status.

Pre-sarcopenic participants spent significantly less time per day in light activity, and did fewer bouts of longer periods of light activity (>5 min), compared with non-sarcopenic patients. Self-reported fatigue and physical functioning were not lower in participants with pre-sarcopenia which raises the possibility that habitually low levels of physical activity may have contributed to reduced muscle mass. However, people with reduced muscle mass need to work closer to their maximum capacity to generate the necessary strength and power to complete activities of daily living. Therefore, reduced muscle mass could result in increased fatigue and compensatory reductions in activity levels. Further research is required to determine if interventions which enhance muscle mass, could improve participation in daily physical activity for patients with MPM.

We observed a significant inverse association between malnutrition and quality-of-life, in particular poorer self-rated physical functioning, which supports work in other cancer survivor populations.[11, 14, 15] However, the relationship between malnutrition and quality-of-life is complex, particularly as malnourished participants had higher IL-6 concentrations and fatigue levels which could be indicative of greater disease burden.[44] While patients with MPM can maintain quality of life with chemotherapy,[45] there are limited effective treatments available.[5] For patients who do not respond to treatment, supportive care strategies could offer some benefit. An important next step will be to test interventions to address malnutrition in MPM to determine their impact on quality-of-life. Notably, nutritional interventions consisting of dietary counseling and oral nutrition supplements alone, provided to patients with cancer receiving chemotherapy or

radiotherapy, have had no impact on quality-of-life.[46] This suggests that interventions may need to do more than increase dietary intake or weight to impact on quality-of-life. Interventions which also address the psychosocial aspects of eating may be an integral part of optimizing quality-of-life in patients with MPM.[47]

Overall energy and protein intake did not differ between nutritional status or body composition groups. High rates of reported nutrition supplement consumption amongst malnourished participants suggest that participants may have already made changes to their diet to address malnutrition. These results indicate malnourished patients with MPM can meet their recommended energy and protein intake with nutrition support. Although, given the higher IL-6 concentrations amongst participants with malnutrition and pre-sarcopenia, these conditions may not be resolved without addressing the underlying inflammation.[17] Anti-inflammatory agents (e.g., eicosapentanoic acid or non-steroidal anti-inflammatory drugs) have the potential to offer some benefit but are yet to be tested in MPM and may be contraindicated for patients receiving active cancer treatment.[17]

There are several limitations to the current study. The study is cross-sectional and therefore cannot draw causative conclusions. The study has a small sample size and was underpowered to detect differences in quality-of-life scores, as demonstrated by the clinically meaningful differences between body composition groups that were not statistically significant (e.g., a 6-point median difference in the vitality domain of quality-of-life; **Figure 4a**). However, a larger, retrospective study of patients with advanced lung cancer (n=734) has reported a significant association between skeletal muscle and quality-of-life.[10]

There is also heterogeneity in the sample with regard to time from diagnosis and treatments received. One of the most common reasons for non-inclusion in the study was being too unwell. Therefore, this study possibly included patients who were in better health, as indicated by longer the median survival of our sample, and may not be representative of the larger MPM population. Additionally, we were unable to obtain body composition data for 15% of participants and being too unwell was the most common reason for not completing a DXA **(Figure 5.1)**. Compared with participants who completed a DXA, participants without a DXA were significantly older, and had a poorer appetite. This data suggests that in cancer patients who are older with significant symptoms, body composition analysis techniques that do not add to participant burden e.g. computed tomography scan analysis, could be more feasible.

Our study is the first to investigate body composition and nutritional status specifically in patients with MPM and provides valuable information on the extent of pre-sarcopenia and malnutrition in this population. Gold standard assessments were employed to comprehensively assess body composition, nutritional status, patient-rated outcomes and objective physical activity. We have included a relatively homogenous sample of patients with MPM. As MPM is a unique disease with a different disease process, prognosis and treatment options to advanced lung cancer, it is important that MPM is studied independently.

5.5 Conclusion

Despite good performance status and a normal or high BMI, participants with MPM had high rates of pre-sarcopenia and malnutrition. Both pre-sarcopenia and malnutrition were associated with negative outcomes for participants. For the first time in MPM, we report that pre-sarcopenia was associated with lower activity levels whilst malnutrition was associated with poorer quality-of-life. Interventions that aim to address reduced muscle mass and weight loss, should be tested in MPM to assess their impact on activity levels and quality-of-life.

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Supplementary Tables

Supplementary Table 5.3 Accelerometer data collection and analysis methods

Paradata	Method
Raw data collection	Accelerometers were programmed to record raw data at a frequency of 30 Hz.
Epoch length	Data were reduced to vertical axis movement counts per 60-second epoch.
Software used	Accelerometer data were downloaded and processed in Statistical Analysis Software (version 9.3, SAS Institute, Cary, NC, USA).
Non-wear time	Waking wear time was determined by visual inspection by a trained rater and an automated algorithm.[1]
Minimum wear time	A valid day was classified as ≥10-hours of waking wear time.
Minimum valid days	Participants with at least one valid day of data were analyzed.

Reference in table

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Supplementary Table 5.4 Manufacturer information for ELISA kits used in serum biomarker analysis

Biomarker	ELISA kit manufacturer
Interleukin-6	Thermo Fisher Scientific, Waltham, MA, USA
Insulin-like growth factor	elisakit.com, Melbourne, Australia
Ghrelin	Thermo Fisher Scientific, Waltham, MA, USA
Leptin	eBioscience Inc., San Diego, CA, USA
Myostatin	R&D Systems Inc., Minneapolis, MN, USA
Adiponectin	R&D Systems Inc., Minneapolis, MN, USA
Vascular endothelial growth factor-A	R&D Systems Inc., Minneapolis, MN, USA
Vascular endothelial growth factor-C	R&D Systems Inc., Minneapolis, MN, USA
Tumor necrosis factor-alpha	Thermo Fisher Scientific, Waltham, MA, USA
Interferon-gamma	Thermo Fisher Scientific, Waltham, MA, USA

Supplementary Table 5.5 Differences in demographic and medical characteristics according to body composition and nutritional status

	Body composition					Nutritional status				
	Non-sarcopenic (n=24)		Pre-sarcopenic (n=28)			Well-nourished (n=38)		Malnourished (n=23)		
	n	%	n	%	p value	n	%	n	%	p value
Age, years	65.0	59.0–70.0^	69.0	62.5–74.0^	0.042*	67.0	61.5–74.0^	70.0	67.0–74.0^	0.171
Gender, male	19	79.2	22	78.6	0.958	31	81.6	17	73.9	0.479
BMI, kg/m^2	26.4	25.0– 29.7^	24.6	23.5–27.2^	0.012*	25.8	24.6–28.2^	25.4	23.7–28.7^	0.592
BMI category										
Underweight	0	0.0	0	0.0	0.064	0	0.0	0	0.0	0.799
Normal weight range	6	25.0	16	57.1		15	39.5	10	43.5	
Overweight	14	58.3	9	32.1		18	47.4	9	39.1	
Obese	4	16.7	3	10.7		5	13.2	4	17.4	
Time since diagnosis, months	2.0	1.0–9.0^	3.0	1.0–12.0^	0.809	2.0	1.0–9.0^	2.0	1.0–12.0	0.502
Histological subtype*										
Epithelioid	20	83.3	17	60.7		31	81.6	12	52.2	
Sarcomatoid	2	8.3	2	7.1		2	5.3	3	13.0	
Desmoplastic	0	0.0	2	7.1		1	2.6	2	8.7	
Biphasic	1	4.2	3	10.7		2	5.3	2	8.7	
Unspecified	0	0.0	4	14.3		1	2.6	4	17.4	
Unknown	1	4.2	0	0.0		1	2.6	0	0.0	

	Body composition					Nutritional status				
	Non-sarcopenic (n=24)		Pre-sarcopenic (n=28)			Well-nourished (n=38)		Malnourished (n=23)		
	n	%	n	%	p value	n	%	n	%	p value
ECOG performance status										
0-1	23	95.8	26	92.9	0.646	38	100.0	18	78.3	0.003*
≥2	1	4.2	2	7.1		0	0.0	5	21.7	
Received treatment prior to study, yes	8	33.3	9	32.1	0.927	13	34.2	8	34.8	0.964
Type of treatment*										
Chemotherapy	4	50.0	4	44.4		7	53.8	3	37.5	
Radiotherapy	1	12.5	1	11.1		1	7.7	2	25.0	
Surgery	1	12.5	0	0.0		1	7.7	0	0.0	
Surgery and radiotherapy	1	12.5	0	0.0		0	0.0	1	12.5	
Chemotherapy & radiotherapy	0	0.0	2	22.2		1	7.7	2	25.0	
Chemotherapy, radiotherapy and surgery	0	0.0	2	22.2		2	15.4	0	0.0	
Other	1	12.5	0	0.0		1	7.7	0	0.0	
Grade of pleural effusion (n=52)*										
0 – 2	12	66.7	13	56.5	0.509	22	66.7	8	42.1	0.043
3 – 4	6	33.3	10	43.5		11	33.3	11	57.9	
Side of pleural effusion, right (n=52)	15	62.5	21	75.0	0.446	25	65.8	16	69.6	0.872

	Body composition					Nutritional status				
	Non-sarcopenic (n=24)		Pre-sarcopenic (n=28)			Well-nourished (n=38)		Malnourished (n=23)		
	n	%	n	%	p value	n	%	n	%	p value
Pleural effusion treatment¤*										
IPC	8	33.3	10	35.7		11	28.9	12	52.2	
ICC	3	12.5	5	17.9		5	13.2	4	17.4	
VATS	3	12.5	2	7.1		4	10.5	1	4.3	
Therapeutic aspirate	1	4.2	4	14.3		4	10.5	1	4.3	
Talc poudrage	1	4.2	1	3.6		2	5.3	0	0.0	
Pleurectomy	0	0.0	1	3.6		1	2.6	0	0.0	
None	7	29.2	5	17.9		10	26.3	5	21.7	
Unknown	1	4.2	0	0.0		1	2.6	0	0.0	
Comorbidities*										
Hypertension	8	33.3	11	39.3		14	36.8	9	39.1	
Hypercholesterolemia	6	25.0	3	10.7		6	15.8	6	26.1	
Ischemic heart disease	2	8.3	3	10.7		2	5.3	4	17.4	
Atrial fibrillation	1	4.2	2	7.1		1	2.6	2	8.7	
Type 2 diabetes	2	8.3	4	14.3		4	10.5	5	21.7	
COPD	0	0.0	1	3.6		0	0.0	1	4.3	
Osteoarthritis	1	4.2	2	7.1		2	5.3	1	4.3	
Hip or knee replacement	0	0.0	3	10.7		1	2.6	2	8.7	
Back pain or spinal surgery	1	4.2	3	10.7		1	2.6	3	13.0	

^Median, interquartile range; ¤Last treatment prior to date of assessment; BMI – Body mass index; IPC – indwelling pleural catheter; ICC – intercostal catheter; VATS – video-assisted thoracoscopic surgery; ECOG – Eastern Cooperative Oncology Group; COPD – chronic obstructive pulmonary disease; *statistical comparisons not carried out

Supplementary Table 5.6 Differences in demographic and medical characteristics between participants with and without DXA scans, n=61

	DXA available (n=52)		DXA missing (n=9)		
	n	%	n	%	p value
Age, years	68.0^	62.0-74.0^	73.0^	69.5-78.0^	0.026*
Gender, male	41	78.8	7	77.8	0.942
BMI, kg/m^2	25.8^	24.1-28.5^	25.4^	24.8-28.9^	0.745
Time since diagnosis, months	2.0^	1.0-9.8^	2.0^	1.0-5.0^	0.483
Histological subtype (n=55)					
Epithelioid	37	78.7	6	75.0	0.814
Non-epithelioid	10	21.3	2	25.0	
Received treatment prior to study, yes	17	32.7	4	44.4	0.493
Side of effusion, right (n=60)	36	70.6	5	55.6	0.371
Grade of effusion (n=50)					
0-2	25	61.0	5	55.6	0.764
3-5	16	39.0	4	44.4	
Effusion treatment¤ (n=60)					
IPC	18	35.3	5	55.6	0.223
Other	21	41.2	1	11.1	
None	12	23.5	3	33.3	
ECOG performance status					
0-1	49	94.2	7	77.8	0.097
≥2	3	5.8	2	22.2	
Comorbidities					
≤1	16	30.8	4	44.4	0.420
>1	36	69.2	5	55.6	
PG-SGA global rating					
A – well-nourished	35	67.3	3	33.3	0.052
B – suspected malnutrition or malnourished	17	32.7	6	66.7	
C – severely malnourished	0	0.0	0	0.0	
Self-reported weight loss in 6 months					
<5%	39	75.0	4	44.4	0.024*
5-10%	8	15.4	1	11.1	
>10%	5	9.6	4	44.4	
Poor appetite (n=53)	15	33.3	8	100.0	<0.001*
FACT-G (n=53)	80.3#	14.9#	70.9	21.3	0.132

^Median, interquartile range; #mean ± SD, *p<0.05; ¤Last treatment prior to date of assessment; IPC – indwelling pleural catheter; PG-SGA – Patient-Generated Subjective Global Assessment, FACT-G – Functional Assessment of Cancer Therapy - General

Chapter Six

6

Functional and Nutritional Impairments in Patients with Malignant Pleural Mesothelioma across the Disease Course

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Abstract

Context: There is little information on the functional and nutritional characteristics of patients with malignant pleural mesothelioma (MPM).

Objectives: To report the prevalence of functional and nutritional impairment across the 2-years following diagnosis of MPM and to describe functional and nutritional status over time.

Methods: This was a prospective observational study and participants were followed for up to 18-months. Functional data were collected using the: Short-Form Health Survey (SF-36) – physical functioning domain and Timed Up and Go (TUG). Nutritional data were collected using the: Anorexia Cachexia Scale (ACS) and Patient-Generated Subjective Global Assessment (PG-SGA). Two analyses were performed: the prevalence of impairment at six time intervals within 2-years of diagnosis and status over time in participants with ≥2 assessments.

Results: Thirty-six patients with MPM were enrolled (mean age 69.7±7.3 years, 81% male, median survival 17.5 [IQR 10.3–29.3] months). Across all time intervals within 2-years of diagnosis, 57-75% of participants had poor SF-36 physical functioning, 50-88% had a poor TUG result, 56-71% had a poor appetite and 18-38% had a high need for nutrition support. Of the participants studied longitudinally (n=25), 52% had poor SF-36 physical functioning, 69% had a poor TUG result, 69% had a poor appetite and 36% had a high need for nutrition support at ≥2 assessments.

Conclusion: In patients with MPM, functional and nutritional impairment was common. For many participants, impairments persisted or reoccurred during follow-up. Screening for functional and nutritional impairment is recommended from diagnosis to identify those that could benefit from supportive care interventions.

Key message statement: This article describes a prospective observational study that provides new information about the functional and nutritional characteristics of patients with MPM, and indicates that functional and nutritional impairments are prevalent across the 2-years from diagnosis and commonly persist or reoccur over time.

6.1 Introduction

Malignant pleural mesothelioma (MPM) is a universally fatal cancer attributed to asbestos exposure.[1] Given the incurable nature of the disease and short median survival of 12 months,[2] the care of patients with MPM is primarily aimed at optimising quality-of-life.

The ability to perform usual daily life activities is a core component of quality-of-life.[3] Additionally, malnutrition is associated with poorer quality-of-life in patients with thoracic cancer.[4-6] However, currently there is no comprehensive description of the functional and nutritional characteristics of this patient population.

Existing research on physical functioning of patients with MPM is limited to those who have undergone pleurectomy or decortication,[7] which represents a small select proportion of patients with MPM. Information on nutritional status in MPM is limited to a cross-sectional analysis of patients assessed close to the time of diagnosis.[8] Research in patients with lung cancer indicates physical functioning and nutritional status decline following diagnosis,[9-11] suggesting supportive care needs are greater over time.[9-11] However, a greater understanding of the functional and nutritional characteristics of patients with MPM is needed as it is a predominantly localised disease,[12] with a longer median survival,[2] which could impact on physical functioning and nutritional outcomes. Therefore, the aim of our study was to report the prevalence of functional and nutritional impairment across the 2 years following diagnosis of MPM and to describe functional and nutritional status over time.

6.2 Methods

6.2.1 Participants

Recruitment took place between August 2015 and March 2017 from a tertiary specialist pleural disease clinic in Western Australia (WA). Inclusion criteria for participation in the study were cytological or histological confirmation of MPM. Patients could enrol any time following MPM diagnosis. Patients were excluded from the study if they were aged <18 years, pregnant or lactating or unable to read and understand English, to give informed consent, or to comply with the protocol or participating in a concurrent exercise intervention study. Patient consent and physician approval were required for participation in the study.

6.2.2 Study design and setting

In this prospective observational study, participants completed study assessments during routine hospital visits approximately every 3 months and were followed until death or for a maximum of 18 months. The study was approved by the Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255).

6.2.3 Measures

Demographic and medical variables

Participants' medical records were reviewed for demographic and medical data.

Self-reported physical functioning

Self-reported physical functioning was assessed with the physical functioning domain of the Short-Form Health Survey (SF-36).[3] Participants were classified as having a poor self-reported physical functioning if they had a norm-based score <45.[3]

Objective physical functioning

Objective physical functioning was assessed with the Timed Up and Go test.[13] Participants were instructed using a standard procedure to get out of a chair, walk 2.44 meters, turn around a marker and return to sitting as quickly as possible. Participants completed three trials with a one minute rest between each test. All tests were timed using a stopwatch, with the best time used in the analysis. We applied the age and sex specific criterion-reference standards that are associated with maintaining physical independence in older adults, which range from 4.8 – 8.0 seconds for men and 5.0 – 8.0 seconds for women.[14] Participants were classified as having poor objective physical functioning if they had a result that exceeded the criterion-reference standard range, i.e. greater than 8 seconds.

Appetite

Appetite status was assessed using the validated Anorexia Cachexia Scale (ACS).[15] Participants were classified as having a poor appetite if they had an ACS score ≤37.[16]

Nutritional status

Nutritional status was assessed using the scored Patient-Generated Subjective Global Assessment (PG-SGA).[17] Participants were classified as having a high need for symptom control and nutrition support if they had a PG-SGA score ≥9.[17]

6.2.4 Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (v. 26, IBM Corporation, Somers, NY, USA). Data were expressed as mean ± SD or median [IQR] where the data were not normally distributed. To report on the prevalence of nutritional and functional impairment, data were allocated into six time intervals across the 2 years following diagnosis of MPM **(Analysis 1)**. Participants with no assessments within 2 years of diagnosis were excluded from this analysis. The number of months between diagnosis and each participant assessment was calculated and participant data were then categorised into the corresponding time interval. Participants were included in multiple time intervals if they completed more than one assessment, however no participant was included in the same time interval twice. To provide a description of functional and nutritional status over time **(Analysis 2)**, we examined outcomes longitudinally at five time intervals within the 18 months of study enrolment. Participants who did not complete ≥2 assessments were excluded from this analysis. The number of months between study enrolment and each participant assessment was calculated and participant data were then categorised into the corresponding time interval. Due to small numbers in each time interval, statistical tests were not used to compare differences in outcomes between time intervals.

6.3 Results

6.3.1 Participant characteristics

Thirty-six participants with MPM enrolled in the study with 34 (94%) included in **Analysis 1** and 25 (69%) in **Analysis 2** (**Figure 6.1**). Participants were predominantly male (81%) with the epithelioid subtype of MPM (69%). The mean age of participants was 69.7 ± 7.3 years and median survival was 17.5 [IQR 10.3 – 29.3] months. Demographic and medical characteristics are presented in **Table 6.1**.

6.3.2 Analysis 1: Prevalence of functional and nutritional impairment between diagnosis and 2-years post-diagnosis

Self-reported physical functioning

At all time intervals, there was a consistently high proportion of participants with a poor physical functioning score on the SF-36. At diagnosis, 74% of participants had below average self-reported physical functioning and of these participants, 14% were receiving cancer treatment. At each of the remaining time intervals, 57 – 75% of participants reported the poor physical functioning and of these participants, 42 – 75% were receiving cancer treatment **(Figure 6.2)**.

Objective physical functioning

At all time intervals, there was a consistently high proportion of participants with a poor result from the Timed Up and Go test. At diagnosis, 91% of participants had a poor Timed Up and Go result and of these participants, 10% were receiving cancer treatment. At each of the remaining time intervals, 50 – 88% of participants had a poor Timed Up and Go result and of these participants, 25 – 50% were receiving cancer treatment **(Figure 6.2)**.

Appetite

At all time intervals, there was a consistently high proportion of participants with a low appetite score on the ACS. At diagnosis, 68% of participants had a poor appetite and of these participants, 31% were receiving cancer treatment. At each of the remaining time intervals, 56 –71% of participants had a poor appetite and of these participants, 25 – 80% were receiving cancer treatment **(Figure 6.2)**.

Nutritional status

Diagnosis was the time interval where the greatest proportion of participants had a high PG-SGA score indicating a high need for symptom control and nutrition support. At diagnosis, 57% of participants had a high need for symptom control and nutrition support and of these participants, 23% were receiving cancer treatment. At each of the remaining time intervals, 18 – 38% of participants had a high need for symptom control and nutrition support and of these participants, 33 – 67% were receiving cancer treatment **(Figure 6.2)**.

6.3.3 Analysis 2: Longitudinal description of functional and nutritional status between enrolment and 18 months

Self-reported physical functioning

Seventeen percent of participants had normal SF-36 physical functioning scores for the duration of follow-up. The remaining participants had poor SF-36 physical functioning scores at one (32%), two (16%) or three or more (36%) assessments (**Figure 6.3**).

Objective physical functioning

Seventeen percent of participants had normal Timed Up and Go results for the duration of follow-up. The remaining participants had poor Timed Up and Go results at one (13%), two (26%) or three or more (43%) assessments (**Figure 6.3**).

Appetite

Twenty-two percent of participants had a normal appetite score for the duration of follow-up. The remaining participants had a poor appetite at one (9%), two (30%) or three or more (39%) assessments (**Figure 6.3**).

Nutritional status

Thirty-two percent of participants did not have a high need for symptom control and nutrition support for the duration of follow-up. The remaining participants had a high need for symptom control and nutrition support at one (32%), two (32%) or three or more (4%) assessments (**Figure 6.3**).

Table 6.1 Participant characteristics

	All participants (n=36) *n (%)*
Sex, *% men*	29 (80.6)
Histological subtype	
Epithelioid	25 (69.4)
Sarcomatoid	3 (8.3)
Desmoplastic	2 (5.6)
Biphasic	2 (5.6)
Unspecified	4 (11.1)
Time since diagnosis	
≤ 3 months	24 (66.7)
4-12 months	8 (22.2)
13-24 months	2 (5.6)
>24 months	2 (5.6)
Survival	
≤ 3 months	2 (5.6)
4-12 months	12 (3.3)
13-24 months	10 (27.8)
>24 months	12 (33.3)
Co-morbidities	
Hypertension	12 (34.3)
Hypercholesterolemia	9 (25.7)
Ischemic heart disease	3 (8.6)
Atrial fibrillation	3 (8.6)
Type 2 diabetes	8 (22.9)
COPD	1 (2.9)
Osteoarthritis	3 (8.6)
Hip or knee replacement	3 (8.6)
Chronic back pain	2 (5.7)
Cancer treatment prior to study, *yes*	9 (25.7)
Type of cancer treatment	
Chemotherapy	4 (44.4)
Radiotherapy	1 (11.1)
Chemotherapy and radiotherapy	3 (33.3)
Chemotherapy, radiotherapy and surgery	1 (11.1)
Cancer treatment during study, *yes*	22 (62.9)
Type of cancer treatment	
Chemotherapy	19 (86.3)
Radiotherapy	1 (4.5)
Chemotherapy and radiotherapy	2 (9.1)

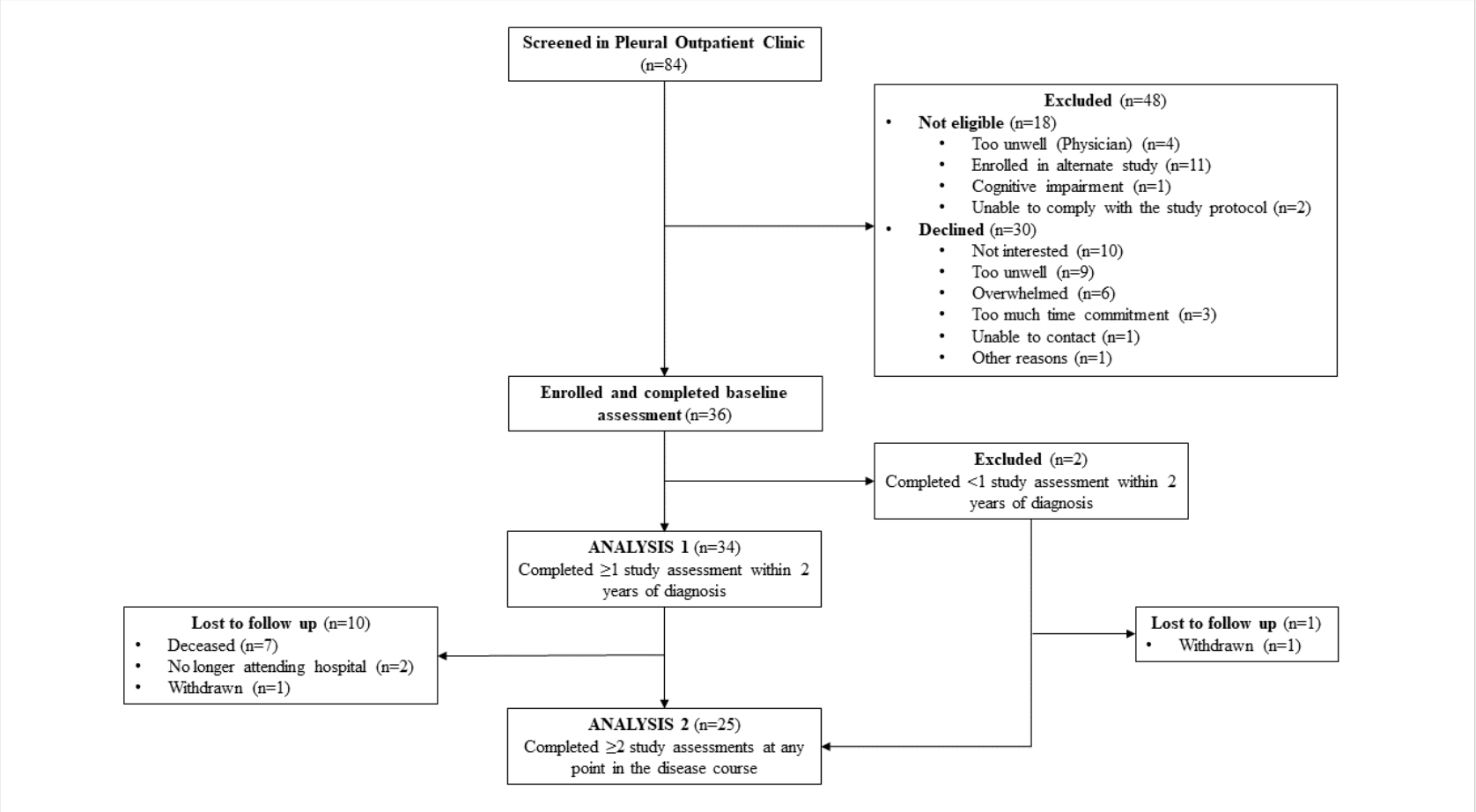

Figure 6.1 Participants included in the prospective observational study.

Thirty-six participants were enrolled at baseline: 2 were excluded and the remaining participants included in Analysis 1 (n=34); 10 were lost to follow up and the remaining 24 were included in Analysis 2 plus 1 extra participant who was excluded from Analysis 1 but eligible for Analysis 2.

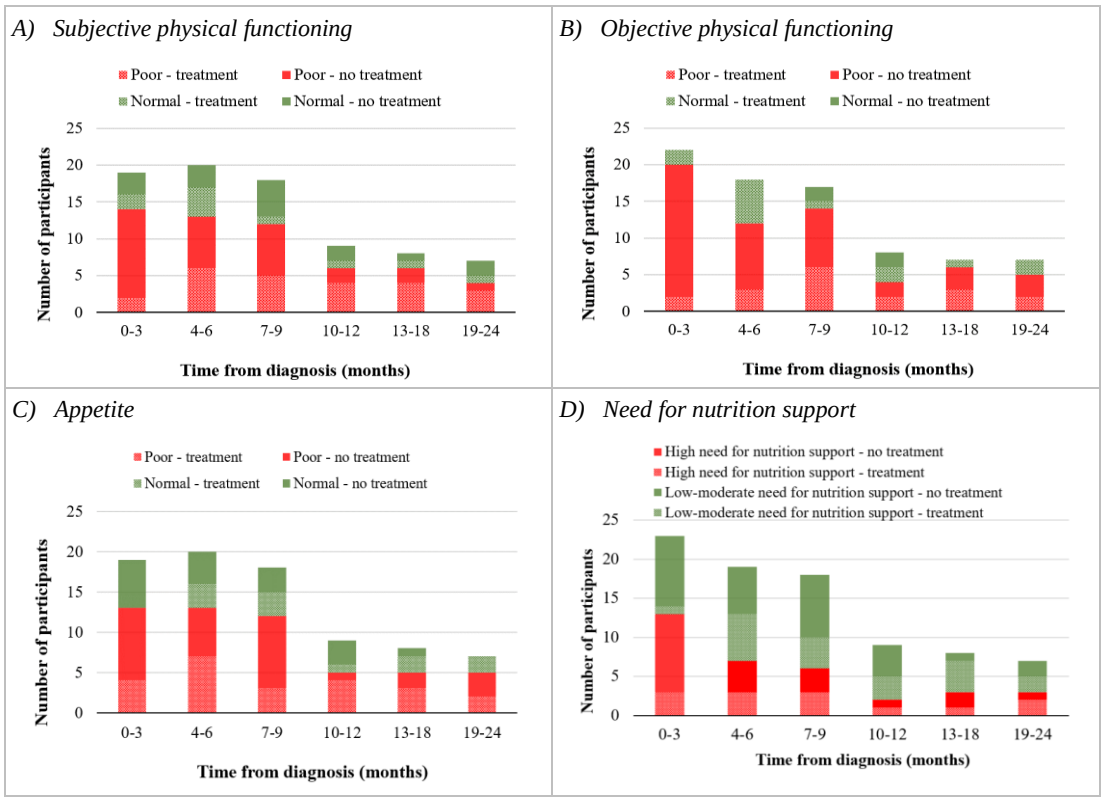

Figure 6.2 Prevalence of poor subjective and objective physical functioning, poor appetite and high need for nutrition support across the 2 years from MPM diagnosis

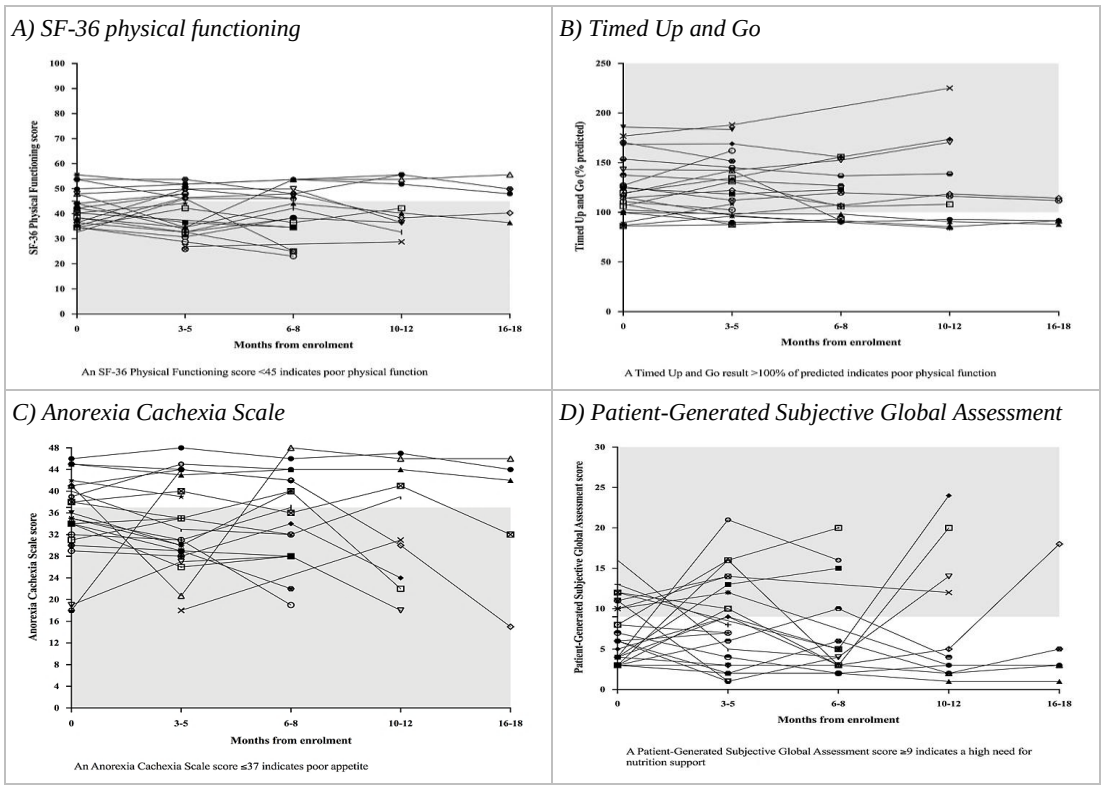

Figure 6.3 Line graphs of individual participants depicting changes in SF-36 physical functioning, Timed Up and Go, Anorexia Cachexia Scale and Patient-Generated Subjective Global Assessment from baseline, n=25

6.4 Discussion

This study provides new information about the functional and nutritional characteristics of patients with MPM. We report that functional and nutritional impairment was common in the 2 years following MPM diagnosis and occurred in the presence and absence of cancer treatment. For many participants in our longitudinal analysis, functional and nutritional impairment persisted across multiple assessments.

