Guro Birgitte Stene

Classification, assessment and treatment of cancer cachexia

Thesis for the degree of Philosophiae Doctor

Trondheim, December 2014

Norwegian University of Science and Technology
Faculty of Medicine
Department of Neuroscience/Department of Cancer Research and Molecular Medicine, European Palliative Care Research Centre

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the degree of Philosophiae Doctor

Faculty of Medicine
Department of Neuroscience/Department of Cancer Research and
Molecular Medicine, European Palliative Care Research Centre

ISBN 978-82-326-0656-6 (printed ver.)
ISBN 978-82-326-0657-3 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2014:371

Printed by NTNU-trykk

Norsk sammendrag

Kakeksi er en hyppig forekommende tilstand hos kreftpasienter som har alvorlige konsekvenser for funksjonsnivå, livskvalitet og overlevelsesevne. Kakeksi kjennetegnes ved et ufrivillig vekttap som følges av appetittløshet og redusert matinntak, metabolske endringer og lav muskelmasse (sarkopeni). Blant klinikere og forskere har det vært liten enighet om hvordan kakeksi skal defineres og klassifiseres hos kreftpasienter. Behandlingen av kakeksi hos kreftpasienter har vært mangelfull. I de senere år, har økt kunnskap om underliggende sykdomsmekanismer bedret forståelsen av kakeksi som et flerdimensjonalt syndrom. Det er behov for objektive og presise metoder for å måle ulike dimensjoner av kakeksi og mer kunnskap om hvilke behandlingstiltak som har effekt. Denne avhandlingen har som overordnet mål å bidra til forbedret klassifisering og måling av kakeksi samt gi økt kunnskap om behandling av kakeksi hos kreftpasienter.

Vekttap og KMI er etablerte diagnostiske kriterier for kakeksi, og avhandlingen bekrefter at disse er valide kriterier for å skille pasienter med kakeksi fra de som ikke har kakeksi. Videre vises det at måling av andre diagnostiske kriterier som tap av muskelmasse, appetittløshet og økt inflammasjon er nødvendig for å klassifisere kakeksi i flere stadier innen sykdomsutviklingen.

Måling av diagnostiske kriterier som muskelmasse og fysisk aktivitet kan bidra med viktig informasjon i et klassifiseringssystem for kakeksi. Validering av en kroppsbåren aktivitetsmåler i denne avhandlingen viste at den måler nøyaktig tid i oppreist stilling og antall forflytninger mellom sittende og stående, men ikke antall steg og energiforbruk. Videre viser måling av muskelmasse ved bruk av CT-basert analyse at pasienter med ikke-kurerbar lungekreft kan ivareta og øke muskelmasse under kreftbehandling. Dette til tross for at flere av pasienten var sarkopeniske før de startet kjemoterapi og uten at de fikk noen tilleggsbehandling for kakeksi. Det ble videre vist at endring i muskelmasse, og ikke sarkopeni målt før behandling, var en signifikant predikator for overlevelse. Fysisk trening er i denne avhandlingen vist å være effektivt for å øke muskelstyrke, men ikke muskelmasse under kreftbehandling. Måling av muskelmasse var kun gjennomført

i noen få studier. Det er en mangel på randomiserte kontrollerte studier som er gjennomført i pasienter som er i tidlig fase av kakeksi eller som har kakeksi til å kunne konkludere om fysisk trening kan anbefales som
en integrert del av behandling en for kakeksi. Fysisk trening er imidlertid trygt og gjennomførbart for de fleste kreftpasienter og bør anbefales som en del av multimodale intervensjoner for å forebygge eller forsinke utviklingen av kakeksi.

Kandidatens navn: Guro Birgitte Stene
Institutt for nevromedisin, Det medisinske fakultet, NTNU
The European Palliative Care Research Centre

Hovedveileder: Jorunn Lægdheim Helbostad
Bi-veiledere: Stein Kaasa og Line Merete Oldervoll

Finansiering: Samarbeidsorganet Helse Midt-Norge RHF og NTNU

Denne avhandlingen er funnet verdig til å forsvares for graden PhD Palliative care. Disputas finner sted i auditoriet ØHA11 i Øya Helsehus, kl. 12.15, fredag 19.desember 2014.

Abstract

Cachexia is a prevalent condition in cancer patients that has severe consequences for physical function, quality of life and survival. Cachexia is characterized by involuntary weight loss followed by loss of appetite and reduced food intake, metabolic changes and low muscle mass (sarcopenia). Among clinicians and researchers there has been little agreement on how to define and classify cachexia in cancer patients, and adequate treatments are so far lacking. Knowledge about the underlying mechanisms of disease has increased the understanding of cachexia as a multidimensional syndrome. There is a need for objective and accurate methods to measure various dimensions of cachexia and to improve knowledge on effective treatments. The overall aim of this thesis is to contribute to improved classification and assessment of cancer cachexia and evidence-based knowledge about treatment of cachexia in cancer patients. The thesis includes two cross-sectional studies, a prospective cohort study and a systematic literature review where the specific aims are as follows:

1) To evaluate two different classification models of cachexia based on information about weight loss, BMI and other relevant diagnostic criteria (disease progression, nutrition status, function) in an international patient population of cancer patients with advanced, incurable cancer.

2) To evaluate the accuracy of a body-worn accelerometer-based activity meter to identify positions (lying, sitting and standing), transfers (sit to stand) and stepping (number of steps), and energy expenditure, in cancer patients with advanced, incurable cancer and different levels of physical performance.

3) To assess changes in muscle mass during chemotherapy in patients with advanced lung cancer and how changes in muscle mass are related to treatment response and survival.

4) To systematically review scientific literature to examine the effect of different types of exercise (endurance, strength, or combined training) on muscle mass and muscle strength in patients with cancer who are at risk of developing cachexia.

This thesis provides new knowledge about the classification, assessment and physical exercise as a potential treatment of cachexia in patients with advanced, incurable cancer. Weight loss and BMI are established diagnostic criteria for cachexia, and findings in this thesis confirm that these are valid criteria for classifying patients with cachexia from those with no cachexia. Furthermore, it seems that the measurement of other diagnostic criteria such as loss of muscle mass, loss of appetite, and increased inflammation is necessary to classify cachexia into different stages of cancer cachexia according to disease progression.

Measurement of diagnostic criteria, such as muscle mass and physical activity, can provide important information in a classification system for cancer cachexia. Validation of a body-worn activity meter in this thesis demonstrated high accuracy for measurement of time in an upright position and number of transfers between sitting and standing, but not the number of steps and energy expenditure. Furthermore, measurement of muscle mass using CT-based analysis showed that patients with advanced, incurable lung cancer can maintain and even gain muscle mass during cancer treatment despite being sarcopenic before starting chemotherapy and without having received any additional treatment for cancer cachexia. It was further shown that changes in muscle mass and not sarcopenia measured before treatment was a significant predictor of survival.

Physical exercise was in this thesis shown to be effective for increasing muscle strength, but not muscle mass during cancer treatment. Measurement of muscle mass was only included in a few studies. There is a lack of randomized controlled trials conducted in patients who are in the early stages of cachexia or who have cachexia in order to conclude whether physical exercise can be recommended as an integral part of treatment for cancer cachexia. Physical exercise is, however, feasible and safe for most cancer patients and should be recommended as a part of multimodal interventions to prevent or delay the development of cancer cachexia.

Acknowledgement

The work in this thesis has been carried out at The European Palliative Care Research Centre (PRC) in collaboration with the Department of Neuroscience at the Norwegian University of Science and Technology (NTNU) and the Cancer Clinic at St. Olav's University Hospital in Trondheim. The Liaison Committee between the Central Norway Regional Health Authority and NTNU funded the work in this thesis.

This thesis had not been possible without the patients that have volunteered to participate in the clinical studies. I am grateful for their valuable contribution to the research conducted in this thesis.

I would like to thank my supervisor, Professor Jorunn Lægdheim Helbostad. You invited me into your field of research more than seven years ago and since then, you have been my mentor, a good colleague and a friend. Thanks for sharing your knowledge, your time and your positive energy during these years and for your support in completing my thesis. Your work achievements and dedication in building an active research group for geriatrics, movement and stroke (GeMS) are impressive. I am truly grateful to have had the opportunity to be part of this, and look forward to future cooperation with you and the GeMS.

I would also like to thank my co-supervisors, Professor Stein Kaasa and senior researcher Line Merete Oldervoll. I am truly grateful to have had the opportunity to learn about clinical research from Stein and to be part of the excellent research environment at the PRC. Line, thank you so much for good supervision in the writing of Paper IV and this thesis, and for inviting me into the network for cancer rehabilitation in Norway.

All co-authors contributing to the planning and conduction of the papers included in this thesis deserves sincere thanks. Thanks to David and Tora for sharing your experience and knowledge about cancer cachexia and for all the discussions and hard work in Paper I. Thanks to international collaborators in Edinburgh including my co-author for Paper

II, Richard Skipworth. Thanks to Ingrid Riphagen for tidying up my literature search and for your contribution to Paper IV. Peter Fayers, thank you for statistical help. Finally, thanks to Bjørn Henning Grønberg for including me in your research, for good supervision in planning, analysis and writing of Paper III.

Completing a PhD is not possible without the support of good colleagues. Thanks to the research nurses at the Cancer Clinic that have helped out in my studies, especially Vanja and Cinzia. Thanks to Gunn-Heidi and Ragnhild for your good humour and excellent administrative skills. I would like to thank all my colleagues at the PRC and a special thanks to the girls in the "Kaffekroken" and to Trude. At the GeMS, my special thanks go to Kristin and Pernille who always share their knowledge and make me feel welcome, and to Gro, for being such a good friend. I would also like to thank my colleagues at Vardesenteret og Pusterommet St.Olavs Hospital and the Cancer Clinic for being supportive in the completion of my thesis. I look forward to work together with you all in the time to come.

I want to thank my family and friends for your encouragement and for always being there for me. Finally, I thank my husband Per Ståle. You are always loving, optimistic and strong and give me courage to be as good as I can possibly be. I thank you for your patience and for caring so lovingly for our two wonderful boys, Erlend and Andreas.

List of papers

PAPER I. Blum D., Stene G.B., Solheim T.S., Fayers F., Hjermstad M., Baracos V.E., Fearon K. E., Strasser F., Kaasa S. Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification system – A study based on data from international multicentre project (EPCRC-CSA). Annals of Oncology. 2014 Aug;25(8):1635-42

PAPER II. Skipworth R.J.E., Stene G.B., Dahele M., Hendry P.O., Small, A.C., Blum D., Kaasa, S., Trottenberg, P., Radbruch, L., Strasser, F., Preston, T., Fearon K.C.H., Helbostad, J.L. Patient-focused endpoints in advanced cancer: Criterion-based validation of accelerometer-based activity monitoring. Clinical Nutrition, 2011, 30(6), pp. 812-821.

PAPER III. Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, Grønberg BH. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncologica, 2014 Sep 16, pp 1-9. [Epub ahead of print]

PAPER IV. Stene G.B., Helbostad J.L., Balstad T.R., Riphagen I.I., Kaasa S., Oldervoll L.M. Effect of physical exercise on muscle mass and strength in cancer patients during treatment - A systematic review. Critical Reviews in Oncology/Hematology. 2013 Dec;88(3):573-93

Abbreviations

AE	Aerobic exercise
AM	Activity meter
BI	Bioelectric Impedance
BMI	Body mass index
CAE	Combined aerobic and resistance exercise
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRP	C-reactive protein
CSA	Computerised symptom assessment
CSA	Cross sectional area
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
DC	Disease Control
DEXA	Dual energy x-ray absorptiometry
DLW	Doubly labelled water
ECOG	Eastern cooperative oncology group
EE	Energy expenditure
EEA	Energy expenditure of activity
EORTC	European organization for research and treatment of cancer
EPA	Eicosapentaenoic acid
EPCRC	European palliative care research collaboration
ESAS	Edmonton symptom assessment system
FFM	Fat-free mass
HU	Hounsfield units
ICD	International classification of diseases
IL-6	Interleukin-6
KPS	Karnofsky performance status
L3	Level of third lumbar vertebrae
LBM	Lean body mass
LOA	Limits of agreement
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ONS	Oral liquid nutritional supplements
PA	Physical activity
PAL	Physical activity level
PD	Progressive disease
PF	Physical functioning
PG-SGA	Patient-generated subjective global assessment
PIF	Proteoglycan proteolysis-inducing factor
PR	Partial response
PRC	European palliative care research centre
QOL	Quality of life
RCT	Randomised controlled trial
RE	Resistance exercise
RECIST	Response evaluation criteria in solid tumours
REE	Resting energy expenditure
RM	Repetition maximum
RPE	Rate of perceived exertion
SD	Stable disease
SD	Standard deviation
SMCA	Skeletal muscle cross-sectional area
SMD	Standardised mean difference
SMI	Skeletal muscle index
TBW	Total body water
TEE	Total free-living energy expenditure
TNF-α	Tumour necrosis factor
TNM	Classification of malignant tumours
UC	Usual care
$VO2^{max}$	Maximal oxygen uptake
WHO	World health organisation
WL	Weight loss

List of tables and figures

Figures

Tables

1. Introduction

1.1 Perspectives

Cancer is one of the leading causes of premature death, with 7.6 million deaths worldwide in 2008. Globally, the incidence (the number of new cancer cases per 1,000 population) of cancer is estimated to increase from 11.3 million new cases in 2007 to 15.5 million in 2030 (1). The real increase in incidence of some cancer types and a growing aging population are factors that might explain these trends (2).

According to the Norwegian Cancer Registry, the number of people that are alive following a cancer diagnosis is expected to increase in the next decades (3). Today, approximately 60 % of all cancer patients live at least five years after receiving their diagnosis (2). Complete recovery from cancer is however not always possible (4). When a cure or long-term remission (no signs of cancer) becomes unlikely or impossible, the disease is considered to be advanced (5). As an example, nearly all patients with non-small cell lung cancer (NSCLC) develop advanced, incurable disease. Still, incurable does not mean untreatable, and thus, these patients can live with their diagnosis for months or even years (6).

1.2 Topic of this thesis

More than 50 % of all cancer patients, and up to 80 % of patient with advanced, incurable cancer develop a condition known as cachexia (7, 8). Cachexia is a complex condition characterised by loss of skeletal muscle mass (with or without the loss of fat mass) that is followed by progressive functional impairment and result in poor quality of life and reduced survival (9, 10). The presence of cachexia and, in particular the severe loss of muscle mass associated with this condition compromise the patient's ability to receive, tolerate and respond to cancer therapy (11, 12).

The lack of consensus among clinicians and researchers on how to define and classify cancer cachexia has resulted in slow development of evidence-based guidelines for diagnosis and treatment of this condition. However, during the last decades, increased knowledge about the underlying pathophysiology of cancer cachexia has emerged from

basic research and improved the understanding of this condition. Several groups of experts have attempted to develop classification systems for cachexia (13) and cancer cachexia (14, 15) using multiple diagnostic criteria i.e. loss of weight (incl. lean tissue and fat), reduced food intake and altered metabolism, anorexia, inflammation and physical and psychological impairments. There is consensus that these criteria represent clinically relevant domains and should be incorporated into a new formal classification system for cancer cachexia. However; more knowledge is needed about the clinical relevance of different diagnostic criteria and how they should be operationalised and assessed, and used to classify cancer cachexia (16).

In 2006, an EU-funded project, the European Association of Palliative Care Research Collaborative (EPCRC), was launched to contribute to the development of new international standards for classification of cancer cachexia (17). The work in this Ph.D. is closely related to work package 2.3 "Assessment and Classification of Cancer Cachexia" in the EPCRC project. One of the more long-standing aims of the EPCRC was to establish international research collaboration within palliative care research, and in 2009, the Palliative Care Research Centre (PRC) was established. The work in this thesis is conducted as part of the planning and initiation of one of the clinical trials initiated from PRC, the MENAC trial (Clinicaltrials.gov Identifier: NCT01419145). The MENAC trial is a multicentre, open, randomized controlled trial comparing a multimodal intervention (Exercise/Nutrition/Anti-inflammatory Medication) for cachexia versus standard cancer care in patients with advanced, incurable cancer receiving palliative chemotherapy.