Functional impairment was prevalent across the 2 years from MPM diagnosis. Between 50 and 91% of participants at each time interval had poor subjective and objective physical functioning. Previous studies have shown that patients with lung cancer have poorer physical functioning than healthy adults, and that function deteriorates over time,[10] however there is a lack of information on the prevalence of functional impairment. In a study of older adults with cancer, 76% of participants reported limitations in physical functioning and 70% of participants had suboptimal objective physical functioning.[18] Our results are consistent with these findings and comparable as many patients with MPM are older adults at diagnosis due to the long latency period between asbestos exposure and diagnosis.[19] Together, the results suggest that functional impairment is common among older patients with cancer.

Poor appetite was prevalent across the 2 years from MPM diagnosis. Poor appetite was reported by 56 – 71% of participants across all time intervals in our study, which is higher than the 40% reported by patients with advanced lung cancer.[5] The participants with advanced lung cancer were assessed prior to cancer treatment,[5] and as chemotherapy can adversely affect appetite, this could have contributed to the higher prevalence of poor appetite reported in our study. Notably, the majority of participants with a poor appetite at diagnosis were not receiving cancer treatment, which indicates poor appetite can occur irrespective of treatment status. This indicates that an evaluation of appetite should be included in management of patients with MPM regardless of whether they are receiving cancer treatment.

As MPM is an incurable cancer and median survival is 12 months,[1] it is encouraging that a proportion of participants had normal function and nutritional status throughout follow-up. However, it is concerning that more than half of participants had persistent or recurrent functional and nutritional impairment, as the extended duration of impairment could have a more profound impact on patient quality-of-life.

Patients with MPM who have functional and nutritional impairment could benefit from supportive care interventions, however these impairments could go undetected in clinical practice. Existing guidelines recommend routine assessment of physical

functioning to identify functional impairment[20] and the use of screening tools to identify nutritional impairment.[21] Our findings suggest that screening or assessment tools which identify functional and nutritional impairment should be recommended for all patients with MPM from the point of diagnosis. Functional impairment can be identified with self-report questionnaires such as the SARC-F[22] or objective tests such as the Short Performance Physical Battery[23] while nutritional impairments can be identified with the use of a validated nutrition screening tool such as the Malnutrition Screening Tool.[21] Resistance exercise training could be used to improve physical functioning in patients with MPM[23] although to date, interventions to address nutritional impairments via nutritional support have not been tested in MPM.

There are several limitations to this study. Our study may not be representative of all patients with MPM. The enrolment rate was 43% and poor health was the most common reason for non-participation; therefore the actual prevalence of functional and nutritional impairment in this clinical group may be higher than we have reported. Additionally, participants identified as malnourished during the study were referred to a dietitian. Dietitian intervention, including nutritional counselling and nutrition supplements, may have contributed to improved nutritional status at subsequent assessments. We did not track which participants received nutritional intervention. Functional and nutritional impairments are associated with multiple factors including cancer stage[25] and treatment,[26, 27] baseline co-morbidities,[28] and physical activity level.[29] As the sample size of our study was relatively small, we could not adjust for these confounding factors. Further research with a larger sample size is needed to gain an understanding of the factors that contribute to changes in functional and nutritional outcomes in patients with MPM.

This study is the first to provide a description of the functional and nutritional characteristics in an unselected group of patients with MPM. The majority of participants in our study received non-surgical cancer treatment or no cancer treatment, which is representative of standard care pathways for patients with MPM. A strength of our study is the prospective collection of functional and nutritional data from participants for up to 18 months from enrolment. Additionally, we used validated measures to evaluate self-reported as well as objective physical functioning, appetite and nutritional status.

In patients with MPM, functional and nutritional impairment was common and not exclusive to participants receiving cancer treatment. For many participants, functional and nutritional impairments were persistent or reoccurred during follow-up. Screening for functional and nutritional impairment is recommended for all patients with MPM from the time of diagnosis to identify those who could benefit from supportive care interventions.

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Chapter Seven

7

Changes in Body Composition in Patients with Malignant Pleural Mesothelioma and Relationship with Activity Levels and Dietary Intake

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Abstract

Background: Cachexia is common in advanced cancer and is associated with negative patient outcomes. In malignant pleural mesothelioma (MPM), no study has reported body composition changes or factors associated with these changes. This study aimed to describe changes in body composition over time and its relationship with activity levels and dietary intake.

Methods: The study was a secondary analysis of data collected from a longitudinal observational study of patients with MPM. Participants completed 3-monthly assessments for up to 18 months. Participants with two dual-energy x-ray absorptiometry (DXA) scans were included. Change in appendicular skeletal muscle mass (ASM) and total fat mass (FM) were used to categorise participants into phenotypes. Activity levels were measured with an Actigraph GT3X+ accelerometer and energy and protein intake were measured with a 3-day food record and 24-hour recall.

Results: Eighteen participants were included (89% male, mean age 68.9±7.1 years). Median time between DXA was 91 [IQR 84–118] days. Compared to participants with ASM maintenance (n=8), fewer participants with ASM loss (n=10) survived ≥12 months from follow-up (p=0.04). Participants with ASM loss increased sedentary time (p=0.028), and decreased light activity (p=0.028) and step count (p=0.008). Activity levels did not change in participants who maintained ASM (p>0.05). Energy and protein intake did not change in either group (p>0.05).

Conclusion: Multiple patterns of change in body composition were identified in patients with MPM. Muscle loss was associated with poorer survival and decreased activity levels. Interventions that improve physical activity or muscle mass could benefit patients with MPM.

7.1 Introduction

Malignant pleural mesothelioma (MPM) is an incurable cancer that results from asbestos exposure.[1] Patients with MPM have limited treatment options and a short median survival of 12 months.[1] It has been hypothesised that cancer cachexia could contribute to the cause of death in MPM.[2]

Cancer cachexia is a form of malnutrition characterised by the loss of skeletal muscle mass in the presence or absence of loss of fat mass, and is often accompanied by anorexia and systemic inflammation.[3] Cancer cachexia can lead to the development of low skeletal muscle mass, which is associated with a range of negative outcomes in some advanced cancer populations including poorer quality of life,[4] lower activity levels,[5] increased treatment toxicity[6] and poorer survival.[6] Further, people with both low skeletal muscle mass and excess fat mass (i.e. sarcopenic obese) have had an even greater risk of negative outcomes.[7]

In our previous research we reported that 50% of patients with MPM had low skeletal muscle mass close to the time of diagnosis, and of these 11% were obese.[8] Although clinicians report patients with MPM become emaciated over the disease course, and often die with a low BMI,[2] there are no studies in patients with MPM on changes in body composition over time. Information on the patterns of change in body composition could improve our understanding of the need for interventions which can prevent and treat cancer cachexia in MPM.

Physical activity and dietary intake are modifiable factors which could be central to the development of cancer cachexia. Physical activity and dietary protein intake stimulate muscle protein synthesis[9] and in sufficient quantities could protect against the development of low skeletal muscle mass.[10, 11] Additionally, lower levels of physical activity and high dietary energy intake can create a positive energy balance resulting in weight gain that is largely an increase in fat mass.[12] There is little research into the relationship between physical activity, dietary intake and changes in body composition in cancer populations. Understanding these complex relationships is critical for the design of interventions to prevent and treat cancer cachexia.

The aims of this study in patients with MPM were to describe the changes in body composition over time and the relationship between body composition changes and activity levels and dietary intake.

7.2 Methods

7.2.1 Study design and participants

The study was a secondary analysis of data collected from a longitudinal observational study which aimed to describe the functional and nutritional status of patients with MPM. Patients were recruited from a tertiary specialist pleural disease clinic in Perth, Western Australia and were eligible if they had cytological or histological confirmation of MPM. Exclusion criteria were: aged <18 years, pregnant or lactating, unable to read and understand English, unable to comply with the protocol or were participating in an intervention study likely to influence body composition. Participant consent and physician approval were required before commencing the study. Participants completed assessments of body composition, activity levels and dietary intake during routine hospital visits, approximately every 3 months and were followed until death or for a maximum of 18 months. Participants that did not complete body composition scans at two consecutive assessments were excluded from this analysis. The study was approved by the Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255).

7.2.2 Measurements

Demographic and medical variables

Demographic and medical data were obtained from participant medical records. Disease progression at the time of follow up was determined by clinician examination of the Computed Tomography scan completed closest to the time of the second body composition scan. The Eastern Cooperative Oncology Group (ECOG) performance status was recorded on the date of assessment.[13]

Anthropometric measures

Weight and height, measured with participants dressed in light clothing with shoes removed, were used to calculate the BMI. Participants were classified as underweight, normal weight, overweight or obese based on World Health Organisation (WHO) BMI criteria.[14]

Body composition

Body composition was assessed using whole body dual-energy x-ray absorptiometry (DXA) scans (Hologic Discovery A, Hologic Inc., Marlborough, MA, USA). Appendicular

skeletal muscle and fat mass was segmented from trunk lean and fat mass at the acromio-humeral and pelvic-femoral joints.[15] Low skeletal muscle mass was defined as an appendicular skeletal muscle mass/height^2 of ≤7.26 kg/m^2 for males and ≤5.45 kg/m^2 for females. Participants with low skeletal muscle mass were categorised as pre-sarcopenic, consistent with diagnostic criteria from the European Working Group on Sarcopenia in Older People.[16] Participants with low skeletal muscle mass and a BMI ≥30.0 kg/m^2 were categorised as sarcopenic obese.[7] Change in body composition variables were calculated as the percent change between the second and first measurements.

To characterise changes in body composition over time, participants were categorised into body composition phenotypes according to changes in skeletal muscle mass and fat mass. Total lean mass measured with DXA includes both skeletal muscle and residual mass (i.e., organs), however appendicular lean mass is predominantly skeletal muscle.[17] Therefore, to report on changes in skeletal muscle mass we considered it more accurate to use appendicular lean mass, also known as appendicular skeletal muscle mass, which represents, on average 75% of whole-body skeletal muscle.[17] The four body composition phenotypes were: 1) loss of appendicular skeletal muscle mass and loss of total fat mass; 2) loss of appendicular skeletal muscle mass and maintenance or gain of total fat mass; 3) maintenance or gain of appendicular skeletal muscle mass and loss of total fat mass and 4) maintenance or gain of appendicular skeletal muscle mass and maintenance or gain of total fat mass. A loss was defined a change of <0.00 kg between the first and second measurements; maintenance or gain was defined as a change of ≥0.00 kg between the first and second measurements.

Activity levels

Sedentary behaviour and physical activity were objectively assessed following each body composition scan using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA). Participants were instructed to wear the accelerometer on their hip continuously 24 hr/day for 3 days, to only remove for bathing or swimming and to record any non-wear time in a logbook. Cut-points were applied to classify sedentary behaviour as <100 counts/minute (cpm), light activity as 100-1952 cpm and moderate and vigorous physical activity (MVPA) as >1952 cpm.[18, 19] Variables were calculated per day and then averaged across all valid days, defined as at least 10 hours of data per day. Additional accelerometer methodology for this study has been reported previously.[5]

Dietary intake

Dietary intake was measured following each body composition scan using a 3-day estimated food record at the initial assessment and a 24-hour recall at subsequent assessments. To assist participants with completion of the food record, written and verbal instructions were provided explaining how to complete the food record and accurately estimate portion sizes using household measures. Returned food records were visually inspected by the researchers and incomplete details were clarified with participants. Participants completed the 24-hour recall in a face-to-face interview with a dietitian using the multiple pass method.[20] The food records and 24-hour recalls were analysed using Foodworks 8 software (Xyris Software Pty Ltd, Queensland, Australia). Intake variables were calculated per day, and for the food records, intake was averaged across all three days. Energy (kJ) and protein intake (g) were expressed per kg of body weight per day respectively.

7.2.3 Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (v. 23, IBM Corporation, Somers, NY, USA). Data were expressed as mean ± SD or median [IQR] where the data were not normally distributed. To examine the relationship between changes in body composition and participant characteristics, activity levels and dietary intake, participants were condensed into two groups: 1) muscle loss group; and 2) muscle maintenance group, with definitions provided above. Fisher's exact test was used to test for differences in characteristics between participants with muscle loss and muscle maintenance where the data were categorical. As the data were not normally distributed, the Mann-Whitney test was used to test for differences in characteristics between participants with muscle loss and muscle maintenance where the data were continuous, and for differences in change in activity levels and dietary intake between muscle groups. The Wilcoxon signed-rank test was used to test for differences in body composition, activity levels and dietary intake between the first and second measurements.

7.3 Results

7.3.1 Participant characteristics

Of the 36 patients recruited to the longitudinal observational study, 18 (50%) were included in the current study (**Figure 7.1**).

The median time between the first and second body composition scans was 91 (IQR 84 – 118) days. Participant characteristics are presented in (**Table 7.1)**. The majority of participants were male (89%) and the mean age was 68.9 ± 7.1 years. Nine participants (50%) received cancer treatment during the follow up period. Ten participants (56%) met the criteria for muscle loss and eight participants (44%) met the criteria for muscle maintenance. Three participants (30%) with muscle loss survived more than 12 months from the second body composition scan, while all participants (100%) with muscle maintenance survived more than 12 months from the second scan (p=0.04). No other differences in participant characteristics were observed between muscle groups (p>0.05) (**Table 7.1**).

7.3.2 Changes in sarcopenia status

There was a 17% increase in the proportion of participants who were pre-sarcopenic between the first and second body composition scans. Eight participants (44%) were pre-sarcopenic at the first measurement and eleven participants (61%) were pre-sarcopenic at the second scan. Three participants (30%) who were non-sarcopenic at the first measurement were pre-sarcopenic at the second scan. None of the participants who were pre-sarcopenic at the first measurement became non-sarcopenic. Of the participants who were pre-sarcopenic at the first scan, none (0%) were obese. Of the participants who were pre-sarcopenic at the second scan, one (9%) was obese.

7.3.3 Changes in body composition

When participants were condensed into the four body composition phenotypes, eight participants (44%) had a loss of appendicular skeletal muscle and fat mass, two participants (11%) had a loss of appendicular skeletal muscle and maintained fat mass, four participants (22%) maintained appendicular skeletal muscle and lost fat mass and, four participants (22%) maintained appendicular skeletal muscle and fat mass (**Figure 7.2**).

There were no significant changes in total, lean or fat mass during the follow up period in the whole group **(Table 7.2)**. Participants with muscle loss (n=10) experienced a significant decrease in total mass (p=0.005), trunk lean mass (p=0.009), appendicular skeletal muscle mass (p=0.005) and trunk fat mass (p=0.013) but not appendicular fat mass (p=0.721). Participants with muscle maintenance (n=8) experienced a significant increase in appendicular skeletal muscle mass (p=0.012) but not total mass (p=0.093) trunk lean mass (p=0.484), trunk fat mass (p=0.401) or appendicular fat mass (p=0.889).

7.3.4 Change in activity levels according to muscle change group

There were no significant changes in activity levels during the follow up period in the whole group (**Table 7.3**). Participants with muscle loss had a significant decrease in median step count (p=0.008), an increase in the proportion of waking hours spent as sedentary (p=0.028) and a decrease in the proportion of waking hours spent in light activity (p=0.028) (**Table 7.3**). There was no significant change in the proportion of waking hours spent in moderate and vigorous physical activity (p=0.260). Participants with muscle maintenance maintained step count (p=0.176), and the proportion of waking hours spent as sedentary (p=0.499), in light activity (p=0.499) or in moderate and vigorous physical activity (p=0.176) (**Table 7.3**).

There was a significant difference between participants with muscle loss and muscle maintenance for change in step count (-1020 [IQR -4667 – 56] vs. 1234 [IQR -204 – 2221] steps/day; p=0.008; **Figure 7.3**) and for the proportion of waking hours spent in light activity (-4.8 [IQR -9.2 – 0.2] vs. -0.7 [IQR -2.0 – 7.5]; p=0.023; **Figure 7.3**) but not for the proportion of waking hours spent as sedentary (4.9 [IQR -2.3 – 11.1] vs. 0.5 [IQR -8.6 – 2.2]; p=0.142; **Figure 7.3**).

7.3.5 Change in dietary intake according to muscle change group

There were no significant changes in energy and protein intake during the follow up period in the whole group (**Table 7.3**) or in participants with muscle loss and those with muscle maintenance (**Table 7.3**).

There was a significant difference between participants with muscle loss and muscle maintenance for change in protein intake (-0.28 [IQR -0.48 – 0.15] vs. 0.74 [IQR -0.14 – 0.82] g/kg/day; p=0.025; **Figure 7.3**) but not for energy intake (-7.9 [IQR -45.0 – -0.9] vs. 28.9 [IQR -23.6 – 123.1] kJ/kg/day; p=0.193; **Figure 7.3**).

Table 7.1 Participant characteristics, n=18

	All participants (n=18)	Muscle loss (n=10)	Muscle maintenance (n=8)	P value
Age, *years*	68.9 ± 7.1	67.0 [61.5-74.3]	71.5 [62.5-75.0]	0.633
Sex, *male*	16 (88.9%)	8 (80%)	8 (100%)	0.477
BMI, *kg/m2*	25.2 [23.9-28.7]	25.9 [24.1-29.5]	24.3 [23.8-27.7]	0.237
BMI category				
Underweight	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Normal weight range	9 (50.0%)	3 (30.0%)	6 (75.0%)	
Overweight	7 (38.9%)	5 (50.0%)	2 (25.0%)	
Obese	2 (11.1%)	2 (20.0%)	0 (0.0%)	
Pre-sarcopenic, *yes*	8 (44.4%)	4 (40.0%)	4 (50.0%)	0.520
Histological subtype, *epithelioid*	15 (83.3%)	8 (80%)	7 (87.5%)	1.000
ECOG performance status at first scan*, 0-1	18 (100%)	10 (100%)	8 (100%)	-
Time from diagnosis to first scan*				
<3 months	10 (55.6%)	5 (50.0%)	5 (62.5%)	-
3-12 months	5 (27.8%)	3 (30.0%)	2 (25.0%)	
>12 months	3 (16.7%)	2 (20.0%)	1 (12.5%)	
Time from first to second scan, *days*	91.0 [84.0-118.0]	87.5 [82.5-92.5]	105.5 [87.5-143.5]	0.083
Cancer treatment during follow up, *yes*	9 (50%)	5 (50%)	4 (50%)	1.000

	All participants (n=18)	Muscle loss (n=10)	Muscle maintenance (n=8)	P value
Type of cancer treatment				
Cisplatin and Pemetrexed	3 (33.3%)	1 (20.0%)	2 (50.0%)	-
Carboplatin and Pemetrexed	3 (33.3%)	2 (40.0%)	1 (25.0%)	
Vinorelbine	1 (11.1%)	1 (20.0%)	0 (0.0%)	
Clinical trial – Cisplatin, Pemetrexed and Durvalamab	2 (22.2%)	1 (20.0%)	1 (25.0%)	
Disease progression at second scan*				
Progressed	10 (55.6%)	6 (60.0%)	4 (50.0%)	-
Stable	4 (22.2%)	2 (20.0%)	2 (25.0%)	
Response to treatment	2 (11.1%)	0 (0.0%)	2 (25.0%)	
Data not available	2 (11.1%)	2 (20.0%)	0 (0.0%)	
Time from second scan* to death				
<12 months	7 (38.9%)	7 (70.0%)	0 (0.0%)	0.04
≥12 months	11 (61.1%)	3 (30.0%)	8 (100.0%)	

*First or second body composition scan

Table 7.2 Participant changes in body composition, n=18

	All participants (n=18)			Muscle loss (n=10)			Muscle maintenance (n=8)		
Mass (kg)	**First scan**	**Second scan**	**P value**	**First scan**	**Second scan**	**P value**	**First scan**	**Second scan**	**P value**
Total	75.0 (70.3-87.4)	74.1 (67.3-88.7)	0.133	75.0 (70.4-91.6)	72.5 (66.9-88.7)	0.005*	74.1 (68.4-87.1)	75.7 (68.8-90.9)	0.093
Lean mass									
Total	50.4 (47.3-53.9)	49.5 (46.9-53.9)	0.248	51.4 (46.9-56.4)	48.7 (43.9-54.6)	0.005*	49.6 (46.8-53.5)	50.8 (49.0-53.7)	0.012*
Trunk	26.6 (24.8-29.1)	25.4 (24.5-28.3)	0.085	26.9 (25.2-29.9)	25.2 (23.8-29.0)	0.009*	25.2 (24.7-28.9)	26.5 (24.8-28.2)	0.484
Appendicular	21.4 (18.9-22.2)	20.5 (19.7-22.2)	0.306	21.4 (18.6-23.0)	20.4 (17.3-21.8)	0.005*	21.2 (18.5-22.0)	21.8 (20.3-22.2)	0.012*
Fat mass									
Total	24.3 (20.1-30.1)	24.2 (19.8-28.7)	0.215	25.9 (20.1-30.1)	24.3 (20.5-28.0)	0.037*	22.9 (16.8-30.1)	23.6 (16.2-31.1)	0.575
Trunk	12.3 (9.8-15.1)	11.2 (9.4-15.1)	0.184	12.4 (10.1-15.3)	10.8 (9.4-14.0)	0.013*	11.9 (7.8-15.5)	11.8 (7.7-17.0)	0.401
Appendicular	11.3 (8.3-13.8)	11.5 (8.4-13.9)	0.679	11.9 (8.3-15.2)	11.5 (8.7-14.2)	0.721	10.2 (8.2-13.0)	10.1 (7.5-14.0)	0.889

Data is presented as median (interquartile range); *p<0.05

Table 7.3 Participant activity levels and dietary intake, n=17

	All participants (n=17)			Muscle loss (n=10)			Muscle maintenance (n=7)		
	First scan	Second scan	P value	First scan	Second scan	P value	First scan	Second scan	P value
Activity behaviours									
Steps, *n*	5505 (4603-6404)	4736 (3608-6843)	0.196	6013 (4111-9117)	4251 (1738-5372)	0.008*	5039 (4582-5653)	5590 (4196-7404)	0.176
Sedentary behaviour, *%*	70.3 (61.7-73.1)	73.1 (64.0-76.0)	0.196	67.0 (58.1-72.7)	73.7 (66.8-84.2)	0.028*	72.6 (62.8-73.2)	73.1 (63.4-75.7)	0.499
Light activity, *%*	27.5 (26.4-35.0)	25.5 (22.3-34.5)	0.215	28.4 (26.0-39.6)	25.3 (15.4-30.8)	0.028*	27.1 (26.3-35.1)	26.2 (22.7-35.7)	0.499
MVPA, *%*	0.8 (0.5-3.1)	0.9 (0.7-1.7)	0.836	1.0 (0.4-5.3)	0.7 (0.3-1.5)	0.260	0.6 (0.5-1.4)	1.7 (0.8-1.7)	0.398
Dietary intake									
Energy intake, *kJ/kg*	129.6 (90.1-143.8)	121.8 (102.3-147.2)	0.981	122.8 (94.2-140.2)	119.0 (90.5-135.0)	0.241	135.3 (61.4-141.0)	139.3 (110.0-263.3)	0.176
Protein intake, *g/kg*	1.5 (0.9-2.0)	1.4 (1.1-1.8)	0.492	1.0 (0.9-1.8)	1.2 (0.7-1.6)	0.333	1.6 (0.8-1.7)	1.5 (1.4-2.9)	0.091

Data is presented as median (interquartile range); MVPA – Moderate and Vigorous Physical Activity; *p<0.05

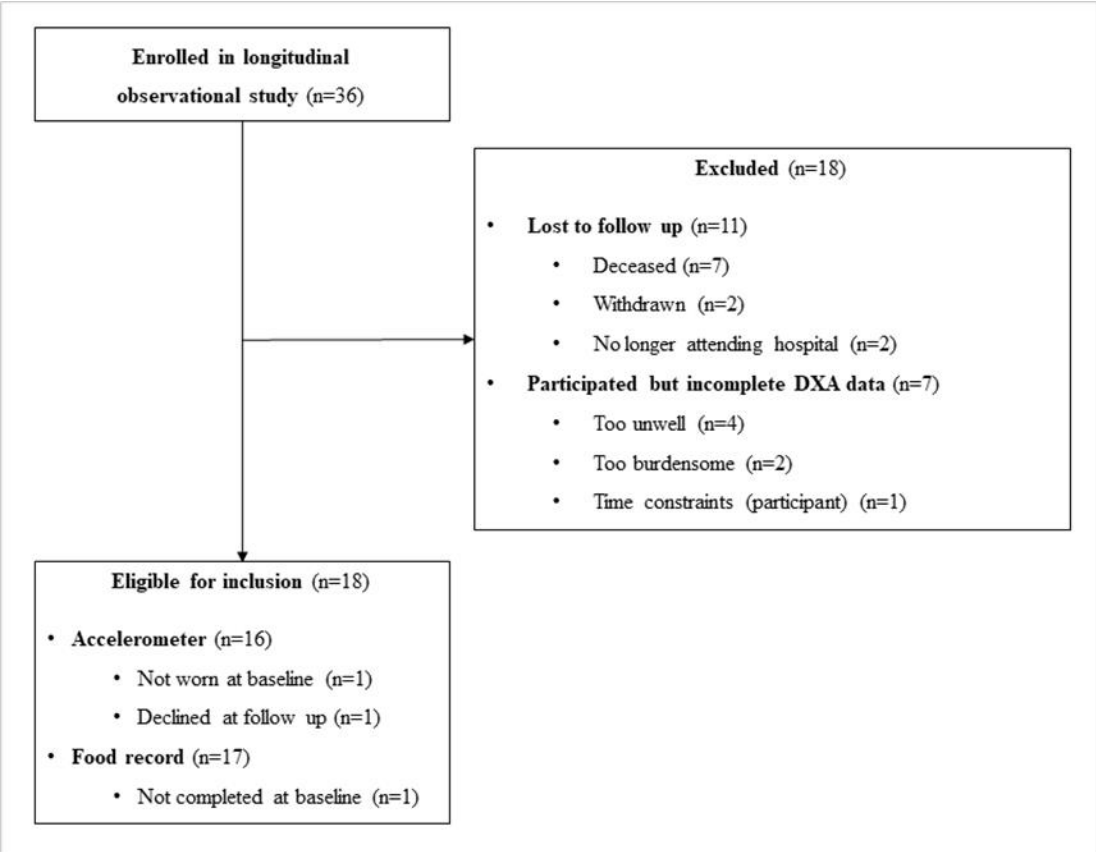

Figure 7.1 Participants included in the secondary analysis

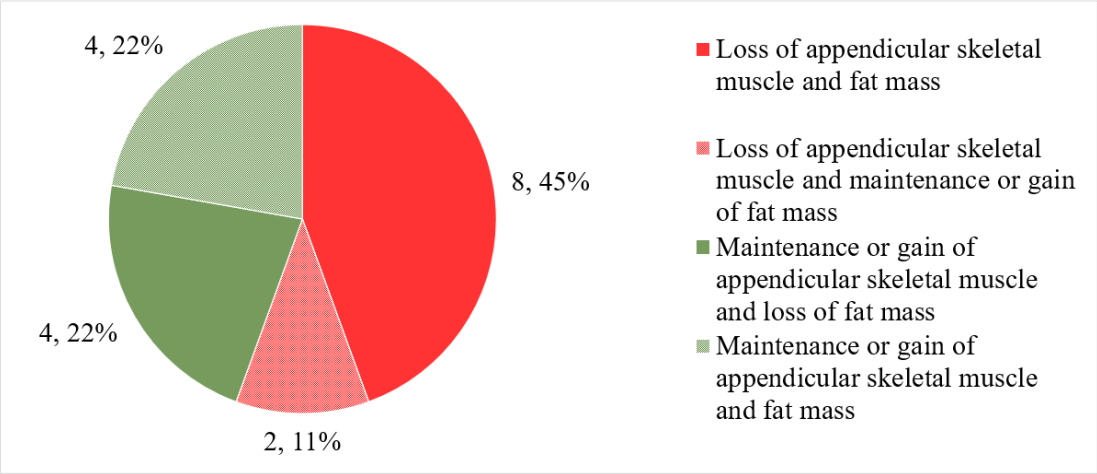

Figure 7.2 Proportion of participants within each body composition phenotype, n=18

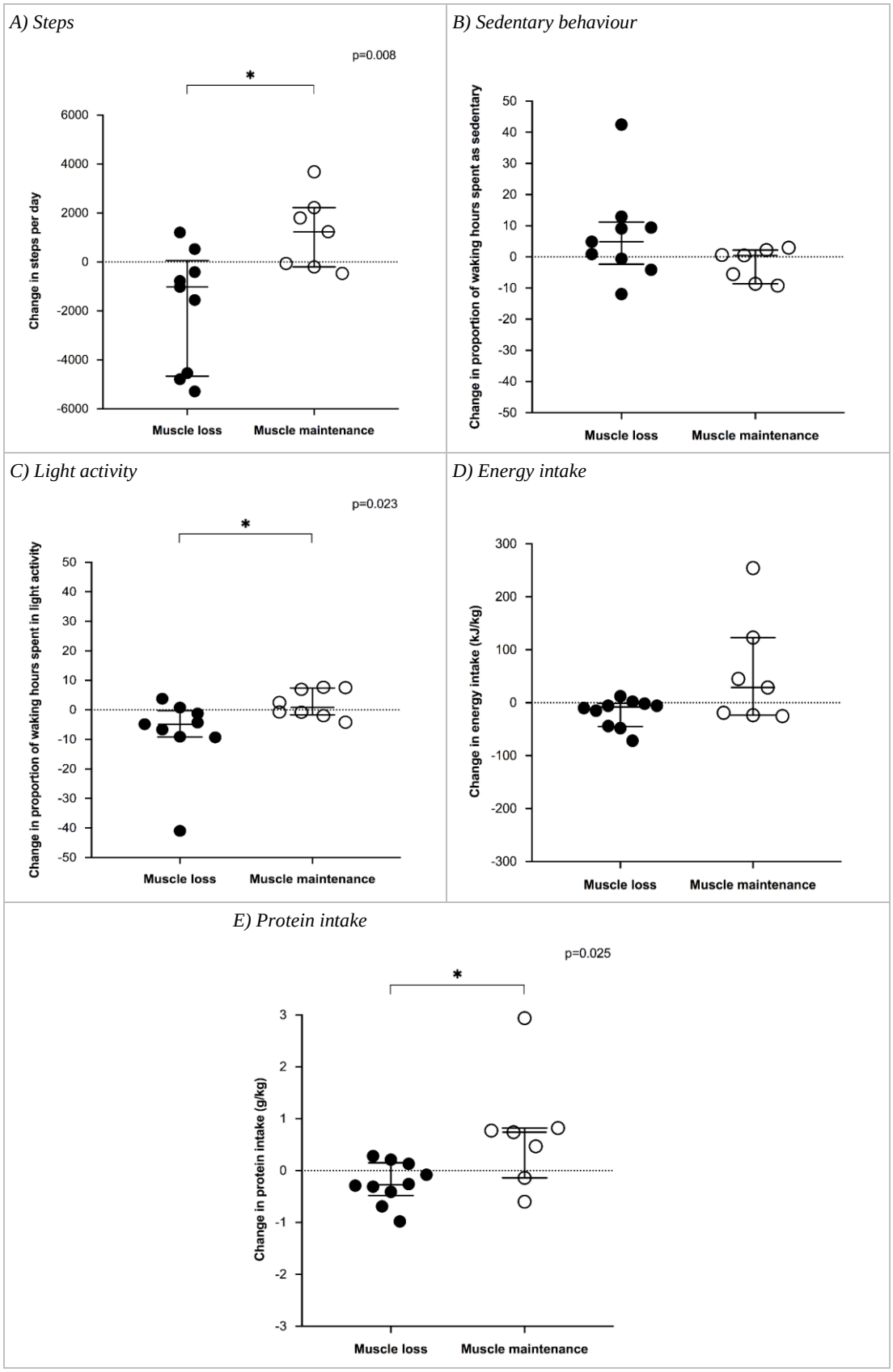

Figure 7.3 Change in physical activity and dietary intake according to muscle change group

7.4 Discussion

Our study is the first to prospectively assess changes in body composition in relation to activity levels and dietary intake in patients with MPM. We identified multiple patterns of body composition change among our participants. Notably, participants with muscle loss and muscle maintenance had distinct survival, physical activity and dietary intake characteristics.

Our participants could be categorised across all four body composition phenotypes. The most common phenotype, which included 44% of participants, was the loss of appendicular skeletal muscle mass and fat mass, which is consistent with the cachexia phenotype.[3] When we condensed the four body composition phenotypes into two groups: 1) muscle loss and 2) muscle maintenance; 56% of participants had muscle loss and 44% had muscle maintenance. This result is particularly notable as the low mean BMI reported in a previous post-mortem study indicated patients with MPM become emaciated over the disease course.[2] While muscle loss was common, our results suggested that a proportion of participants with MPM had the ability to maintain muscle, at least for a fraction of the disease course.

There were significant differences in survival between participants with muscle loss and muscle maintenance. A small proportion (30%) of participants with muscle loss survived at least 12 months from the second body composition scan while all (100%) participants with muscle maintenance survived at least 12 months from the second body composition scan. Therefore, muscle loss could be indicative of shorter survival in patients with MPM. Similar findings have been reported in a large retrospective study of patients with advanced cancer (n=368)[21] where the authors stated that muscle loss became more common as death approached. Tumour burden is thought to mediate the metabolic changes that cause loss of muscle and fat mass[22] highlighting the importance of efficacious cancer treatments for the management of cachexia.[3] There are currently limited treatment options for those with MPM and in a previous clinical trial only 40% of patients responded to first-line chemotherapy treatment.[23] Therefore, addressing lifestyle factors that contribute to cancer cachexia could offer benefit.

Participants with muscle loss had a significant decline in activity levels over the follow up period of 3 months, while participants with muscle maintenance sustained their activity levels. As physical activity is required for muscle protein synthesis,[9] a decrease in physical activity may have contributed to muscle loss among our participants.

Additionally, as the majority of participants (70%) with muscle loss were categorised as pre-sarcopenic at follow up, participants may not have had the strength and endurance to participate in their usual physical activity. The lack of physical activity could result in an even greater reduction in muscle loss. Therefore, regardless of the causal pathway between muscle loss and activity levels, resistance exercise training may offer benefit to patients with MPM as it can improve skeletal muscle mass, strength and physical function.[24]

There were no statistically significant changes in dietary intake over the follow up period for participants with muscle loss and muscle maintenance, however we made clinically meaningful observations. Participants with muscle loss had a median energy and protein intake that was within the recommended energy and protein intake range of 105 – 126 kJ/kg and 1.0 – 1.5 g/day, respectively,[25] while median energy and protein intake among participants with muscle maintenance exceeded these recommendations. In a larger study (n=52) of patients with incurable non-small cell lung cancer (NSCLC), higher energy and protein intakes (149 kJ/kg and 1.4 g/kg, respectively) were associated with maintenance of skeletal muscle mass during chemotherapy.[26] Approximately 40-50% of patients with NSCLC are reported to have an elevated resting energy expenditure,[27, 28] which could lead to muscle and fat loss unless dietary intake is increased proportionally. As muscle loss developed in our participants meeting dietary intake recommendations, it is possible that an elevated resting energy expenditure could have been a contributing factor in these patients with MPM. Intakes of energy and protein that exceed recommendations may be needed to preserve skeletal muscle mass in patients with MPM.

This study has several potential limitations worthy of consideration. Several factors are known to affect muscle and fat metabolism, including disease progression, inflammation, cancer treatment and older age.[29] While these characteristics were compared between participants with and without muscle loss, the sample size was too small to allow further evaluation in relation to changes in body composition. Energy and protein intake at baseline and follow up were measured using different dietary assessment methods. Participant feedback indicated that a 3-day food record was too burdensome, therefore we used 24-hour recalls at follow up assessments. Compared with a 24-hour recall, a 3-day food record could be more representative of usual dietary intake as measurement is carried out over a greater number of days. However, a 24-hour food recall is not less accurate than a food record.[20] Considering this population of advanced cancer patients, participant burden was a key consideration in our study that should also be taken into account in future investigations.

Our study provides an insight into changes in body composition experienced by patients with MPM. A strength of our study is the use of DXA for body composition analysis, which enabled us to complete reliable evaluation of appendicular skeletal muscle mass and whole-body and regional fat mass.[17] This data cannot be obtained through computed tomography evaluation of body composition, which employs a single cross-section analysis, and existing prediction equations used to convert cross-sectional data to appendicular skeletal muscle mass may be inaccurate.[30] Additionally, we report device-assessed sedentary behaviour and physical activity using an accelerometer, which has greater accuracy when compared with self-report questionnaires.[31]

7.5 Conclusion

For the first time, we report on body composition changes over time in patients with MPM. Our results indicate that multiple patterns of change in body composition exist in this patient population. Muscle loss was associated with poorer survival and decreased activity levels. Interventions that improve physical activity or muscle mass could benefit patients with MPM.

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Chapter Eight

8

Nutritional Status, Dietary Intake and Resistance Exercise Adherence and Outcomes in Patients with Malignant Pleural Disease

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Abstract

Purpose: Little is known about the effects of nutritional status and dietary intake on response to exercise interventions in advanced cancer. This study aimed to determine if completion rates and response to an exercise intervention differ according to nutritional status and dietary intake in patients with malignant pleural disease (MPD).

Methods: Patients with MPD participated in a 6-week resistance exercise intervention. Outcome measures were assessed before and after the intervention. Nutritional status was assessed with the Patient-Generated Subjective Global Assessment (malnutrition defined as a rating of B or C). Dietary intake was assessed with 3-day food records (adequate intake defined as energy ≥25 kcal/kg/day and protein ≥1.0 g/kg/day). Appendicular skeletal muscle mass (ASM, kg) was segmented from whole-body dual-energy x-ray absorptiometry and adjusted for height (kg/m^2). Physical functioning was assessed with repeated chair rise, Timed Up and Go, one-repetition maximum leg press and Six-Minute Walk Test.

Results: Thirty-three participants were recruited (median age 68 [IQR 62-73] years, 68% men). Study completion rates were not significantly different between well-nourished and malnourished participants (84% vs. 75%; p=0.616). Gain in ASM was significantly greater in participants with adequate compared to inadequate intake (mean difference 0.40 [95% CI 0.14-0.67] kg/m^2; p=0.005). There were no differences between those with adequate and inadequate intake for change in repeated chair rise (p=0.504) Timed Up and Go (p=0.734), relative one-repetition maximum leg press (p=0.643) and Six-Minute Walk Test (p=0.600).

Conclusion: There were acceptable study completion rates for participants with malnutrition. Dietary intake may not affect the physical functioning response to resistance exercise, however adequate intake could optimize muscle gains. This could have implications for the development of exercise and multimodal interventions in advanced cancer populations.

8.1 Introduction

Malignant pleural disease (MPD) indicates the presence of advanced cancer, and occurs as a result of malignant pleural mesothelioma (MPM) or the metastatic spread of cancer to the pleura.[1] Malnutrition is common in patients with advanced cancer, including those with MPM.[2] Malnutrition is characterized by changes in weight and body composition that result from inadequate dietary intake or the impaired absorption or utilization of nutrients.[3]

A high proportion of malnourished patients with advanced cancer have low skeletal muscle mass[2] which has been associated with poorer quality of life,[4] greater treatment toxicity[5] and shorter overall survival.[6] Therefore, interventions which increase skeletal muscle mass have the potential to improve quality of life, treatment tolerance and survival.

Resistance exercise training can increase skeletal muscle mass and improve physical functioning in patients with cancer.[7] While malnourished patients are represented in exercise interventions targeting patients with advanced cancer,[8] little is known about the feasibility of exercise interventions in cancer patients with malnutrition, as nutritional status is rarely assessed.[8, 9] Due to higher fatigue levels,[2] combined with the negative impact of low skeletal muscle mass on physical functioning,[10] malnourished patients could have poorer adherence to exercise interventions than well-nourished patients. This could indicate the need for additional support during exercise interventions for patients that are malnourished.

There is a lack of data on the relationship between dietary intake and the response to resistance exercise training in advanced or poorer prognosis cancer populations. Dietary intake plays a central role in skeletal muscle homeostasis, yet intake is inadequate in a high proportion of patients with advanced cancer.[2] When dietary intake is inadequate, amino acids from the diet may be used as an energy source, reducing availability for skeletal muscle synthesis,[11] and skeletal muscle may be broken down to provide the body with amino acids for energy.[11] Therefore, skeletal muscle growth and functional responses to exercise could be impeded in cancer patients with inadequate dietary intake.[7]

The aim of this study in patients with MPD was to determine whether: 1) completion rates, adherence and tolerance to a resistance exercise intervention differed according to nutritional status and dietary intake; and 2) the body composition and physical functioning response to resistance exercise training differed according to dietary intake.

8.2 Methods

8.2.1 Participants

Participants were recruited from tertiary specialist pleural disease and medical oncology clinics in Perth, Western Australia (WA). Participants were eligible if they had cytological or histological confirmation of MPD. Exclusion criteria were aged <18 years, pregnant or lactating, unable to read and understand English, unstable bone metastases or metastases of the long bones, acute illness or disorder precluding exercise, physician recommendation against participation and patient unable to give informed consent or comply with the protocol. The study was approved by the Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255).

8.2.2 Measures

Assessment schedule

Participants completed a baseline assessment fewer than 7 days prior to commencing the exercise intervention and a post-intervention assessment fewer than 7 days after completing their final exercise training session.

Demographic and medical data

Participant medical records were reviewed for demographic and medical data. At baseline and post-intervention, participants were assigned an Eastern Cooperative Oncology Group (ECOG) performance status rating of 0 to 4.[12]

Anthropometric data

Height (m) was measured at baseline and weight (kg) was measured baseline and post-intervention. Participants were dressed in light clothing with shoes removed. Weight and height data were used to calculate the body mass index (BMI) (kg/m^2).

Nutritional status, appetite and dietary intake

Nutritional status was assessed at baseline and post-intervention using the Patient-Generated Subjective Global Assessment (PG-SGA).[13] Participants were categorized with a global rating of A – well nourished, B – suspected malnutrition/malnutrition or C – severe malnutrition. Participants with malnutrition (global rating of B and C) were combined for data analysis. Participants who were well-nourished at baseline and post-

intervention were considered well-nourished and participants who were malnourished at either or both time-points were considered malnourished.

Participants completed a validated questionnaire at baseline and post-intervention to assess appetite (Anorexia Cachexia Scale; ACS).[14] A poor appetite was defined as a score of ≤37 on the ACS, consistent with previously reported cut-points.[15]

Dietary intake was collected following the baseline and post-intervention assessments with a 3-day food record. Written and verbal instructions were provided to participants, explaining how to complete the food record and estimate portion sizes using household measures (including measuring cups and spoons). Food records were analysed by an Accredited Practising Dietitian (EJ) using FoodWorks 8 Professional (Xyris Software Pty Ltd, Australia). Intake variables were calculated per day and averaged across three days for each participant. Energy (kcal) and protein intake (g) were expressed per kilogram (kg) of body weight per day.

The recommendations of the European Society of Parenteral and Enteral Nutrition (ESPEN) expert group were used to classify energy and protein intake as adequate or inadequate.[16] These guidelines recommend patients with cancer achieve a minimum energy intake of 25 kcal/kg/day and protein intake 1.0 g/kg/day.[16] Participants with an intake that met the ESPEN expert group recommendations at baseline and post-intervention were considered to have adequate dietary intake. Participants with an intake below the ESPEN expert group recommendations at either or both time-points were considered to have inadequate dietary intake.

Body composition

Body composition was measured at baseline and post-intervention using whole body dual-energy x-ray absorptiometry (DXA) (Hologic Discovery A, Hologic Inc., Marlborough, MA, USA). Appendicular skeletal muscle mass was segmented from trunk lean mass at the acromio-humeral and pelvic-femoral joints and adjusted for height (kg/m^2).[17] Low appendicular skeletal muscle mass was defined as ≤7.26 kg/m^2 for males and ≤5.45 kg/m^2 for females.[18] Change in appendicular skeletal muscle mass (kg/m^2) and body fat (%) were determined by the absolute difference between the baseline and post-intervention measurements.

Physical functioning

Participants completed a series of standardized tests at baseline and post-intervention to assess physical functioning. Lower body function was assessed with the repeated chair rise (sec), where participants were asked to rise from a seated position and return to sitting, five consecutive times.[19] Functional mobility was assessed with the Timed Up and Go (sec), where participants were asked to rise from a seated position, walk 8-feet forward, turn around, walk back to the chair and sit down.[20] Lower body strength was assessed with the one-repetition maximum (1RM) leg press, or the maximum weight (kg) that can be lifted one time.[21] Relative 1RM was calculated as 1RM leg press divided by current weight. Functional capacity was assessed with the Six-Minute Walk Test (m), where participants were asked to walk as far as possible on a flat 50 m course in six minutes.[22]

Exercise intervention

Supervised resistance exercise training was undertaken by participants in small groups, three times per week for six weeks with a total of 18 sessions. Participants had an additional two-week period where they could make up for any missed sessions. Exercise training was supervised by an Accredited Exercise Physiologist. The training involved resistance exercises that were designed to target the major muscles of the upper and lower body, with 1 – 3 sets of each exercise performed at an intensity of 8 – 12 repetition maximum, defined as the maximum weight that could be lifted 8 – 12 times. Exercise prescription was progressive and modified by the Accredited Exercise Physiologist according to the individual's response.

Adherence and tolerance to the exercise intervention

Completion of the study was defined as attendance at both the baseline and post-intervention assessments. Adherence to the exercise intervention was recorded as the total number of exercise sessions attended out of a possible 18. Following each exercise session, participants were asked to rate their perceived exertion during exercise and their tolerance of the session. Perceived exertion was assessed with the Borg scale, where a score of 6 represents no exertion and a score of 20 represents maximal exertion.[23] Tolerance was assessed using a 7-point Likert scale, where a score of 1 indicated the exercise session was extremely intolerable and a score of 7 indicated an extremely tolerable session. Average perceived exertion and average tolerance of the exercise intervention were calculated for each participant and determined by the sum of each participant's data divided by the number of exercise sessions attended.

8.2.3 Statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (v. 25, IBM Corporation, Somers, NY, USA). Data are expressed as mean ± SD or median [IQR] where the data were not normally distributed. Fisher's Exact Test was used to assess differences in study completion rates between well-nourished and malnourished participants. Two-tailed independent t-tests, or the Mann-Whitney test where the data were not normally distributed, were used to test for differences in participant characteristics and change scores of variables according to nutritional status or dietary intake. Paired t-tests, or the Wilcoxon signed rank test where the data were not normally distributed, were used to assess if body composition and physical functioning variables changed significantly from baseline to post-intervention.

8.3 Results

8.3.1 Participant characteristics

Participant flow through the study and baseline participant characteristics have been reported previously (**Appendix B**).[24] Briefly, thirty-three patients enrolled in the study with a median age of 68 [IQR 62 – 73] years and a mean BMI of 25.7 ± 3.4 kg/m^2. Participants were predominantly male (68%), with a diagnosis of MPM (85%) and an ECOG performance status rating of 0-1 (97%). All participants completed the PG-SGA and eight (24%) were classified as malnourished. Thirty participants (91%) completed the appetite questionnaire and food record, and of these, nine (30%) had a poor appetite and eleven (37%) did not meet energy and protein requirements.

8.3.2 Nutritional status and dietary intake among participants who completed the intervention

Of the 27 participants who completed the intervention, 26 (96%) had complete nutritional status data available and 25 (93%) had complete dietary intake data. Regarding the incomplete data, one participant did not complete the 3-day food record at baseline and one participant declined to complete the PG-SGA and weight measurement post-intervention; therefore energy (kcal/kg/day) and protein (g/kg/day) intake could not be calculated for these participants. No differences were observed in demographic or disease characteristics between participants according to nutritional status or dietary intake group (**Table 8.1 and Table 8.2**). The majority of participants (73%) who completed the intervention were well-nourished at baseline and post-intervention (**Figure 8.1**). Only 40% had adequate energy and protein intake at both baseline and post-intervention (**Figure 8.1**).

8.3.3 Differences in completion rates, exercise adherence and tolerance according to nutritional status and dietary intake

Study completion rates were not significantly different between participants who were well-nourished or malnourished at baseline (84% vs. 75%; p=0.616). Among participants who completed the intervention, there were no significant differences between participants well-nourished and malnourished with regard to the number of exercise sessions attended (median 18.0 [IQR 18.0 – 18.0] vs. median 18.0 [IQR 13.0 – 18.0]; p=0.427), the average tolerance of exercise sessions (median 6.1 [IQR 5.8 – 6.5] vs. median 5.7 [IQR 5.2 – 5.9]; p=0.073) or the average rating of perceived exertion of exercise sessions (median 12.7 [IQR 12.1 – 13.8] vs. median 12.3 [IQR 12.3 – 12.8]; p=0.611; **Table 8.3**).

Study completion rates were not significantly different between those with adequate and inadequate dietary intake at baseline (89% vs. 82%; p=0.611), although three participants did not complete the baseline food record. Among participants who completed the intervention, there were no significant differences between participants with adequate and inadequate intake with regard to the number of exercise sessions attended (median 18.0 [IQR 14.5 – 18.0] vs. 18.0 [IQR 18.0 – 18.0]; p=0.567), the average tolerance of exercise sessions (median 6.0 [IQR 5.9 – 6.3] vs. median 5.8 [5.3 – 6.5]; p=0.495) or the average rating of perceived exertion of exercise sessions (median 12.6 [IQR 12.3 – 13.7] vs. median 12.3 [IQR 12.0 – 12.9]; p=0.338; **Table 8.3**).

8.3.4 Changes in body composition following the exercise intervention, according to dietary intake

Change in appendicular skeletal muscle mass differed significantly between the adequate and inadequate dietary intake groups (mean difference 0.40 [95% CI 0.14 – 0.67] kg/m^2; p=0.005; **Figure 8.2**). Following exercise training, appendicular skeletal muscle mass significantly increased in participants who had adequate dietary intake (mean change +0.43 [95% CI 0.18 – 0.67] kg/m^2; p=0.004); there was no significant change in participants with inadequate dietary intake (mean change +0.03 [95% CI -0.13 – 0.19] kg/m^2; p=0.737).

Change in body fat (%) did not differ significantly between the adequate and inadequate dietary intake groups (median difference -0.15 %; p=0.765; **Figure 8.2**). Following exercise training, body fat (%) did not change significantly in participants with adequate dietary intake (median change -0.45 [IQR -2.7 – 0.4] %; p=0.314) or inadequate dietary intake (median change -0.3 [IQR -1.2 – 0.5] %; p=0.414).

8.3.5 Changes in physical functioning following the exercise intervention, according to dietary intake

There were no differences between those with adequate and inadequate dietary intake for change in the repeated chair rise (mean difference 0.43 [95% CI -0.90 – 1.76] sec; p=0.504), Timed Up and Go (median difference -0.09 sec; p=0.734), relative one-repetition maximum leg press (median difference 0.02; p=0.643) or Six Minute Walk Test (median difference -4.7 m; p=0.600; **Figure 8.3**).

Following exercise training, the chair rise improved significantly in participants with both adequate dietary intake (median change -0.93 [IQR -2.25 – -0.37] sec; p=0.021) and inadequate dietary intake (median change -1.23 [IQR -2.75 – -0.24] sec; p=0.004). Timed up and go improved significantly in participants with adequate dietary intake (median change -0.30 [IQR -1.55 – 0.39]; p=0.012) but not in those with inadequate dietary intake (median change -0.39 [IQR -0.65 – 0.17] sec; p=0.221). Relative 1RM leg press improved significantly in participants with both adequate dietary intake (median change 0.23 [IQR 0.06 – 0.38]; p=0.008) and inadequate dietary intake (median change 0.21 [IQR 0.05 – 0.32]; p=0.001). Six Minute Walk Test improved significantly in participants with adequate dietary intake (median change 46.8 [IQR 27.7 – 100.0] m; p=0.011) but not in those with inadequate dietary intake (median change 42.1 [IQR -11.3 – 120.0] m; p=0.075).

Table 8.1 Demographic, disease and nutritional characteristics of participants who were well-nourished and malnourished, n=26

	All participants (n=26)		Well-nourished (n=19)		Malnourished (n=7)		
	n	%	n	%	n	%	P value
Age[#], *years*	67.0^	62.0 – 72.3^	68.0^	62.0 – 72.0^	62.0^	62.0 – 74.0^	0.651
Gender							
Male	19	73.1	14	73.7	5	71.4	1.000
Female	7	26.9	5	26.3	2	28.6	
BMI[#], *kg/m2*	25.9	3.4	26.0^	24.7 – 30.0^	23.7^	19.8 – 26.3^	0.055
Cancer type							
Mesothelioma	21	80.8	16	84.2	5	71.4	0.588
Non-mesothelioma	5	19.2	3	15.8	2	28.6	
ECOG performance status at baseline							
0-1	25	96.2	19	100.0	6	85.7	0.269
≥2	1	3.8	0	0.0	1	14.3	
Cancer treatment prior to intervention, *yes*	9	34.6	5	26.3	4	57.1	0.188
Cancer treatment during intervention, *yes*	7	26.9	4	21.0	3	42.9	0.340
Appendicular lean mass at baseline (DXA)							
Low[□]	14	53.8	9	47.4	5	71.4	0.391
Normal	12	46.2	10	52.6	2	28.6	
Normal appendicular lean mass over study period	11	42.3	9	47.4	2	28.6	0.658

	All participants (n=26)		Well-nourished (n=19)		Malnourished (n=7)		
	n	%	n	%	n	%	P value
Dietary intake at baseline*							
Inadequate	8	30.8	5	27.8	3	42.9	0.640
Adequate	17	65.4	13	72.2	4	57.1	
Adequate intake over study period	10	38.5	8	44.4	2	28.6	0.659
Appetite at baseline							
Poor▪	7	26.9	2	10.5	5	71.4	0.006
Normal	19	73.1	17	89.5	2	28.6	
Normal appetite over study period*	17	65.4	16	88.9	1	14.3	0.001

ECOG – Eastern Cooperative Oncology Group; DXA – Dual-Energy X-Ray Absorptiometry; #assessed at baseline, ^median, IQR, □DXA measured appendicular lean mass ≤7.26 kg/m2 for men and ≤5.45 kg/m2 for women; ▪Score ≤37 on Anorexia Cachexia Scale; *Well-nourished, n=18 and malnourished, n=7

Table 8.2 Demographic, disease and nutritional characteristics of participants with adequate and inadequate intake, n=25

	All participants (n=25)		Adequate intake (n=10)		Inadequate intake (n=15)		
	n	%	n	%	n	%	P value
Age[#], *years*	67.0^	62.0 – 72.5^	67.0^	59.3 – 71.0^	68.0^	62.0 – 73.0^	0.723
Gender							
Male	18	72.0	7	70.0	11	73.3	0.856
Female	7	28.0	3	30.0	4	26.7	
BMI[#], *kg/m2*	25.9	3.5	25.6	4.1	26.0	3.0	0.775
Cancer type							
Mesothelioma	20	80.0	9	90.0	11	73.3	0.307
Non-mesothelioma	5	20.0	1	10.0	4	26.7	
ECOG performance status at baseline							
0-1	24	96.0	9	90.0	15	100.0	0.211
≥2	1	4.0	1	10.0	0	0.0	
Cancer treatment prior to intervention, *yes*	9	36.0	4	40.0	5	33.3	0.734
Cancer treatment during intervention, *yes*	7	28.0	3	30.0	4	26.7	0.856
Appendicular lean mass at baseline (DXA)							
Low[□]	14	56.0	7	70.0	7	46.7	0.250
Normal	11	44.0	3	30.0	8	53.3	
Normal appendicular lean mass over study period	10	40.0	3	30.0	7	43.8	0.405

	All participants (n=25)		Adequate intake (n=10)		Inadequate intake (n=15)		
	n	%	n	%	n	%	P value
Nutritional status at baseline (PG-SGA)							
Well-nourished	20	80.0	8	80.0	12	80.0	1.000
Suspected malnutrition/ moderately malnourished	5	20.0	2	20.0	3	20.0	
Severely malnourished	0	0.0	0	0.0	0	0.0	
Well-nourished over study period	18	72	8	80.0	10	66.7	0.467
Appetite at baseline							
Poor▪	7	28.0	3	30.0	4	26.7	0.856
Normal	18	72.0	7	70.0	11	73.3	
Normal appetite over study period*	16	64.0	6	66.7	10	66.7	1.000

ECOG – Eastern Cooperative Oncology Group; DXA – Dual-Energy X-Ray Absorptiometry, PG-SGA – Patient-Generated Subjective Global Assessment; #assessed at baseline, ^median, IQR, □DXA measured appendicular lean mass ≤7.26 kg/m2 for men and ≤5.45 kg/m2 for women; ▪Score ≤37 on Anorexia Cachexia Scale *inadequate intake, n=15 and adequate intake, n=9

Table 8.3 Differences in adherence and tolerance to exercise between nutritional status and dietary intake groups

	Well-nourished (n=19)		Malnourished (n=7)			Adequate intake (n=10)		Inadequate intake (n=15)		
	Median	IQR	Median	IQR	P value	Median	IQR	Median	IQR	P value
Sessions attended, #	18.0	18.0 – 18.0	18.0	13.0 – 18.0	0.427	18.0	14.5 – 18.0	18.0	18.0 – 18.0	0.567
Average tolerance	6.1	5.8 – 6.5	5.7	5.2 – 5.9	0.073	6.0	5.9 – 6.3	5.8	5.3 – 6.5	0.495
Average RPE	12.7	12.1 – 13.8	12.3	12.3 – 12.8	0.611	12.6	12.3 – 13.7	12.3	12.0 – 12.9	0.338

RPE – Rating of Perceived Exertion

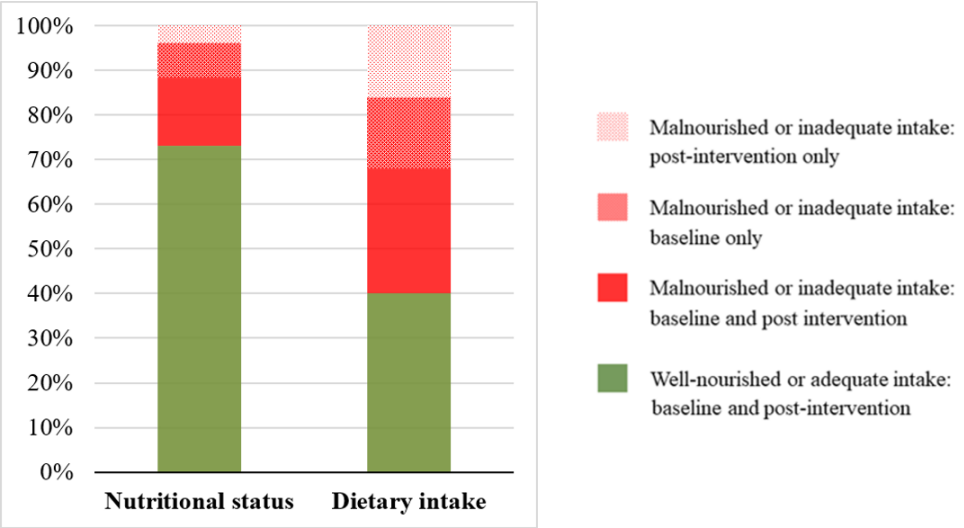

Figure 8.1 Nutritional status and dietary intake at baseline and post-intervention