The main topic of this thesis is therefore classification and assessment of cancer cachexia with a particular focus on muscle mass and strength and physical activity, and finally, treatment of cancer cachexia. The thesis includes four published papers, two method studies on classification (Paper I) and assessment (Paper II), one prospective cohort study (Paper III), and finally, a systematic literature review (IV).

2. Theoretical background

2.1 Pathophysiology of cancer cachexia

Early in the third century B.C, Hippocrates describes a condition that might have been cancer cachexia: *"The flesh is consumed and becomes water… the abdomen fills with water; the feet and legs swell, the shoulders, clavicles, chest, and thighs melt away….The illness is fatal."*(7). As an early description of cachexia pathophysiology, this could illustrate how involuntary weight loss was considered an ominous sign of poor prognosis (18). For centuries, cachexia was recognised as an inevitable, non-specific, serious complication of various underlying chronic illnesses, and in the early twentieth century, it was described as a progressive, end-stage manifestation of cancer (19). Great advances both within basic and clinical research have improved knowledge about the underlying pathophysiology of cancer cachexia (20). As a primary condition, cancer cachexia is a result of a complex interaction between the tumour and the body's response to the tumour. This host-tumour interaction includes several processes including a systemic inflammatory response, altered tumour metabolism, anorexia (i.e. abnormal neuro-hormonal changes that regulate appetite) and the rapid breakdown of proteins (muscle) and lipids (fat) (13, 14). These interactions are complex but as a simple overview, Figure 1 shows the main pathophysiological pathways for primary cachexia.

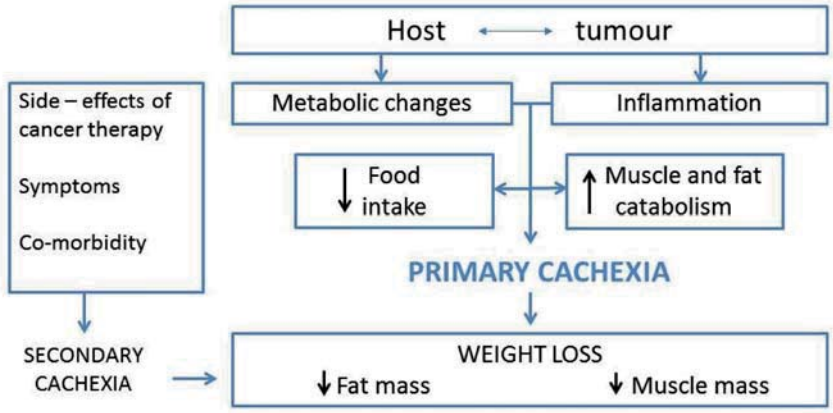


Figure 1. Pathophysiology of cancer cachexia.

Activation of several pro-inflammatory cytokines (e.g. Interleukin-1 and -6, tumour necrosis factor (TNF)-α), is an important part of the host's anti-tumour response. However, these cytokines are also involved in the progression of the tumour, and might, in combination with alterations in metabolic pathways and other neuro-hormonal changes, be important factors to explain the increased catabolism of muscle and fat in cancer cachexia (21-23). Furthermore, the progressive loss of muscle is caused by an abnormal activation of proteolytic pathways that reduce the rate of protein synthesis and increases protein degradation (24, 25). The proteoglycan proteolysis-inducing factor (PIF) might seem to account for the increased muscle protein degradation and decreased protein synthesis (26). Furthermore, levels of other catabolic mediators i.e. Myostatin and Angiotensin II have been shown to be increased in experimental cancer cachexia and act as negative regulators of muscle proteolysis (27).

A primary cause of reduced food intake in cancer cachexia includes the decreased central drive to eat or loss of appetite, also known as cachexia-anorexia syndrome (28). The underlying pathophysiology of this syndrome is not fully understood. However, a main theory is that the inflammatory cytokines released by the tumour affect hormonal pathways that control the regulation of appetite and causes anorexia (26). Secondary cachexia is caused other factors that might impair food intake i.e. stomatitis, diarrhoea, constipation, dyspnoea, depression and pain (29). These symptoms are, in contrast to primary cachexia, often readily reversible with appropriate treatment and are therefore important to identify (30).

2.2 Classification of cancer cachexia

In medicine, classification is used to assign individual patients into separate and distinct groups on the basis of some shared diagnostic criteria that are typical of a specific disease or condition.

There have been several attempts to identify diagnostic criteria and classify cancer cachexia, as shown in Table 1.

Table 1. Former attempts to classify cancer cachexia

Authors	Proposed classification systems
Cancer Cachexia Study Group ***Fearon et al., 2006*** [31]	Cachexia defined as: a) Weight loss: ≥10% last six months b) Low food intake: ≤1500 kcal/d c) Systemic inflammation: C-reactive protein ≥10 mg/L
Society for Cachexia and Wasting Disorders ***Evans et al., 2008*** [13]	Cachexia defined as weight loss of at least 5% (oedema free) in 12 months or less in the presence of underlying illness (or BMI<20kg/m^2). PLUS 3 out of 5 factors: Decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry (CRP, Haemoglobin, Albumin) No staging proposed
SCRINIO Working Group ***Bozzetti et al., 2009*** [32]	Cachexia defined as weight loss ≥ 10% Pre - cachexia: Weight loss ≤10% AND additional diagnostic criteria: anorexia, early satiety and fatigue
Special interest groups (SIGs): Cachexia-anorexia in wasting diseases' and 'Nutrition in geriatrics.' ***Muscaritoli et al., 2010*** [14]	Cachexia defined according to Evans 2008. Pre – cachexia: a) underlying chronic disease b) unintentional WL ≤ 5% of usual body weight during the last 6 months c) chronic or recurrent systemic inflammatory response d) anorexia or anorexia - related symptoms
EPCRC consensus definition and classification of cancer cachexia ***Fearon et al., 2011*** [15]	Weight loss > 5% the last six months, OR BMI <20 kg/m and any degree of weight loss > 2%, OR Appendicular skeletal muscle index consistent with sarcopenia and any degree of weight loss > 2% Classifies into stages: pre-cachexia, cachexia and refractory cachexia. Proposes additional criteria: anorexia/reduced food intake and systematic inflammation. Refractory cachexia: a) Not responsive to anti-cancer treatment b) Low performance score (Karnofsky) c) < 3 months expected survival

The CASCO Score ***Argiles et al., 2011*** [33]	Classifies cachexia into mild (0-25), moderate (26-50), severe (51-75), and terminal (76-100) according to five domains: a) WL (5 cut- offs for severity) or LBM loss (> 10%) c) Anorexia d) Inflammation (plasma IL-6 and CRP; three cut –offs), immunological (lymphocytes etc.), and metabolic (albumin, anaemia, etc.) disturbances d) Physical performance (PA, hand-grip strength, stair climb, 6 min walk) e) Quality of life (3 cut-offs based on QoL questionnaire)
The cachexia clinic ***Vigano et al., 2012*** [34]	Classifies into pre-cachexia, cachexia and refractory cachexia according to different combinations of clinical criteria: a) Anorexia (ESAS appetite score) b) Nutritional intake (PG- SGA Box 2) c) WL (> 5% last 6 months) or BMI>20 + any WL>2%, or sarcopenia + any WL>2 % d) Hand grip strength e) Biological measurements (anaemia, CRP, albumin or white blood count)

Many diagnostic criteria have been proposed, but the far most common criterion is weight loss (35, 36). Various cut-offs for weight loss (2%, 5%, 10%, 15% and 20%) as well as different time frames (e.g. weight loss during the past 1, 3 and 6 months) have been used in clinical studies (16). In 2006, Fearon et al (31) tested a classification model including multiple diagnostic criterions i.e. weight loss, reduced food intake and systemic inflammation. They suggested that all these criteria and not only weight loss could be used to better classify cancer cachexia. Later, an international group of researchers and clinicians formally agreed to add five diagnostic criteria in addition to weight loss, namely decreased muscle strength, reduced muscle mass, fatigue, anorexia and biochemical alteration (including inflammation) (13). This proposal was later approved by the Special Interest Group (SIG) on cachexia-anorexia in chronic wasting diseases (14).

These attempts to classify cancer cachexia are supported by a strong clinical and pathophysiological rationale; however not all the included criteria were specific to cancer, nor validated as diagnostic criteria in classification system for cancer cachexia.

These proposals were however the basis for the work towards a consensus-based framework for classification of cancer cachexia proposed by the EPCRC in 2011 (15).

In the EPCRC consensus, it was agreed that weight loss greater than 5% or alternatively, weight loss greater than 2%, and a BMI<20 kg/m² are established diagnostic criteria for cancer cachexia. In addition, a measurement of muscle mass was highly advocated as a diagnostic criterion. Several sex-specific cut-off values using different methods of measurement of muscle mass were recommended (Table 2).

Table 2. Sex-specific cut-off values for loss of muscle mass according to different measurements methods (15).

Method of measurement	Muscle mass measurements	Cut-off values
Anthropometry	Mid upper-arm muscle area	men <32 cm²; women <18 cm²
Bioelectrical impedance	Fat-free mass index (without bone)	men 14·6 kg/m²; women <11·4 kg/m²
Dual energy x-ray absorptiometry	Appendicular skeletal muscle index	men <7·26 kg/m²; women <5·45 kg/m²
CT- image analysis	Skeletal muscle index	I) men <55 cm²/m²; women <39 cm²/m² i) men ≤ 52.4 cm²/m²; women ≤ 38.5 cm²/m²

Furthermore, the EPCRC consensus proposed that cancer cachexia can progress along a continuum of various stages from early (pre) cachexia, cachexia to late (refractory) cachexia (Figure 3).

Since 2011, others have proposed systems that classify cancer cachexia into stages (33, 34). Staging as part of a classification for cancer cachexia is important for guiding clinical decision making about treatment and prognosis. This is because treatments that are given to prevent or delay the development of cancer cachexia need to be initiated at an early stage (pre-cachexia). For patients in a late (refractory) stage, preventive treatment strategies have few benefits and might cause more side-effects and distress for patients.

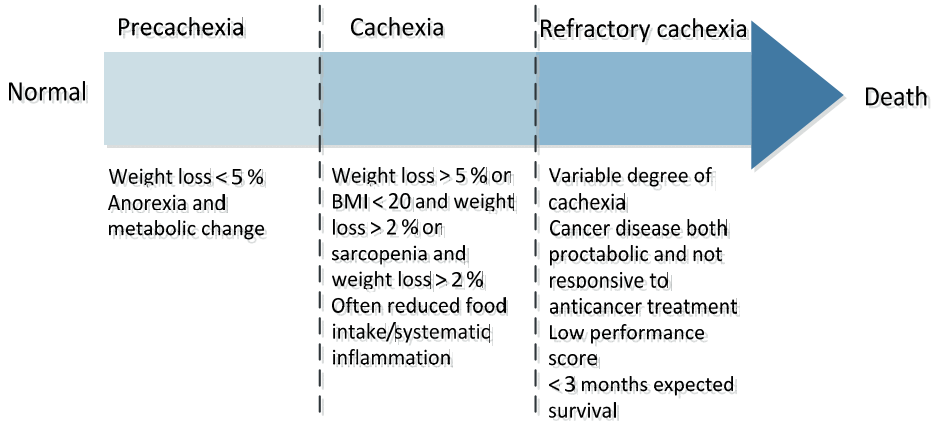


Figure 3. Staging of cancer cachexia.

2.3 Assessment of cancer cachexia domains

Assessment can be defined as "the evaluation or estimation of the nature, ability, or quality of a certain phenomenon." (37). To classify cancer cachexia, an accurate, appropriate and standardized assessment of relevant diagnostic criteria is essential.

The EPCRC consensus proposed several key cancer cachexia domains as part of the framework for a new classification of cancer cachexia, namely stores, catabolism, nutrition and function. Although the EPCRC consensus agreed about some important diagnostic criterions for these domains (Figure 4), they did not agree on how to assess these. In the following, examples of tools and methods that can be used to assess cancer cachexia domains are presented.

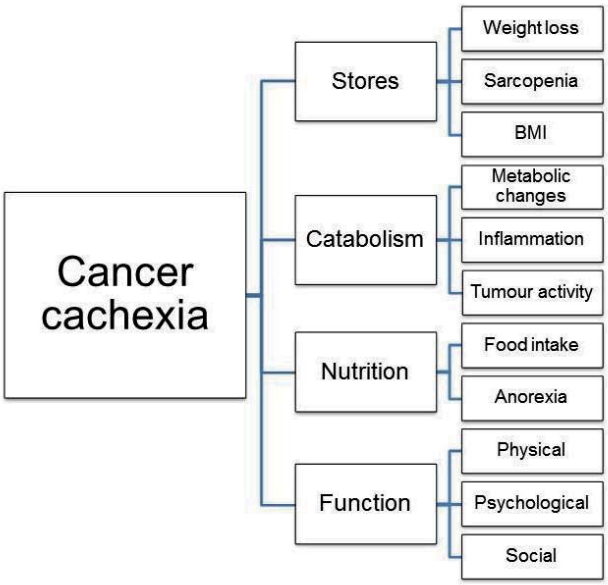


Figure 4. Cancer cachexia domains and sub-domains

2.3.1 Stores

Body weight and BMI can be assessed using readily available methods, e.g. simple scales, or by asking the patients themselves in interviews or by self-report questionnaires. These tools might be time-efficient and require limited resources. However, they cannot measure muscle mass. Bioelectric Impedance (BI) is a method that can give estimates of fat-free mass (FFM). A measure of FFM includes all non-fat components of the human body such as skeletal muscle, bone and water. BI is easily administrated and therefore much used as an outcome in cachexia trials. BI is most suitable for group comparisons between groups of patients with substantial alterations in body composition (38).

Dual Energy X-ray Absorptiometry (DEXA) is a technique used to derive the mass of one material in the presence of another through knowledge of their unique X-ray attenuation at different energies. This method provides a direct measure Lean body mass (LBM) in kilograms (39). LBM primarily consists of skeletal muscle, with the

remainder comprised of metabolic tissues (i.e. kidney and liver) and intracellular and extracellular water and thus, DEXA cannot separate skeletal muscle from other lean tissues in the body (38). This method is however considered the gold standard for measurement of body composition and is commonly used as a surrogate measure of skeletal muscle mass in clinical trials.

CT-image based assessment of muscle mass is preferable to other body composition methods as it can precisely distinguish skeletal muscle from other tissues (i.e. visceral and subcutaneous fat; intra-muscular fat) and it can also separate between individual skeletal muscles (39). The estimates of skeletal muscle mass from CT-images are derived from the different attenuation characteristics of the different tissues and are measured in Hounsfield Units (HU). In the measurement of skeletal muscle mass, an HU ranging from – 29 to 150 HU is used to separate muscle mass from other tissues e.g. fat (40). A single CT-image taken at the third lumbar vertebral level is used as a standard landmark for body composition analysis (41) and can be used to develop algorithms to predict whole body muscle mass in healthy individuals (40), and in cancer patients (42).

CT-image analysis was first performed for body composition analysis by Heymsfield and colleagues (43). In the past decade, the methods have been increasingly used to measure body composition in various cancer populations for the purpose of predicting prognosis (12, 44-48) and to assess longitudinal changes in muscle mass during the course of cancer disease (11, 44, 49-51).

CT- scans are commonly performed for diagnostic and follow-up purposes in routine oncological care and can thus also be used retrospectively to assess body composition. There is however some limitations as CT-imaging are expensive, exposes the patients to high dose of radiation, and it requires high technical skills (38). Thus, the assessment of muscle strength is sometimes proposed to be a “proxy” and a more feasible alternative to sophisticated measurements of muscle mass (52, 53). Muscle strength is a direct result of physiological factors such as muscle mass but is also determined by neurological and biomechanical factors. It has been shown that muscle strength is

affected, regardless of changes in muscle mass in patients with advanced cancer, and that these two variables are not linearly correlated (54).