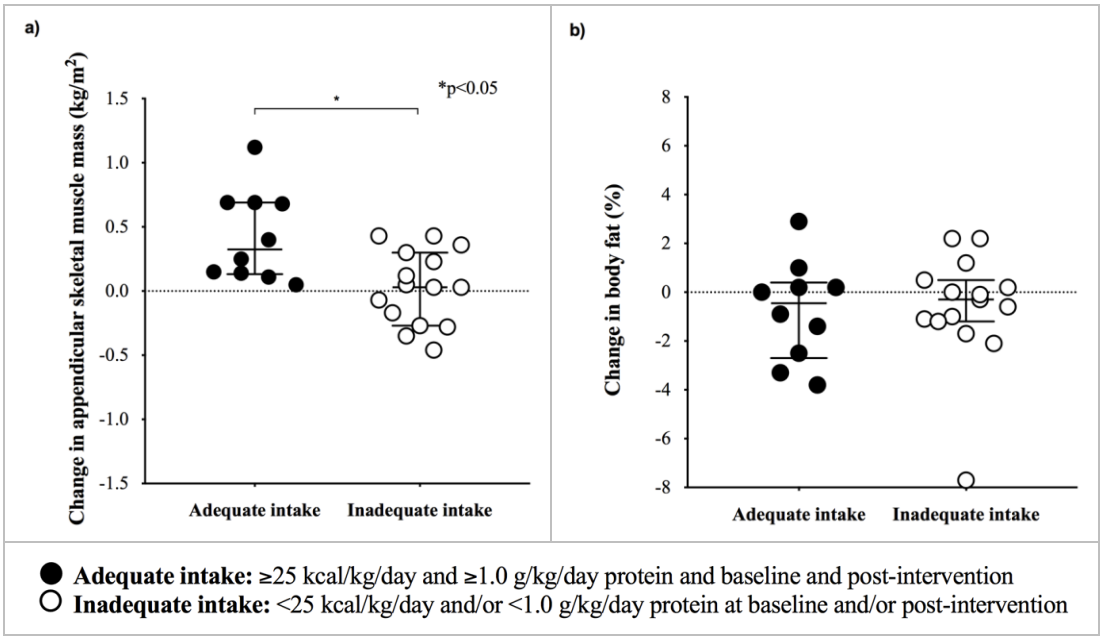

Figure 8.2 Differences in the change in body composition. a) appendicular skeletal muscle mass and b) body fat percentage according to dietary intake group, n=25

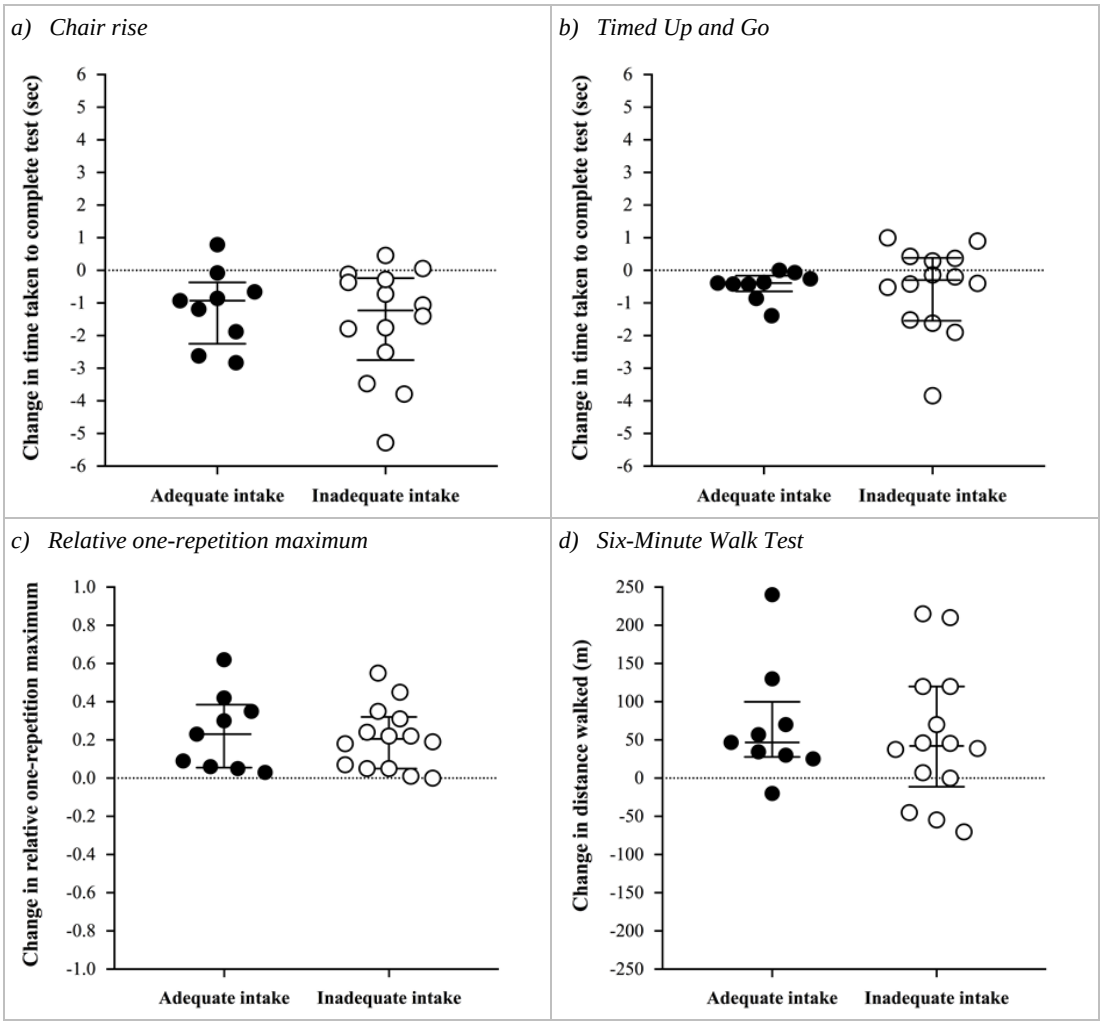

Figure 8.3 Differences in change in physical functioning outcomes according to dietary intake group, n=23

8.4 Discussion

We examined if nutritional outcomes impacted completion or efficacy of a 6-week resistance exercise intervention. The majority of participants (73%) were well nourished over the course of the intervention, however only 40% of participants maintained adequate intake at pre and post intervention. There were no differences in completion rates, adherence to, or tolerance of the exercise sessions according to nutritional status or dietary intake group. Participants with adequate intake had a significant increase in appendicular skeletal muscle mass, while those with inadequate intake had no change in appendicular skeletal muscle mass. Notably, there were no significant differences in the physical functioning response to exercise according to the dietary intake group.

We previously reported excellent adherence and tolerance to the exercise intervention overall, and in this study we report that there were acceptable study completion rates among both well-nourished and malnourished participants (84% and 75%, respectively) and both nutritional status groups reported the exercise sessions were tolerable. Our results indicated that malnourished patients with MPD are capable of completing a short resistance exercise training program. To our knowledge, no other study in advanced cancer has directly compared exercise intervention completion rates according to nutritional status. However, in a previous 3-month combined nutrition and exercise intervention, where one-third of the participants with advanced cancer were at nutritional risk, the majority of participants (97%) completed the intervention.[25] The individualized prescription of exercise was a central component of our study and the previous intervention. Having flexibility in the exercise prescription for participants with malnutrition, who have poorer baseline physical functioning and greater fatigue, may be integral to their successful completion of exercise interventions.

Participants with MPD who consumed adequate intake had a significant increase in appendicular skeletal muscle mass following the exercise intervention. There was no change in appendicular skeletal muscle mass among participants with inadequate intake. To our knowledge, this is the first study in patients with an advanced cancer to evaluate the relationship between dietary intake and body composition outcomes from resistance exercise training. Our results raise the possibility that addressing inadequate intake or maintaining adequate intake could optimize the skeletal muscle response to exercise. This is a particularly important finding as low muscle mass is associated with a range of negative outcomes for patients, including poorer quality of life,[4] increased risk of

treatment toxicities[6] and poorer survival.[6] Nutrition screening, using a tool such as the Malnutrition Screening Tool (MST)[26] could be a fast and effective way to identify patients eating less than usual and requiring nutritional counselling and oral nutrition supplements to meet dietary intake recommendations.[26] As patients with MPD are at high risk of inadequate intake,[2] routine screening and access to nutrition support should be considered alongside exercise interventions.

Optimizing physical functioning is also important for patients with advanced cancer. We found no significant differences in physical functioning outcomes between participants with inadequate and adequate energy and protein intake. Following the exercise intervention, we observed positive changes among both dietary intake groups for the chair rise and 1RM leg press. This suggests that resistance exercise training is beneficial even for cancer patients who are unable to meet dietary intake recommendations. This is particularly relevant for advanced cancer patients, as dietary intake can remain suboptimal even following nutritional intervention.[27]

A limitation of the current study is the small sample size, therefore we were unable to incorporate other confounding health issues such as cancer progression and treatment into our statistical analysis and cannot draw conclusions about causality. The majority of participants with malnutrition also had a good performance status and therefore may not be representative of the broader population of malnourished patients with advanced cancer, particularly those with poorer performance status. More unwell patients could be less likely to commence, complete, adhere to and tolerate the exercise intervention. Exertion and tolerance of the exercise intervention were measured using the Borg scale and a 7-point Likert scale, respectively. Both measures are participant-rated and therefore subjective and may not represent the level of objective physiological exertion or tolerance experienced by participants. Additionally, as dietary intake was only assessed at two time points, before and after the intervention, we are unable to determine the duration and stability of any inadequate energy and protein intake. More frequent monitoring of dietary intake for example weekly or fortnightly could capture the duration of inadequate intake. Repeated 24-hour dietary recalls[28] could be one way to increase the frequency of dietary intake monitoring, without substantially increasing participant burden.

As resistance exercise interventions can increase skeletal muscle mass and improve physical functioning, they have the potential to improve quality of life, treatment tolerance and survival in patients with advanced cancer. However, the response to resistance

exercise could be impeded by poor tolerance to exercise prescription and inadequate intake. Compared to patients with early stage cancer, patients with advanced cancer, as in the current study, are more likely to experience malnutrition and a poor appetite,[29] which may negatively affect their ability to participate in exercise and eat adequately during an exercise intervention.

As exercise oncology research begins to include more patients with advanced cancer,[30] the impact of the unique nutritional issues that characterize this patient group needs to be evaluated to determine how to best optimize patient outcomes. This study offers insight into how nutrition and exercise outcomes interact in patients with MPD and the potential to improve response to exercise with combined interventions.

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Chapter Nine

9

Conclusions and Implications for Future Research

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9.1 Overview

This research aimed to provide information on the physical activity, nutritional status and body composition of patients with MPD and their relationship with patient outcomes, as well as examine the effects of nutritional status and dietary intake on outcomes of an exercise intervention. This chapter is a summary of the findings from a literature review and three experimental studies that were conducted in patients with MPD, and acknowledges the strengths, limitations and implications of the work.

Chapter Two is a critical review of the literature. There is a lack of information in the literature regarding the prevalence of inactivity, functional impairment, malnutrition and low muscle mass in patients with MPD, and their associations with patient outcomes, confirming the value of further investigation. There is also a limited understanding on the effect of different body composition assessment methods on the classification of low muscle mass and the subsequent conclusions that are drawn. Furthermore, there is little information on the nutritional status and dietary intake of participants included in exercise interventions, and the impact that these nutritional factors have on exercise outcomes.

In Chapter Three, the aim was to use accelerometry to characterise physical activity levels and their relationship with patient outcomes. The majority of participants did not meet physical activity guidelines; and compared to participants with good performance status, participants with a poor performance status spent a greater proportion of their day as sedentary and a lower proportion of their day participating in light activity. These results indicated that patients with MPD were inactive, and performance status and survival were associated with activity levels. Accelerometry was well tolerated as a tool for assessing physical activity levels in this population.

In Chapter Four, the aim was to compare body composition assessment methods, namely CT and DXA, which are commonly used in the classification of low muscle mass in research. There was a moderate positive correlation between skeletal muscle index and appendicular skeletal muscle index and a moderate agreement between the CT cut-points from Prado et al[1] and the DXA cut-points from Baumgartner et al[2], but no significant agreement between the other cut-points evaluated. These findings highlighted that although the body composition assessment methods of CT and DXA were correlated, there were differences between methods when they were used to classify low muscle mass.

In Chapter Five, the aim was to determine the prevalence of low muscle mass and malnutrition and investigate their relationship with physical activity levels and quality of life in patients with MPM. There were high rates of low muscle mass and malnutrition.

Compared to participants with normal muscle mass, participants with low muscle mass were more sedentary and participated in less light activity; and compared to participants who were well-nourished, those with malnutrition had poorer quality of life. These results indicated that low muscle mass and malnutrition were common among patients with MPM and were associated with negative outcomes.

In Chapter Six, the aim was to determine the prevalence of poor physical functioning and nutritional outcomes in the two years from MPM diagnosis and provide a description of functional and nutritional status over time. Functional and nutritional impairment were common throughout the 2 years post diagnosis and for many participants, impairments persisted or reoccurred during the follow-up. These results indicate a need for screening in clinical practice to identify patients with functional and nutritional impairment who could benefit from supportive care interventions.

In Chapter Seven, the aim was to describe changes in body composition over time and their relationship with activity levels and dietary intake. Multiple patterns of change in body composition were found. Ultimately, compared to participants with muscle maintenance, those with muscle loss had poorer survival and decreased activity levels over time. Interventions that target muscle loss or physical activity may benefit patients with MPM.

In Chapter Eight, the aim was to determine if completion rates and response to an exercise intervention differed according to nutritional status and dietary intake. There were acceptable study completion rates for participants with malnutrition. Compared to participants with inadequate dietary intake, participants with adequate intake had a greater increase in muscle mass, however there were no differences in the physical functioning response to exercise. This result suggests that adequate intake could optimise muscle gains. Importantly, those with malnutrition or inadequate intake can still complete and gain benefit from an exercise intervention. This could have implications for the development of exercise and combined interventions in advanced cancer populations.

9.2 Limitations and strengths

The research has a small sample size relative to studies completed in other cancer populations, such as those with advanced lung cancer.[3, 4] This was expected given MPM is a rare cancer with fewer than 800 new cases diagnosed across Australia each year.[5] Despite the anticipated small sample size, research in MPM was needed given the lack of existing data on physical activity, nutritional status and body composition. Research in this field was particularly important as supportive care interventions could offer benefit to a patient population with incurable disease and limited treatment options. Therefore, the

overarching purpose of this research was to provide a platform from which intervention studies could be developed.

The research includes a heterogeneous population of patients with MPM. Patients with MPM could enrol in the studies at any time from the point of diagnosis and regardless of their past, present or future cancer treatment plans. As a result, there are multiple confounding factors that were not adjusted for in the statistical analysis due to the relatively small sample size, which limit the conclusions that can be drawn from the research. The alternative would have been to control for these confounding factors and include patients at specified time points within the disease course or treatment journey. However, this would have had a negative impact on the sample size for two reasons. Firstly, the time of diagnosis was a particularly challenging time to recruit participants. Twenty percent of the participants who declined to participate reported feeling too overwhelmed with their recent diagnosis. Second, there is no standard treatment pathway for patients with MPM and while approximately half of participants had treatment during the course of their disease, the other half of participants did not. Therefore, the research would not have been feasible if the eligibility criteria were restricted to patients who were newly diagnosed or due to commence chemotherapy.

A lack of benefit to patients is a commonly reported barrier to participation in clinical trials.[6] Two of the experimental studies conducted, the cross-sectional and longitudinal observational studies offered no direct benefit to participants. The recruitment rate for the longitudinal observational study was 43%. Of the patients excluded, approximately one-third were ineligible, however the remaining two-thirds declined to participate. None of the patients who declined participation reported a lack of benefit to themselves as a reason for non-participation, however this may have been due to social desirability bias. Therefore, the lack of benefit to patients may have had a negative effect on the participation rate.

The health of the patients with MPM may also have had an impact on the participation rate. Almost one-third of patients who declined to participate reported being too unwell. Assessments for this research were completed over one hour, which could be inconvenient for unwell patients. Consequently, this research most likely included the more well patients with MPM and the results may not be generalisable to the larger MPM population. Considering ways that patients can participate with minimal time and effort could improve future participation rates of unwell patients with MPM.

Previous research has reported that the inconvenience and cost of travel for patients with cancer are also important considerations for participation in clinical trials.[7] Similarly during the recruitment process in this research, patients indicated that one of the main considerations for study participation was whether they would need to make additional visits to the hospital. A high proportion of the participants were from regional or remote Western Australia, and additional travel would have been a significant burden. Consequently, the timing of study assessments in the longitudinal observational study was flexible. This meant that on occasion there was a longer than expected time between study assessments. The differences in the timing of follow up between participants created some challenges during data analysis. However, the alternative would substantially limit participation. The burden associated with attending assessments should be carefully considered when planning future research in patients with MPD.

As the study was conducted in an advanced cancer population, participant burden was a key consideration when planning the research. For example, informal feedback from participants during the longitudinal observational study indicated that completing a 3-day food record was burdensome. Therefore, an amendment was made to the study protocol and participants were asked to complete a 3-day food record at the baseline assessment only; and the shorter 24-hour recall was completed at subsequent assessments. Participants appeared to be more engaged in the 24-hour recall process. While results of a 24-hour recall may not represent habitual dietary intake, the method was more acceptable to patients. Compared with a 3-day food record, the 24-hour recall could be more feasible in patients with advanced cancer when dietary intake needs to be assessed at multiple time points. This also indicates the need to be pragmatic in these types of studies.

The completion of body composition assessments was a significant challenge in this study population. The DXA machine used for this study was a 10-minute walk from the Respiratory and Medical Oncology clinics, which was difficult for most participants. This was managed by using wheelchairs and the hospital buggy service to transport participants to the DXA machine. Some participants were not able to lie flat on the DXA bed or independently get on and off the DXA bed. This was managed by providing pillows and physical assistance to participants. Although these challenges understandably led to some participants declining to complete a DXA scan, there were no serious adverse events related to body composition assessment or any other measurements, indicating that the assessments were safe. However, this experience highlighted that DXA may not be the most practical way to assess muscle mass in patients with advanced cancer; particularly in

prospective research where participants have disease progression and become more unwell over time. For future research it may be more feasible to measure muscle mass using CT.

9.3 Implications for practice and future research

This research provides preliminary data on functional and nutritional impairment in MPM and indicates that these issues are prevalent in this patient population. While this research did not investigate the proportion of participants who had received a referral to an exercise physiologist, physiotherapist or dietitian for supportive care, current figures suggests that functional and nutritional impairment in patients with cancer goes undetected in a high proportion of cases,[8, 9] which could have a negative impact on patient-centred outcomes. Several factors could contribute to this finding, including a lack of awareness of the benefits of interventions to address functional impairment,[10] and insufficient clinician skills to identify nutritional issues.[11] Exercise physiologists, physiotherapists and dietitians have an important role to play in providing education to clinicians to increase awareness of functional and nutritional impairment in MPM, and to improve clinician skills in identifying these problems. Existing guidelines recommend the integration of functional assessment[10] and nutrition screening[12] into routine clinical care for patients with cancer to facilitate timely access to supportive care interventions. The high rates of functional and nutritional impairment reported in this research indicate there is a need for health services to implement functional assessment and nutrition screening into routine care of patients with MPM. At present, routine assessment of function and nutrition is not conducted in the pleural outpatient clinic in Western Australia. Consequently, future research will focus on implementing functional assessment and nutritional screening practices into routine clinical care using an implementation science approach that considers the barriers and enablers of change.

As MPM has no cure, improving survival and the ability to tolerate cancer treatments is of high importance. A growing body of research suggests that low muscle mass and poor muscle quality is associated with reduced time to disease progression and overall survival[13] and could increase the likelihood and severity of toxicity from chemotherapy.[14] A study investigating muscle mass, muscle quality, survival and treatment toxicity in MPM presents several methodological challenges. First, the study would require a much greater sample size than the one recruited in this research. Based on the research in this thesis, using DXA prospectively is unlikely to be feasible due to low incidence of disease[5] and the additional burden associated with DXA in unwell patients with advanced cancer.

Additionally, DXA does not measure muscle quality.[15] CT could be a more practical way to undertake this research as scans are performed as part of routine clinical care, accessible for retrospective analysis. CT also has the capacity to measure both muscle mass and quality.[15] Although CT is more practical, the findings of this work indicate existing cut-points may have limited utility. Therefore, the relationship between muscle mass, muscle quality, survival and treatment toxicity will be evaluated with data as continuous variables as recommended by the American Society of Parenteral and Enteral Nutrition.[16]

Research presented in this thesis indicates that inadequate dietary intake and malnutrition are common in patients with MPD and associated with poor outcomes such as reduced quality of life. Additionally, adequate dietary intake may be required to increase muscle mass during exercise training. Therefore, the next phase of this research will be to determine if a multi-modal program of nutritional support with exercise training could optimise the therapeutic effect of exercise. Considering aerobic exercise may interfere with muscle maintenance or gain in patients with cancer,[17] resistance training will be the primary mode of exercise. Existing research indicates that intervention with dietary counselling and oral nutrition supplements can improve energy and protein intake in patients with cancer.[16, 17] These interventions will be the foundation of the nutritional support program. Additionally, preliminary research indicates amino acid supplementation with beta-hydroxy-beta-methylbutyrate (HMB), the active metabolite of leucine, slows the breakdown of protein in muscle tissue and enhances muscle protein synthesis, resulting in improvements in muscle mass.[18] Given the substantial challenges to maintaining and improving muscle mass in advanced cancer patients, HMB supplementation could be a novel way to improve the effects of traditional nutrition support in combination with resistance exercise training.

9.4 Conclusion

This research investigated physical activity, functional and nutritional status and body composition in patients with MPD and its relationship with patient outcomes. In an effort to better understand supportive care outcomes, this research also evaluated the effects of nutritional status and dietary intake on outcomes of an exercise intervention. There were high rates of inactivity, poor physical function, malnutrition and low muscle mass among patients with MPD. Low muscle mass and malnutrition were associated with negative outcomes. Muscle loss over time was associated with a decline in physical activity, therefore interventions that target muscle mass or physical activity could offer

benefit to these patients. The results of the exercise intervention indicated that malnutrition should not preclude participation, however dietary intake could influence body composition outcomes. Therefore, combined nutrition and exercise interventions could be most impactful. Research is needed to investigate the relationship between low muscle mass and survival, as well as the feasibility and efficacy of combined interventions in patients with MPD.

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APPENDICES

Appendix A Accelerometer-based Activity Monitoring in Cancer Survivorship Research

A Review of Accelerometer-based Activity Monitoring in Cancer Survivorship Research

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EPIDEMIOLOGY

ABSTRACT

PEDDLE-MCINTYRE, C. J., V. CAVALHERI, T. BOYLE, J. A. MCVEIGH, E. JEFFERY, B. M. LYNCH, and J. K. VALLANCE. A Review of Accelerometer-based Activity Monitoring in Cancer Survivorship Research. *Med. Sci. Sports Exerc.*, Vol. 50, No. 9, pp. 1790–1801, 2018. **Background**: In the cancer survivorship context, physical activity and sedentary behavior have been measured using different methods. **Purpose**: To conduct a narrative review of published research in cancer survivor populations to summarize the quality and identify gaps in reporting on accelerometer data collection, data processing, and outcome measures in cancer survivors. **Methods**: An initial PubMed® search of articles published in English was conducted in January 2017, and a final search was conducted in May 2017. Variables extracted included study characteristics, methods for accelerometry data collection (e.g., device used), data processing (e.g., cut points used), and data reporting (e.g., time spent in different activity intensities). **Results**: A total of 46 articles were eligible for inclusion in the review. The majority of studies (34 of 46) targeted a single cancer group and 18 of these 34 studies were in survivors of breast cancer. Half (54%) of the studies used an ActiGraph® accelerometer. Methods of accelerometer data processing varied across studies. Definitions of non–wear time, vectors used during processing, and filters applied during processing were reported by 51%, 60%, and 8% of studies, respectively. Most studies reported moderate and vigorous physical activity (78%), 50% reported sedentary time, and 43% reported light-intensity activity. Cut points to categorize these activities varied between studies. **Conclusions**: This narrative review highlights inconsistency in the methods used to collect, process, and report accelerometry data across cancer survivor studies. Accelerometry has potential to add detailed knowledge of the levels and patterns of physical activities and sedentary behaviors across the cancer spectrum. Recommendations are made to improve data processing and reporting methods to maximize the scientific validity of future accelerometer research in this field. **Key Words:** PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR, ACCELEROMETER, CANCER, MEASUREMENT

The past two decades have witnessed a plethora of research examining the health benefits of physical activity in people with cancer. Studies have demonstrated associations of physical activity and important cancer outcomes including a lower risk of cancer recurrence, improved mortality, and beneficial effects on a range of patient-reported outcomes (1,2). More recent research has indicated that sedentary behavior may also impact the health of cancer survivors (3). While physical activity and sedentary behavior are important targets for cancer survivorship research, accurate and reliable measurement of these constructs remains a challenge.

Most research to date on physical activity and sedentary behavior in cancer survivors has been characterised by the use of self-reported assessments, most often using measures that rely on a person's recall of their physical activity and/or sedentary behavior. The reliability and validity of self-report physical activity questionnaires are dependent on participants' activity levels (i.e., active adults have more measurement error than less active adults) (4–6). Additionally, high-volume and less discrete behaviors, such as sedentary time and light

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intensity activity that occur throughout the day are difficult to capture by self-report. Self-reported measures of sedentary time and physical activity have been shown to have only poor to fair agreement with objective measures of these behaviors using accelerometry (7), although it could be argued that these two methods are not measuring the same constructs (6).

Using accelerometers to measure activity and sedentary behavior is becoming increasingly common in the cancer survivorship context. As accelerometry provides an objective measure of important patient-centered outcomes, it is appealing to both researchers and clinicians. Accelerometry also enables precise and reliable measurement across the movement continuum (i.e., sleep, sedentary, and physical activity behaviors) that occur at different intensities and patterns throughout the 24-h day. Accurate quantification of physical activity and sedentary behavior via accelerometry facilitates a better understanding of these exposures and how they relate to health outcomes in cancer survivors. Accelerometer data also allow for the complex characterisation of physical activity accumulation patterns, including the identification of times of day and days of the week in which individuals are more or less active or sedentary. This information is valuable for developing interventions aimed at changing these behaviors (8). Given the potential clinical applications of accelerometers for cancer populations, differences in population characteristics (compared to the general population), and the increasing research focus on cancer survivorship, understanding how accelerometers have been applied in cancer research is of particular importance.

Although accelerometers have the capacity to provide richer and more accurate data about physical activity and sedentary behaviors compared with self-report measures, the quality of the data produced is dependent on an array of decisions made during data collection and processing. These critical decisions include device type and placement, wear-time protocols, epoch length, filter application, criteria for non–wear time, criteria for a valid day of wear time, and how to process data to obtain summary measures of sedentary time, light-intensity activity and moderate and vigorous physical activity (MVPA) (9,10). These decisions can affect the summary measures derived (e.g., minutes of MVPA per day) and also the observed associations between these summary measures and health outcomes. It is therefore vital that accelerometer data collection and processing decisions are clearly reported in journal articles summarizing accelerometer-based studies. Failure to report this information means that studies are not replicable and also makes it difficult to determine if discrepant results across studies are "real" differences or simply due to measurement and data processing decisions (11). In this narrative review we aimed to: (a) summarize the quality of reporting on accelerometer data collection, data processing, and outcome measures of published research that has used accelerometers in cancer survivor populations; (b) identify gaps in reporting accelerometer data collecting, data processing, and outcome measures; and (c) provide recommendations to improve the quality of future accelerometer-based research.

METHODS

A comprehensive PubMed® search of articles published in English was conducted. The initial search was run in January 2017, and a subsequent final search was conducted in May 2017. The natural language and MeSH terms included were as follows: "physical activity," "sedentary," "sitting," "neoplasms," "cancer," "malignancy," "tumor," "tumor," "accelerometry," "actigraphy," "acceleromet,*" "monitor," "device," "tracker," "global positioning." Reference lists of relevant review articles were also screened. Two review authors (V.C. and J.V.) independently examined the studies identified for inclusion in the review. Reviews, abstracts, editorials, study protocols, and studies that only used pedometers/step counters or physical activity trackers to measure physical activity were excluded. Data from the included studies were independently extracted and tabulated by four review authors (C.P.-M., E.J., T.B., and J.M.), with data from each study reviewed by at least two of these authors. The parameter was recorded as not applicable (NA) when it did not apply to the given study because of the device used (e.g., non–wear time protocol does not apply for studies that used the SenseWear Armband device because it only records when being worn), or when the outcome measures were not relevant (e.g., sedentary time was not reported in the article, therefore no sedentary cut point was reported). In all cases, disagreements or discrepancies were resolved by consensus.

Outcome Measures

Study characteristics. Data were extracted regarding population characteristics (e.g., cancer population, average age), study design, timing of observations, and the accelerometer used.

Accelerometer data collection and analysis. Information was extracted regarding how the device was delivered (i.e., in person or via mail), device used (e.g., activPAL™), device placement (e.g., hip), wear time protocols (i.e., instructions to participants on daily time of wear and the total number of days of wear), software used for processing, the vector used in processing, any filters applied during processing, epoch length (in data collection and during processing), how non–wear time was identified, how a valid day of wear time was defined, minimum number of valid days of wear time required for inclusion in analysis, which cut points were used to create summary measures of sedentary time, light intensity activity and/or MVPA, and any additional information on how total physical activity was calculated. Where one of the included articles referred to a previously published article rather than describing any of the above items in their own methods section, the relevant information was extracted from the cited study.

Accelerometer data reporting. Data were collected regarding time spent in: 1) sedentary time or sitting/lying, 2) light intensity activity or standing activity, and 3) MVPA or stepping. The proportion of participants meeting physical activity guidelines (i.e., ≥150 min MVPA or 75 min of vigorous activity) was also extracted, as well as any additional information on how physical activity guideline cut points were applied (e.g., 10-min bouts, physical activity over 5 d of the week). Compliance with accelerometer wear (i.e., number of participants that wore the device and were included in the analysis) was recorded along with the average valid days of data, average wear time, and whether the analysis was adjusted for waking wear time.