2.3.2 Catabolism

The assessment of catabolic drive implies some type of measurement of the underlying disease and can be assessed by indirect measures such as tumour size and/or tumour progression, in addition to more direct measures of tumour metabolism such as systemic inflammation. The Response Evaluation Criteria in Solid Tumours (RECIST) are used to measure tumour size and/or tumour progression and is a standard for evaluation of response to cancer treatment (55).

The most widely accepted index of systemic inflammation is serum C-reactive protein (CRP) (15). It should however be recognised that cachexia can exist without overt systemic inflammation and therefore, measures of tumour activity, as well as other metabolic factors that might contribute to catabolism (e.g. insulin resistance, prolonged high-dose corticosteroid therapy, hypogonadism, increased resting energy expenditure) should be considered (15).

2.3.3 Nutrition

A nutritional assessment should include some measurement of oral food intake and any secondary causes of reduced food intake, i.e. constipation, dyspnoea and pain. The patients can for example be asked to recall their diet during the last 24 hours or three days (56). The patient-generated subjective global Assessment (PG-SGA) is a patient-reported outcome. In addition to addressing weight loss, it grades the amount and type of intake and addresses secondary causes of reduced food intake (57).

Anorexia or loss of appetite is most often assessed by self-report in advanced cancer patients. For instance, appetite items from patient reported outcomes (PRO's) such as the Edmonton Symptom Assessment System (ESAS) (58) or the European Organization for Research and Treatment of Cancer (EORTC) Quality of life questionnaire, QLQ C30 (59) are commonly used and shown to be both practical and feasible to use in the assessment of advanced cancer patients (60).

2.3.4 Function

Physical function

Physical function refers to the patients' physical performance in everyday life activities. Assessment of physical function includes both the patient's perception of what he can do (self-report), the health providers perception of what the patient can do (observer-based methods) and what he can actually do (performance measures) (61). In clinical studies, it is common to ask the patients about their physical function using self-report methods; for instance, questionnaires that assess average physical function over a specified period. These are used because they are easily administered. However, recall bias is a challenge, especially for elderly and very sick patients (62, 63).

Observer based indexes (health care provider rated) are commonly used to measure physical performance in the clinical setting, like for instance, the ECOG or Karnofsky Performance Status, and they are known as powerful prognostic tools (64) and used as entry criteria into clinical trials (29).

Physical performance tests are used to measure what the patient is capable of doing, and can capture different aspects of physical function i.e. muscle strength, balance or gait speed, at a single point in time. The challenge with this method is that performance may vary within and between days for patients with advanced, incurable cancer and the results may be influenced by how well the patient feels at the time of testing (65).

Physical activity

Assessment of physical activity (PA) can capture what the patients is doing; such as the type of activity, the frequency (how much) and duration (how long) of activity as well as the intensity (how hard a person works, or how much energy is used) (66). Overall PA and these different sub-domains of PA can be measured using a variety of methods such as activity diaries, recall questionnaires and interviews, and even behavioural observation, but these methods are subject to bias, can be time-consuming and not all are feasible for long-term registrations (67). Assessment of PA can also include measurement of energy expenditure (EE). Methods such as the doubly labelled water technique (DLW) (68) and indirect calorimetry (69) can give reliable and valid

information about energy expenditure; however both are comprehensive and expensive to use in routine clinical practice and do not indicate what activities the patients are doing (70, 71).

Activity meters can give objective measurements of everyday activities over longer time periods by using the amplitude and frequency of the acceleration signal embedded in the device (72, 73). Small sensors fixed to the skin can record free-living physical activity for many days without changing battery, enabling continuous monitoring of physical activities in the home setting (74). Activity meters are capable of identifying episodes of walking, standing, and sitting/lying and can record number of steps and step rate (cadence) while walking (75). They also provide information about energy expenditure by assigning each activity an estimated energy cost in metabolic equivalents (76).

There are some aspects that should be noted in terms of using activity meters to assess PA in advanced cancer patients who are in a pre-cachectic or cachectic state. These patients have limited spare capacity and will function close above the thresholds need to perform daily functions (61). Their PA is shown to be much lower than in a healthy individual (77, 78) and non-cachectic cancer patients (79), and characteristically, they might only move short distances, and walk at slow speeds. In studies of elderly hip fracture patients, this type of physical activity behaviour has shown to compromise the validity of the activity meters (80). It is therefore important that the activity meters derive outcomes of high accuracy and thus, they should be validated on the particular population of interest (81).

The ActivPAL™ is a small, lightweight single axis accelerometer that is attached to the patient's thigh and has a battery capacity for continuous recording of seven days. The accelerometer embedded in the ActivPAL meter produce signals reflecting thigh inclination while wearing it and samples data at 10 Hz (82). This device has shown to give valid estimates of physical activity in both young adults and community-dwelling older adults (75, 82, 83). ActivPAL data has also been validated against other accelerometer-based systems (84, 85). Feasibility studies conducted in patients with advanced cancer has shown that the ActivPAL is easy to use and safe (74, 86).

However, the accuracy of recognition of PA from acceleration signals derived from activity meters in cancer patients with advanced disease is not yet determined and thus, the validity of previous reports on activity levels and patterns remains uncertain.

Psychosocial function

Cachexia is a significant emotional burden for many cancer patients (87). Assessment of psychosocial function in cancer cachexia is about measuring the negative emotions associated with reduced dietary intake, involuntary weight loss and the social consequences of these symptoms (88). There is an abundance of tools that are used to assess different aspects of psychosocial functioning e.g. quality of life questionnaires (89), anxiety and depression questionnaires (90, 91) or interviews with patients and their families (92).

2.4 Treatment of cancer cachexia

2.4.1 Treating the cancer

The most efficient treatment for cancer cachexia is to treat the underlying cause; to cure the cancer. Treatment that is directly targeting the tumour (tumour – targeting therapies) includes surgical procedures to remove the tumour and lymph nodes, hormone therapy to suppress tumour growth and ionizing radiation or cytotoxic "anti-neoplastic" drugs that destroy cancer cells. These treatments can be given as single therapies or as combination therapy. It is common to refer to tumour-targeting therapy as either curative or palliative. In patients with advanced stage cancer, a cure is not a likely outcome. Thus, the aim of the tumour- targeted treatment is to delay progression or reduce the size of the tumour to relieve symptoms and sometimes to prolong life.

A less appreciated effect of tumour-targeted treatment is its role in the treatment of cancer cachexia (93). As both the progression of the tumour and cancer cachexia is influenced by the same inflammatory factors (46, 93, 94), tumour targeted treatments used to delay tumour progression, might thus possibly contribute to attenuate the catabolic effects caused by the primary cachexia (11). Based on journal review, one study found that patients with substantial gains in muscle mass had a better response to treatment, ate well and had good symptom control, whereas those who lost muscle

mass, had progressive disease and a short survival (11). These are important findings, as it has been shown that weight loss can lead to patients receiving significantly less chemotherapy and develop more toxicity i.e. nausea, vomiting and appetite loss during tumour-targeted treatment (95, 96).

2.4.2 Treating cancer cachexia

A number of promising therapeutic drugs that target the underlying skeletal muscle catabolism and tumour-induced inflammation that drives cancer cachexia is under development. Still, the efforts have so far not resulted in approved therapies. This can be due to a number of factors. Firstly, clinical studies have mainly investigated the therapeutic effect of single pharmacological or nutritional treatments (29). Secondly, the have been initiated at a time where cachexia is manifest or in a late stage and thus not responsive to treatment (97).

There has however been a paradigm shift towards more comprehensive, early onset multimodal treatment approaches in the management of cancer cachexia (20). It is now recognised that cancer cachexia can have an early onset and that treatments must be initiated at a pre-cachectic stage. Furthermore, it is appreciated that adequate tumour control and control of symptoms given concurrent with cachexia treatments is essential. Finally, a unified therapeutic approach that incorporates nutrition, physical exercise and combinations of drugs to enhance anabolism and reduce catabolism is considered important.

So far the evidence supporting multimodal treatment is limited. However, there are ongoing clinical trials (98, 99). A recent review synthesised current evidence of multimodal treatment for cancer cachexia (99). The review showed that it might be possible to increase weight and to some degree muscle mass if a combination of anti-inflammatory approaches such as non-steroidal anti-inflammatory drugs (NSAIDs) and Eicosapentaenoic acid (EPA) is used. It further concluded that the effects of these drugs, or any drug to combat cancer cachexia, cannot be maximised unless additional interventions to maintain nutritional status, prevent muscle loss, and maintain physical function is administered.

Anti-inflammatory drugs

NSAIDs have the potential to reduce muscle wasting by modulating inflammation and regulation of appetite (100). A systematic review of use of NSAIDs in cancer cachexia interventions studies demonstrated positive effects of NSAIDs on body weight, and lean body mass, but the evidence was not found sufficient to recommend the administration of NSAIDs outside clinical trials (101).

EPA is an n-3 fatty acid that has anti-inflammatory properties including the capacity to down-regulate pro-inflammatory cytokine production and the acute phase protein response in cancer patients (99). There is some evidence that EPA can increase lean body mass (LBM) and other cachexia related symptoms. However, these findings are based on small, uncontrolled clinical trials, and not confirmed in RCTs (102).

Nutrition

Nutrition is an essential part of cachexia treatment as it is not considered possible to improve or stabilize weight if nutritional needs are not met (56). Strategies to increase energy intake in patients are parenteral nutrition (feeding distributed intravenously), enteral nutrition (tube feeding) or dietary counselling with advice aiming to increase oral intake. Studies on the effect of aggressive feeding in cancer patients such as parental and enteral nutrition have shown limited effect in reversing weight loss and are not recommended by cancer cachexia guidelines (56).

Dietary counselling can be used to increase intake of energy-dense foods, increase meal frequency and/or to use oral liquid nutritional supplements (ONS) (103). It has been shown that ONS are useful to increase weight and energy intake in cancer patients. Whether this applies to different types and stages of cancer is however not clear (104). According to a recent systematic literature review there is a positive effect of dietary counselling on weight loss and energy intake in patients with advanced cancer at different stages of cachexia (56).

Physical exercise

The possibility that physical exercise might contribute to reverse the pathophysiology of cancer cachexia and thus might play an important part of anti-cachexia treatment is currently debated (105-108). It has been suggested that physical exercise may attenuate

muscle protein degradation by down-regulating the activity of pro-inflammatory cytokines and enhance immune function (109). Strength training in particular is a potent stimulus of growth in muscle mass and increased strength (105). So far, evidence to support this in cancer cachexia is only provided by experimental animal studies (110, 111) and in chronic diseases other than cancer, i.e. COPD (112, 113) and chronic heart failure (114).

An active lifestyle, including regular physical exercise, is associated with health gains in terms of improved fitness, disease prevention, improved mental health and longer survival (115). Studies of patients with different types and stages of cancer have shown that participation in physical exercise programs increases muscle strength and aerobic capacity, reduces fatigue and anxiety, and improves self-esteem and quality of life (116-118). Physical exercise is considered to be well tolerated, feasible and safe during and following cancer treatment (116), even by patients with advanced stage cancer (119).

Table 3. Cancer-specific guidelines for physical exercise prescriptions during cancer treatment (120-122).

Type	Aerobic – based exercise	Resistance – based exercise
Frequency	At least 3- 5 times per week depending on the intensity	1-3 times per week with rest days in between
Intensity	Moderate – 50 – 75 % VO2 max or Borg RPE 11-14	0 – 80 % of 1 RM or 6-12 RM
Duration	At least 20 – 30 min continuous exercise or 3-5 min bouts with rest intervals	8-10 exercise, 1-4 sets per muscle group
Progression	Should meet frequency and duration goals before increase in intensity.	

In principle, the same physical exercise recommendations that are given in the general population (123) are also included in cancer-specific guidelines, as shown in Table 3 (120-122). Prescribing physical exercise in patients with advanced, incurable cancers is

challenging due to their progressive disease and short survival (124, 125). Drop out-rates from physical exercise interventions are often high due to poor tolerance, fatigue and lack of motivation (126). Thus, evidence-based guidelines for physical exercise is largely based on studies conducted in cancer patients treated with curative intent (122).

3. Aim and research questions

The overall aim of this thesis is to contribute to the improved understanding of cancer cachexia through clinical research on classification, assessment and treatment of cachexia in cancer patients.

The following research questions were answered in this Ph.D.:

Is information about weight loss and BMI sufficient to classify cancer cachexia in patients with advanced, incurable cancer and can information from other domains (intake, catabolism and function) improve a classification of cancer cachexia into several stages?

How accurate is a body-worn activity meter in measuring different dimensions of physical activity in patients with advanced cancer?

Is a change in muscle mass during palliative chemotherapy associated with treatment response in patients with advanced non-small cell lung cancer; and is a change in muscle mass a prognostic factor for survival?

What is the effect of physical exercise performed during cancer treatment on muscle mass and strength across cancer patient cohorts with different diagnoses and stage of disease?

4. Materials and methods

4.1 Study designs for papers included in the thesis

The thesis comprises of four papers based on data from three clinical studies (Paper I-III) and a systematic review (Paper IV). Design and study populations for the clinical studies are shown in Table 4.

Table 4. Design and study populations for the clinical studies (Paper I-III) and the systematic review (Paper IV)

Paper	Study	Design	Population	N included (analysed)
I	EPCRC - Computerised Symptom Assessment Study (CSA)	Cross-sectional, method study Multicentre	Metastatic or locally advanced cancer	1070 (861)
II	EPCRC - Activity Monitoring by use of Electronic Body Worn Sensors Study (AMOEBS)	Cross-sectional method study Multicentre	Advanced, incurable cancer (Controls: healthy adults)	66 (59)
III	HELIK – Assessment of Change in Muscle Mass during Chemotherapy by Computer Tomography (CT-HELIK)	Prospective cohort study Single centre	Advanced non-small cell lung cancer (NSCLC)	52 (35)
IV	Systematic literature review		All types and stages of cancer Undergoing active cancer treatment	16 randomised controlled trials

Abbreviations: EPCRC: The European Palliative Care Research Collaboration. HELIK: The Health Related Quality of Life during Chemotherapy Study.

4.2 The clinical studies (Paper I-III)

4.2.1 EPCRC-CSA Study

In Paper I, data from the Computerized Symptom Assessment Study (CSA) initiated by The European Palliative Care Research Collaborative (EPCRC) was used.

The EPCRC-CSA study is a cross-sectional, multicentre, observational study including 1070 patients with advanced cancer. In the period from October 2008 until December 2009, in-and out-patients were recruited from palliative care units, hospices and general oncology and medical wards in several European countries (Norway, United Kingdom, Austria, Germany, Switzerland, and Italy) and in Canada and Australia. Patients were eligible if they were aged ≥ 18 years, had an incurable metastatic or locally advanced cancer diagnosis and were able to complete questionnaires.

In the CSA study, data were collected by use of touch sensitive computers (HP Compaq TC4200 1200 tablet PCs made by Hewlett-Packard Development Company LD) (127). Data was entered by tapping directly on the computer screen with an electronic pen. Assessment consisted of two parts, one completed by the study coordinators and the other completed by the patients. If necessary, help was provided to the patients by a study nurse.

Of the 1070 patients assessed in the EPCRC-CSA study, 209 patients were excluded from the Paper I study due to withdrawn consent (n=4), technical failure during data collection (n=15) or incomplete or missing data from questionnaires (n=190).

4.2.2 EPCRC-AMOEBS study

In Paper II, data from the AMOEBS study (Activity Monitoring by use of Electronic Body Worn Sensors), was used.

The AMOEBS is a multicentre study that includes data from two cross-sectional method studies initiated by the EPCRC project. These studies were the Video study and the Doubly Labelled Water (DLW) study. In the Video study, forty-nine patients with advanced cancer (predominantly aero-digestive and urogenital) were included from

cancer clinics (in-and out-patients) at three European study centres (Norway, Switzerland and Germany). The data collection was conducted in the period between November 2007 and April 2008 by research teams at the respective study sites. Four patients were excluded from the Video study due to disease progression (n=1) and missing data (n=3), leaving 45 patients for final analysis. In the DLW study, seven patients with advanced oesophago-gastric cancer were included from a cancer in- and out-patient clinic in Edinburgh. In addition, ten healthy volunteers were recruited as controls. Three study participants (one cancer patients and two healthy adults) were excluded from the final data analysis due to missing data.

4.2.3 CT-HELIK study

In paper III, data from a larger clinical trial, Health Related Quality of Life during Chemotherapy (HELIK), conducted by the European Palliative Care Research Centre (PRC) and the Lung Department at St. Olav University Hospital was used.

The HELIK study included fifty-four patients diagnosed with advanced, stage IIIB/IV Non-Small Cell Lung Cancer (NSCLC) from the lung ward (day-care unit) in the period from August 2009 to May 2010. Out of these, 35 patients were concurrently selected to participate in a single centre prospective cohort study (CT-HELIK study) based on the following eligibility criteria: i) patients had received at least one course of chemotherapy, ii) had abdominal CT-scans including images taken at the third lumbar vertebral level taken, and iii) two consecutive CT-scans were taken before starting chemotherapy and after chemotherapy. Reasons for exclusion were discontinuation from the HELIK- study (n=10), or not fulfilling the eligibility criteria for the CT-HELIK study (n=9).

4.3 Methods (Paper I-III)

4.3.1 Classification models for cancer cachexia

In paper I, two classification models based on information about weight loss (last six months prior to study entry) and body mass index (BMI) was used. These models consisted of 1) a two-group model (Model 1) to validate the diagnostic criteria (no-

cachexia versus cachexia) and 2) a four-group model (Model 2) to examine a preliminary framework for classification of cancer cachexia into stages (Figure 4A and 4B). To further explore the consensus framework definition of pre-cachexia, a weight loss model adding information from the cachexia domains catabolism (CRP < or > 10 mg/l) and food intake (appetite ESAS > 3), was tested in term of survival.

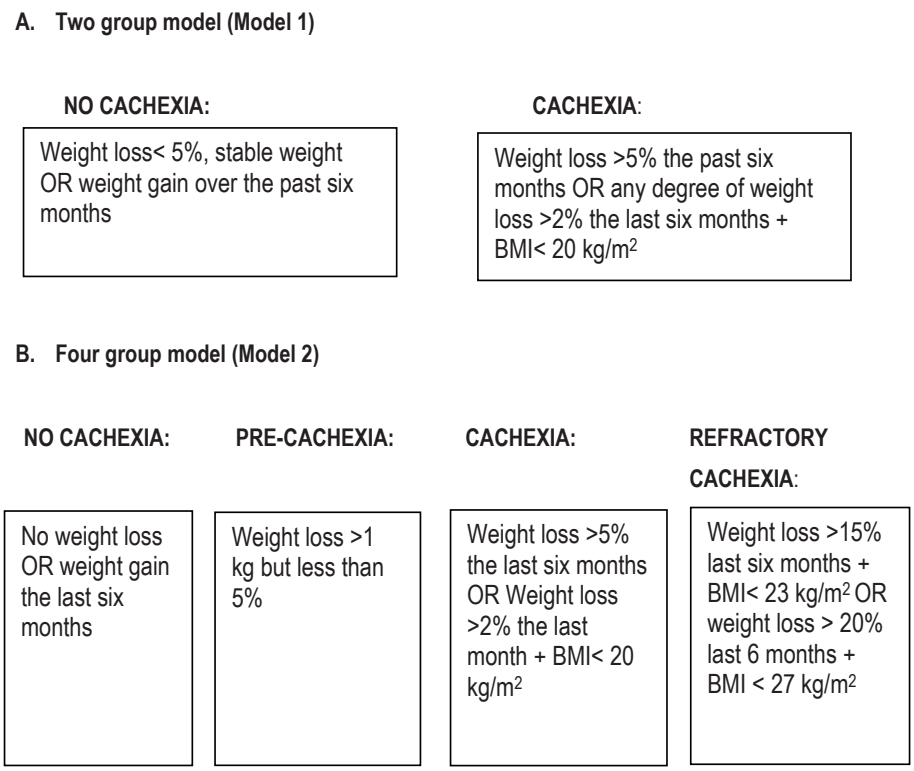


Figure 4A and B: Classification models for cancer cachexia used in Paper I

4.3.2 Accelerometer-based physical activity monitoring

In Paper II, accelerometer-based activity monitoring was used for physical activity recognition (time spent in body position, transfers and steps) while performing an in-lab mobility test protocol (Video Study) and for long term recording of total free-living energy expenditure (DLW study).

In both studies, the ActivPAL was attached to according to a standardised protocol on the patient right thigh using self-adhesive stickers. During the long-term registration of data in the DLW study, the patients were asked to remove the device during water-based activity.

The software package provided by the manufacturer (PAL Technologies Ltd, Glasgow, UK) was used to download accelerometer data from the activity meter via an USB interface docking station. From the software, data on time spent in body position (lying, sitting, standing, and walking), transfers from lying/sitting to standing/walking, step counts and estimates of energy expenditure was derived.

Video study

In the Video study, a two-dimensional digital video camcorder (Sony Handycam DCR-HC96) was used to record activities performed by the patients as part of the mobility test protocol while concurrently wearing the ActivPAL™. To synchronise time between the camcorder clock and the ActivPAL™, both devices were connected to the same PC before starting the test procedure. The validation protocol (Appendix 1) consisted of two series of activities selected from physical test batteries developed for use in old and frail persons (128, 129). Testing lasted 30-45 minutes and was performed in a controlled environment in the hospital ward. Series I included 10 standardised activities such changing body position from sitting to standing, transfers and walking at different speeds. Series II included 10 free-living activities intended to mimic everyday life situations in the home environment, and each participant completed three randomly selected activities. Participants were offered physical support or to use a walking aid if required during all activities.

DLW study

In the DLW study, a minimum of seven days of continuous recording using the ActivPAL™ was completed for each patient. Except during water-based activities, the patient wore the ActivPAL™ at all hours during the day and at night in the assessment period.

Doubly labelled water technique

Total free-living energy expenditure (TEE) was measured over a two-week period using the DLW technique. In the preparation of the doubly labelled water (DLW), doses of deuterium (100 % $^{2}_{H}$-H_2O) and Oxygen -18 (10 % ^{18}O- H_2O) were made from a common stock for the whole study, optimized for body weight of 70 kilograms (kg) and assuming 40 kg total body water (TBW). A five kg dose stock was prepared, and this was aliquoted into 125ml leak proof, wide neck polypropylene bottles (#2105-0004, Nalgene, NY, USA) and stored at -20 degrees Celsius until required.

On the first day of the study (day 0), the subject collected a urine sample and poured an aliquot (of urine) into a 30 ml universal container. A bottle of the prepared dose of DLW was consumed by the patient ensuring that all DLW had been ingested. Identical procedures were repeated by the patient on study day 1, 2, 3, 7, 12, 13 and 14. Urine samples were frozen at -20°C prior to analysis. Urine samples were prepared using methods described by Scrimgeour et al. (130) and Prosser et al. (131).

Indirect calorimetry

Resting energy expenditure (REE) was measured by indirect calorimetry using a ventilated hood technique (GEM; NutrEn Technology Ltd, Lancashire, UK) (132). Patients attended the hospital lab at 08:00 AM following an overnight fast and were instructed to rest in a supine position for at least 30 min before starting testing. Measurements were performed for at least 30 min. Indirect calorimetry provides measurements of V^{O2} and V^{CO2}, which have an error of less than 2.3% (133).

4.3.3 Image-based assessment of muscle mass

In Paper III, electronically stored computerised tomography (CT) images of the abdominal region were collected from the medical records of individual patients and assessed using a commercially available medical imaging software program (Slice O' Matic v 4.3 Tomovision, Canada). This software has been used in several publications to quantify skeletal muscle cross-sectional area and had an estimated measurement error of < 2.0 % (39, 40, 42). From a series of CT-images, one single image taken at the level

of the third lumbar vertebra (L3) was selected using a scrolling function in the imaging software.

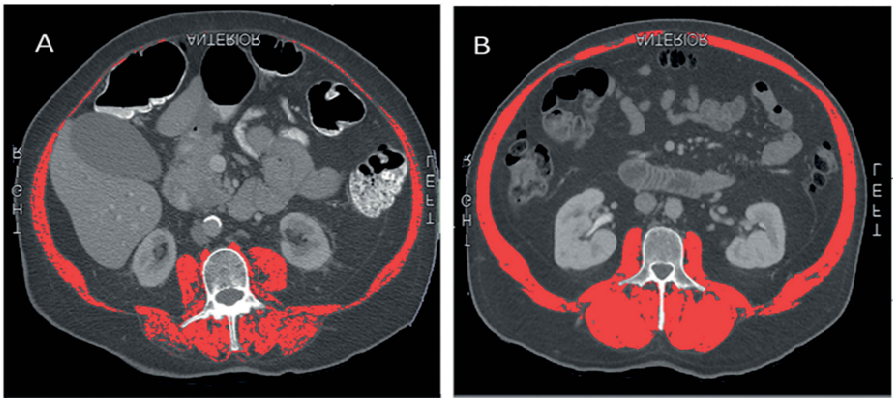


Figure 5. CT- images from two individuals, one with sarcopenia (A) and one with no sarcopenia (B). Skeletal muscle mass is tagged in red using the Slice O Matic software.

To ensure correct anatomical land marking, the first image in which both vertebral transverse processes at the L3 were clearly visible, was used for analysis. All muscles at the L3 region (tagged in red in Figure 5) were identified and assessed by means of the quantitatively measuring radio density in Hounsfield units (HU) with thresholds from −29 to +150 and the sum of all muscles were expressed as total skeletal muscle CSA (cm2).

4.4 Outcome variables (Paper I-III)

A number of outcome variables were used in the clinical studies (Paper I-III). An overview is given in Table 5.

4.4.1 Demographic information

Information about the participant's age and gender was collected in all three papers (Paper I-III).

4.4.2 Medical status

Information about the patient medical status included cancer diagnosis using the International Classification of Diseases (ICD-10) (134), stage of cancer assessed

according to Classification of Malignant Tumours (TNM v. 7.0) (5) and comorbidity using the Charlson Comorbidity Index (135).

4.4.3 Anthropometric data

Weight and weight-change the last six months was assessed by the Patient-Generated Subjective Global Assessment in Paper I (see details on PGS-SGA below). In paper II, height and body weight was measured with manual scales to the nearest 0.1 cm and 0.1 kg respectively, and with the patients wearing light clothes and no shoes. In paper III, data on weight and height were based on self-report.

4.4.4 Biological samples

Serum samples of C-reactive protein, albumin and haemoglobin reported in Paper I, were measured in blood samples collected from patients within three days after study entry into the EPCRC-CSA.

4.4.5 Performance Status

Performance status was measured by the Karnofsky Performance Scale (136) in Paper I and II (Appendix 2) and by the European Collaborative Oncology Group (ECOG) Performance Score (137) in paper III (Appendix 3). Both scales are physician-reported outcomes, clinically orientated and have well documented predictive value in the cancer patient (138). The ECOG Performance Score classifies patients on a scale from 0 to 5 and a higher score predicts a worse prognosis (138).

The Karnofsky Performances Scale classifies the functional impairment of patients on a scale from 0 to 100, with intervals of 10 (139), with higher scores indicating better function (138). The primary purpose the KPS was to allow physicians to evaluate a patient's ability to survive chemotherapy for cancer (140) and it is commonly used as an entry criteria into clinical trials.

4.4.6 Patient-generated questionnaires

Symptom burden

Symptoms were measured by the Edmonton Symptom Assessment System (ESAS) in Paper I (58) (Appendix 4). This patient-reported questionnaire consists of eight items

about the severity of most common symptoms experienced by cancer patients and two items of the overall burden of symptoms. Each question is scored on an 11-points numeric rating scale (NRS-11). The ESAS is extensively used in cancer research and has been validated various cohorts of cancer patients (141).

Quality of life

Quality of life was measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of life questionnaire, version 3.0 (QLQ) C30 (59) in Paper III (Appendix 5). This instrument is a well-validated and extensively used tool specifically developed for cancer patients (142, 143). The 30-item pool forms five functional scales, three symptoms scales and six single items. In Paper III, appetite loss (symptom scale) was used. This item is measured on a four-point categorical scale (not at all –very much).

Food intake

In Paper I, food intake was measured by the PG-SGA Box 2 Question (Appendix 6) which asks the patient about any change in food intake compared to normal on a three-point categorical scale (less than usual, no change and more than usual) (144). The PG-SGA has been validated in cancer patients (145) and correlates closely with quality of life (146).

4.4.7 Accelerometer-based physical activity monitoring

Activity recognition

Data on time (in seconds) spent in different positions i.e. lying, sitting and upright (standing and walking) and changes in body positions (sit to stand and/or stand to sit transitions), as well as recognition of the number of steps taken while walking, were derived from the activity meter and the video recording.

Energy expenditure

Resting energy expenditure (REE) derived from indirect calorimetry, was calculated by use of the Weir equation (147). Total energy expenditure (TEE) was calculated by multiplying number of METs per day derived from DLW with the patient's body weight. Physical activity levels (PALs) were calculated from the formula

PAL=TEE/REE. Energy expenditure of activity (EEA) derived by the DLW, was calculated from the formula EEA=TEE-REE (148). To derive a variable for EEA from the ActivPAL, the number of METs recorded for non-activity was subtracted from the total number of METs per day.

4.4.8 CT-image-based assessment of muscle mass

Skeletal muscle cross-sectional area

The sum of the total muscle mass at the level of the third lumbar vertebral was expressed as skeletal muscle cross-sectional area (SMCA) and expressed in cm^2 (149).

Cut-off for sarcopenia

Skeletal muscle cross-sectional area (cm^2) was normalized for body height to derive a skeletal muscle index (SMI), expressed in unit cm^2/m^2 (45). A SMI below 55.4 cm^2/m^2 for men, and 38.9 cm^2/m^2 for women, was used to classify patients as sarcopenic (150).

Lean Body Mass

Lean body mass (LBM) in kg was calculated by means of the formula: 0.30 x [skeletal muscle at L3 using CT (cm^2)] + 6.06, as reported by Mourtsakis et al. (42).

4.4.9 Evaluation of treatment response

In Paper III, response to cancer treatment was assessed according to the RECIST 1.1 (55). These criteria are used in routine clinical practice to evaluate treatment response and are defined as follows:

- Complete response (CR): disappearance of all target lesions.
- Partial response (PR): at least 30 % decrease in the sum of diameters of target lesions
- Progressive disease (PD): At least 20 % increase in the sum of target lesions
- Stable disease (SD): Not sufficient decrease to quality for neither PR nor sufficient increase to qualify for PD.

Categorisation of treatment response was done by using the Disease Control (DC) system, including CR, PR and SD. Response rates for DC in patients with advanced lung cancer are approximately 30 % (151, 152).

Table 5. Outcomes used in the clinical studies.

Outcome	Variable used and unit of measurement	Method or assessment tool	Paper I	Paper II	Paper III
Demographic information	Age, years	Interview, medical charts or questionnaire	x	x	x
	Gender, male/female		x	x	x
Medical status	Diagnosis	ICD-10	x	x	x
	Stage of disease	TMN	x	x	x
Anthropometric data	Height	Interview, medical charts or self-report questionnaire	*x*	*x*	x
	Weight		x	x	x
	Weight loss		*x*		*x*
	Body Mass Index		x	*x*	x
Biological samples	Albumin	Blood tests	x		
	Haemoglobin		x		
	C-reactive protein		x		
Physical function	Performance score 0 -100	KPS	x	x	
	Performance score 0-5	ECOG			x
PRO's	Symptom burden (fatigue, appetite loss, depression, anxiety, well –being)	ESAS	x		
	Food intake	PG-SGA	x		
	Quality of life	EORTC QLQ-C30			x
Activity monitoring	Time in upright	ActivPAL		x	
	Number of transitions			x	
	Step count			x	
	Total Energy Expenditure	DLW		x	
	Resting energy expenditure	Indirect Calorimetry		x	
Muscle mass assessment	Cross sectional area of skeletal muscle, cm2	Slice O' Matic			x
	Skeletal muscle index, cm^2/m^2				x
	Lean Body Mass, kg				x
Evaluation of treatment response	Response;	RECIST			x
	Stable disease				x
	Progression				x
Toxicity	Haematological, grade III-IV	CTCAE			x
	Non-haematological, grade III-IV				x

4.4.10 Toxicity

Haematological and non- haematological toxicity was assessed and scored according to the Common Terminology Criteria for Adverse Events version 3.0 (153) in paper III. Grade III and IV events were reported.