RESULTS

The initial search in January 2017 yielded a total of 271 records. The final search in May 2017 detected 43 additional records and four additional articles were detected through other sources, making a total number of 314 records identified in the search. After screening of titles, abstracts, and full text, 46 articles were deemed eligible for inclusion in the review (see Figure, Supplemental Digital Content 1, study flow diagram, http://links.lww.com/MSS/B279). Where there was more than one article reporting on the same data set, only the primary article reporting accelerometry outcomes were included. Secondary articles were excluded. In randomized controlled trials (RCTs) or cohort studies, only the baseline data were included, and in the case where the intervention and control group data were presented separately, only intervention group data were included.

Study characteristics. Study characteristics are reported in Table 1. The majority of studies (72%) targeted a single cancer group, namely breast (n = 17) (12,14,16,20,22,29,36,40–46,48,52,57), lung (n = 6) (17,18,21,27,38,39), colorectal (n = 5) (31,32,49,53,58), prostate cancer (n = 4) (19,25,37,54), and non–Hodgkin lymphoma (n = 1) (13). Other study populations were based on clinical characteristics, such as advanced cancer (34), cachexia (24), or sites of disease, such as brain metastasis (35) or malignant pleural effusion (28). Most study designs were cross-sectional (n = 28), with a further 10 prospective studies (16,20,22–24,26,27,48,49,52), six RCTs (19,39,43–46), one nonrandomized clinical trial (33), and one case series (34). The majority of cross-sectional and RCT studies (n = 35) were either following completion of active treatment (34%) (12,17,21,25,30,32,38,43,45,47,51,53) or "postdiagnosis" (17%) (13,14,40,50,54,55), with fewer studies focusing on before (11%) (15,33,39,41) or during treatment (9%) (44,46,56), whereas a portion of studies did not specify (26%) (18,19,28,29,31,36,37,42,57). For the prospective studies and case series (n = 11), assessments often began during treatment (27%) (20,23,52), or following completion of primary treatment (30%) (16,22,26,48,49), with only one beginning at diagnosis (27) and two unspecified (24,34).

Over half (54%) of the studies used an ActiGraph® accelerometer. SenseWear Armband (11%) and activPAL (11%) devices were the next most common accelerometer models used. Most studies measured physical activity and/or sedentary behavior with one accelerometer (98%), with only a single study using more than one research-grade accelerometer simultaneously (2%) (20). The majority of studies (63%) used a waist placement. Most studies used protocols of 7 d of wear time (76%) and waking hours only wear time (65%).

How have studies reported physical activity and sedentary behavior data? Table 1 and the Supplementary Table 1 (Supplemental Digital Content 2, description of accelerometry data analysis methods, http://links.lww.com/MSS/B280) report study characteristics, data reporting, and data analysis methods of the reviewed studies. Of the 46 studies included, 45 reported physical activity or sedentary behavior data. One study only reported methods (20). Of these studies, outcomes were most often reported as hours or minutes per day (52%), with other studies reporting data as hours per minute per week (20%) (12,19,26,29,32,44,45,50,56), steps per day (15%) (17,23,27,34,35), total physical activity counts (n = 5) (18,24,30,46,51), or kilocalories per week (n = 1) (43).

Sedentary time was reported in 50% of studies. Of those, three studies did not report the cut point used to define sedentary behavior (15,16,22). Among those reporting cut points, the most commonly used sedentary cut points were Matthews et al. (59) (i.e., <101 counts per minute, 61%) (7,13,14,21,25,28,29,32,36,37,40,42,47,48,53), or using METs (60) [i.e., ≤1.5 MET; 22% (17,39,41,52,55)]. Sedentary time ranged in the studies from 189 min per waking day (52) to 713 min per waking day (41). Bouts of sedentary time were reported in six studies (14,17,21,28,31,53). Prolonged sedentary bouts were described as 20+ min (13,14,28,31) or 30+ min (17,21,28,53). Time in 20-min sedentary bouts ranged from 185 min per waking day (14) to 339 min per waking day (31). Time in 30-min sedentary bouts ranged from 153 min per waking day (53) to 185 min per waking day (21).

Light intensity activity was reported in 43% studies. Cut points to categorize light intensity activity were not reported in one study (22) and were most often listed as a combination of Freedson and Matthews cut points (59,61) (i.e., 100–1951 counts per minute; 55%) (13,14,19,21,28,36,37,40,47,49,53). Light intensity activity ranged from 125 min·d^{-1} (54) to 551 min·d^{-1} (40).

Moderate and vigorous physical activity was reported in 78% of studies. Cut point references were provided for all but three studies (22,43,50). Five studies cited cut points and analysis methods from a primary article (15,16,19,44,46). The most commonly used MVPA cut points were Freedson (61) [i.e., ≥1,952; 50% (12–14,19,21,25,28,32,36,37,40,44–49,53)], or a MET cut point (62) (most commonly ≥ 3 METs, 20%) (17,29,39,41,52,56,57). Time in MVPA ranged from 3.7 min·d^{-1} (36) to 150 min·d^{-1} (22). MVPA in 10-min bouts was reported in eight studies (13,14,17,21,31,32,41,53), and ranged from 5.7 min·d^{-1} (21) to 51 min·d^{-1} (31).

TABLE 1. Study characteristics and accelerometer data reporting.

Author	Study Population/ Average Age	Study Design/ Sample Size	Timing of Observation	Device	Physical Activity Participation				Compliance	No. Valid Days	Wear Time
					Sedentary Time or Sitting/Lying	Light Intensity Time or Standing	MVPA Time or Stepping	Participants Meeting PA Guidelines (%)			
Arnireault, 2015 (12)	Breast cancer Stage I to III 55 [11] yr	Cross-sectional, $n = 199$	Posttreatment	Actigraph GT3X	NR	NR	107.3 min·wk^{-1}	27.2%	98%[a]	Median, 7 d; range, 4–7 d	NR
Boyle, 2017 (13)	Non-Hodgkin lymphoma Stage NR 62 [6.9] yr	Cross-sectional, $n = 156$	Postdiagnosis	Actigraph GT3X[b]	8.6 h·d^{-1}	5.3 h·d^{-1}	30.6 min·d^{-1}	52.6%[c]	94%[d]	NR	145 h·d^{-1}
Boyle, 2016 (14)	Breast cancer Stage I to IV	Cross-sectional, $n = 340$	Postdiagnosis	Actigraph GT3X[b]	8.2 h·d^{-1}	345.7 min·d^{-1}	31.6 min·d^{-1}	14.7%[c]	NR[e]	NR	14.5 h·d^{-1}
Broderick, 2014 (15)	Nonhematological All stages 55 [16] yr	Cross-sectional, $n = 107$	Pretreatment (chemotherapy or radiotherapy)	RT3	ECOG 0 = 7.5 h·d^{-1}	ECOG 0 = 4.7 h·d^{-1}	ECOG 0 = 0.9 h·d^{-1}	NR	97%[a]	5.6 d	NR[f]
Broderick, 2014 (16)	Breast cancer Stage I to IIIB 51 [16] yr	Prospective $n = 27$	Posttreatment	RT3	6.8 h·d^{-1}	5.1 h·d^{-1}	1.1 h·d^{-1}	4%[c,g]	NR[e]	NR	NR[f]
Cavalheri, 2015 (17)	Lung cancer Stage I to IIIA 68 [10] yr	Cross-sectional $n = 20$	Posttreatment	SenseWear Armband	68% of waking wear time	21% of waking wear time	11% of waking wear time	NR	NR[e]	NR	NR[f]
Chen, 2015 (18)	Lung cancer Stage I to IV 64 [11] yr	Cross-sectional $n = 111$	NR	Actigraph MicroMini with Action W2	NR	Up activity mean: 149.2 min·d^{-1}		NR	≥96%[a]	NR	NR
Cormie, 2013 (19)	Prostate cancer Metastatic 73 [8] yr[h]	RCT $n = 20$	NR	Actigraph GT3X	NR	341.7 min·wk^{-1}[h]	Moderate: 179.6 min·wk^{-1}[h] Vigorous: 1.8 min·wk^{-1}[h]	20%[h]	NR[e]	NR	NR
Courneya, 2016 (20)	Breast cancer Stage ≥ T1c 56 [11] yr	Prospective $n = 500$	On treatment or postsurgery	Actigraph GT3X and activPAL	NR	NR	NR	NR	Actigraph: 90%[d] ActivPAL: 88%[d]	NR	NR
D'Silva, 2018 (21)	Lung cancer Stage I to IV 71 yr	Cross-sectional $n = 127$	Posttreatment	Actigraph GT3X[b]	587.2 min·d^{-1}	245.5 min·d^{-1}	14 min·d^{-1} In bouts ≥10 min: 5.7 min·d^{-1}	23%[c]	NR[e]	6.6 d	848 min·d^{-1}
De Jesus, 2017 (22)	Breast Stage I to III 53 [8] yr	Prospective, $n = 20$	Posttreatment	Actical	5.8 h·d^{-1}	1.3 h·d^{-1}	2.5 h·d^{-1}	NR	78%[d]	3.9 d	68.7 h·wk^{-1}
Ferrioli, 2012 (23)	Mixed diagnoses Mixed stages 60 [11] yr	Prospective	On treatment	activPal	18.5 h·d^{-1}	3.7 h·d^{-1} standing	1.6 h·d^{-1} stepping	NR	100%	Median 7 d Range 2–7	NR
Fouladiun, 2007 (24)	Cachexia Advanced cancer 71 [2] yr	Prospective, $n = 53$	NR	AM 71256, Actigraph	NR	Total PA counts per day: 627		NR	74%[a]	NR	NR
Gaskin, 2016 (25)	Prostate cancer Stage I to III 66 [9] yr	Cross-sectional, $n = 147$	Posttreatment	Actigraph GT1M	9 h·d^{-1}, standardized for accelerometer wear time	NR	38 min·d^{-1}	NR	77%[a] 91%[d]	NR	14 h·d^{-1}
Gell, 2016 (26)	Mixed All stages 58 [10] yr	Prospective, $n = 24$	Not currently receiving chemotherapy or radiation treatment	Actigraph GT3X	NR	NR	317.5 min·wk^{-1}	NR	NR[e]	NR	NR

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TABLE 1. *(Continued)*

Author	Study Population/ Average Age	Study Design/ Sample Size	Timing of Observation	Device	Physical Activity Participation			Participants Meeting PA Guidelines (%)	Compliance	No. Valid Days	Wear Time
					Sedentary Time or Sitting/Lying	Light Intensity Time or Standing	MVPA Time or Stepping				
Granger, 2014 (27)	Lung cancer Stage I to III 69 [9] yr	Prospective, $n = 50$	At diagnosis	KinetaMap	NR	NR	6182 steps per day	NR	74%[d]	NR	NR
Jeffery, 2017 (28)	Malignant pleural effusion Advanced cancer 69 [8] yr	Cross-sectional, $n = 46$	NR	Actigraph GT3X	11 h·d^{-1}	4.2 h·d^{-1}	9.5 min·d^{-1}	10.9%	96%[a] 98%[d]	5.9 d	15.3 h·d^{-1}
Johnson-Kozlow, 2006 (29)	Breast cancer Stage I to III 57 yr	Cross-sectional $n = 178$	NR	Actigraph 7164	8.3 h·d^{-1}	NR	175 min·wk^{-1} Moderate: 162 min·wk^{-1} Vigorous: 13 min·wk^{-1}	17%[g]	82%[d]	NR	15.2 h·d^{-1}
Kampshoff, 2016 (30)	Breast cancer Stage NR 54 [9] yr	Cross-sectional $n = 180$	Completed primary cancer treatment	ActiTrainer	NR	Activity Counts: 252.3		NR	NR[e]	NR	NR
Lawrence, 2017 (31)	Colorectal cancer Stage I to IV 69 [8]	Cross-sectional $n = 36$	NR	Actigraph GT3X	Median 339 min·d^{-1}	NR	Median 51 min·d^{-1}	NR	86%[d]	6.7 d	NR
Lewis, 2017 (32)	Bowel cancer Dukes stage A-C 68 [7] yr	Cross-sectional, $n = 58$	Posttreatment	Actigraph GT3X	3919 min·wk^{-1}	NR	Total MVPA: 120 min·wk^{-1} In bouts ≥10 min: 53 min·wk^{-1}	NR	90%[d]	NR	NR
Loughney, 2017 (33)	Rectal cancer Locally advanced 64 [45–82][b] yr	Nonrandomized, intervention, $n = 33$	Pretreatment	SenseWear Pro armband	NR	Total PA: 61 min·d^{-1}[h]		NR	NR[e]	NR	NR
Lowe, 2013 (34)	Mixed diagnoses Metastatic 55 [6] yr	Prospective case series, $n = 3$	NR (individual data only)	activPAL	NR (individual data only)	NR (individual data only)	NR (individual data only)	NR	100%[f]	NR	NR
Lowe, 2014 (35)	Brain metastases Metastatic 64 [10] yr	Cross-sectional, $n = 31$	Completing or completed whole brain radiotherapy	activPAL	20.2 h·d^{-1}	2 h·d^{-1}	0.9 h·d^{-1} stepping	NR	84%[a]	Range, 3–7 d	NR
Lynch, 2010 (36)	Breast cancer Stage NR 69 [16] yr	Cross-sectional, $n = 111$	NR	Actigraph 7164	9.3 h·d^{-1}	4.5 h·d^{-1}	3.7 min·d^{-1}	NR	NA[f]	NR	NR[f]
Lynch, 2011 (37)	Prostate cancer Stage NR 75 [7] yr	Cross-sectional, $n = 103$	NR	Actigraph 7164	9.9 h·d^{-1}	4 h·d^{-1}	6 min·d^{-1}	NR	NA[f]	NR	NR[f]
Maddocks, 2012 (38)	Lung cancer Advanced 66 [9] yr	Cross-sectional, $n = 84$	No chemotherapy or radiotherapy	activPAL	19.7 h·da^{-1}	3.3 h·d^{-1} standing	1.1 h·d^{-1} stepping	NR	NR[e]	NR	NR
Maeda, 2016 (39)	Lung cancer Stage I to II 72 [8] yr[b]	RCT, $n = 19$	Presurgery	Actimarker EW4800 P-K	214 min·d^{-1}[h]	214 min·d^{-1}[h]	16 min·d^{-1}[h]	NR	NR[e]	NR	NR
Marinac, 2015 (40)	Breast cancer Stage I to III 63 [7] yr	Cross-sectional, $n = 136$	Postdiagnosis	Actigraph GT3X[b]	510.4 min·d^{-1}	550.6 min·d^{-1}	21.1 min·d^{-1}	NR	99%[a]	NR	NR[f]
Mazzoni, 2017 (41)	Breast cancer Stage NR 58 [11] yr	Cross-sectional, $n = 84$	Postsurgery and preadjuvant treatment	SenseWear Armband Mini	713 min·d^{-1}	NR	Moderate: 41 min·d^{-1} Vigorous: 2 min·d^{-1}	NR	96%[a]	NR	NR

Phillips, 2015 (42)	Breast cancer Stage 0 to IV 56 [9] yr	Cross-sectional, $n = 500$	NR	Actigraph GT1M	553.4 min·d^{-1}	Light = 202.9 min·d^{-1} Lifestyle = 64.3 min·d^{-1}	MVPA = 22.5 min·d^{-1} Moderate = 20.9 min·d^{-1} Vigorous = 1.5 min·d^{-1}	43.3%	88%[d] Of these 95% with valid wear ≥3 d	6.8 d	NR[f]
Pinto, 2005 (43)	Breast Stage 0 to II 53 [10] yr[h]	RCT, $n = 86$	Posttreatment	Caltrac	NR	NR	Moderate: 76.1 min·wk^{-1}[h] Vigorous: 0.7 min·wk^{-1}[h]	NR	NR[e]	NR	NR
Pinto, 2015 (44)	Breast cancer Stage 0 to III 56 [10] yr	RCT, $n = 76$	On treatment	Actigraph GT3X	NR	NR	13.4 min·wk^{-1}[h]	25.6%[h,i]	NR[e]	NR	NR
Rogers, 2015 (45)	Breast cancer Stage I to IIIA or DCIS 55 [9] yr	RCT, $n = 222$	Postprimary treatment	Actigraph GT1M or GT3X	NR	NR	178 min·wk^{-1}*	49.8%*	NR	NR	NR
Rogers, 2009 (46)	Breast cancer Stage I to IIIA 53 [9] yr	RCT, $n = 41$	On hormonal therapy	Actigraph GT1M	NR	NR	Moderate: 14.2 min·d^{-1}[h] Vigorous: 0.2 min·d^{-1}[h]	35%[h]	NR[e]	NR	NR
Ruiz-Casado, 2014 (47)	Mixed diagnoses Nonmetastatic 54 [11] yr	Cross-sectional, $n = 180$ (cancer)	Postprimary treatment	Actigraph GT3X	548 min·d^{-1}	228 min·d^{-1}	MVPA: 49 min·d^{-1} Moderate: 48 min·d^{-1} Vigorous: 1 min·d^{-1}	94%[c]	93%[a] 88%[d]	NR	NR[f]
Sabiston, 2014 (48)	Breast cancer Stage I to III 55 [11] yr	Prospective, $n = 199$	Postprimary treatment	Actigraph GT3X	647.5 min·d^{-1}	NR	16.3 min·d^{-1}	29%	NA[j]	Median 7 d Range 4–7 d	NR
Skender, 2015 (49)	Colorectal cancer Stage I to IV 61 [16] yr	Prospective, $n = 198$	Postsurgery	Actigraph GT3X[b]	NR	NR	38.7 min·d^{-1}	NR	83%[d] Of these 95% with valid wear ≥7 d	NR	NR
Sloane, 2009 (50)	Breast and prostate cancer *In situ*, localized or regional 58 [10] yr	Cross-sectional, $n = 139$	Postdiagnosis	RT3 Triaxial	NR	NR	227.8 min·wk^{-1}	16%	~85%[d]	5.7 d	NR
Timmerman, 2015 (51)	Mixed diagnoses Stage NR 57 [10] yr	Cross-sectional, $n = 18$	Posttreatment	MTx inertial 3-DMotion Sensor	NR	Mean daily activity level: 1108 counts per minute		NR	78%[d]	94% of all possible measurement days included	NR
Tonosaki, 2014 (52)	Breast cancer Stage I to III 50 [10] yr	Prospective, $n = 31$	On treatment	Panasonic EW-4800	Days 2–7 = 189 min·d^{-1}	Days 2–7 = 310.7 min·d^{-1}	Days 2–7 = 23.3 min·d^{-1}	NR	NR[e]	NR	NR
Vallance, 2014 (53)	Colon cancer Stage I to III 64 [10] yr	Cross-sectional, $n = 197$	Posttreatment	Actigraph GT3X[b]	527.9 min·d^{-1}	310.6 min·d^{-1}	Total: 28.5 min·d^{-1} In bouts ≥10 min: 8.8 min·d^{-1}	16%[c]	NR[e]	6.6 d	867 min·d^{-1}
Van Blargain, 2017 (54)	Prostate cancer Stage T1c–T2a Median 66 yr	Cross-sectional, $n = 22$	On active surveillance	Actigraph GT3X[b] and Fitbit	NR	Actigraph: 125 min·d^{-1} Fitbit One: 190 min·d^{-1}	Actigraph: 51 min·d^{-1} Fitbit: 100 min·d^{-1} Moderate: Actigraph: 47 min·d^{-1} Fitbit: 81 min·d^{-1} Vigorous: Actigraph: 4 min·d^{-1} Fitbit: 19 min·d^{-1}		96%[a] 92%[d]	5.8 d	NR

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TABLE 1. *(Continued)*

Author	Study Population/ Average Age	Study Design/ Sample Size	Timing of Observation	Device	Physical Activity Participation					Wear Time
					Sedentary Time or Sitting/Lying	Light Intensity Time or Standing	MVPA Time or Stepping	Participants Meeting PA Guidelines (%)	Compliance	No. Valid Days	
van Roekel, 2016 (55)	Colorectal cancer Stage I to III 70 [9] yr	Cross-sectional, $n = 155$	Postdiagnosis	MMOXX1	Total = 10.2 h·d^{-1}	Total = 3.4 h·d^{-1}	Total = 1.7 h·d^{-1}	NR	97%[a] 99%[d]	6.8 d	15.3 h·d^{-1}
Vassbakk-Brovold, 2016 (56)	Mixed diagnoses Stage I to IV 59 [11] yr	Cross-sectional, $n = 84$	On treatment	SenseWear Armband	NR	NR	NR	48%[c]	94%[d]	3.6 d	23.7 h·d^{-1}
Yee, 2014 (57)	Breast cancer Metastatic 58 [10] yr	Cross-sectional, $n = 71$	NR	SenseWear Armband	NR	NR	82 min·d^{-1}	NR	NR[e]	NR	NR

[a]Wore device.
[b]%, Female of whole study.
[c]Guidelines calculated with 10-min bout criteria.
[d]Provided valid accelerometer data.
[e]Insufficient detail provided.
[f]Adjusted data for waking wear time.
[g]≥30 min·d^{-1}.
[h]Intervention group.
[i]Participants only included in analysis/study if provided valid accelerometer data or completed the intervention/study.
[j]Only reported postintervention.
DCIS, ductal carcinoma *in situ*.

The current physical activity guidelines for cancer survivors [i.e., ≥ 150 min of MVPA per week (63)] were applied in 38% of studies. Seven studies specified that MVPA must occur in 10-min bouts (13,14,16,21,47,53,56), and two specified that activity must occur on at least 5 d out of 7 d of the week (16,29). In studies that applied the guidelines, the percentage of participants meeting current physical activity guidelines for cancer survivors ranged from 4% (16) to 94% (47).

Quality of reporting on data collection and processing. Quality of accelerometer reporting for data collection and processing-related items is outlined in Figure 1. Additional information regarding data collection and processing-related items is available in Supplemental Table 1 (Supplemental Digital Content 2, description of accelerometry data analysis methods, http://links.lww.com/MSS/B280) and Supplemental Table 2 (Supplemental Digital Content 3, summary of methods used in accelerometer-based studies, http://links.lww.com/MSS/B281). Accelerometer data collection-related items were generally well reported and included accelerometer brand and model (100%), monitor placement (91%), and wear protocol (98% for number of days; 91% for hours per day). Delivery method was the exception, with only 54% of studies reporting this information.

In contrast, accelerometer data processing-related items were generally poorly reported, particularly the definition of non–wear time (reported by 51% of studies), filters applied during processing (reported by 8% where applicable), valid day definition and minimum number of valid days (reported by 62% and 57% of studies, respectively), software and epoch length for processing the accelerometer data (53% and 61% respectively), and vectors used during processing (reported by 60% where applicable). The most reported data processing-related items were cut points used to define sedentary time (87%) and MVPA (91%). Device-specific software was most commonly used to process accelerometer data (40% of all studies), and just over half of the studies (54%) reported processing the accelerometer data using 60-s epochs.

Compliance was not reported in sufficient detail in 17 studies; three were not applicable as participants and were only included in the study if they had provided valid accelerometer data (36,37,48). Compliance with accelerometer wear ranged from 74% (24,27) to 99% (40). The average (or median) number of valid days of data was reported in 13 studies. A minimum wear-time criterion of 600 min was the most common (40%). A variety of criteria were used to define non–wear time and minimum number of valid days. When reported, this ranged from 3.6 (56) to 7.0 d (12,48). Wear time was reported in 10 studies and ranged from 14.1 h·d^{-1} (21) to 23.7 h·d^{-1} (56). Nine studies did not report wear time, but did adjust analysis for wear time.

DISCUSSION

In our review, we identified accelerometer studies in cancer survivor populations differed in how they defined and reported on sedentary behavior and physical activity. With

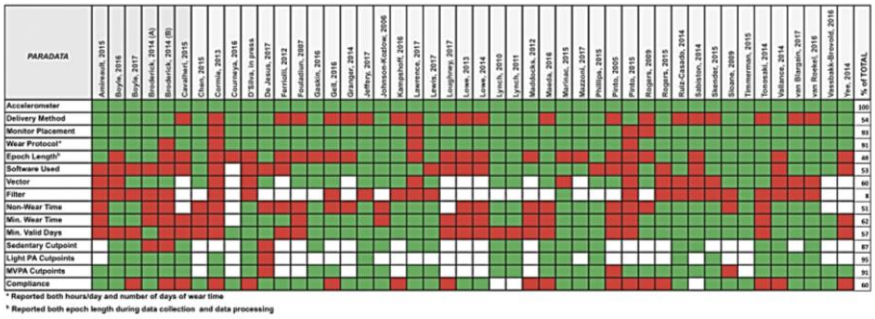

FIGURE 1—Percentage of accelerometer paradata items reported (n = 46). *Green cells*, reported; *red*, not reported; *white*, NA.

regard to the quality of reporting on data collection and processing methods, data collection-related items were reported in the majority of studies, whereas data processing-related items were described in a smaller proportion of studies.

Accelerometry has potential to generate detailed knowledge of the levels and patterns of physical activity and sedentary behavior in cancer survivors. It also provides opportunities for the investigation of associations between physical activity and sedentary behavior with health outcomes (including clinical outcomes such as fatigue, mortality, and recurrence), and insight on how cancer treatments impact engagement in physical activity and sedentary behavior. Accelerometry research can contribute to identifying minimal clinically important differences in physical activity and sedentary behavior, as well as the specific characteristics of what amounts of physical activity (or reductions in sedentary behavior) are needed to facilitate improved cancer outcomes. Accelerometry output can also be translated into meaningful messages for cancer survivors (i.e., convert metrics into behavior targets for patients). The decreasing cost of accelerometers and increasing access to open-source data extraction and processing methodologies will make it easier to integrate objective activity monitoring into cancer survivor studies (64). However, to achieve beneficial health outcomes in oncology and public health, carefully considered data processing and reporting decisions must be made.

In comparison to a recent review by Montoye et al. of accelerometer-based intervention studies in the general population (10), a similar percentage of studies in our review failed to report on epoch length (36% [present study] vs 38%), days of data collected (9% vs 2%), minimum valid days (52% vs 44%), and brand of accelerometer (0% vs 2%). However, we found that the cancer survivorship literature reported fewer studies failing to report compliance (40% [present study] vs 64%), delivery method (46% vs 69%), non–wear time definition (49% vs 69%) and minimum wear time (38% vs 50%). One possible reason for this difference is that the earliest study included in our review was published in 2005, whereas the Montoye review included studies dating back to 1998, before standards/checklists of accelerometry data collection and reporting had been published. Overall, the completeness of reporting on methods used to collect, process, and report accelerometry data in cancer survivor studies needs improvement. A formal consensus process for internationally agreed standards for accelerometer data collection, processing, and reporting has been suggested to help address such limitations (65). However, such guidelines have not yet been developed and published. Therefore, as in other recent reviews (9,10), we recommend that authors report all data collection and processing-related accelerometer paradata (in the main text and/or as supplementary material) to ensure that data can be accurately compared across studies and that others are able to replicate their methods. Examples of adequate reporting of accelerometer paradata and a template for reporting paradata are available in the recent review by Montoye et al. (10). Guidance related to data collection and data processing decisions relating specifically to Actigraph® devices, which were used in 54% of the studies included in the present review, are available in a recent review by Migueles et al. (9).

Three quarters of the studies included in this review used cut points to summarize accelerometer data into discrete variables (e.g., sedentary behavior, MVPA). The most commonly used cut points across studies of cancer survivors were <101 counts per minute for sedentary behavior (59) and >1952 counts per minute for MVPA (61). Although the widespread adoption of these particular cut points allows comparison across studies (provided data collection and processing protocols are comparable), their use requires careful consideration in cancer survivor research. The same "intensity" measured by an accelerometer will impart a different level of physiological stress on different people. The commonly used >1952 counts per minute cut point for MVPA was developed by Freedson et al. (61) based on indirect calorimetry data collected during treadmill activities in a group of university students with a mean age 24 yr. In the current review, the mean age of participants ranged from 50 (52) to 73 (19). Cancer survivors are often older, have comorbid conditions as well as ongoing cancer-related side effects, that impact functional capacity. Therefore, cut points developed from young healthy volunteers may not be

representative of physiologically "light" or "moderate" intensity activity in cancer survivor populations. Thus, consideration of accelerometer cut point algorithms validated for specific cancer survivor populations (and subpopulations) will be important (9). When appropriate, using the total volume of physical activity could also allow comparisons to be made across studies, while avoiding some of the issues of generic application of cut points which could be problematic in certain cancer groups (e.g., advanced cancer or those on treatment). When cut points are applied, we recommend authors acknowledge that there may indeed be limitations of this approach and should be mindful to justify their choice of cut points.

Almost 40% of the studies reviewed here report the percentage of survivors that were meeting current physical activity guidelines (e.g., 150 min·wk^{-1} of MVPA). Recent studies have highlighted some concerns with using accelerometer-measured MVPA to classify individuals as sufficiently active based on public health guidelines, and it has been argued that there may be situations where it is preferable to consider the total volume of physical activity rather than simply MVPA (66). These concerns could be particularly salient for cancer survivors who often face functional limitations and ongoing side effects of disease and treatments that could impact functional capacity. For example, an individual may have functional/mobility issues, or a particular tumour (e.g., lung), stage (e.g., stage IV), and/or treatment regime (e.g., lung resection resulting in reduced pulmonary capacity) that precludes participation in what accelerometers categorize as MVPA. Thus, the application of physical activity guidelines (developed in a young and healthy population) may not be appropriate. Development of cancer population-specific (or functional state-specific) physical activity guidelines could help with this issue and would also add value to oncology care, by providing more specific guidelines for survivors and cancer care professionals. Additionally, the development of minimal clinically important differences for these populations could assist with interpreting a meaningful change in physical activity and sedentary behavior levels beyond the application of physical activity guidelines. Further research into this area will help determine the optimal strategies to determine whether cancer survivors are achieving sufficient levels of MVPA to confer health benefits. We recommend that authors carefully consider the use of physical activity guidelines as an outcome measure, and when used, the rationale for including this outcome should be articulated and the limitations of this approach acknowledged.

The most commonly used device in the studies included in our review was the Actigraph®, with the majority of these studies using a waist placement. Used in this manner, the Actigraph® device is not able to differentiate between sitting and standing. Although some standing activities (standing quietly) require little to no movement (<101 counts per minute) and low-energy expenditure (<1.5 METs), they are not considered sedentary behaviors because the individual is not in a seated posture. For an individual standing still, the Actigraph® will record the subject as engaging in sedentary time (i.e., <101 counts per minute or <1-5 METs). This issue is likely to be exacerbated in populations, which may have high amounts of sedentary time, such as people with advanced cancer. This has implications for assessing interventions designed to reduce sedentary behavior (i.e., sitting time). Only 10% of studies reviewed here used thigh-worn accelerometers, which have higher accuracy when measuring sitting and reclining than waist or wrist worn accelerometers. However, it is important to note that thigh-worn devices are less accurate in capturing activities involving primarily upper body motion (e.g., rowing, upper body resistance training). Although the choice of device and body placement is dependent on several issues such as the study aims, cost, and availability, future studies with a primary focus on sedentary behavior should consider the use of devices which are able to better differentiate between sitting and standing (e.g., activPAL™).