4.5 Data analysis and statistics (Paper I-III)

4.5.1 Paper I

An independent sample t-test for continuous variables and a Chi-Square test for categorical variables were used to compare groups in the two-stage classification model (Model 1) for demographic, medical and patient-reported variables.

One Way Analysis of Variance (ANOVA) was used for multiple comparisons between the four groups in the four-stage classification model (Model 2). Bonferroni correction was used to account for multiple testing. For non-parametric data, the equivalent Kruskal-Wallis test was used for comparison between two and two groups separately in Model 2. The contribution of individual items representing the main cachexia domains (catabolism, intake, function) to the model was further tested in a multinomial logistic regression, forced entry model, using "no cachexia" as the reference category for the outcome variable. CRP was not normally distributed and a logarithmic transformation was performed before entering the variable in the regression analysis.

Survival was defined as the time between the date of clinical assessment and the date of death. Patients alive by January 1st 2011 were treated as censored data. Uni-variate survival analysis was performed using the Kaplan-Meier method and Cox regression (log-rank tests) to compare survival curves between groups in the two classification models.

4.5.2 Paper II

Data derived from the ActivPAL were converted into second-by-second outputs using an Excel Spreadsheet provided by the manufacturer, and identification of relevant sequences was performed in a custom-made Mat Lab program. Test Series I included walking at three different speeds (slow, preferred and fast). Data from all 3 speeds were

analysed. Video data from all participating centres were analysed by the study coordinator in Trondheim prior to analysis of the ActivPAL data. Each forward movement of the foot in an upright position recorded by video was counted as a step (82, 154). Walking speed was calculated as meters walked (6 meters) divided by time taken to walk in seconds, for all walking trials.

Ordinal and continuous variables were presented as means, SD and ranges, and dichotomous variables as absolute numbers and percentages. Activity data were compared between patients with KPS 70 - 100 and KPS 40 - 60 in order to analyse differences between self-caring and non-self-caring populations. Differences between groups were determined using Student's Independent Sample t-test. Statistical significance was set at $p<0.05$ level using exact, two-sided p-values. Bi-variate relationships were assessed by Pearson's product-moment correlation (r). Linear regression models were used to determine the contribution of independent PA variables on dependent EE variables.

In the DLW study, retrospective mathematical modelling was used to derive EE from the ActivPAL. The ActivPAL software assigns an energy cost in METs to body postures and a linear scaling of stepping where one MET equals 1 kcal/kg/h. A non-linear correction was applied to correct for the actual measurement of REE by the ActivPAL in the study population (0.84 kcal/kg/h).

Bland-Altman plots with 95% limits of agreement (LOA) and absolute percentage errors were used to assess agreement between ActivPAL and the two comparative methods; video recordings or DLW and results were expressed in absolute units (155).

4.5.3 Paper III

Ordinal and continuous variables were presented as means, SDs and ranges, and dichotomous variables as absolute numbers and percentages.

Change in SMCA was categorized according to relative change from pre- to post-chemotherapy ((post-chemotherapy SMCA – pre-chemotherapy SMCA)/pre-

chemotherapy SMCA) x 100) into two groups: a) SMCA Loss (> 2 % loss of SMCA, b) SMCA Stable/Gain (≤ 2 % loss or gain in SMCA). The cut-off values for SMCA were based on a previously reported measurement error for CT-image based assessment of 2 % (4). Response to treatment was categorized as "Disease control" (complete response, partial response and stable disease) or "Progressive disease" for the purpose of statistical analysis.

Chi-square and Fisher's exact tests were used to compare categorical variables for response to treatment (responders vs. non-responders) and change in skeletal muscle mass ($SMCA_{Stable/Gain}$ vs. $SMCA_{Loss}$) at the group level. A significance level of $p<0.05$ was regarded as statistically significant, and $p<0.1$ as a trend.

Survival time was defined as the time from inclusion until death and was estimated using the Kaplan-Meier method. The log-rank test was used for uni-variate survival comparisons. The Cox proportional hazard method was used for multivariate survival analyses adjusting for known prognostic factors in advanced NSCLC (referring to Table 3 in Paper III).

4.6 Ethical consideration (Paper I-III)

Written informed consent was obtained from all subjects for the studies reported in Paper I, II and III (copy of consent letter and form, enclosed in appendix).

Ethical approval was granted by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK) for all data collected at the Trondheim study site in the Papers I, II and III.

In collaborating national and international study sites, ethical approval was granted by the local, regional ethics committees at each study site. Data collection was approved by the Norwegian Social Science Data service (NSD). Procedures were in accordance with International Committee for Harmonization, Good Clinical Practices and the Helsinki Declaration.

4.7 The systematic literature review (Paper IV)

Established methodology for the conduct and reporting of systematic literature reviews was used in Paper IV (156).

4.7.1 Searching the literature

A systematic review should seek to identify all relevant published and unpublished records (157). Electronic searches were performed on January 11th 2012 in selected electronic databases (PubMed, Embase, Pedro, and Cochrane Central) by a trained research librarian. A combination of controlled terminology and free-text terms was used: (1) physical exercise, (2) cancer and (3) muscle mass and strength (including terms such as cachexia, anorexia, malnutrition, wasting, and asthenia), and were adapted to each database.

4.7.2 Selection of studies and data extraction

The identified studies were screened for eligibility using the following criteria:

a. Study had to have a randomised controlled trial design
b. Include patients aged 18 years or more with a confirmed cancer diagnosis and who were about to start or undergoing active cancer treatment at trial entry
c. Physical exercise had to be repetitive (more than once), consist of aerobic or strength exercise or a combination of both, and be delivered either as a single intervention or as part of a multimodal approach
d. Published in English and in a peer-reviewed journal

All identified records were screened for duplicates and irrelevant titles. Two reviewers screened the remaining abstracts and subsequently full-text papers were reviewed independently in pairs of two and two reviewers. In both instances, cases of disagreement about eligibility between two reviewers warranted a third reviewer's opinion.

Data extraction from the included studies was performed using a custom made pre-piloted electronic form and plotted in a Microsoft Office Excel 2010 software spreadsheet. Data on study design, participants, interventions, outcome measures

(muscle mass and strength), results and conclusions were extracted. Disagreements on final inclusion and exclusion were resolved by consensus by two of the authors.

4.7.3 Assessment of study quality

All included studies were assessed for quality. The assessment was performed independently by two reviewers and based on the criteria for "risk of bias" within the GRADE system for rating quality of evidence (158). These criteria are randomisation procedures, allocation concealment, blinding, power-estimation, loss to follow-up, intention-to-treat analysis and selective end-point reporting.

4.7.4 Synthesis of data from included studies

In the included trials treatment effects for each of the two or more groups are shown as differences in change between the groups. In order to compare results across studies and outcomes (muscle strength and muscle mass) effect sizes were calculated according to Cohen's method (159). The formula used to calculate standardised mean difference (SMD) was: mean values for the experimental group, minus mean values for the control group, divided by the pooled standard deviation (160). Pooled standard deviation is calculated using the formula: square root of SD for experimental group^2 + SD of control group^2 divided by 2. SMDs were interpreted in accordance to Cohen's "rule of thumb" stating that an SMD of 0.2- 0.5 is small to moderate, 0.51 - 0.8 moderate to large and greater than 0.8 large (159).

5. Summary of results

5.1 The clinical studies (Paper I-III)

A summary of results from three clinical studies, two method studies (Paper I and II) and one prospective cohort study (Paper III) are presented below. The patient characteristics for these studies are shown in Table 6.

Table 6. Patient characteristics in the clinical studies (Paper I-III)

Column1	Paper I	Paper II		Paper III
		VIDEO STUDY	*DLW STUDY*	
Number of patients analysed	861	45	6 [a]	35
Age; years mean (range)	62 (18-89)	65 (28-86)	65 (59-76) [b]	67 (27-85)
Gender; females n (%)	401 (47)	26 (51)	2 (33)	17 (49)
Diagnosis	Digestive, breast, lung, prostate and other	Aero-digestive, urogenital	Oesophago-gastric adenocarcinoma	Non-small cell lung cancer
Stage of cancer	Advanced loco-regional or metastatic	Advanced, stage IV	Advanced, stage IV	Advanced, stage IIIB and IV
KPS 0-100 mean (range)	72 (40-100)	64 (40-100)	87 (80-100)	NA
ECOG 0-5 n (%)	NA	NA	NA	0 (11) 1 (83) 2 (6)
BMI kg/m^2 mean (SD)	24.2 (4.3)	22.2 (4.3)	29.0 (4.2)	24.2 (4.2)
WL [c]**, kg** mean (SD)	3.9 (4.1)	NA	NA	3.4 (4.5)

[a] The sample consisted of six advanced cancer patients and 8 controls (healthy adults)
[b] Healthy adults: mean age 28 (range 25-31) years
[c] Last three months prior to diagnosis

Abbreviations: KPS=Karnofsky Performance Status, ECOG= European Collaborative Oncology Group, BMI=Body Mass Index, WL=Weight loss; NA=not assessed.

5.1.1 Paper I

Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model-A study based on data from international multi-centre project (EPCRC-CSA)

In Paper I, the aim was to examine i) a two group model validating the diagnostic criteria for cancer cachexia (Model 1) and ii) a four-group model for classification of cancer cachexia into stages based on weight loss and BMI as a preliminary framework (Model 2).

Data from eight hundred sixty-one patients were analysed. Model 1 resulted in 399 cachectic and 462 non-cachectic patients. In comparison to non-cachectic patients cachectic patients had significantly higher levels of inflammation (CRP 44.9 ml/g vs. 30.0 ml/g; $p<0.001$), lower food intake (58.6 % vs. 29.8 %, $p<0.001$), more appetite loss (3.9 vs. 2.6; $p< 0.001$) and a lower performance status (KPS score: 68 vs. 75, $p<0.01$). Model 2 resulted in 536 patients classified into the three groups representing cachexia stages; pre-cachexia (n=147), cachexia (n=305) and refractory cachexia (n=86). Three hundred and twenty patients were weight stable or had weight gain (non- cachectic group). The scores on criteria representing key cachexia domains are shown in Table 7.

CRP was higher in the refractory cachexia group compared to pre-cachexia ($p<0.01$) and no-cachexia ($p<0.001$) groups. The proportion of patients reporting reduced food intake (“eating less than usual”) and poorer appetite were higher in the three groups (pre-cachexia, cachexia and refractory cachexia) compared to the no-cachexia group ($p<0.001$). Patients in the cachexia and refractory cachexia group had lower performance status compared to patients in the pre-cachexia and cachexia group ($p<0.001$).

The median overall survival for all patients was 207 days. In model 1, median survival for patients classified as cachectic was shorter than for non-cachectic patients (139 days vs. 269 days; $p<0.001$). In Model 2, the median survival for patients with cachexia (148

days) or late cachexia (123 days) was significantly shorter than for patients with no cachexia (269 days; p<0.001), but not for early cachexia (269 days; p=0.245). Median survival was significantly shorter for patients with pre-cachexia defined as; WL > 5% weight loss + CRP >10 ml/g + appetite loss >3; compared to patients with pre-cachexia defined as WL< 5% (143 versus 377 days; p < 0.001).

Table 7. Mean values for the cancer cachexia domains in Model 2. Data is extracted from Table 2 in Paper I. All values are presented as mean, except for the item "Reduced food intake" that is shown in %.

Domains	Sub-domains	No cachexia	Pre - Cachexia	Cachexia	Refractory cachexia
Stores	Weight gain/loss [a], kg	+ 2.8	-2.4	-7.9	-16.8
	BMI, kg/m^2	25.4	25.1	23.8	19.9
Catabolism	CRP, ml/g	30.3	29.3	40.6	60.6
Nutrition	Reduced food intake [b], %	20	47	56	68
	Appetite loss [c]	2.5	2.9	3.7	4.6
Function	Performance Status (KPS) [d]	74.7	75.0	68.2	66.8

[a] (+) mean weight gain. (-) mean weight loss
[b] Proportion of patients scoring on PG-SGA Item "Eating less than usual" versus 'Unchanged' and 'More than usual'.
[c] Measured by ESAS on a scale from 0-10. A high score represents worse symptoms compared to a low score.
[d] Performance is scored on a scale from 0(death) to 100 (normal functioning).
Abbreviations: kg=kilograms; BMI=body mass index; CRP=C-reactive protein; KPS= Karnofsky Performance Score.

5.1.2 Paper II

Patient-focused endpoints in advanced cancer: Criterion-based validation of accelerometer-based activity monitoring.

In paper II, the objective was to assess whether a small light-weight activity meter (ActivPAL) could be used as an objective measure of daily physical activity (Video Study) and energy expenditure (DLW Study) in advanced cancer patients.

Video study

45 patients (51% females), with a mean age of 64.8 years, were stratified according to performance status at study entry, using the Karnofsky Performance Score (KPS).

Twenty four of the patients had high scores on KPS (scores 70-100) and were categorised as self-caring. The remaining 21 had low KPS (scores 40-60) indicating that they required physical assistance with everyday life activities (non-self-caring). Non-self-caring patients were predominantly males (63%), used walking aids (60%) and had a significantly lower walking speed compared to self-caring patients (0.48 m/s vs. 0.67 m/s; $p>0.001$).

Systematic error measurement for ActivPAL™ compared with video for time spent in different postures was < 0.1sec and there was a 100% agreement between ActivPAL™ and the video for number of transfers between body postures.

For recognition of steps in the whole sample, there was an absolute error of 28.6 % between ActivPAL™ and the video. In non-self-caring patients, absolute error in step count was 33% compared with 24% in self-caring patients ($p>0.001$). A correlation between walking speed and difference in step count between video and ActivPAL™ was $r=-0.51$ ($p<0.01$).

DLW study

Six cancer patients and eight healthy controls (one control had two assessments) participated in the DLW study. Cancer patients were older than the healthy controls (median years 62 vs. 29; $p<0.001$), but did not differ significantly in measures of nutritional status, including BMI, LBM and fat mass and predicted or measured REE.

When assessed by DLW, cancer patients had a lower mean total TEE (2321 vs. 3202 kcal/day; $p = 0.044$) and EEA (742 kcal/day vs. 1609 kcal/day; $p =0.036$) compared with healthy controls.

Absolute errors between the measurement of EEA and TEE between ActivPAL and DLW were small. 1.4% and 0.4 %, respectively. A within-subject variability of 55 % between the ActivPAL and DLW measurements was demonstrated.

5.1.3 Paper III

Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer.

The aim of Paper III was to investigate whether changes in muscle mass is associated with response to treatment and overall survival. Thirty-five patients with advanced NSCLC evaluated for response after three cycles of chemotherapy were analysed. Patients were 48% females, mean age 67 years (range 56-86) with predominantly stage IV (metastatic) disease (83%). More than 70 % of the patients were sarcopenic before starting chemotherapy.

Mean reduction in SMCA from before starting chemotherapy to after chemotherapy was 4.6 cm^2 (CI 95 % -7.3 to -1.9; $p<0.002$), equal to the loss of whole body muscle mass of 1.4 kilograms. As illustrated in Figure 6 (Figure extracted from paper III), 16 patients remained stable or gained SMCA. Out of these, 14 responded to chemotherapy, while two progressed (p=0.071).

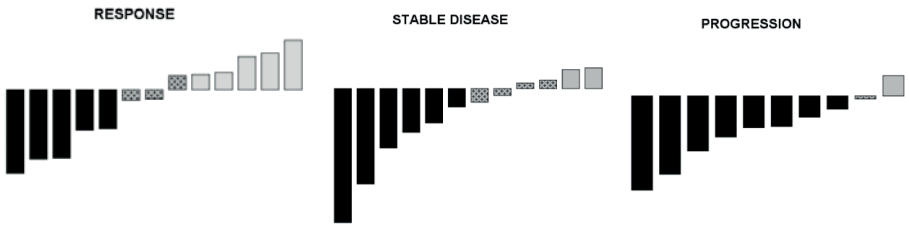


Figure 6. Changes in muscle mass shown according to response to chemotherapy. Changes in muscle mass, SMCA, for each patient is shown according to the evaluation of treatment response (response, stable disease and progression). Patients are presented by individual bars representing: black (> 2 % loss), dotted grey (stable – 2 % to +2 %) and light grey (> 2 % gain).

Those with a stable or increased SMCA had longer median overall survival than patients who lost muscle mass (loss: 5.8, stable/gain: 10.7; p=0.073). Stage of disease ($p<0.003$), treatment regimen

($p<0.023$), response to treatment ($p<0.007$) and stable/gain in SMCA ($p<0.040$) but not sarcopenia at baseline, were significant prognostic factors in the multivariate survival analysis.

5.2 The systematic literature review (Paper IV)

Effect of physical exercise on muscle mass and strength in cancer patients during treatment-A systematic review.

In the systematic review presented in Paper IV, the aim was to evaluate the scientific evidence of effects of physical exercise on muscle mass and strength in patients with cancer. Electronic searches were performed up to January 2012, identifying 16 randomised controlled trials for final data synthesis (118, 161-175). The included studies were comparing either aerobic (AE) or resistance exercise (RE) or a combination of these (CAE) against usual care (UC). An overview of setting, duration and frequency, dose and intensity of the physical exercise interventions is presented in Table 8.

Table 8 Summary of the delivery of physical exercise interventions for all included studies.

	Aerobic	Resistance
Setting/delivery	Supervised individual or group using treadmill or stationary bike cycling, by physiotherapists or exercise physiologists at exercise facility at hospital Home-based (outdoor walking)	Supervised individual or group using stationary machines, by physiotherapists or exercise physiologists at exercise facility at hospital Home-based (free weights or elastic bands)
Duration/ Frequency	Median duration of 8 weeks ranging from 4 to 52 weeks with median number of sessions per week (frequency) of 3.	
Dose	6-45 minutes	2-3 series of 8-12 repetitions
Intensity	60 – 95% of max heart rate (HR) or 12-15 on Borg Ration of Perceived Exertion (RPE) scale	65 – 90% of one repetition maximum (1RM) or moderate to hard (15 – 17) on the Borg RPE scale

A significant better effect of physical exercise compared to UC was shown for muscle mass in three studies (162, 165, 166), in which one study showed that RE was superior to AE (166). Moderate to large effects on both upper and lower muscle strength, was demonstrated in favour of physical exercise (AE, RE and CAE) across different cohorts of cancer patients (118, 161, 166, 169, 172-175). The majority of the included studies were conducted in patients with early stage cancer. One study included only patients with advanced stage cancer (118). Patient characteristics of the samples in all the included studies are presented in Table 9 (unpublished results).

Table 9. Patient characteristics for clinical trials included in the review.

Author	n	Age *	Cancer diagnosis	TNM stage
Adamsen 2009 (161)	269	47 (20-65)	Solid tumours: breast 44%, bowel 13% + haematological malignancies	nr
Battaglini, 2007 (162)	20	56.6±16	Solid tumours: Breast 100%	nr
Baumann 2010 (163)	64	44.9±12.4	Mixed haematological malignancies (mainly acute and chronic leukaemia)	nr
Baumann 2011(164)	47	41.4±11.8	Mixed haematological malignancies (mainly acute and chronic leukaemia with severe aplasia)	nr
Coleman 2003 (165)	24	55 (42-74)	Multiple myeloma	nr
Courneya 2007(166)	242	49.2 (25-78)	Solid tumours: Breast 100%	I – IIIA
Cunningham 1986(167)	30	26.0 (15-38)	Acute Leukaemia 100%	nr
Demark- Wahnefried, 2008 (168)	90	41.8 (25-65)	Solid tumours: Breast 100%	I-IIIA
Jarden, 2009 (169)	42	39.1 ± 12.2	Mixed haematological malignancies	nr
Monga 2007 (170)	30	68±4.2	Solid tumours: Localized prostate 100 %	nr
Mustian 2009 (171)	38	60 (36-82)	Breast 71 % and prostate 29 %	nr
Oldervoll 2011(118)	231	62.2±11.3	Solid tumours: gastro-intestinal tract 32%, breast 22%, lung 16%	IV
Schwartz 2007(173)	66	50.1±8.7	Solid tumours: Breast 100%	I - III
Schwartz 2009 (172)	101	47 (27-71)	Solid tumours: breast 76%, colon 13%, lymphoma 11%	I-III
Segal 2009 (174)	121	66.3±7.0	Solid tumours: Prostate 100%	I-IV
Wiskemann 2011 (175)	105	48.8 (18-71)	Mixed haematological malignancies	nr

* Age is shown as mean and range or standard deviation as reported in studies.
Abbreviations: nr= not reported in study

Quality assessment of the included trials demonstrated large variation in sample size and considerable loss to follow up and furthermore revealed that the majority of the trials had some methodological shortcomings, mainly related to blinding of assessor, concealed allocation and sample size estimation.

6. Discussion

6.1 Main findings

The overall aim of this thesis is to contribute to improved classification, assessment and treatment of patients with cancer cachexia. Results from the included studies indicate that the classification of cancer cachexia based on information about weight loss and BMI is valid in patients with advanced, incurable cancer; however additional information such as food intake and inflammation can contribute to an improved classification of cancer cachexia. Cancer cachexia is associated with inactivity and loss of muscle mass. In this thesis, it has been shown that a body worn activity meter can provide accurate measures of some aspects of physical activity in patients with advanced, incurable cancer. Furthermore, it was found that muscle mass can be stabilised or even reversed for patients responding to chemotherapy, and that change in muscle mass during the course of chemotherapy is an independent predictor of survival. Finally, this thesis shows that physical exercise can be recommended concurrent with cancer treatment to improve muscle strength across cancer patient populations. Few studies have so far measured muscle mass, and thus, there is not sufficient evidence to recommend physical exercise as a single treatment for cancer cachexia.

6.2 Methodological considerations

The research questions asked in this thesis were investigated through three clinical studies; two cross-sectional studies (Paper I and II) and one prospective cohort study (Paper III), and finally, one systematic review of randomised controlled trials (Paper IV). This chapter discusses internal and external validity of the included studies.

6.2.1 The clinical studies (Paper I-III)

Study designs

Cross-sectional design

Cross-sectional designs are commonly used to describe prevalence, to estimate the association between variables, and to detect differences between subgroups of the study sample (176). The exposures and outcomes are observed or measured simultaneously, or within a short period (177). Hence, this study design fitted the aims of Paper I and Paper II.

An advantage in a cross-sectional study design is that large numbers of participants can easily be included, and significant amount of information can be collected (178). This study design was therefore useful in Paper I, as information about a large number of variables and their distribution patterns in a patient cohort representative for cancer cachexia was necessary in order to validate the cancer cachexia classification models. Detection of differences between the sub-groups representing the different stages of cancer cachexia was also possible. However, the main limitation of using a cross-sectional design was that no causal interferences could be drawn, and information about the natural history of cancer cachexia could not be derived. Still, as the study presented in Paper I was a first step in the development of a standardized classification system for cancer cachexia, the cross-sectional design was regarded as appropriate to generate hypotheses that can be more rigorously studied in future longitudinal studies.

A cross- sectional study design is also commonly used in method comparison studies to test agreement between two measurement methods, as was the purpose of Paper II. In method comparison studies, agreement between different methods of measurements is quantified by comparing the 'new' method against a "criterion" to test validity (155). In Paper II, the accuracy of a body-worn accelerometer-based activity meter (ActivPAL) to measure activity (body positions, transfers and stepping) and energy expenditure was tested. The cross-sectional design was thus suitable as measurements from the ActivPAL and the criterion methods (video recordings and DLW) could be taken at precisely the same point in time on the same patients.

Prospective cohort design

In prospective cohort studies, patients are identified and classified according to exposure factors at study baseline and are then followed over time (179). The design is suitable to study the association between exposure and outcome variables, which was the primary research question in Paper III. Cohort studies are furthermore used to answer research questions about prognosis (i.e. whether exposure to a given factor is associated with the risk of having a certain outcome), which was a secondary aim in this study.

A limitation of a prospective cohort study is that it is purely observational (un-controlled, no randomisation) and thus, the possibility to draw conclusions on causal effects are restricted. However, reporting changes in muscle mass during chemotherapy by use of CT-image analysis is not common in cohorts of patients with advanced incurable cancer. A pilot study was therefore important to generate hypotheses that can be more rigorously studied in future larger clinical trials.

Internal validity

Internal validity is the extent to which the result of a study can be interpreted accurately (176). Selection procedures, missing data and measurement errors are possible sources of bias that may be a threat to the internal validity of the studies included in this thesis. In the further, some actions that were taken to minimize potential bias are discussed.

Selection bias and missing data

Ideally, all available patients filling the inclusion criteria should be included in a study and there should be no missing data; however, this is a challenge in the majority of clinical studies (176). The selection of patients into the EPCRC-CSA study (Paper I) was not based on random procedures, and there are no estimates of the patients that were not willing to participate. Therefore, volunteer bias cannot be excluded. In addition, the eligibility criteria required patients to be capable of completing several self-reported questionnaires. Using a paper and pen format, completing an extensive number of questionnaires can be time-consuming and burdensome for patients that have advanced disease, are hospitalised and might suffer from fatigue or reduced physical function or mental capacity. To accommodate this challenge, computerised assessment was tested out in the EPCRC-CSA study. Patients could lie in bed and use their index finger to answer questions on a tablet PC. Most of the patients included found this feasible (> 95% response rate) however, “healthy effect bias” was possible as it was observed that elderly men with a low KPS did not comply so well with computerised assessment (180).

In the selection of a sample for Paper I, a proportion (15%) of the patients from the original EPCRC-CSA study sample were excluded from the data analysis because it was not possible to obtain data on weight loss. In cross-sectional surveys, where information

is collected from a large number of patients, such as the EPCRC-CSA study, self-report is a feasible method of reporting subjective symptoms. However, the use of self-report could explain the missing data on weight loss as some patients might have had difficulties in recalling their weight history.

The exclusion of patients that did not have data on weight loss was necessary, as this was the validation criteria for the cancer cachexia classification models in Paper I. However, the exclusion of these patients could possibly have led to a biased selection if weight loss data was not missing at random. Analysis (not presented in Paper I), show that patients excluded due to lack of weight loss data had similar BMI as the included patients (24.3 vs 24.2 kg/m^2; p=.861; however they were older (66.7 vs 61.9 years: $p<0.001$) and had a lower score on KPS (63.1 vs 71.1; $p<0.001$). These findings could suggest that the excluded patients were more frail compared to the sample used in the analysis.

The lack of data on muscle mass was a major limitation in the attempts to classify cancer cachexia in Paper I. Information about muscle mass could have contributed to better classifying patients in a pre-cachectic stage, as slight muscle loss can be obscured due to oedema (12). One previous study including muscle mass to validate a cancer cachexia classification systems did however not show that differences in muscle mass contributed to characterise different stages of cancer cachexia (34).

In paper III, it was only possible to obtain two consecutive and evaluable CT-images in a subset of 35 patients out of the original sample of 54 patients. There were however no statistical differences in baseline characteristics between the subset and the original sample which could indicate that data were missing at random. The study sample of 35 patients can be regarded as small. Sample size calculations were not performed because the investigation was considered to be exploratory and hypothesis generating for future investigations (181). However, a small sample can reduce the statistical power and thus undermine the results from survival analysis.

Measurement errors

In paper II, video recording was used as a criterion measure to test the accuracy of the activity meter. Video has been used as gold standard for similar purposes in previous reports (82, 154). Video recording was feasible in this study as the test protocol was performed in a controlled in-lab setting. The recordings were synchronised with the activity meter and the set-up standardised for the individual patients to ensure comparability of data derived from both methods. Still, the part of the protocol attempting to test everyday life activity (Test protocol II) provided to be challenging as video recording of steps in "real life" conditions was not easily detected.

Slow gait speed gives lower acceleration amplitudes than higher gait speeds and can explain why the activity meter's failed to detect steps in Paper II (76, 80). Furthermore, short walking sequences result in atypical gait characteristics with low acceleration amplitudes during start and stop, and this may also have contributed to the high step count errors observed (182). Inspection of the raw acceleration data confirmed that steps had been registered by the activity meter but were left unrecognised following software calculations. Similar high step count errors have also been demonstrated in slow walkers (<0.8 m/sec) when using other AM-systems (183-186). Together, these observations suggest that, at the present time, algorithms imbedded in the software of commercially available activity meters may not be sophisticated enough to detect steps accurately enough in frail and slow walkers (81). The accuracy of step count measurements using the ActivPAL meter can therefore not be trusted to give estimates of "true" effect in clinical studies on patients with cancer cachexia.

CT-image analysis of muscle mass has been reported to have a small measurement error of 1.5-2 %, with a minimum detectable change of ~ 2% (40, 42). It was therefore an ideal method to detect small changes in skeletal muscle body composition in the CT-HELIK study (Paper III). The image analysis was conducted by a trained researcher and standardizes procedures based on previous reports were used to minimize systematic error. Cut-off values used to categorize changes in muscle mass (loss, stable and gain) was based on previous reports (11). Further studies in other and larger samples within the same population have to be performed in order to confirm findings in Paper III.

External validity

External validity refers to the extent to which the results of a study can be generalized to other patients and settings. In the clinical studies included in this thesis (Paper I, II, III), the main study population was patients with an advanced, incurable cancer diagnosis. In the further text aspects that need consideration with regards to external validity will be discussed.

The EPCRC-CSA study (Paper I) was a large multicentre study recruiting patients from multiple study sites across Europe and in Canada. The advantage of multicentre studies is that they can secure a rapid inclusion and provide large study samples with high external validity. As a limitation, the centres recruiting patients into the EPCRC-CSA study was not randomly selected and thus, bias cannot be excluded.

In the EPCRC-AMOEBS study (Paper II) convenience sampling was considered most appropriate to ensure a wide distribution across a range of physical functioning (187). In the video study, it was possible to obtain an equal distribution of patients with KPS ranging from 40 – 100. In the DLW study, a low number of advanced, cancer patients and inclusion of healthy controls might have reduced the external validity of the conclusions drawn regarding validity of the activity meter in patients with low physical function.

In the prospective cohort study (Paper III) the original sample consisted of a selected group of patients with advanced, inoperable NSCLC recruited to participate in a small, single centre RCT. Ideally, estimates of muscle mass used in the final analysis for Paper III, should have been based on a larger, randomly selected population of NSCLC patients. The small sample size and strict eligibility criteria could have limited the external validity of the results from the survival analysis. Still, the findings in Paper III demonstrated that the response rate to chemotherapy and prognostic factors for survival (stage of disease, loss of appetite and response to treatment) were similar to reports from other studies of NSCLC (152).

6.2.2 The systematic literature review (Paper IV)

Study design

The systematic review included in this thesis (Paper IV) was conducted to guide planning of a randomized controlled trial (RCT) about the effect of multimodal treatment on cancer cachexia with muscle mass as the primary outcome (Clinical Trials.gov nr. NCT01419145). It was thus considered appropriate to collect and summarize evidence from RCTs as this would give the best possible estimate of the real effect of physical exercise interventions on muscle mass in different populations of cancer patients.

Systematic reviews and meta-analyses that summarize the evidence from RCTs are placed at the highest level in the 'hierarchy of evidence' as they are considered to give the best possible estimate of any true effect (157). The internal and external validity of a systematic review is however dependent upon the quality of the RCT's included in the review, as well as the conduct and reporting of the systematic review itself.