Although accelerometers offer many advantages over self-reported measures, they do have important limitations. For example, accelerometers do not capture cycling or water-based activities, and they do not detect the context within which physical activity or sedentary behaviors are occurring (e.g., transport, occupational, screen time). In contrast, self-report measures are important for providing the context in which activities are occurring; depending on the self-reported measures used, distinction can be made between transport-related sedentary time and leisure sedentary time (e.g., screen-based), and planned/intentional activity and occupational activity. Thus, we recommend continued use of self-report measures of physical activity and sedentary behavior to complement objective assessment. Current ongoing research initiatives are using both devices as well as self-report measures for a complete assessment of the full activity spectrum (20).

The majority of studies (65%) reported collecting accelerometer data during waking hours. Even in studies that collected 24-h data, often only waking hours are reported (28). Across a 24-h period, individuals engage in a combination of sleep, sedentary behaviors, and physically active behaviors (of light, moderate or vigorous intensity), and recent research has considered these behaviors together rather than in isolation. New statistical techniques, such as compositional analyses or isotemporal substitution modeling, may help generate a clearer understanding of the dynamic interplay between movement behaviors measured during waking hours or the entire day (67). For example, isotemporal substitution modeling allows the researcher to explore associations of alternating allocations of time in one behavior with another while holding total time constant (68,69). Studies in the cancer survivorship context have used this approach to examine the reallocation of time and the projected impact on outcomes such as health-related quality of life, fatigue, and waist circumference (55,70,71). Continued use of new and innovative statistical approaches will help inform intervention research in cancer survivor populations.

CONCLUSIONS

The use of accelerometer-based activity monitors has improved understanding of the spectrum of physical activity and sedentary behavior undertaken in clinical and free-living environments by cancer survivors. However, the specific frequency, intensity, and duration of physical activity (or sedentary behavior) required to improve cancer outcomes remains unknown. The continued expansion of accelerometry in cancer survivor research will help to address these gaps in knowledge and inform more robust and detailed physical activity recommendations for cancer control. However, adequate reporting of accelerometer paradata is needed so that we can more precisely inform physical activity and sedentary behavior recommendations to health care professionals, stakeholders, and patients.

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The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM.

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Appendix B Resistance exercise training improves physical functioning and body composition in patients with malignant pleural disease.

Peddle-McIntyre CJ, Jeffery E, Lee YCG, Nowak A, McVeigh J, Nguyen B, Fitzgerald D, Straker L, Newton RU.

Resistance exercise training improves physical functioning and body composition in patients with malignant pleural disease.

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Abstract

Purpose: To investigate the feasibility and efficacy of exercise to improve muscular strength, physical functioning, body composition, and patient-rated outcomes in patients with malignant pleural disease (MPD).

Methods: Thirty-three patients with MPD were recruited to complete an exercise training intervention of progressive resistance exercise training three times/week for six-weeks. Outcomes assessed at baseline and post-intervention included muscular strength (1-repetition maximum leg press), functional capacity (6-Minute Walk Test), physical functioning (Timed Up and Go; chair rise), body composition (Dual energy X-ray Absorptiometry), quality of life (Short-Form 36 Health Survey; SF-36), physical activity and sedentary behaviour (Actigraph accelerometer), ratings of intervention burden and acceptability (7-point Likert scale; 1, not at all, to 7, very much). Attendance was assessed as the number of exercise sessions attended out of a possible 18. Paired T-test or Wilcoxon Signed Rank Test was used to assess changes over time.

Results: Mean participant age was 64 (SD=11) years. The majority had mesothelioma (93%), Eastern Cooperative Oncology Group Performance Status 0-1 (97%), and were male (70%), and had low appendicular skeletal muscle mass (56%). Twenty-six participants (79%) completed the intervention; 24 (73%) completed post-intervention assessments. Post intervention, significant improvements were found for mean six-minute walk distance (+59 m; 95% CI 24-93; $p<0.05$), 1-repetition maximum leg press (+17 kg; 95% CI 11-23; $p<0.001$), Timed Up and Go (-0.51 sec; 95% CI -0.94 - -0.08; $p<0.05$), chair rise (-1.5 sec; 95% CI -2.2 - -0.9; $p<0.001$), and appendicular lean mass/height squared (+0.19 kg/m2; 95% CI 0.04 – 0.34; $p<0.05$).

For patient-rated outcomes, only the mental health subscale of SF-36 changed significantly (median change +2.6, IQR 0.0, 5.2; $p<0.05$). Overall, no post-interventions changes in activity behaviors were observed (all p's >0.05). Preliminary analysis indicates that changes in body composition might mediate this response. Median attendance at supervised exercise was 100% (inter-quartile range 72%-100%).

Conclusion: This pilot study indicates progressive resistance exercise training in patients was feasibly in MPD and resulted in improvements in muscular strength, physical functioning and body composition.

B.1 Introduction

Despite medical advances, malignant pleural disease (MPD) remains an incurable cancer with limited treatment options. Pleural malignancy can result from primary cancer (i.e., mesothelioma), or from metastatic spread of cancer into the pleural space (common in breast, lung, and ovarian cancer).[1] The pleural effusion causes distressing breathlessness, restricts daily activities, impairs quality of life (QoL), and can be recurrent.[1] The main goals in the treatment of MPD are to alleviate symptom burden and allow patients to take part in their nomal physical activities of daily living for as long as possible.

In MPD, poor performance status, or immobility, is often clinically attributed to symptoms such as breathlessness, pain, fatigue and muscle wasting. Evidence suggests that patients with MPD are very inactive, spending the large majority of their waking hours sedentary.[2] Even amongst patients early in their diagnosis with good performance status, low appendicular skeletal muscle mass (ASM) is common and is associated with reduced participation in daily physical activity.[3] Muscle loss is a hallmark feature of cancer cachexia that severely impacts quality of life, physical functioning, and treatment tolerance. In advanced cancer populations, low muscle mass has been associated with poorer quality of life,[4] worse overall survival,[5] and increased likelihood of dose-limiting toxicities from chemotherapy.[6]

Appropriately prescribed exercise provides a significant opportunity to counteract this aetiology of poor outcomes for patients with MPD. In advanced lung cancer, exercise training has shown promise for increasing functional capacity and health-related quality of life.[7] However, there is little evidence to date on the effects of exercise on body composition in this group.[7] The purpose of this study was to assess the feasibility and efficacy of a 6-week resistance exercise training intervention for improving physical functioning, body composition, and physical activity profile in patients with MPD.

B.2 Methods

B.2.1 Participants

People with cytological or histological confirmation of MPD or those with a recurrent large exudative pleural effusion with cytological or histological proven cancer outside the thorax with no alternative cause were eligible to participate in the intervention. Potential participants were excluded if they were aged <18 years, pregnant or lactating, unable to

read and understand English, unable to give informed consent or comply with the protocol, had unstable bone metastasis or metastasis of long bones, had acute illness or any musculoskeletal, cardiovascular, or neurological disorder that could inhibit or put participants at risk from participating in assessments or exercise intervention, were unable to obtain physician consent, or were participating in a conflicting study.

B.2.2 Design and recruitment

The study was a single group pilot intervention study. Ethical approval was provided by Sir Charles Gairdner Group and Edith Cowan University Human Research Ethics Committees (ID: 2014-124 and 13255). Recruitment took place between September 2015 and July 2017 in a tertiary specialist pleural disease and medical oncology clinic in Western Australia (WA).

B.2.3 Exercise training intervention

Supervised exercise sessions were scheduled to be completed three times a week for 6-weeks. An optional two-week make-up period was provided for participants who chose to make up sessions with the goal of completing 18 exercise training sessions. Exercise sessions began with a 5-minute warm up comprising of low-level aerobic activity such as walking and stationary cycling. The resistance training involved eight resistance exercises that targeted the major upper and lower body muscle groups (e.g., chest press, seated row, leg press, leg extension). Resistance was increased by a 5-10% increment for the next set/training session if participants were able to perform more repetitions than specified during a set. Intensity was manipulated from 8-12-repetition maximum (RM) using 1-3 sets per exercise, with 1-2 minute rest periods between sets.[8] Due to the advanced nature of MPD, the potentially high symptom burden, and changes in participant status due to treatment the exercise intervention was designed to be flexible with adjustments made as required. To achieve this, at the start of every exercise training session, participants were asked to rate their current level of pain (Visual Analog Scale; VAS; no pain/very severe pain), describe any changes in shortness of breath, fatigue, or new symptoms since their previous training session. It was then discussed between the exercise physiologist and participant if the planned exercise program required any changes to the volume, intensity, or rest periods.

B.2.4 Outcome Measures

Demographic and medical variables

Self-report questionnaires were used to obtain demographic information (e.g., marital status, education level, employment status, smoking status). Medical records and chest x-rays were reviewed to obtain data regarding cancer diagnosis, pleural effusion characteristics, cancer treatments, and comorbid conditions. Eastern Cooperative Oncology Group (ECOG) performance status was rated on the day of baseline assessment.[9] Patients were categorised as either good performance status (i.e., ECOG 0-1) or poor performance status (i.e., ECOG ≥2).

Physical functioning

All study endpoints were assessed at baseline and post-intervention. Participants completed a series of tests to assess different aspects of physical functioning. Muscular strength was assessed by 1 RM for lower body using a seated leg press.[10] Lower body 1RM was divided by current body weight to determine relative 1RM. Cardiorespiratory functional capacity was assessed by Six-Minute Walk Test (distance in metres).[11] Participants were asked to walk as far as possible on a flat 50 m course in six minutes.[12] Functional ability was assessed via repeated chair rise (time in seconds taken to rise from seated and return to sitting ten times)[13] and Timed Up-and-Go (TUG; time in seconds required to rise from sitting, walk a distance of 2.44 metres, turn around and return to sitting).[14] Chair rise and TUG were performed in triplicate with one minute rest-periods provided between trials, with the best outcome (i.e., the shortest time) used in analysis. Participants were grouped according to change in leg strength from baseline to post-intervention as gained (change ≥10%), and lost (change <10%). Participants were also grouped for Six-Minute Walk Distance (6MWD) using a cut point of a 9.5% change post intervention as this is considered a clinically meaningful difference.[15]

Anthropometric measures and body composition

Participant weight and height were measured at baseline. Participants were wearing light clothing and footwear was removed. Body mass index (BMI; kg/m^2) was calculated, and participants were categorised according to World Health Organization (WHO) BMI criteria.[16]

Body composition (i.e., regional and whole-body lean and fat mass) was derived from whole-body dual-energy x-ray absorptiometry scans (DXA; Hologic Discovery A, Waltham, MA, USA). Appendicular skeletal muscle (ASM), whole body and regional fat mass were assessed using standard procedures.[3] Low ASM, was defined as an appendicular skeletal muscle mass/height^2 of ≤7.26 kg/m^2 for males and ≤5.45 kg/m^2 for females.[17] Participants with low ASM were categorised as pre-sarcopenic.[18] All participants were grouped according to change in ASM from baseline to post-intervention as gained (change >0.05 kg), and lost (change ≤ 0.05).

Physical activity and sedentary behavior

Objective activity behaviour was assessed via accelerometer (Actigraph GT3X+; Actigraph, Pensacola, FL, USA) the three-days prior to and following the intervention at baseline and post-intervention respectively. Participants were asked to wear the accelerometer on their hip continuously (24hr/day) for three-days and record any non-wear time over that period. Accelerometers were programmed to record raw data at a frequency of 30 Hz, which were later reduced to vertical axis movement counts per 60-second epoch. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA). Waking wear time was determined by an automated algorithm and visual inspection by a trained rater.[19] A valid day was defined as 8hr of waking wear time.[20] Commonly used cut off points were used to classify activity as sedentary time (i.e., <100 counts/minute; cpm), light activity (i.e., 100-1952 cpm) or moderate to vigorous physical activity (MVPA; >1952 cpm).[21,22] All variables were calculated per day and then averaged across all valid days.

Patient-reported Outcome Measures

Patient-reported outcome measures were assessed using a battery of validated questionnaires. Cancer-specific health-related QoL (HRQoL) and symptoms were assessed by the Functional Assessment of Chronic Illness Therapy (FACIT) General,[23] and Fatigue [24] scales. A score of ≤34 on the FACIT-Fatigue was categorised as clinically meaningful fatigue.[25] General HRQoL was assessed by The Medical Outcomes Study Short-Form 36 (SF-36).[26] Dyspnea was assessed using the Cancer Dyspnea Scale (CDS)[27] and 100 mm visual analogue scale (VAS) anchored with “no breathlessness” at 0mm and “maximum possible breathlessness” at 100mm.[28]

Safety, tolerance, and attendance

Safety was measured by tracking the incidence and severity of adverse events related to the intervention. Additionally, an adverse events log was provided to participants to document any adverse events experienced throughout the exercise program. An additional home diary was used to self-report any adverse events that took place at home (e.g., muscle soreness). Following each exercise session participants were asked to rate their perceived exertion using the Borg Scale (range 6-20)[29] as well as session tolerance using a 7-point Likert scale (anchored with '1/extremely intolerable' and '7/extremely tolerable').[30] Ratings of intervention burden and acceptability were assessed post-intervention using 7-point Likert scales (anchored with '1/not at all', and '7/ very much').[31] The number of participants completing the intervention (i.e., attending baseline and post-intervention assessment), as well as the number of exercise sessions attended was recorded. Attendance was reported as the percent of sessions attended out of a possible 18.

B.2.5 Statistical analyses

Statistical analyses were conducted using Statistical Package for the Social Sciences (v. 25, IBM Corporation, Somers, NY, USA). Data are reported using mean and standard deviation or median and interquartile range (IQR) when not normally distributed. Normality of the distribution for outcome measures was tested using the Kolmogorov–Smirnov test. Changes in physical functioning, body composition, quality of life were assessed using paired t-tests. Independent t-tests were used to test for differences between groups in physical activity and sedentary time. The change in the proportion of participants categorised as pre-sarcopenic was assessed using the McNemar test. This was a pilot feasibility study. Therefore, due to the nature of the intervention and variation in ability to complete tests, we used complete cases for the analyses. An alpha of 0.05 was used to determine statistical significance. No adjustment was made for multiple comparisons. Figures were created using GraphPad Prism (version 7, GraphPad Software, La Jolla, California, USA).

B.3 Results

B.3.1 Participant characteristics

Participant flow through the trial is reported in Figure B.1. Briefly, between September 2015 and July 2017, 137 patients with MPD were identified, of whom, 118 (86%) were eligible and 33 (28%) of those enrolled. The main reason for ineligibility was choosing an

alternate conflicting study (n=15), and the main reason for non-enrolment was living too far away from the intervention site (n=27). Twenty-six participants (79%) completed the intervention. Of those enrolled, seven were lost-to-follow up, the main reason cited by participants for dropout was fatigue (n=4).

Participant medical and demographic characteristics are presented in Table B.1. The majority of participants were male (67%), with a diagnosis of mesothelioma (85%), and a good performance status (i.e., ECOG 0-1; 97%) and had received some treatment for pleural effusion (82%). On average, participants were 66 years old (SD 10.0), and half were overweight or obese (54%). Thirteen participants (39%) received anticancer treatment prior to entering the trial, while 11 (33%) received treatment during the intervention. Median time from diagnosis of MPE was 6 months. At baseline, 19 participants (58%) had low appendicular skeletal muscle mass, and 7 participants (23%) were clinically fatigued.

B.3.2 Changes in physical functioning and QoL

Those that completed the intervention demonstrated significant improvements across all measures of physical functioning (all <0.002; Table B.2, Figure B.2). Only the mental component score of the SF-36 changed significantly following the intervention (p=0.022). All other outcomes showed no significant change following the intervention (Table B.2).

B.3.3 Changes in body composition

Changes in body composition following the intervention are reported in Table B.2. Following exercise training there was a significant increase in ASM, [mean change 0.66, (95% CI 0.20, 1.12) kg; p=0.007], and ASM relative to height [mean change 0.19, (95% CI 0.05, 0.34) kg/m^2; p=0.011]. Among those that completed the intervention (n=26), there was a significant change in the proportion of participations that had pre-sarcopenia from baseline (54%) to post-intervention (27%; p=0.039). Following the intervention, 52% remained not sarcopenic (n=11) with an average change of +0.16 (SD 0.30) kg in ASM; 31% (n=8) became not sarcopenic with average increase 0.30 kg ASM (SD 0.19). While, 23% (n=6) remained pre-sarcopenic with mean change of 0.10 kg ASM (SD 0.42), and 4% (n=1) became sarcopenic (change -0.35 kg).

B.3.4 Changes in physical activity behaviours and sedentary time following exericse training

There was no significant change from baseline to post-intervention in accelerometer waking wear time [mean difference 19.9, 95% CI (-25.12 – 64.98) min; p=0.369], or number of valid days of wear (z=-1.633, p=0.102). Overall, between baseline and post-intervention there was no change in the proportion of waking wear time spent as sedentary [67.9 (SD 9.5)% to 67.4 (SD 9.6)%; mean difference -0.4, 95% CI (-3.4 – 2.5)%; p=0.765], in light activity [29.1 (SD 9.6)% to 30.2 (SD 8.8)%; mean difference 1.1, 95% CI (-1.8-4.0)%; p=0.441) or MVPA [3.1(SD 2.5)% to 2.4(SD 2.4)%; mean difference -0.7, 95% 95% CI(-1.5-0.2)%; p=0.122].

B.3.5 Physical activity and sedentary behavior according to changes in body composition, muscular strength, and functional capacity.

Changes in physical activity were examined to determine if they differed based on response to the exercise intervention. Post-intervention, participants with a loss or no change in ASM (n=8) demonstrated an increase in the proportion of waking hours spent as sedentary [+5.1 (SD 6.5)%] compared with those that gained ASM [n=14; -3.4 (SD 6.2)%] resulting a significant difference between groups [mean difference 8.5, 95% CI(3.3, 13.7)%; p=0.003]. Those that lost ASM demonstrated a reduction in light activity (-3.8% SD 6.2) compared to those that gained ASM [+3.8 (SD 5.8)%], resulting in a significant difference between groups [mean difference -7.6 95% CI(-13.0% - -2.1)%; p=0.009]. There was no statistically significant difference between groups for changes in MVPA [+1.9 (SD 3.2)% vs +5.5 (SD 8.1)%; mean difference -3.6, 95% CI(-9.9 – 3.7)%; p=0.244; Figure B.3].

Within group changes indicate for the gain ASM group there was a significant decrease in the proportion of waking hours spent as sedentary [mean change -3.4; 95% CI(-0.5 - -2.5)%; p=0.026], an increase in light activity, [mean change 3.8; 95% CI(0.5 – 7.1)%; p=0.028], but no change in MVPA [mean change 0.4; CI(-1.8 – 1.0)%; p=0.583]. Conversely the loss or no change of ASM group increased sedentary time [mean change 5.1; 95% CI(-0.4 - -10.5)%; p=0.064], with no significant change in light activity [mean change -3.8; CI(-8.9 – 1.4)%; p=0.131], and reduced MVPA [mean change -1.3; 95% CI(-2.1- -0.5)%; p=0.006].

We examined differences in physical activity and sedentary behaviour outcomes by change in strength (leg press 1RM, >10% vs ≤ 10%) and a clinically meaningful change in functional capacity (6MWD, >9.5% vs ≤ 9.5% change). There were no significant differences between those with ≤ 10% increase from baseline 1RM (n=6) and those with >10% increase from baseline 1RM (n=14). Both 1RM groups had a similar change in the proportion of time spent sedentary [0.1 (SD 7.7)% vs -0.4 (SD 7.2)%; mean difference 0.6 95% CI(-7.0, 8.1)%; p=0.874], in light activity [-0.1 (6.5)% vs. 1.1 (7.0)%; mean difference 1.2 (-8.2, 5.0)%; p=0.735], or MVPA [4.2 (5.8)% vs 5.3 (7.2)%, mean difference 1.1 (-8.1, 6.0)%; p=0.754]. There were no significant differences between those with >9.5% (n=8) and those with ≤ 9.5% increase from baseline 6MWD (n=12). Both 6MWD groups had a similar change in the proportion of time spent sedentary time [1.1 (SD 7.6)% vs 1.0 (SD 7.5)%; mean difference 2.0 CI(-9.0, 5.0)%; p=0.552)], light activity [1.2 (SD 6.4)% vs 0.0 (SD 7.5)%; mean difference 1.2 95% CI(-5.4, 7.7)%; p=0.714], and MVPA [5.5 (8.1)% vs 4.0 (4.1)%; mean difference 1.5 95% CI(-5.0, 8.1)%; p=0.632].

B.3.6 Patient Rated Outcomes

Following exercise training there was a significant improvement in the mental health composite score of the SF-36 (p=0.022). There were no significant changes in other patient reported outcomes following the intervention (Table B.2).

B.3.7 Safety, Tolerance and Attendance

There were no serious adverse events related to the intervention. There were two minor adverse events related to exercise reported. Both were resolved with no medical intervention required. One participant experienced a musculoskeletal injury during work (i.e., not related to the intervention). Two participants were admitted to hospital during the intervention for issues unrelated to the intervention (abdominal pain due to disease progression; and pleurodesis). Session rating of perceived exertion with the Borg scale (6-20 scale; higher score is higher exertion) was median 11.6 (IQR 11.4-12.9), perceived tolerance (1-7 scale) was median 6.0 (IQR 5.7, 6.3). For all participants enrolled, the median attendance was 100% (IQR 7-100%; range 6%-100%). The reasons provided for missed sessions included fatigue, undergoing treatment/appointments, vacation, and family obligations. The main reason given for dropping out of the study was fatigue (n=4).

Table B.1 Demographic and medical characteristics of patients, n=33

	n	%
Age, years, mean (SD)	65.7 (10.0)	
Gender, male	23	70
Marital status		
Married/de-facto	31	94
Divorced/widowed	2	6
Education Level		
Primary	4	12
Secondary (high school)	10	30
Trade/certificate/diploma	11	33
Bachelor degree or higher	8	24
Employment Status		
Retired/unemployed	29	88
Part-time/full time	4	12
Smoking status		
Never	18	55
Past smoker	9	27
Current	7	21
BMI, $kg/m^{2,}$ mean (SD)	26 (3)	
Underweight	0	0
Healthy weight range	15	45
Overweight or obese	18	55
Pre-sarcopenic[#] (DXA; n=33)	19	58
Diagnosis		
Mesothelioma	28	85
Other	5	15
Time since diagnosis of cancer, months	7 (2, 14)^	
Time since diagnosis of MPD, months	6 (3, 13)^	
Histological subtype (if mesothelioma)		
Epithelioid	19	58
Biphasic	3	9
Sarcomatoid	2	6
Desmoplastic	1	3
Unspecified	2	6

	n	%
Histological subtype (not mesothelioma)		
Adenocarcinoma	2	6
Other	2	6
Unknown	2	6
ECOG performance status 0/1	32	97
Received treatment prior to study	13	39
Chemotherapy alone	4	24
Radiotherapy	5	15
Surgery	3	9
TKI inhibitor	1	3
Chemotherapy + Immunotherapy	2	6
Chemotherapy + TKI	2	6
Received treatment during study	11	33
Chemotherapy alone	3	9
TKI	2	6
Immunotherapy alone	1	3
Chemotherapy + Immunotherapy	4	12
Side of effusion, right	24	73
Effusion treatment¤		
IPC	12	36
ICC	3	9
VATS	3	9
Therapeutic aspirate	6	18
Pleuroscopy	7	21
None	4	12
Unknown	2	6.
No. of comorbid conditions, mean (SD)	2 (2)	
Arthritis	11	33
Hypertension	9	27
Hypercholesterolemia	7	21
COPD	3	9
Ischemic heart disease	2	6
Clinically fatigued (n=30)**	7	23

IPC – indwelling pleural catheter; ICC – intercostal catheter; VATS – video-assisted thoracoscopic surgery; ECOG – Eastern Cooperative Oncology Group;
COPD – chronic obstructive pulmonary disease; ** score of ≤34 on the FACIT-fatigue; TKI Tyrosine Kinase Inhibitor

Table B.2 Changes in physical functioning, body composition, and quality of life following the intervention.

	Baseline Mean (SD)	Post-intervention Mean (SD)	Mean change (95% CI)	p-value
Physical Functioning (n=24)				
Leg press 1RM, kg	88.2 (37.7)	105.1 (42.1)	16.9 (11.2, 22.6)	<0.001
6MWD, m	524.2 (104.7)	582.7 (108.1)	58.5 (24.4, 92.5)	0.002
Chair rise, sec	12.8 (3.4)	11.3 (3.4)	-1.5 (-2.2, -0.9)	<0.001
TUG, sec	6.4 (1.9)	5.9 (1.8)	-0.5 (-0.9, -0.1)	0.022
Body Composition (n=26)				
Whole Body				
Total Mass, kg	77.78 (11.28)	78.17 (15.44)	0.39 (-0.64, 1.43)	0.443
Lean Mass, kg	49.57 (10.86)	50.18 (11.28)	0.61 (-0.08, 1.31)	0.080
Fat Mass, kg	25.82 (5.86)	25.57 (6.84)	-0.25 (-1.20, 0.70)	0.597
Fat Percentage, %	33.47 (5.63)	32.87 (6.68)	-0.61 (-1.63, 0.42)	0.235
Lean				
Trunk, kg	25.68 (5.64)	25.62 (5.53)	-0.06 (-0.50, 0.38)	0.773
ASM, kg	20.83 (5.04)	21.49 (5.63)	0.66 (0.20, 1.12)	0.007
ASM kg/m2	6.83 (1.10)	7.03 (1.25)	0.19 (0.05, 0.34)	0.011
Fat				
Body Fat Percentage, %	33.47 (5.63)	32.87 (6.68)	-0.61 (-1.63, 0.42)	0.235

	Baseline Mean (SD)	Post-intervention Mean (SD)	Mean change (95% CI)	p-value
Quality of life (n=26)				
FACT-General	83.4 (17.2)	82.6 (18.4)	-0.8	0.703
Fatigue Scale^	39.5 (34.8, 48.3)^	43.5 (27.8, 48.2)^	---	0.736
Physical Component Score (SF-36)	45.2 (11.8)	43.8 (9.8)	-1.3 (-4.9, 2.3)	0.455
Mental Component Score (SF-36)^	52.6 (37.3, 58.8)^	55.4 (47.8, 59.6)^	---	0.022
Dyspnea				
VAS (mm)^	12.5 (1.1, 36.3)^	5.0 (0, 22.5)^	---	0.277
CDS Total^	3.5 (0, 10)^	3.0 (0.5, 10.5)^	---	0.897

6MWD, Six Minute Walk Distance; m, metres; sec, seconds; kg, kilograms; ht, height; ^ Median, IQR; VAS, Visual Analogue Scale; CDS, Cancer Dyspnea Scale

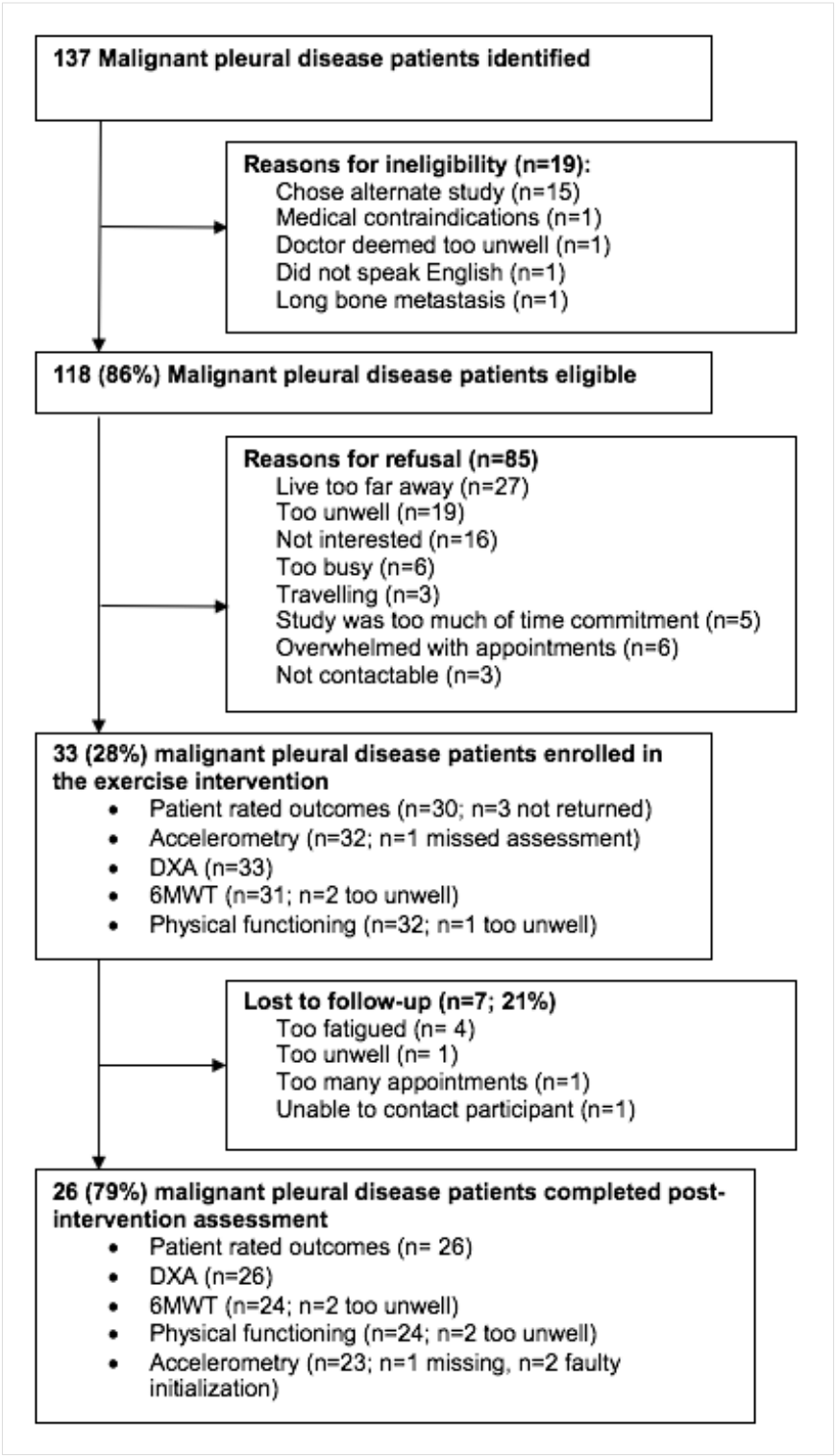

Figure B.1 Participant flow through the trial

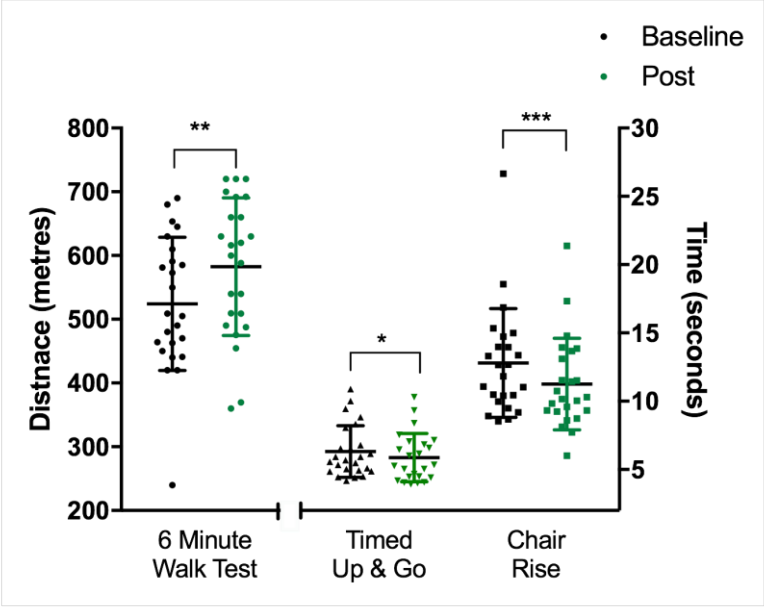

Figure B.2 Changes in physical functioning following exercise training.
* p<0.05

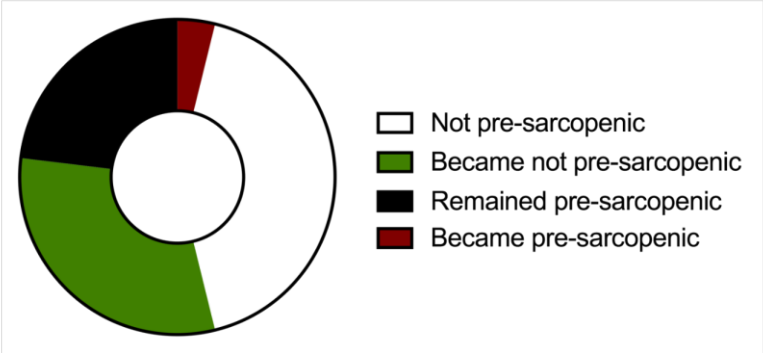

Figure B.3 Sarcopenia status following exercise intervention.