Internal and external validity

The PRISMA statement (156) was used as a guide for the search and selection of studies into the systematic review. According to this statement, the sampling method used in Paper IV had some limitations. Literature searches were for example restricted to English speaking journals only, which could have increased the risk of publication bias (selective reporting of studies). This restriction as well as excluding studies published before 1975, was deemed necessary to limit the number of records identified. Another limitation is that that search terms for outcomes are not always represented in abstracts of indexing terms (i.e. Mesh). Consequently, this could have excluded relevant studies. Indeed, nine records were identified by additional manual searches performed in bibliographies of full-text articles.

The eligibility criteria for the published papers were pre-planned and rigorously used in the selection of trials for inclusion. Except for one RCT, studies that included patients with advanced, incurable cancer were small, pilot studies with no control group. The exclusion of non-randomized studies can therefore have reduced the generalizability

(external validity) of the results as cancer cachexia is most prevalent in advanced stage cancer.

Conclusions that can be drawn from any literature review are based on the quality of the trials included. Thus, identifying possible biases in the conducted trials is essential (158). According to the GRADE criteria for "risk of bias, the RCTs included in the systematic review had some shortcomings, mainly concerning small sample sizes and lack of concealed allocation. Many of the included RCT's were pilot studies and this might explain the small sample sizes. It is not known whether the lack of allocation concealment is due to underreporting of the use of this method or that it was not used at all. Allocation concealment is used to reduce selection bias by preventing the participating patients or the investigators from knowing in advance the treatment to which subjects will be assigned.

Another limitation was that few of the included studies reported muscle mass as the primary outcome of interest. In an RCT, the power of the statistical analysis is determined by sample size and the expected between subject variation (mean and SD) in the primary outcome. Muscle mass or strength was the primary outcome in only two trials, and neither study provided power estimates on this outcome. Secondary outcomes in RCT's are commonly used to provide additional data for descriptive purposes or exploratory investigations of unknown associations. The majority of studies were thus not powered to detect changes in muscle mass and strength and thus, effects might have been underestimated in the interpretations of the results from a systematic review.

6.3 Interpretation of main findings

Cancer cachexia as a clinical condition has been overlooked or not adequately diagnosed and treated in the past, and improved classification systems are needed (7). Publication of the international consensus for classification by the EPCRC in 2001 was a great achievement towards improved management of patients with cancer cachexia (15). However, a lack of validated diagnostic criteria and a formal system to classify cancer cachexia into stages is still slowing the progress of developing effective

treatment strategies. In this thesis, the aim was to contribute to the improved understanding of cancer cachexia through improving classification, assessment and treatment of cancer cachexia.

6.3.1 Classification of cancer cachexia

Weight loss is a well-recognized diagnostic criterion for cancer cachexia that has guided diagnosis and treatment of this condition for centuries (19). Results from Paper I underline the legitimacy of using weight loss and BMI as diagnostic criterions for cancer cachexia. However, information about weight loss and BMI was not sufficient to discriminate different groups of patients representing stages of cancer cachexia with regards to the key cachexia domains (stores, nutrition, catabolism and function) and survival. This finding is in line with previous reports, such as the study by Fearon et al (31), showing that not weight loss alone, but a three-factor profile of weight loss, reduced food intake and systemic inflammation, could identify a distinct group of cachectic patients with adverse functional outcomes and prognosis.

In Paper I, the classification of an early stage of cancer cachexia (pre-cachexia) using information about weight loss alone did not have discriminative impact on survival. However, the results suggested that a combination of weight loss (< 5%) with additional information about anorexia (a score of >3 on ESAS appetite item was used as a categorical variable) and systemic inflammation (CRP > 10 ml/g as cut off) might contribute towards a better classification of the pre-cachexia stage. In comparison, Vigano and colleagues were not able to identify a distinct pre-cachexia stage from their data, but found that other stages (cachexia, refractory cachexia) were related to adverse patients reported outcomes and shorter survival (34).

Previous studies and the findings in Paper I, underline the importance of classification of cancer cachexia into stages in order to guide diagnosis and treatment. However, more importantly, it demonstrates the lack of clear and simple criterions and valid cut-off values for making a correct classification of cancer cachexia into stages.

6.3.2 Assessment of cancer cachexia

Muscle mass and strength

Muscle loss is an increasingly recognised diagnostic and prognostic criterion for cancer cachexia (12, 45) and argued to be an important endpoint in cancer cachexia trials (99).

Results from Paper III demonstrated that muscle loss among patients with advanced cancer might vary considerably during the course of chemotherapy. Changes in muscle mass ranged from large losses to gains over a relatively short period of chemotherapy and were also related to survival. This is in line with previous studies that have used CT-image assessment to study changes in muscle mass during treatment in advanced cancer patients (11, 44, 50, 51) and underline the need for repeated measurements of muscle mass in order to understand the development of cancer cachexia in diagnostic and prognostic studies.

The same was not true for sarcopenia at baseline which, compared to change in muscle mass, did not prove to be a significant predictor of survival. Interestingly, the results showed that patients who were sarcopenic at baseline, did maintain or even gain muscle mass during chemotherapy. This is in contrast to a comparable study by Murphy et al. (50) which reported larger losses among patients with baseline sarcopenia compared to non-sarcopenic patients in patients with advanced NSCLC undergoing chemotherapy.

Except for the study by Prado et al. (11), studies that use CT-images to measure changes in muscle mass during cancer treatment, are all small sampled and there is a lack of validated cut-off values for categorising patients according to loss or gain in muscle mass. This makes comparison of change in muscle mass across studies challenging. In addition, further studies also need to decide on clinically meaningful change in muscle mass in patients at different stages of cancer cachexia.

Assessment of muscle strength has been proposed to be a feasible alternative to sophisticated measurements of muscle mass (15). It has been shown that although muscle mass is reduced in patients with cancer cachexia, muscle strength is not always

affected (188), and it has been suggested that muscle mass and strength might not necessary be highly correlated (54). However, at present it cannot be concluded whether muscle strength can act as a proxy for measurement of muscle mass. It is neither not clear which of the outcomes that are most important when assessing cancer cachexia, and at present, both muscle mass and muscle strength should probably be considered (189).

Physical activity

Progressive functional decline is an inevitable consequence of cancer cachexia. Patients frequently report an experience of weakness and fatigue during everyday life activities (22). As a consequence, many cachectic cancer patients reduce their activity levels (31). Activity monitoring by use of small, body worn activity meters is a relatively new assessment method and is by some considered to be "state of the art" for the assessment of physical activity (81). In this thesis, it was shown that an activity meter provided accurate measures of some important aspects of daily physical activity in patients with advanced, incurable cancer.

Activity meters can provide objective information about everyday activity levels, and importantly, low level of physical activity, that is not so easily captured by other methods such as questionnaire or diaries (190). In this thesis, the activity meter accurately measured time spent in upright (standing/walking) and sedentary (lying/sitting) positions both in non-self-caring and self-caring patients. These findings correspond to other validation studies using the same activity meter in other study populations (75, 80, 82, 85). We found, however an under-report of steps in both self-caring and non-self-caring patients. A measurement error of 33% in patients in non-self-caring, and 24% in self-caring patients was higher than expected but in line with results from similar studies of frail, elderly patients (80). For the estimation of energy expenditure, there was an underestimation of EEA by the activity meter compared to the "gold standard", DLW-derived measurements. These results are in line with or have slightly smaller measurement errors compared with other studies (191-194). For the ActivPAL activity meter used in DLW study, calculation of energy expenditure was

also based on step recognition. Underreport of steps may therefore also have influenced conclusions regarding energy expenditure (195).

We found that the accuracy of step counts was poorest in those with the slowest walking speed or with the lowest functioning. These are patients that probably are most inactive and move only short distances and thus, it is even more important to register the activity that is actually performed. Time in upright activity is an outcome derived from the ActivPAL that has shown to discriminate between high and low activity levels among frail elderly hospitalised following hip-fracture (80). It has also been shown that objective physical activity scores significantly correlate with disease stage, functional status, and QoL in patients with cancer (78). Therefore, activity meters can make meaningful objective estimates of patient function in response to cancer and its treatment and may provide surrogate outcomes for quality of life (195).

6.3.3 Treatment of cancer cachexia

There is a lack of standardised treatments for cancer cachexia. The complexity of the condition warrants development of treatment interventions that aim to optimise treatment of the underlying cancer in combination with treatment that target multiple cancer cachexia domains. As shown in Paper III in this thesis, a relatively short chemotherapy regimen might suppress the catabolic processes driving muscle loss for those patients that respond to treatment. This finding underlines the importance of tumour control in cancer cachexia management, and furthermore, suggests that there is an anabolic potential for therapeutic interventions aimed at preserving and restoring muscle mass and strength. Physical exercise is extensively used for this purpose. However, as shown in this thesis, and by others (196), there is a shortage of studies that specifically address cancer patients in a pre-cachectic or cachectic stage. Thus, at present there is not sufficient evidence to recommend specific prescriptions of physical exercise as a therapeutic intervention to treat cancer cachexia. However, physical exercise is highly advocated as an essential component of multimodal interventions for cancer cachexia, and ongoing studies should provide new evidence in this field (99).

6.4 Clinical implications of the findings

A standardized system for classification of cancer cachexia is highly warranted in the clinical setting as it would help clinicians to identify patients according to where they are in the cancer cachexia trajectory and guide treatment decisions in individual patients. To be feasible in clinical settings, a classification system must be accurate and based upon standardised assessment tools that are commonly available. This thesis has provided new knowledge about the assessment of two key cachexia domains, muscle mass and physical activity. Based on results from study II it is suggested that repeated measurements of muscle mass can be important in a clinical setting in order to identify patients that are developing cancer cachexia. CT-images are available in many cancer clinics. However, image-based analysis of muscle mass so far requires competence and resources not available outside the research setting. Thus, it is not always feasible to obtain sophisticated measures of muscle mass in cancer clinics, and therefore, it can be argued that classification systems for cancer cachexia must be built on more easy applicable assessments, e.g. muscle strength and/or physical activity, which allow bedside diagnostics.

Activity meters can provide clinicians with continuous data about free-living physical activities that might not be so easily captured by other measures of physical function. It seems that most cancer patients, regardless of their functional levels, are able and willing to wear the ActivPAL (74). However, in patients with advanced incurable cancer, there is at present limited use of activity meters outside clinical studies. The acceptability of use as well as the cost of monitors, time to process data, and potential for missing data is all aspects that might challenge the feasibility of the activity meters in the clinical setting. In this thesis, activity meters have shown to provide accurate estimates of time in upright activity and should be considered in a clinical setting where information about activity is regarded important. Feasibility of use in the clinical setting can be enhanced by the proper training of personnel and furthermore, it relies on the continuous development of new and improved technology and methods for analysing data on physical activity.

Results from Paper III in this thesis give an important message to clinicians. In order to treat cancer cachexia, the underlying cancer needs to be managed. This thesis has provided evidence that physical exercise improves muscle strength and possibly prevents muscle loss during cancer treatment and can safely be integrated with cancer cachexia management. There is however so far no evidence concerning effects of physical exercise in patients that are in a pre-cachectic or cachectic stage. Thus, exercise prescriptions need to follow recommendations based on formal guidelines for cancer patients and should take the individual patients medical condition, symptoms burden and physical function into consideration.

7. Conclusions

The research questions and answers raised through this thesis can be summarized as follows:

Is information about weight loss and BMI sufficient to classify cancer cachexia in patients with advanced, incurable cancer and can information from other domains (intake, catabolism and function) improve a classification of cancer cachexia into stages from early to late development?

> *Information about weight loss and BMI can clearly distinguish patients who are cachectic from non-cachectic patients but is not sufficient to classify patient into more than two stages of cancer cachexia. Additional information about food intake and inflammation can be used to improve classification by identifying a group of patients with pre-cachexia.*

How accurate is a body-worn activity meter in measuring different dimensions of physical activity in patients with advanced cancer?

> *A body worn activity meter can be used with accuracy in patients with advanced cancer to assess some dimensions of physical activity such as time spent in different activities (lying/sitting, standing, and walking) and number of transfers from sitting to standing*

Is change in muscle mass during palliative chemotherapy associated with treatment response in patients with advanced non – small cell lung cancer; and is change in muscle mass a prognostic factor for survival?

> *A trend towards a larger gain in muscle mass was demonstrated for patients who responded to treatment. Change in muscle mass during treatment, and not sarcopenia before starting treatment, was an independent predictor of survival.*

What is the effect of physical exercise performed during cancer treatment on muscle mass and strength across cancer patient cohorts with different diagnoses and stage of disease?

There is evidence that physical exercise including either aerobic or resistance exercise or a combination of the two, performed during cancer treatment, improves muscle strength, but not muscle mass. There is a lack of randomised controlled trials in patient cohorts with pre-cachexia or cachexia to draw conclusion about the role of physical exercise as an integrative part of treatment for cancer cachexia. Still, awaiting result of ongoing trials, physical exercise is safe and feasible in all cancer patients and should be recommended as part of multimodal interventions aimed at preventing or delaying the development of cancer cachexia.

8. Future research

Development of an international, formally accepted classification system for cancer cachexia is an ongoing process that requires time and effort from many research areas (genetics, molecular science, clinical research). Importantly, improvements in this area largely depend on large collaborative research initiatives working at an international level, such as the EPCRC. This thesis constitutes part of the work done by the EPCRC and has contributed to extending knowledge about classification, assessment and treatment of cancer cachexia in a way that have implications for planned and ongoing clinical trials.

As part of the EPCRC project, large multicentre cross-sectional studies have been conducted to identify and agree upon the most relevant domains to be included in the new classification system. These were stated in the international consensus report in 2011 (15) and included muscle mass and strength, anorexia and food intake, catabolic drive and physical and psychological function. How these cancer cachexia domains should be assessed, were not decided upon by the EPCRC. However, several investigators in the PRC has the past few years worked to develop validated assessment tools for anorexia and food intake (60, 197) and inflammation (198). This thesis has added knowledge about assessment of muscle mass (Paper III) and physical activity (Paper II). Activity meters represent a new and 'novel' technology but, due to the inaccuracies of the step count recognition in patients with advanced cancer; at present they are not recommended to use outside clinical trials. Further prospective validation with larger cohorts of cancer patients with a full spectrum of physical activity is required to improve knowledge about outcomes that can be used as end-points in therapeutic cancer cachexia trials.

A classification system for cancer cachexia is highly warranted to improve management of patients that suffer from this devastating condition. To further develop a cancer cachexia classification system, large prospective intervention studies should investigate the clinical relevance of the new classification system for categorising patients according to their stage of cancer cachexia. It is therefore important to work towards a clear definition of pre-cachexia, especially because this group of patients should be the

target of future intervention trials. Prospective prognostic studies can contribute to identifying subgroups of patients at particular risk of poor treatment outcomes. Longitudinal assessments of muscle mass in such studies can give new insight on how to treat cachexia.

Interventions in cachexia trials should ideally be multimodal, including a combination of optimal treatment of the underlying cancer; and additional treatments that specifically target cancer cachexia. Improving knowledge about the role of physical exercise as an integrated part of cancer cachexia treatment can be achieved through studies that to a larger extent target patient populations with advanced, incurable cancer.

9. Appendix

APPENDIX 1. Test protocols used in Video Study (Paper II)

APPENDIX 2. Karnofsky Performance Status (Paper I, II)

APPENDIX 3. ECOG Performance Score (Paper III)

APPENDIX 4. Edmonton Symptom Assessment System (Paper I)

APPENDIX 5. EORTC QLQ-C30 version 3.0. (Paper II and III)

APPENDIX 6. PG-SGA (Paper I)

Index of activities in test protocol

Part 1. Activities in bed and sitting

1.1. Lie down on your back on the bed.
1.2. Turn over lying on your right side.
1.3. Return to lying on your back.
1.4. Turn over lying on your left side.
1.5. Return to lying on your back.
1.6. Sit up onto the edge of the bed.
1.7. Lie down on your back on the bed.
1.8. Sit up onto the edge of the bed.
1.9. Move from the bed to sitting in the chair.
1.10. Stand up from the chair.
1.11. Sit down in the chair.