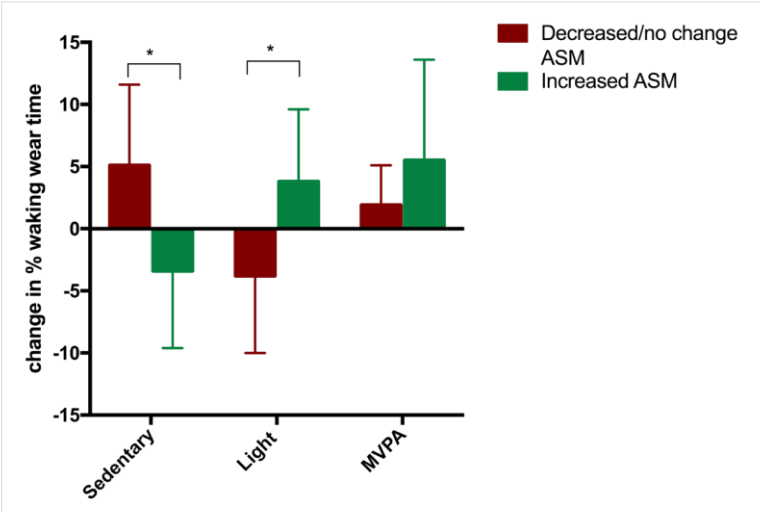

Figure B.4 Changes in proportion of waking hours spent in activity behaviours based on changes in appendicular skeletal muscle mass.
* p=<0.05

B.4 Discussion

This study examined the feasibility and efficacy of a short resistance exercise training program for improving physical functioning and body composition in patients with MPD. There were several important findings: 1) the program was effective at improving muscular strength, physical functioning, and functional capacity; 2) there was an increase in ASM following the intervention and those that increased ASM had an improved physical activity profile; 3) there were no changes in quality of life or fatigue following the intervention, and 4) the program had good compliance and ratings of tolerability among these patients with high disease burden.

Patients with MPD and mesothelioma have not been exclusively studied in the exercise oncology literature. Compared to other thoracic cancer patients, this is a unique subgroup, particularly those with mesothelioma due to the relatively long median survival (~12 months), lack of extrathoracic spread of disease, and low rates of a history of smoking. Improvements in muscular strength, functional capacity, and physical functioning paired with the positive feasibility and safety data presented indicate that exercise training could be a valuable supportive care intervention in this patient population. Average improvements in functional capacity reported here meet the cut-point for a clinical meaningful improvement,[15] and are similar to research in other advanced lung cancer populations.[7,32] Importantly, worse physical functioning has been associated with reduced survival in cancer popualtions.[33] Functional capacity has been identified as a strong independent predictor of survival in those with advanced lung cancer.[34,35] Importantly, there were no serious adverse events and participants report the favourable measure of tolerability. Therefore, a safe and tolerable intervention that improves functional capacity could be particularly important for those with MPD.

Overall, there was an improvement in ASM following the intervention. A proportion of participants (31%) even progressed out of being categorised as pre-sarcopenic. Recent literature in other advanced cancer populations has indicated the importance of adequate muscle mass due to associations with lower risk/rates of treatment toxicity,[6] and improved survival. While this finding is preliminary and requires replication in larger randomised trials, these results suggest that even a short-term individualised resistance exercise training program could be effective for improving ASM, which could have important implications for clinical outcomes. Previous research in advanced cancer populations indicates some success in improving lean mass with exercise training (n=4 studies in prostate cancer, lymphoma, and myeloma).[36] Further research is needed to examine ways

to optimise improvements in muscle mass in advanced cancer populations. Multi-modal interventions that include exercise and nutrition support and pharmacological agents to optimise improvements in body composition have potential to be most effective.[37]

While the exercise intervention showed no overall effect for improving physical activity behaviours, analysis indicated that participants that improved ASM also improved physical activity profile such that less time was spent sedentary and more time was spent in light activity. Previous research in MPD has indicated pre-sarcopenia is associated with a similar physical activity profile; specifically, greater sedentary time and lower light activity.[3] This preliminary finding provides further evidence that ASM could be a key mediator of physical activity. This is particularly important considering the importance that clinicians and patients place on the ability to remain actively engaged in activities of daily living. Further research is needed to more fully elucidate the relationship between changes in ASM and physical activity and sedentary behaviour.

This study has several important limitations to consider. This was a pilot feasibility study and therefore is subject to the inherent limitations of a small sample size, lack of control group, and inability to control for confounding factors that could affect results. One of the main confounders is treatment (including chemotherapy, fluid drainage of effusion, pain control etc.). These treatments could improve some of the outcomes if patient responded, but are unlikely to affect others, particularly body composition and muscular strength. Additionally, while this group was a homogenous sample in terms of MPD diagnosis, participants were heterogeneous in terms of treatment status (on/off), types of treatment completed both during and following the diagnosis, and time since diagnosis. The vast majority of participants had good performance status and the results might not be generalisable to more unwell participants. However, this research does provide important information to inform future research aimed at improving physical functioning and body composition in this population of patients with advanced cancer. The study employed well validated measures of body composition, physical functioning and patient-rated outcomes.

Overall, this work found that resistance exercise training that was provided in flexible and individualised prescription was feasible and beneficial for patients with MPD. Improvements in ASM and reductions in the proportion of patients with pre-sarcopenia indicate that resistance exercise could be an effective tool in addressing muscle loss in a select population of patients with advanced pleural cancers.

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Supplementary Data

Supplemental Table B.3 Differences in baseline physical function and body composition outcomes based on trial completion status.

	Completers (n=26)	**Drop-outs** (n=7)	**Mean Difference (95% CI)**	**p**
Physical Functioning (n=25)				
Leg Press (kg)	89.9 (36.8)	64.0 (22.8)	25.9 (-4.1, 0.1)	0.089
6MWD (m)	530.1 (106.7)	442.8 (81.7)	87.3 (-8.3, 182)	0.072
Chair Rise (sec)	12.8 (3.9)	16.3 (4.4)	-3.4 (-6.9, 0.1)	0.056
TUG (sec)	6.3 (1.9)	7.1 (1.2)	-0.7 (-2.2, 0.8)	0.346
Body Composition (n=26)				
Appendicular lean mass (kg)	20.8 (5.0)	18.5 (4.5)	2.3 (-2.0, 6.6)	0.283
Appendicular lean mass/ht^2 (kg/m^2)	6.8 (1.1)	6.3 (1.2)	0.5 (-0.5, 1.4)	0.339

Appendix C Sir Charles Gairdner Group – Ethical Approval

Government of **Western Australia**
North Metropolitan Health Service
Sir Charles Gairdner Osborne Park Health Care Group

HREC Ref. QI Projects / 11149-2016

Sir Charles Gairdner Hospital

8 August 2016

Ms Emily Jeffrey
Dietitian
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Dear Ms Jeffrey

QUALITY IMPROVEMENT No: 11149
TITLE: Actigraphy: an objective measure of activity levels in malignant pleural effusion patients

The above quality improvement/audit project has been determined to be of negligible risk by the Sir Charles Gairdner Group Human Research Ethics Committee. Therefore the project, as per the National Statement on Ethical Conduct in Human Research (5.1.22), is exempt from review. It was tabled at the HREC meeting on 18 August 2016.

Please quote number 11149 on all correspondence sent to the Human Research Ethics Committee Office.

Yours sincerely

ıir
thics Committee
Sir Charles Gairdner Hospital

Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee,
Level 2 A Block, Hospital Ave, Nedlands, WA 6009
Telephone (08) 6457 2999 Fax (08) 6457 3307 ABN: 13 993 250 709
Email HREC.SCGH@health.wa.gov.au Website www.scgh.health.wa.gov.au

Appendix D Sir Charles Gairdner Group – Ethical Approval

Government of **Western Australia**
Department of **Health**

Our Ref: 2014-124 approval SCGOPHCG

Sir Charles
Gairdner Hospital

16 July 2015

Professor Gary Lee
Respiratory Medicine
B Block
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Dear Professor Lee

HREC No: 2014-124
Project Title: Investigating nutritional status, physical functioning, and the effects of exercise intervention in malignant pleural mesothelioma

On behalf of the Sir Charles Gairdner Osborne Park Health Care Group, I give authorisation for your research project to be conducted at the following site(s):

Sir Charles Gairdner Hospital

This authorisation is based on the approval from the Sir Charles Gairdner Group Human Research Ethics Committee and the review from the Research Governance Office. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' (attached) and with the compliance of all reports as required by the Research Governance Office and approving HREC. Noncompliance with these requirements could result in the authorisation be withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

Yours sincerely

Dr Karen Murphy
A/EXECUTIVE DIRECTOR
SIR CHARLES GAIRDNER AND
OSBORNE PARK HEALTH CARE GROUP

Sir Charles Gairdner Group Human Research Ethics Committee, Level 2 A Block, Hospital Ave, Nedlands, WA 6009
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Appendix E Edith Cowan University – Ethical Approval

HUMAN RESEARCH ETHICS COMMITTEE
For all queries, please contact:
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270 Joondalup Drive
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OFFICE OF RESEARCH AND INNOVATION

270 Joondalup Drive,
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Telephone 134 328
Facsimile: (08) 9300 1257
CRICOS 00279B

ABN 54 361 485 361

31 July 2015

Ms Emily Jeffery
Faculty of Health, Engineering and Science
JOONDALUP CAMPUS

Dear Emily

ETHICS APPROVAL – MULTICENTRE RESEARCH PROJECT

Project Code:	**13255**	
Project Title:	**Investigating nutritional status, physical functioning, and the effects of exercise intervention in malignant pleural mesothelioma**	
Chief Investigator:	Professor Gary Lee	
Approval Dates:	*From:* 31 July 2015	*To:* 1 June 2019

Funding Source: ECU Health and Wellness Institute

Thank you for your recent application for ethics approval. This proposal has been reviewed by members of the Human Research Ethics Committee (HREC). The Committee noted that this project has also been submitted to the Curtin University Human Research Ethics Committee.

I am pleased to advise that the proposal complies with the provisions contained in the University's policy for the conduct of ethical human research and ethics approval has been granted. In granting approval, the HREC has determined that the research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

All research projects are approved subject to general conditions of approval. Please see the attached document for details of these conditions, which include monitoring requirements, changes to the project and extension of ethics approval.

We wish you success with your research project.

Yours sincerely

Kim Gifkins
SENIOR RESEARCH ETHICS ADVISOR

Appendix F Participant Information and Consent Form

HUMAN RESEARCH ETHICS COMMITTEE
For all queries, please contact:
Research Ethics Officer
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270 Joondalup Drive
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AND INNOVATION

270 Joondalup Drive,
Joondalup
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Facsimile: (08) 9300 1257
CRICOS 00279B

ABN 54 361 485 361

31 July 2015

Ms Emily Jeffery
Faculty of Health, Engineering and Science
JOONDALUP CAMPUS

Dear Emily

ETHICS APPROVAL – MULTICENTRE RESEARCH PROJECT

Project Code:	**13255**	
Project Title:	**Investigating nutritional status, physical functioning, and the effects of exercise intervention in malignant pleural mesothelioma**	
Chief Investigator:	Professor Gary Lee	
Approval Dates:	*From:* 31 July 2015	*To:* 1 June 2019

Funding Source: ECU Health and Wellness Institute

Thank you for your recent application for ethics approval. This proposal has been reviewed by members of the Human Research Ethics Committee (HREC). The Committee noted that this project has also been submitted to the Curtin University Human Research Ethics Committee.

I am pleased to advise that the proposal complies with the provisions contained in the University's policy for the conduct of ethical human research and ethics approval has been granted. In granting approval, the HREC has determined that the research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

All research projects are approved subject to general conditions of approval. Please see the attached document for details of these conditions, which include monitoring requirements, changes to the project and extension of ethics approval.

We wish you success with your research project.

Yours sincerely

Kim Gifkins
SENIOR RESEARCH ETHICS ADVISOR

What is the purpose of this study?

Following a diagnosis of mesothelioma there can be declines in health and wellbeing. Many people experience weight loss, poor appetite, tiredness, shortness of breath, and pain. No research has examined how nutritional status (i.e., how well your diet is meeting your nutritional needs), physical functioning (e.g., ability to do tasks such as walking and lifting), and body composition (i.e., how much fat and muscle you have) changes over time for patients with mesothelioma. Therefore, one purpose of this research is to assess changes in nutritional status, body composition, and physical functioning over time.

Research has demonstrated that exercise is a safe and effective intervention for the management of various adverse effects associated with cancer and cancer treatments. However, this information is based on research studies involving predominantly breast and prostate cancer patients. Currently, it is unknown if exercise can help lessen the negative symptoms associated with mesothelioma and its treatment. Therefore the second purpose of this research is to find out if a short, supervised exercise program could be useful for people with mesothelioma.

What does participation in this study involve?

As a participant in this study you will receive standard medical care. There are two groups in this study: 1. the nutrition group, 2. the exercise group.

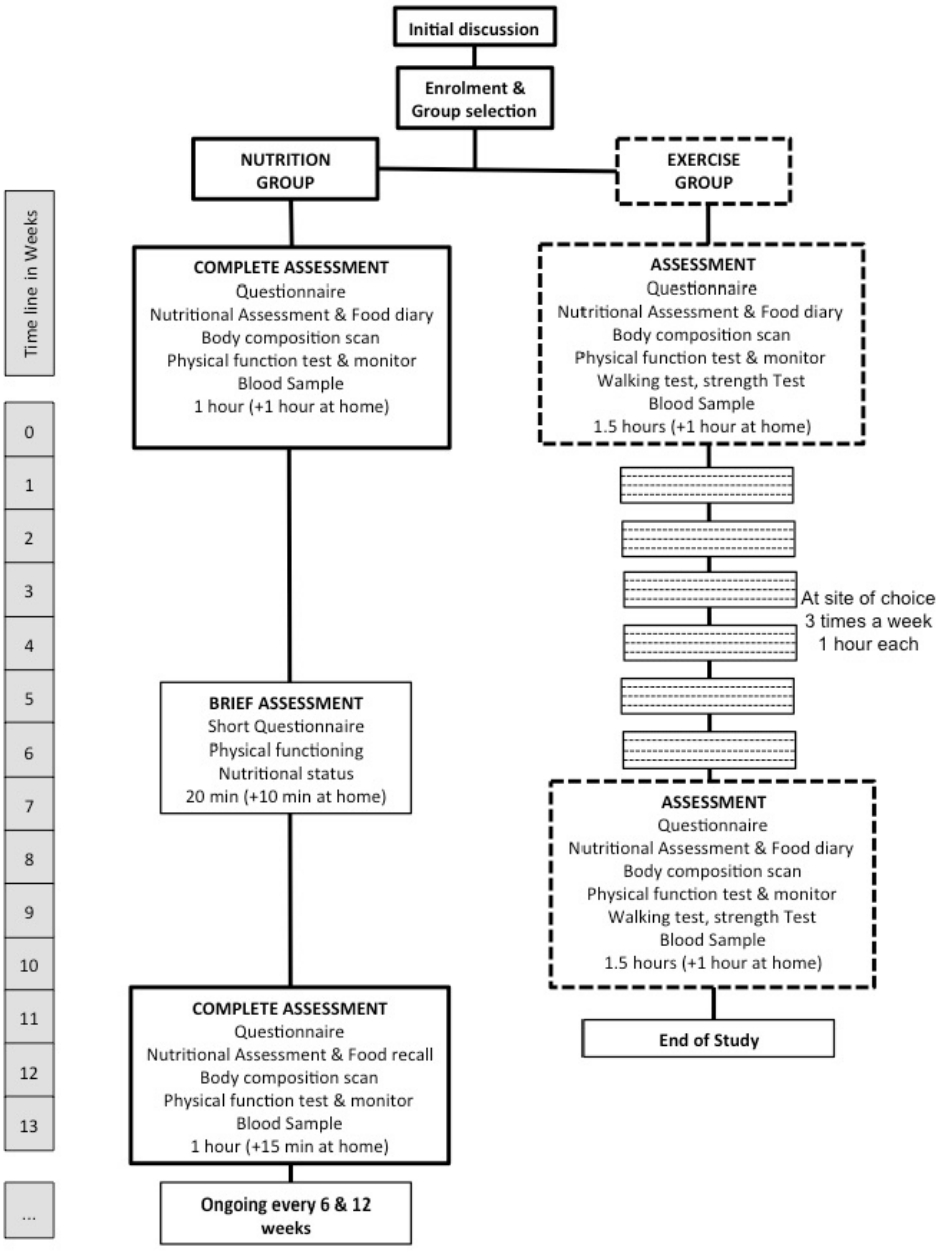
If you have mesothelioma you can choose to take part in the nutrition group. This involves nutrition and physical function assessments every 6 weeks. Assessments will alternate between brief assessments (takes about 30 minutes) and complete assessments (takes about an hour) as described below.

If you have malignant pleural disease as a result of another primary cancer (e.g., lung cancer, breast cancer), or if you have mesothelioma then you may choose to take part in the exercise intervention. This is a 6-week supervised exercise program. You would have assessment before the exercise program, after the exercise program as described below.

All participants will be asked to complete a series of tests or assessments. You will be thoroughly instructed on each of the assessments and supervised by qualified professionals at all times throughout these sessions.

Assessments can be done at Sir Charles Gairdner Hospital (SCGH; in the Cancer Centre Gymnasium, outpatients department), the Harry Perkins Institute of Medical Research, or at the Edith Cowan University (ECU) Health & Wellness Institute in Joondalup. The brief assessments can be done at ECU in Mt Lawley. If you are unwell and unable to travel it could be possible to arrange for us to do the brief assessment at your home.

Study Diagram



Assessments:

- *Questionnaires*

For the brief and complete questionnaires you will be asked to complete standardized questionnaires to assess quality of life and cancer-related symptoms. The brief questionnaire is expected to take you approximately 10 minutes to complete. The complete questionnaire will take approximately 15 minutes of your time. Before starting the exercise program you will be asked to complete a form with details such as your home address and contact phone number and also a health questionnaire that will provide information about your medical history, activity history, and other information that we will need to safely develop your tailored exercise program. Before and after the exercise program you will asked to completed standardized questionnaires to assess your quality of life, fatigue, shortness of breath, psychological distress, sleep quality, your physical activity level, your physical functioning and your motivation towards and thoughts about the exercise program. The questionnaires are anticipated to take you approximately forty minutes to complete at each of the assessment time points.

- *Body Composition Scan*

Dual Energy X-Ray Absorptiometry (known as DXA) will be used to assess your body composition (i.e., how much fat, muscle, and bone you have). This assessment involves lying still on a specifically designed platform for approximately 5 minutes and a scanning arm will move above your total body. A low-dosage x-ray will pass from underneath the platform to the scanning arm. The total radiation dose for all scans undertaken during the scan is very low, only a little more than normal background radiation from an airplane flight and much less than, for example, an international flight. A maximum of five scans will be completed in the nutrition study.

- *Nutritional status*

You will be asked to answer 4 questions about your weight and how much food you have been eating. Then you will undergo a brief physical exam to assess for any signs of muscle wasting and fat loss. The nutritional status assessment will take approximately 15 minutes to complete.

- *Physical Function*

A series of tests will be used to assess physical functional performance. Before physical function tests are performed, demonstrations, practice time, sufficient warm-up will be undertaken. You will be supervised during all tests and your safety will be observed at all times. Each of these tests will be performed three times. These tests involve:

  - Timed up and go: you will be seated in a chair, rise to stand, walk 8 feet, turn around and return to sitting.
  - Hand grip strength: You will be asked to squeeze a hand grip machine as hard as you can for each hand.
  - If you take part in the exercise study you will also complete a chair rise test: You will be seated in a chair and asked to rise and sit 5 consecutive times, without the use of your arms for support, as fast as possible.

- *Walking test*

For the Six-Minute Walk Test, you will be asked to walk 50 meters in a corridor, turn and return to the starting position for a total of six minutes. During this time you can take breaks if you need to.

- *Food diary*

You will be asked to record all of the food and drinks you consume over a 3-day period. It is recommended that you complete the diary at the time of eating or drinking. A food diary and instruction manual will be provided.

- Food recall

You will be asked to recall all of the food and drinks you consumed over the previous day. This will take approximately 15 minutes and can be completed in person or over the phone.

- *Strength Test*

You will be asked to perform a one repetition maximum test, which is the most weight that can be lifted one time with your legs using correct technique. This will be performed on a leg press weight-training machine that you will be using during the exercise training sessions. You will be supervised and instructed by a qualified professional during this test. If you have disease that has spread to the bone you will not have to complete this test.

- *Monitor of Physical activity level*

You will be asked to wear a monitor to measure your activity for 3 days. The device is very small and lightweight and is worn around the waist 24 hours a day.

- *Blood Sample*

You will be asked to have blood taken for this research. Your blood will be analysed for substances that produce an inflammatory response in the body. Your blood samples would be stored in our secure research facilities at Sir Charles Gairdner Hospital for up to 5 years. Blood samples will collected by a member of the Pleural Medicine Clinical staff or at an accredited Australian National Association of Testing Authorities laboratory when you get other blood tests done (i.e., PathWest). You will not receive the results of these blood samples.

Exercise program:

If you are eligible and would like to, you can participate in a 6-week exercise program. If you indicate that you are interested in the exercise study, an exercise coordinator will follow-up with you. Your specialist doctor will be required to give consent for you to take part in this exercise study. Prior to beginning the exercise program, you will be asked to complete a demographics and health history questionnaire. This is to ensure that the exercise program can be individualized so that it is appropriate for you and specific to your current health status.

The exercise program involves 3 supervised exercise sessions each week of resistance exercise (i.e. lifting weights). The sessions will be approximately 60 minutes long and conducted in small groups of up to 5 participants at the exercise clinic in the Cancer Centre at Sir Charles Gairdner Hospital, or at sites throughout Perth (i.e., Murdoch, Mt Lawley, Joondalup, and Crawley). You can choose the location that is most convenient for you. Accredited exercise physiologists experienced in working with people with cancer will be supervising your exercise program, which will be specifically tailored to you and your capabilities. The resistance exercise will involve 6-8 exercises that target the major upper and lower body muscle groups using weight training machines and other forms of resistance such as hand weights. The intensity will be moderate to vigorous (i.e. somewhat hard to hard) and will be manipulated by varying the amount of weight you are lifting, how many times in a row you lift it and how many sets of each exercise you perform. You might also complete aerobic exercise training at a moderate intensity. This could be walking on a treadmill, cycling on a stationary bike or rowing on a stationary ergometer or exercising or a cross trainer machine. Your program will be modified and progressed according to how you are feeling.

At the end of the 6-weeks you will have a two-week period to make up any missed sessions, if you choose to do so. It is completely up to you if you would like to make up any missed sessions or not.

What are the possible benefits of participating?

The direct benefit for you is that all study activities, including the nutrition assessments, exercise program and assessments, are provided at no cost to you. Participating in an exercise program may maintain or improve your physical wellbeing. Additionally, it is hoped that this study will contribute important new information about the management of mesothelioma.

What are the possible side effects and risks?

Because there are no additional medical procedures involved in this study, there are few foreseeable major risks or side-effects associated with participation. However, as is the case with anyone who exercises, any exercise may result in mild discomfort and muscle soreness.

There is also the possibility of muscle pulls or strains associated the functional assessment, exercise assessment or the exercise program, common to any type of physical activity. In line with standard practice in exercise physiology, we will monitor and modify your program whenever necessary. In order to minimize these risks you will perform an adequate warm-up and cool-down before and after any exercise bout, be fully instructed on the correct lifting technique, familiarized with the movements involved in this investigation and supervised at all times by qualified professionals. Risk of falling may exist in the performance of some tasks, however, you will be closely supervised to minimize the risk of falling. During exercise it is possible to experience symptoms such as abnormal blood pressure, fainting, light-headedness, shortness of breath, muscle cramps or strain, nausea, and in very rare cases heart rhythm disturbances or heart attack. These potential risks are common to any form of physical activity. You will be asked to report any symptoms you experience during exercise and your safety will be of primary importance at all times. You will be given a log where you can write this information down. The Sir Charles Gairdner Hospital Cancer Centre gymnasium is associated with full medical facilities in the unlikely event that any medical assistance is needed. The other exercise sites have emergency action procedures in place in the unlikely event that medical assistance is needed.

DXA scans are routine clinical tests but carry a small risk to you as they involve exposure to radiation. The level of radiation exposure is very small (10-30 microSieverts [µSv]) in comparison to the natural annual radiation dose in western communities (approximately 3000µSv). A person would receive radiation exposure of approximately 80 µSv on an airline flight of 8 hours or 30 to 40 µSv during a typical chest x-ray.

The discomforts associated with having blood taken are minimal. There is a risk that sometimes bruising and infection may occur and that the arm might become sore. Risk of bruising or infection will be minimised because all samples will be taken by a trained phlebotomist, medical doctor or nurse with extensive experience. The total amount of blood needed during each testing session will not be less than 10 ml (2 teaspoons). No syringes, needles or other devices capable of carrying infection from one person to another shall be reused. All of these items, which are disposable, will be destroyed after each use. All contaminated items will be disposed of promptly in special containers.

If you experience discomfort during any of the tests, please let the study staff know immediately. You may experience some anxiety or discomfort in answering the questions about your quality of life, distress, and well-being. If you do experience this, you can choose to stop filling out the questionnaire at any time. Your responses will be kept strictly confidential. Some of the questions before and after the exercise program will ask about the level of distress you are experiencing. If our study identifies that you are experiencing significant distress, we will ask you if we can notify your GP or cancer specialist so that the appropriate referral for support services can be made.

You may experience some distress when responding to questions about you weight and food intake during the nutritional status assessment. If you do experience any distress during assessment please tell the researcher. You can choose to stop any assessments at any time. If you are found to be malnourished, and are not currently under the care of a dietitian, your permission will be sought to contact your GP or cancer specialist who can make a referral to a dietitian.

What will happen to the information collected as part of this research study?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. They may also need to get some of your health information from other health service providers e.g., another hospital, pathology laboratory, radiography (please note that your CT/MRI scans may be reviewed), GP or

other medical specialist. Any information obtained in connection with this research project that can identify you will be kept private and confidential. It will be stored securely and only authorised persons, who are aware that it must be kept confidential, will have access to it. Your study details will be given a unique number so your identity will not be revealed. As required for safety reasons, your emergency contact details (their name, phone number, and relationship to you) as well as any medical history relevant for exercise training will be given to the exercise physiologist who will be supervising your exercise training and kept in your exercise-training diary. This information will be kept in a secured locked location at the exercise-training site while not in use. Your exercise-training log will not have your full name on it, only your study id. The trial records will be kept in the Department of Respiratory Medicine during the study in a locked filing cabinet in a locked office and archived. A copy of the data without identifying information will be kept at ECU Joondalup. This data will be kept for at least 5 years from the time the study is closed. They may be destroyed at any time thereafter. Your exercise training log will contain only information required for exercise training and will be transferred to and from exercise sites with care and stored in a locked area at all possible times. Your health records and any information obtained during the research project are subject to inspection for the purpose of verifying the procedures and the data. This review may be done by the relevant authorities and authorised representatives of the institution relevant to this Participant Information Sheet, *Sir Charles Gairdner Hospital* or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as noted above. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected. Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information. Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Are there any costs involved?

There will be no direct costs incurred as a result of participation in this study. However, there will be expense associated with travelling to, and parking at, Sir Charles Gairdner Hospital or ECU Joondalup to complete the assessments or exercise training. About one hour of parking will be required If you attend exercise training or an assessment at Sir Charles Gairdner Hospital (approximately $3.00/hour) or ECU Joondalup (approximately $1.50/hour). You will not be paid for participation in this study.

Voluntary participation and withdrawal

Participation in this study is entirely voluntary. Whether you decide to participate in the study or not, your decision will not prejudice you in any way. No explanation or justification is needed if you choose not to participate. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time without reason or justification. If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. A member of the research team will provide a form for *Withdrawal of Participation* for you to sign.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

Will I receive any feedback?

A summary of study results will be made available to all interested participants upon completion of the trial. On request, we will provide you with a brief summary report of your individual results with relation to how your physical function test results changed following the exercise intervention.

Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Sir Charles Gairdner Hospital.*

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Further information and who to contact?

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, Professor Y C Gary Lee on phone 6457 4968, or any of the following people:

Dr Carolyn McIntyre	Phone: (08) 6304 3987	Email: c.mcintyre@ecu.edu.au
Ms Emily Jeffery	Phone: (08) 6304 2082	Email: ejeffery@our.ecu.edu.au

Complaints contact person

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*Sir Charles Gairdner Group*
HREC Executive Officer	*Sean Howarth*
Telephone	*08 6457 2999*
Email	*sean.howarth@health.wa.gov.au*

Consent Form - *Adult providing own consent*

Title	*Investigating nutritional status, physical functioning, and the effects of an exercise intervention in malignant pleural mesothelioma*
Protocol Number	*version 1.2*
Coordinating Principal Investigator/	*Professor YC Gary Lee*
Principal Investigator	*Dr Carolyn McIntyre, Ms Emily Jeffery*
Associate Investigators	*Prof Rob Newton, Assoc/Prof Philippa Lyons-Wall* *Prof Jeanette Creaney, Prof Anna Nowak*
Location	*Sir Charles Gairdner Hospital, Perth, Western Australia* *Edith Cowan University Health and Wellness Institute*

Declaration by Participant

1. I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
2. I understand the purposes, procedures and risks of the research described in the project.
3. I have been able to have a member of my family or a friend with me while I was told about the study if I so wish. I have had an opportunity to ask questions and I am satisfied with the answers I have received.
4. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I understand that my personal details and the details of my emergency contact will be kept by the exercise physiologist for safety reasons.
6. I understand that I will be given a signed copy of this document to keep.
7. I understand that, if I decide to discontinue the research project treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

If you are unclear about anything you have read in the Patient Information Sheet or this Consent Form, please speak to your doctor before signing this Consent Form.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/

Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Appendix G Participant Screening Form

INTERMIx – Nutrition Study
SCREENING/ELIGIBILTY - CRF 1

Patients Initials:					Age:		
Date of Birth: (dd/mm/yy)	_____/_____/_____				Sex:	M ○ F ○	
Patient ID no: *(First name/Nutr/no.) e.g James/NUTR/01*	_____/_____						

DATE_____/_____/_____ **Current ECOG** _____

1. ELIGIBILITY/INELIGIBILITY CHECKLIST

a. Eligible:

• Established diagnosis of malignant pleural mesothelioma: • Histo-cytologically proven pleural mesothelioma	Yes ○ No ○

b. Ineligible (any "Yes' answers means the patient is INELIGIBLE):

• Age <18 years	Yes ☹ No ○
• Patients who are pregnant or lactating	Yes ☹ No ○
• Inability to read and understand English	Yes ☹ No ○
• Inability to give informed consent or comply with the protocol	Yes ☹ No ○
• Unable to obtain physician consent	Yes ☹ No ○
• Participation in the exercise intervention	Yes ☹ No ○

I confirm that the patient <u>meets all the criteria for entry into the trial</u> and is eligible for participation	Yes ○ No ☹

☐ **Informed consent form signed by patient and a copy of the Patient Information Sheet has been given to the participant.**

☐ **This patient is in sufficient health to participate in the study**

Physician's Name (PRINT):	Signature:	Date:

Please photocopy this form. File the original in the patient trial notes

Sir Charles Gairdner Hospital

Patient-Generated Subjective Global Assessment

Edith Cowan University Health and Wellness Institute

vario wellness clinic

Participant ID: _____ **Date:** _____

Please answer the questions in the four boxes.

1. Weight

In summary of my current and recent weight:

I currently weight about _____ kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:

☐ decreased (1) ☐ not changed (0) ☐ increased (0)

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:

☐ Unchanged (0)
☐ More than usual (0)
☐ Less than usual (1)

I am now taking:

☐ Normal food but less than normal amount (1)
☐ Little solid food (2)
☐ Only liquids (3)
☐ Only nutritional supplements (3)
☐ Very little of anything (4)
☐ Only tube feedings/only nutrition by vein (0)

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

☐ No problems eating (0)
☐ Nausea (1)
☐ Constipation (1)
☐ Mouth sores (2)
☐ Things taste funny or have no taste (1)
☐ No appetite, just did not feel like eating (3)
☐ Feel full quickly (1)
☐ Smells bother me (1)
☐ Problems swallowing (2)
☐ Pain; where? (3) _____
☐ Other** (1) _____
☐ Vomiting (3)
☐ Diarrhoea (3)
☐ Dry mouth (1)

**Examples: depression, money or dental problems

4. Activities and function: over the past month, I would generally rate my activity as:

☐ Normal with no limitations (0)
☐ Not my normal self but able to be up & about with most things (1)
☐ Not feeling up to most things, but in a bed or chair less than half the day (2)
☐ Able to do little activity and spend most of the day in bed or chair (3)
☐ Pretty much bedridden, rarely out of bed (4)

The researcher will complete the rest of the form:

	Additive score of the Boxes 1-4	**A**

5.	**Disease and its relation to nutritional requirements** (See Worksheet2) All relevant diagnoses (specify) _____ Primary disease stage (if known) _____ Age _____	**Numerical score from Worksheet 2**	**B**
6.	**Metabolic demand** (See Worksheet 3)	**Numerical score from Worksheet 3**	**C**
7.	**Physical** (See Worksheet 4)	**Numerical score from Worksheet 4**	**D**

Global Assessment (See Worksheet 5)

☐ Well nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total PG-SGA Score

(Total numerical score of A+B+C+D above)

Worksheets for PG-SGA Scoring

Boxes 1-4 of the PG-SGA are designed to be completed by the patient. The PG-SGA numerical score is determined by 1) the parenthetical points noted in boxes 1-4 and 2) the worksheets below for items not marked with parenthetical points. Scores for boxes 1 and 3 are additive within each box and scores for boxes 2 and 4 are based on the highest scored item checked off by the patient.

Worksheet 1 – Scoring Weight (Wt) Loss

Wt loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10-19.9%
3-4.9%	2	6-9.9%
2-2.9%	1	2-5.9%
0-1.9%	0	0-1.9%

Score for Worksheet 1

Worksheet 2 – Scoring Criteria for Condition

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of open wound, fistula	1
Presence of trauma	1
Age greater than 65 years	1

Score for Worksheet 2

Worksheet 3 – Scoring Metabolic Stress

Score for metabolic stress is determined by a number of variables known to increase protein and calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg prednisolone chronically (2 points would have an additive score for this section of 5 points

Stress	**None (0)**	**Low (1)**	**Moderate (2)**	**High (3)**
Fever	no fever	> 99 and <101	≥101 and <102	≥ 102
Fever duration	no fever	=< 72 hours	72 hours	> 72 hours
Steroids	no steroids	< 10 mg	≥ 10 and < 30 mg	≥ 30 mg

Score for Worksheet 3

Worksheet 4 – Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition; fat, muscle & fluid status. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ moderate deficit, 3+ severe deficit

Fat stores:				
Orbital fat pads	0	1+	2+	3+
Triceps skin fold	0	1+	2+	3+
Fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	**0**	**1+**	**2+**	**3+**
Muscle status				
Temples (temporalis muscle)	0	1+	2+	3+
Clavicles (pectoralis & deltoids)	0	1+	2+	3+
Shoulders (deltoids)	0	1+	2+	3+
Interosseous muscles	0	1+	2+	3+
Scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
Thigh (quadriceps)	0	1+	2+	3+
Calf (gastrocnemius)	0	1+	2+	3+
Global muscle deficit rating	**0**	**1+**	**2+**	**3+**
Fluid status				
Ankle oedema	0	1+	2+	3+
Ascites	0	1+	2+	3+
Global fluid status rating	**0**	**1+**	**2+**	**3+**

Point score for the physical exam is determined by the overall subjective rating of total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Score for worksheet 4 ☐

Worksheet 5 – PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss OR Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) OR No wt stabilisation or wt gain (i.e. continued wt loss)	> 5% wt loss in 1 month (or >10% in 6 months) OR No wt stabilisation or wt gain (i.e., continued wt loss)
Nutrient intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition impact Symptoms	None OR Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms	Presence of nutrition impact symptoms
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible oedema)

Global PG-SGA rating (A, B or C) _____

Appendix I Questionnaire – Baseline

Sir Charles Gairdner Hospital

Edith Cowan University Health and Wellness Institute

vario wellness clinic

Nutritional Status, Activity, and the Effects of Exercise in Mesothelioma

Assessment: Complete

Study ID: _____

Date: ____/____/____

Instructions:

- Please take your time completing these important questionnaires and answer all questions as honestly as you can.
- Please note: there are questions on both sides of each page in this package.
- Your responses provide extremely valuable information regarding the effects of exercise in cancer survivors and have the potential to influence the information and services provided to cancer survivors worldwide.
- We really appreciate your time and value the contribution you are making to advancing the scientific knowledge surrounding exercise for cancer survivors.
- If you have any questions whatsoever please don't hesitate to ask.

THANK YOU!

These first questions ask for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. For each of the following questions, please circle the one number that best describes your answer.

1. In general, would you say your current health is:

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

2. **Compared to one year ago**, how would you rate your health in general **now**?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

3. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	1	2	3
c) Lifting or carrying groceries.	1	2	3
d) Climbing **several** flights of stairs.	1	2	3
e) Climbing **one** flight of stairs.	1	2	3
f) Bending, kneeling, or stooping.	1	2	3
g) Walking **more than a mile**.	1	2	3
h) Walking **several hundred yards**.	1	2	3
i) Walking **one hundred yards**.	1	2	3
j) Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities.	1	2	3	4	5
b) **Accomplished less** than you would like.	1	2	3	4	5
c) Were limited in the **kind** of work or other activities.	1	2	3	4	5
d) Had **difficulty** performing the work or other activities (for example, it took extra effort).	1	2	3	4	5

5. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities.	1	2	3	4	5
b) **Accomplished less** than you would like.	1	2	3	4	5
c) Did work or other activities **less carefully than usual**.	1	2	3	4	5

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

7. How much **bodily** pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
1	2	3	4	5	6

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	1	2	3	4	5
b) Have you been very nervous?	1	2	3	4	5
c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d) Have you felt calm and peaceful?	1	2	3	4	5
e) Did you have a lot of energy?	1	2	3	4	5
f) Have you felt downhearted and depressed?	1	2	3	4	5
g) Did you feel worn out?	1	2	3	4	5
h) Have you been happy?	1	2	3	4	5
i) Did you feel tired?	1	2	3	4	5

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

11. How TRUE or FALSE is **each** of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people.	1	2	3	4	5
b) I am as healthy as anybody I know.	1	2	3	4	5
c) I expect my health to get worse.	1	2	3	4	5
d) My health is excellent.	1	2	3	4	5

Below is a list of statements that other people with cancer have said are important to their quality of life. Please indicate the extent to which you have experienced each of the statements during the past 7 days by circling the appropriate number using the following scale.

During the PAST 7 DAYS:	not at all	a little bit	some-what	quite a bit	very much
PHYSICAL WELL - BEING					
1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by side effects of treatment	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4
SOCIAL/FAMILY WELL - BEING					
8. I feel close to my friends	0	1	2	3	4
9. I get emotional support from my family	0	1	2	3	4
10. I get support from my friends	0	1	2	3	4
11. My family has accepted my illness	0	1	2	3	4
12. I am satisfied with family communication about my illness	0	1	2	3	4
13. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section					
14. I am satisfied with my sex life	0	1	2	3	4

During the PAST 7 DAYS:	not at all	a little bit	some-what	quite a bit	very much
EMOTIONAL WELL - BEING					
15. I feel sad	0	1	2	3	4
16. I am satisfied with how I am coping with my illness	0	1	2	3	4
17. I am losing hope in the fight against my illness	0	1	2	3	4
18. I feel nervous	0	1	2	3	4
19. I worry about dying	0	1	2	3	4
20. I worry that my condition will get worse	0	1	2	3	4
FUNCTIONAL WELL - BEING					
21. I am able to work (include work at home)	0	1	2	3	4
22. My work (include work at home) is fulfilling	0	1	2	3	4
23. I am able to enjoy life	0	1	2	3	4
24. I have accepted my illness	0	1	2	3	4
25. I am sleeping well	0	1	2	3	4
26. I am enjoying the things I usually do for fun	0	1	2	3	4
27. I am content with the quality of my life right now	0	1	2	3	4

ADDITIONAL CONCERNS

	not at all	a little bit	some-what	quite a bit	very much
1. I have a good appetite	0	1	2	3	4
2. The amount I eat is sufficient to meet my needs	0	1	2	3	4
3. I am worried about my weight	0	1	2	3	4
4. Most food tastes unpleasant to me	0	1	2	3	4
5. I am concerned about how thin I look	0	1	2	3	4
6. My interest in food drops as soon as I try to eat	0	1	2	3	4
7. I have difficulty eating rich or “heavy” foods	0	1	2	3	4
8. My family or friends are pressuring me to eat	0	1	2	3	4
9. I have been vomiting	0	1	2	3	4
10. When I eat, I seem to get full quickly	0	1	2	3	4
11. I have pain in my stomach area	0	1	2	3	4
12. My general health is improving	0	1	2	3	4

FATIGUE SYMPTOMS

	not at all	a little bit	some-what	quite a bit	very much
1. I feel fatigued	0	1	2	3	4
2. I feel weak all over	0	1	2	3	4
3. I feel listless ("washed out")	0	1	2	3	4
4. I feel tired	0	1	2	3	4
5. I have trouble starting things because I am tired	0	1	2	3	4
6. I have trouble finishing things because I am tired	0	1	2	3	4
7. I have energy	0	1	2	3	4
8. I am able to do my usual activities	0	1	2	3	4
9. I need to sleep during the day	0	1	2	3	4
10. I am too tired to eat	0	1	2	3	4
11. I need help doing my usual activities	0	1	2	3	4
12. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13. I have to limit my social activity because I am tired	0	1	2	3	4

Please circle the number that best describes how you feel **NOW:**

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness (Tiredness = lack of energy)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness (Drowsiness = feeling sleepy)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression (Depression = feeling sad)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety (Anxiety = feeling nervous)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem (for example constipation)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Appendix J Activity Monitor Instructions and Log

ACTIVITY MONITOR INSTRUCTIONS

The activity monitor measures the amount of physical activity you do in your everyday life. It is also used to measure the amount and quality of your sleep.

1. Please start wearing the monitor from:

_____

2. Please take off the monitor:

_____

If you have any questions about the activity monitor please call and leave a message: 6304 2329
If there is no answer, please leave a message. It will be checked and responded to as soon as possible between 8:00am and 4pm Monday to Friday.

- **Where do I wear the activity monitor?**
  - The monitor needs to be worn at the hip area of your waist with the black button facing the top (Do not twist the button).
  - The monitor can be worn either above or beneath clothing, and it is not necessary for it to make contact with the skin.
  - The monitor must be held snugly against the body to work properly (i.e. must be secure and not bounce or slide when you're moving).

- **How long do I wear the activity monitor for?**
  - We ask that you wear the monitor for a period of 3 days.
  - It is very important to wear the monitor 24 hours a day if possible.
  - This includes when you are asleep at night.
  - The monitor should be taken off to bath/shower.
  - You need to take off the activity monitor on the date and time listed above.

- **What happens if I get the activity monitor wet?**
  - It's preferable if the monitor doesn't get wet but it is water resistant so will not be affected by getting slightly wet.
  - If you are a swimmer please take the device off before getting into the pool/ocean.
  - Note the device is water *resistant* and not water *proof*.

ACTIVITY MONITOR LOG

Study ID: _____

Date: ____/____/____

Please use this form to document any time that you didn't wear the monitor during the three-day period, or any issues you had wearing the monitor

	DETAILS
Day 1	
Day 2	
Day 3	

Appendix K Food Record

Sir Charles Gairdner Hospital

Edith Cowan University Health and Wellness Institute

vario wellness clinic

Food Diary

Participant ID: _____

Started diary on:_____(date)

Finished diary on:_____(date)

You are welcome to contact the researcher during business hours to discuss your questions or concerns about the food diary.

Contact person: Emily Jeffery

Contact details: (08) 6304 2082

ejeffery@our.ecu.edu.au

Food diary guidelines

1. Record everything that you eat and drink for three (3) consecutive days

- Start each day on a new page
- You can use more than one page for each day
- Record the date at the top of the page
- We recommend you carry your food diary with you at all times throughout the three day recording period, so that nothing is forgotten
- Write down the time that you eat and drink
- Write down what you eat and drink as close as possible to the time that you consume it

2. Describe your food and drink in as much detail as possible

- Record the type and brand of each item e.g. Sunblest *(brand)* multigrain *(type)* bread
- If eating meat, include the cut of meat (e.g. rump steak) and whether fat has been trimmed (e.g. chicken skin removed)
- Describe your cooking method. For example, boiling, frying, BBQ, roasting or baking. If fat (e.g. oil) has been added, please state the brand and the amount
- Where foods or drinks have been eaten outside the home (e.g. take-away) please describe what it is and where it has been bought
- Record all accompaniments such as butter, gravy, sauce, salt and sugar

3. Describe the amount of food and drink you consume

- Use household measures (cups and spoons) to record the amount of food and drink you consume. For example, 1 cup of boiled, white rice or 1 tsp of Flora canola margarine.
- You can weigh your food and drink if you like, but it is not required.
- For mixed dishes (e.g. a salad or stir fry), estimate each ingredient separately. For example, garden salad: 1 lettuce leaf, 4 slices cucumber, 4 cherry tomatoes and 1 tsp Kraft 99% fat free French dressing.
- You can also record your recipes in the 'notes' section at the end of each page. Then just tell us how much is your portion e.g. half or one-quarter.
- Ensure you record all fluids (including water) and estimate the volume consumed in mL or by the type of cup e.g. pint glass, paper cup, coffee mug.

Food diary example

Time	Food and Drink Eaten	
	Description eg. Weetbix	**Quantity** eg. 3 biscuits / 45g
7.30am	*Cornflakes – Kelloggs* *Milk – Brownes Calcium Plus* *Sugar - white* *Toast, white bread – Helgas* *Margarine – Flora Light* *Tea – Lipton* *Milk – Brownes Skim* *Sugar - white*	45g 1.5 cups 2 tsp 2 large thick slices 3 teaspoons 1 cup 30ml 3 tsp
10.30am	*Granita – Arnotts* *Black Coffee* *Green Apple – Granny Smith*	1 biscuit 1 cup 1 medium
1 pm	*Bought from deli:* *1 x cheese & salad sandwich* *White bread – unknown* *Butter – unknown* *Cheese grated, unknown* *Lettuce* *Tomato* *Beetroot, canned* *Apple – Red Delicious*	 2 standard slices Thickly spread ½ a cup 2 small leaves 3 medium slices 3 slices 1 large
3.30pm	*Water – Mount Franklin* *Homemade chocolate slice from deli*	1 bottle 750ml 1 medium slice
7.30pm	*Spaghetti, white – Maggi* *Bolognaise Sauce – lean mince* *Parmesan Cheese – Kraft* *Red wine, Shiraz* *Salad* - *carrots* - *tomatoes* - *lettuce* *French dressing – Kraft Fat Free*	320g 1.5 cups (half the recipe) 3 tsp 2 glasses 3 slices 1 whole 4 small leaves 1 tbsp
9.00pm	*Ice cream (vanilla) –Streets Blue Ribbon*	3 large scoops

Notes:
Bolognaise Sauce: 500g lean mince, 1 x 420g can tinned whole tomatoes, 2 tablespoons Leggo tomato paste, 1 tablespoon canola oil, ½ cup dry white wine, oregano, thyme, basil, salt and pepper

Date:

Time	Food and drink consumed	
	Description	Quantity

Notes:

Appendix L Standard Operating Procedure – Dual Energy X-Ray Absorptiometry

INTERMIx

DXA standard procedures

Prior to the scanning day

- Advise participants:
  - ☐ Wear comfortable clothing with no metal (e.g. zips, metal buttons)
  - ☐ Not to undertake strenuous exercise on the morning of the scan
  - ☐ Eat breakfast but avoid a very large breakfast

Equipment

- Hologic DXA (Horizon A), Level 2, Harry Perkins Institute of Medical Research
- Sample spine (calibration equipment)

Set up

1. Calibration
   - Turn on computer.
   - Turn on DXA by pressing the green button.
   - Double click on QDR account.
   - A pop-up will show asking to back up computer, click "**no**".
   - Make sure **NHANES-BCA** is enabled:
     - Click **"Utilities"**.
     - Click **"System Configuration"**.
     - Click **"Analysis"**.
     - At the bottom of the screen, make sure the box is ticked.
   - Click and open up **"Daily QC"**.
   - Collect sample spine from calibration equipment cupboard and remove the outer black cover.
   - Place the spine on DXA bed (largest vertebral body is closest to computer) and adjust position ensuring the red lasers crossover in the middle of the small air bubble and the middle number 1 at the opposite end of spine.
   - On computer click continue.
   - If the spine has been correctly positioned and scanned then the message **'daily QC passed'** should appear and click **OK**.

Testing Instructions

1. Ask patient if there is any chance of pregnancy. **DO NOT** scan if pregnant.
2. Ask the patient to remove any metallic items they have on/with them e.g. glasses, loose change, zips, metal buttons etc. Provide a towel/robe if necessary i.e. if they had to remove their jeans.
3. Ask the patient if they have any internal objects that could interfere with the scan such as:
    a. Pacemaker leads
    b. Radioactive seeds
    c. Metal implants
    d. Surgical staples
    e. Radio-opaque catheters or tubes
    f. Wedding rings that cannot be removed
        i. **Make a note on testing sheet if any of the above has been identified.**
4. Measure and record the patient's height and weight.
5. Make sure **'NHANES-BCA'** is enabled prior to scanning each client.
6. Click on **'perform exam'** and then **'new patient'.**
7. Enter the patient details including height, weight, gender, DOB, ID and press **'ok'.**
8. Instruct the client to lie supine with their feet closest to the computer.
9. Position the individual so that they are central and within the scanning field as marked by the black lines with their head positioned 2cm from the end of the bed.
10. Palms are faced down on the bed. If patient does not fit within scanning field, ask them to place their hands vertical.
11. Feet are positioned wide and angled towards each other and held together by strapping tape. Explain to client that this position is used to scan both bones of the lower limbs.
    a. **For hygienic reasons, new strapping tape is to be used for each patient.**
12. Explain to the patient what the scan is looking at, i.e. body composition and BMD and that the scanning process will last for 3-4 minutes.
13. Instruct the patient to lie motionless on the table as movement can affect the scan quality.
14. Select perform **'whole body'** scan and click on **'scan now'** when the patient is correctly aligned on the table.
15. DEXA table must be cleaned with alcohol wipe after use.

Appendix M Standard Operating Procedure – Timed Up and Go Test

INTERMIx

'Timed up and go test' standard procedures

Equipment required

- Armed chair
- Tape measure
- Masking tape
- Small marker or bean bag
- Stop watch

Set up

1. Position armed chair up against a wall
2. Measure 2.44 m (8 ft) from the front of the chair and mark the distance with masking tape
3. Position a marker at the 2.44 m line

Testing instructions

1. Explain the purpose of the test
    a. *This test is designed to mimic the activities of daily living*
2. Explain the process of the test
    a. *In this test, you begin seated, stand up (unassisted if able), walk around cone and return to sitting as quickly as possible. You may use the arms on the chair when you return to sitting.*
3. Inform participant that they will be tested 3 times with a 1 minute rest in between
4. Demonstrate the timed up and go
5. Ask participant if they have any questions before they start

6. Instruct participant to sit in the chair with back firmly against the back of the chair and arms across chest. Feet are shoulder width apart on the floor with knees positioned at 90°
7. Instruct participant to commence with "3, 2, 1, Go"
8. Researcher to start stopwatch on "Go" and stop the stopwatch once the participant returns their upper back to the backrest
9. Participant to have a 1-minute rest. If greater than a 1-minute rest is required, document this on the data collection form
10. Complete two more trials to give three trials in total. If participants are unable to complete 3 trials, document this on the data collection form

Appendix N Data Collection Form

COMPLETE ASSESSMENT --- DATA COLLECTION SHEET

ID number:_____ Initials: _____

Date:_____ Assessor Name: _____

1. ☐ **Baseline** ☐ _____ **Weeks**
2. ☐ **Informed Consent** ☐ **Physician Consent** ☐ **Demographic Info & Health History**
3. ☐ **Check medical history**: (Is there any reason not to do the functional testing?)

_____

_____

4. **Performance Status:** _____
5. **Height**:_____cm (only at baseline) **Weight**:_____kg
6. **Grip Strength:** (30 second rest between trials)
   - ☐ Seated, elbow flexed at 90°, forearm neutral, wrist 0-30° of dorsiflexion
   - ☐ Instructed to exhale when squeezing dynamometer
   - ☐ Hand dominance (R or L) _____
   - ☐ Hand dynamometer position used (1-5) _____

   RIGHT: Trial 1: _____ Trial 2: _____ Trial 3: _____ **BEST**: _____

   LEFT: Trial 1: _____ Trial 2: _____ Trial 3: _____ **BEST**: _____
7. **Timed up and go** (1 min rest between trials)

   ☐ Used arms to assist in standing

   Trial 1:_____sec Trial 2:_____sec Trial 3:_____sec **BEST**:_____sec
8. ☐ **DXA full body scan**: remove shoes, socks, ALL metal (jewellery, underwire bra) and any prosthetics
9. ☐ **PGSGA Completed**
10. ☐ **3 Day diet record and ActiGraph explained (baseline)**

11. Collect/Give out:

Give out:

☐ Questionnaire (complete)

☐ 3 day food record

☐ ActiGraph

How will the ActiGraph, questionnaire, and food diary be returned?

☐ Drop off

☐ Mail (Return Tracking ID:)

☐ Date for next assessment confirmed

Collect:

☐ Check all data has been returned from previous assessment

Appendix O Sample Resistance Exercise Training Program

EXERCISE TRAINING LOG

Participant ID:_____/ EXER /_____

First name / EXER/ number

Emergency Contact Details:

Name: _____

Contact Details: _____

Relationship: _____

Relevant Medical information:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Medications:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

If there are any medical issues with participants, please contact our physician support:

Dr Maree Azzopardi – 0412 866 477

In a last resort, contact the Pleural Medicine Hotline:

0421 253 918

SESSION RATING OF PERCEIVED EXERTION (RPE)

6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

TOLERANCE OF SESSION

Please rate the number that best represents how you feel

I have found the exercise session to be:

1	2	3	4	5	6	7
Extremely Intolerable	Quite Intolerable	Slightly Intolerable	Neutral	Slightly Tolerable	Quite Tolerable	Extremely Tolerable

Date Session Missed	Reason (if available)

Adherence Log:

Participant ID:_____/EXER/_____ **Date**: _____

TRAINING PROGRAM LOG – WEEK 1 (session 1)

1. **Please rate your current level of pain (if any):**

No pain ——————————————— Very severe pain

2. **Has pain affected your ability to undertake usual activities of daily living since your last exercise training session?** Yes No
   - **If yes, has the interference increased or decreased?** Increased Decreased
3. **Has shortness of breath changed since your last exercise training session?** Yes No
   - **If yes, has it increased or decreased?** Increased Decreased
4. **Has how tired you feel changed since your last exercise training session?** Yes No
   - **If yes, has it increased or decreased?** Increased Decreased
5. **Have you experienced any other pain, new symptoms/issues?** _____

   _____
6. **Warm up:** 5 mins cardio – Cycling or Walking
7. **Resistance Exercises:** Target = 2 sets of 12 reps

1.	Leg Press	reps X	kg	reps X	kg
2.	Chest Press	reps X	kg	reps X	kg
3.	Seated Row	reps X	kg	reps X	kg
4.	Leg Extension	reps X	kg	reps X	kg
5.	Shoulder Press	reps X	kg	reps X	kg
6.	Leg Curl	reps X	kg	reps X	kg
7.	Lat Pull Down	reps X	kg	reps X	kg

8. **Cool down**: Stretching
   - Hamstrings: _____x 15-30 sec • Quadriceps: _____x 15-30 sec • Calf: _____x 15-30 sec
9. **Session RPE**: _____ 10. **Tolerance of Session**: _____

   Notes:_____

   _____

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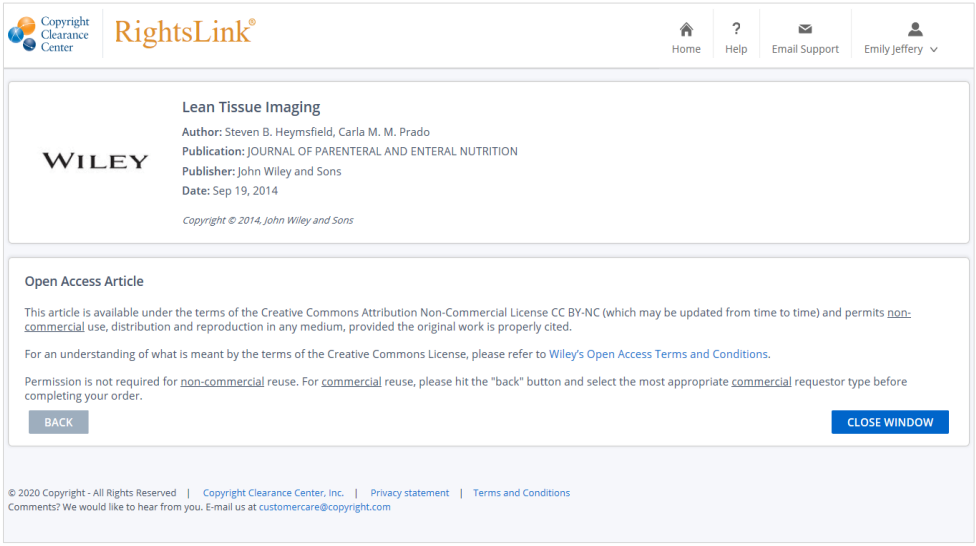

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Lean Tissue Imaging

Author: Steven B. Heymsfield, Carla M. M. Prado
Publication: JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Publisher: John Wiley and Sons
Date: Sep 19, 2014

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Appendix Q Statement of Contributions of Others

Chapter 3

To Whom It May Concern,

I, Emily Jeffery, was responsible for most of the data collection, data analysis and interpretation, and manuscript preparation for the publication entitled *'feasibility of objectively measured physical activity and sedentary behavior in patients with malignant pleural effusion'* (Jeffery E, Lee YCG, McVeigh J et al. Support Care Cancer, 2017; 25:3133-3141).

[redacted]

I, as a Co-Author, endorse that this level of contribution by the Candidate indicated above is appropriate.

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I, Emily Jeffery, was responsible for most of the data collection, data analysis and interpretation, and manuscript preparation for the publication entitled *'agreement between computed tomography and dual energy x-ray absorptiometry for the classification of low muscle mass in patients with malignant pleural mesothelioma'* (Jeffery E, Lee YCG, Newton RU et al. prepared for submission to Appl Physiol Nutr Metab).

[redacted]

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[redacted]

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[redacted]

I, as a Co-Author, endorse that this level of contribution by the Candidate indicated above is appropriate.

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Chapter 8

To Whom It May Concern,

I, Emily Jeffery, was responsible for some of the data collection, and most of the data analysis and interpretation, and manuscript preparation for the publication entitled *'nutritional status, dietary intake and resistance exercise adherence and outcomes in patients with malignant pleural disease'* (Jeffery E, Newton RU, Lee YCG et al. prepared for submission to Med Sci Sports Exerc).

[redacted]

I, as a Co-Author, endorse that this level of contribution by the Candidate indicated above is appropriate.

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