Part 2. Walking activities

2.1. Starting with your right foot first: walk slowly as if you where strolling around.
2.2. Turn around to face the other direction.
2.3. Starting with your right foot first: walk as you would normally do.
2.4. Turn around to face the other direction
2.5. Starting with your right leg first: walk as fast as you can safely walk.

Part 3. Daily activities

3.1. Walk over to the table and make yourself a drink and drink it up.
3.2. Walk over to the bed and put the duvet cover and pillow case on the duvet and pillow on the bed
3.3. Walk over to the sink and clean the mirror.
3.4. Walk over to the television and sit down to watch.
3.5. Walk over to the sink and clean the dishes
3.6. Sit down in the chair and read the newspaper
3.7. Pick up the phone and pretend to make a telephone
3.8. Walk over to the sink and wash and dry your hands.
3.9. Sit down by the table and write a letter.
3.10. Prepare a meal and eat it

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS RATING (%) CRITERIA

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing
0	Dead

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Capital Health

CARITAS HEALTH GROUP

Edmonton Symptom Assessment System: Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Patient's Name _____

Date _____ Time _____

Complete by *(check one)*
- ☐ Patient
- ☐ Caregiver
- ☐ Caregiver assisted

BODY DIAGRAM ON REVERSE SIDE

CH-0202 May 2001

ENGLISH

EORTC QLQ-C30 (version 3)

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

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

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

During the past week:

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

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

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

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 nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

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)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3)_____
☐ other** (1) _____
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)

** Examples: depression, money, or dental problems

Box 3 ☐

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 and about with fairly normal activities (1)
☐ not feeling up to most things, but in 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 (3)

Box 4 ☐

Additive Score of the Boxes 1-4 ☐ A

The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements *(See Worksheet 2)*

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

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) ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other___ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

FD Ottery, 2001 email: fdottery@savientpharma.com or noatpres1@aol.com

10. References

1. Cancer Fact sheet N°297: World Health Organisation Available from: http://www.who.int/mediacentre/factsheets/fs297/en/.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-2917.

3. Fagrapport: Status, utviklingstrekk og utfordringer på kreftområdet. Helsedirektoratets innspill til nasjonal strategi på kreftområdet 2013–2017. Juni 2013. Report No.

4. Advanced Cancer Care Planning. A Desicion-making Guide for Patients and Families Facing Serious Ilness Cancer.Net: American Society of Clinical Oncology. Available from: http://www.cancer.net/navigating-cancer-care/advanced-cancer/advanced-cancer-care-planning_truncated.

5. Sobin LH, Gospodarowicz, M.K..Wittekind, C. . TNM Classification of Malignant Tumours. 7th ed: Wiley-Blackwell; 2009.

6. Kaasa S. Palliativ behandling. In: Wist E, Kåresen, R. , editor. Kreftsykdommer - en basisbok for helsepersonell. 4th ed. Oslo, Norway: Gyldendals Norsk Forlag; 2012. p. 113-125.

7. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle. 2010;1(1):1-5.

8. Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. CurrOpinClinNutrMetab Care. 2008;11(4):400-407.

9. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2012.

10. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. J Cachexia Sarcopenia Muscle. 2013;4(3):173-178.

11. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr [Internet]. 2013 Aug 21. Available from: http://ajcn.nutrition.org/content/98/4/1012.full.pdf.

12. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-1547.

13. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008;27(6):793-799.

14. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr. 2010;29(2):154-159.

15. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-495.

16. Baracos VE. Pitfalls in defining and quantifying cachexia. J Cachexia Sarcopenia Muscle. 2011;2(2):71-73.

17. Kaasa S, Loge JH, Fayers P, Caraceni A, Strasser F, Hjermstad MJ, et al. Symptom Assessment in Palliative Care: A Need for International Collaboration. J Clin Oncol. 2008;26(23):3867-3873.

18. Doehner W, Anker SD. Cardiac cachexia in early literature: a review of research prior to Medline. Int J Cardiol. 2002;85(1):7-14.

19. Bennani-Baiti N, Walsh D. What is cancer anorexia-cachexia syndrome? A historical perspective. J R Coll Physicians Edinb. 2009;39(3):257-262.

20. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44(8):1124-1132.

21. Lundholm K, Korner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P, et al. Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. ClinCancer Res. 2007;13(9):2699-2706.

22. Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annu Rev Med. 2011;62:265-279.

23. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-166.

24. Baracos VE. Regulation of skeletal-muscle-protein turnover in cancer-associated cachexia. Nutrition. 2000;16(10):1015-1018.

25. Baracos VE. Management of muscle wasting in cancer-associated cachexia: understanding gained from experimental studies. Cancer. 2001;92(6 Suppl):1669-1677.

26. Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. J Cachexia Sarcopenia Muscle. 2010;1(1):9-21.

27. Busquets S, Toledo M, Marmonti E, Orpi M, Capdevila E, Betancourt A, et al. Formoterol treatment downregulates the myostatin system in skeletal muscle of cachectic tumour-bearing rats. Oncol Lett. 2012;3(1):185-189.

28. Tisdale MJ. Pathogenesis of cancer cachexia. JSupportOncol. 2003;1(3):159-168.

29. Baracos VE. Clinical trials of cancer cachexia therapy, now and hereafter. J Clin Oncol. 2013;31(10):1257-1258.

30. Muscaritoli M, Molfino A, Gioia G, Laviano A, Rossi Fanelli F. The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. Intern Emerg Med. 2011;6(2):105-112.

31. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. AmJClinNutr. 2006;83(6):1345-1350.

32. Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. JPEN J Parenter Enteral Nutr. 2009;33(4):361-367.

33. Argiles JM, Lopez-Soriano FJ, Toledo M, Betancourt A, Serpe R, Busquets S. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. J Cachexia Sarcopenia Muscle. 2011;2(2):87-93.

34. Vigano A, Del Fabbro E, Bruera E, Borod M. The cachexia clinic: from staging to managing nutritional and functional problems in advanced cancer patients. Crit Rev Oncog. 2012;17(3):293-303.

35. Blum D, Omlin A, Baracos VE, Solheim TS, Tan BH, Stone P, et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol. 2011;80(1):114-144.

36. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491-497.

37. Concise Medical Dictionary: Oxford University Press; 2010. Available from: http://www.oxfordreference.com/10.1093/acref/9780199557141.001.0001/acref-9780199557141.

38. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. Appl Physiol Nutr Metab. 2012;37(5):811-821.

39. Baracos V, Caserotti P, Earthman CP, Fields D, Gallagher D, Hall KD, et al. Advances in the science and application of body composition measurement. JPEN J Parenter Enteral Nutr. 2012;36(1):96-107.

40. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1998;85(1):115-122.

41. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. JApplPhysiol. 2004;97(6):2333-2338.

42. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

43. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr. 1997;17:527-558.

44. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973-6979.

45. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-635.

46. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920-2926.

47. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. ClinCancer Res. 2007;13(11):3264-3268.

48. Parsons HA, Baracos VE, Dhillon N, Hong DS, Kurzrock R. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. PLoS One. 2012;7(1):e29330.

49. Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, et al. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr. 2013;109(2):302-312.

50. Murphy RA, Mourtzakis M, Chu QS, Reiman T, Mazurak VC. Skeletal muscle depletion is associated with reduced plasma (n-3) fatty acids in non-small cell lung cancer patients. J Nutr. 2010;140(9):1602-1606.

51. Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in

patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manage. 2012;44(2):181-191.

52. Blum D, Strasser F. Cachexia assessment tools. Curr Opin Support Palliat Care. 2011;5(4):350-355.

53. Strasser F. Diagnostic criteria of cachexia and their assessment: decreased muscle strength and fatigue. Curr Opin Clin Nutr Metab Care. 2008;11(4):417-421.

54. Collins J, Noble S, Chester J, Coles B, Byrne A. The assessment and impact of sarcopenia in lung cancer: a systematic literature review. BMJ Open. 2014;4(1):e003697.

55. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

56. Balstad TR, Solheim TS, Strasser F, Kaasa S, Bye A. Dietary treatment of weight loss in patients with advanced cancer and cachexia: A systematic literature review. Crit Rev Oncol Hematol. 2014.

57. Martin L, Watanabe S, Fainsinger R, Lau F, Ghosh S, Quan H, et al. Prognostic factors in patients with advanced cancer: use of the patient-generated subjective global assessment in survival prediction. J Clin Oncol. 2010;28(28):4376-4383.

58. Bruera E, Kuehn N, Miller MJ, Selmser P, MacMillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. JPalliatCare. 1991;7(2):6-9.

59. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNatlCancer Inst. 1993;85(5):365-376.

60. Solheim TS, Blum D, Fayers PM, Hjermstad MJ, Stene GB, Strasser F, et al. Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: Three peas in a pod? - analysis from a multicenter cross sectional study. Acta Oncol. 2014;53(4):539-546.

61. Stene GB, Kaasa S, Helbostad JL. Assessment of physical functioning in palliative cancer patients. European Journal of Palliative Care. 2008.

62. Guralnik JM, Branch LG, Cummings SR, Curb JD. Physical performance measures in aging research. JGerontol. 1989;44(5):M141-M146.

63. Wood CA, Anderson J, Yates JW. Physical function assessment in patients with advanced cancer. MedPediatrOncol. 1981;9(2):129-132.

64. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations--a study by the Steering Committee of the European Association for Palliative Care. JClinOncol. 2005;23(25):6240-6248.

65. Montoya M, Fossella F, Palmer JL, Kaur G, Pace EA, Yadav R, et al. Objective evaluation of physical function in patients with advanced lung cancer: a preliminary report. JPalliatMed. 2006;9(2):309-316.

66. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-131.

67. Lissner L, Potischman N, Troiano R, Bengtsson C. Recall of physical activity in the distant past: the 32-year follow-up of the Prospective Population Study of Women in Goteborg, Sweden. AmJEpidemiol. 2004;159(3):304-307.

68. Psota T, Chen KY. Measuring energy expenditure in clinical populations: rewards and challenges. Eur J Clin Nutr. 2013;67(5):436-442.

69. Zhang K, Pi-Sunyer FX, Boozer CN. Improving energy expenditure estimation for physical activity. MedSciSports Exerc. 2004;36(5):883-889.

70. Kumahara H. The use of uniaxial accelerometry for the assessment of physical-activity-related energy expenditure: a validation study against whole-body indirect calorimetry. The British journal of nutrition. 2004;91(2):235-243.

71. Chen KY. Development and validation of a measurement system for assessment of energy expenditure and physical activity in Prader-Willi syndrome. Obesity research. 1999;7(4):387-394.

72. Chen KY, Bassett DR, Jr. The technology of accelerometry-based activity monitors: current and future. MedSciSports Exerc. 2005;37(11 Suppl):S490-S500.

73. Zhang K, Werner P, Sun M, Pi-Sunyer FX, Boozer CN. Measurement of human daily physical activity. ObesRes. 2003;11(1):33-40.

74. Maddocks M, Byrne A, Johnson CD, Wilson RH, Fearon KC, Wilcock A. Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study. Support Care Cancer. 2010;18(12):1539-1544.

75. Grant PM, Dall PM, Mitchell SL, Granat MH. Activity-monitor accuracy in measuring step number and cadence in community-dwelling older adults. J Aging Phys Act. 2008;16(2):201-214.

76. Harrington DM, Welk GJ, Donnelly AE. Validation of MET estimates and step measurement using the ActivPAL physical activity logger. J Sports Sci. 2011;29(6):627-633.

77. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.

78. Ferriolli E, Skipworth RJ, Hendry P, Scott A, Stensteth J, Dahele M, et al. Physical activity monitoring: a responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? J Pain Symptom Manage. 2012;43(6):1025-1035.

79. Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. JPain SymptomManage. 2007;33(6):676-685.

80. Taraldsen K, Askim T, Sletvold O, Einarsen EK, Bjastad KG, Indredavik B, et al. Evaluation of a body-worn sensor system to measure physical activity in older people with impaired function. Phys Ther. 2011;91(2):277-285.

81. Taraldsen K, Chastin SF, Riphagen, II, Vereijken B, Helbostad JL. Physical activity monitoring by use of accelerometer-based body-worn sensors in older adults: a systematic literature review of current knowledge and applications. Maturitas. 2012;71(1):13-19.

82. Grant PM, Ryan CG, Tigbe WW, Granat MH. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. BrJSports Med. 2006;40(12):992-997.

83. Busse ME. Quantified measurement of activity provides insight into motor function and recovery in neurological disease. Journal of neurology, neurosurgery and psychiatry. 2004;75(6):884-888.

84. Godfrey A, Culhane KM, Lyons GM. Comparison of the performance of the activPAL Professional physical activity logger to a discrete accelerometer-based activity monitor. MedEng Phys. 2007;29(8):930-934.

85. Maddocks MM, Petrou AA, Skipper LL, Wilcock AA. Validity of three accelerometers during treadmill walking and motor vehicle travel. British Journal of Sports Medicine. 2008.

86. Maddocks M, Wilcock A. Exploring physical activity level in patients with thoracic cancer: implications for use as an outcome measure. Support Care Cancer. 2012.

87. Hopkinson JB. Psychosocial impact of cancer cachexia. J Cachexia Sarcopenia Muscle. 2014.

88. Oberholzer R, Hopkinson JB, Baumann K, Omlin A, Kaasa S, Fearon KC, et al. Psychosocial Effects of Cancer Cachexia: A Systematic Literature Search and Qualitative Analysis. Journal of Pain and Symptom Management. 2013;46(1):77-95.

89. Jordhoy MS, Fayers P, Loge JH, hlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. JClinOncol. 2001;19(18):3884-3894.

90. Rayner L, Loge JH, Wasteson E, Higginson IJ, Epcrc EPCRC. The detection of depression in palliative care. Curr Opin Support Palliat Care. 2009;3(1):55-60.

91. Wasteson E, Brenne E, Higginson IJ, Hotopf M, Lloyd-Williams M, Kaasa S, et al. Depression assessment and classification in palliative cancer patients: a systematic literature review. Palliat Med. 2009;23(8):739-753.

92. Reid J, McKenna H, Fitzsimons D, McCance T. The experience of cancer cachexia: a qualitative study of advanced cancer patients and their family members. Int J Nurs Stud. 2009;46(5):606-616.

93. MacDonald N. Cancer cachexia and targeting chronic inflammation: a unified approach to cancer treatment and palliative/supportive care. JSupportOncol. 2007;5(4):157-162.

94. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-1179.

95. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503-509.

96. Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? Br J Cancer. 2004;90(10):1905-1911.

97. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90-99.

98. Rogers ES, MacLeod RD, Stewart J, Bird SP, Keogh JW. A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), resistance training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients--ACCeRT study. BMC Cancer. 2011;11:493.

99. Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Curr Opin Support Palliat Care. 2012;6(4):424-431.

100. Reid J, Hughes CM, Murray LJ, Parsons C, Cantwell MM. Non-steroidal anti-inflammatory drugs for the treatment of cancer cachexia: A systematic review. Palliat Med. 2012.

101. Solheim TS, Fearon KC, Blum D, Kaasa S. Non-steroidal anti-inflammatory treatment in cancer cachexia: A systematic literature review. Acta Oncol. 2012.

102. Ries A, Trottenberg P, Elsner F, Stiel S, Haugen D, Kaasa S, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. Palliat Med. 2012;26(4):294-304.

103. Wallengren O, Lundholm K, Bosaeus I. Diet energy density and energy intake in palliative care cancer patients. Clin Nutr. 2005;24(2):266-273.

104. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(5):371-385.

105. Al-Majid S, Waters H. The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. Biol Res Nurs. 2008;10(1):7-20.

106. Maddocks M, Murton AJ, Wilcock A. Improving muscle mass and function in cachexia: non-drug approaches. Curr Opin Support Palliat Care. 2011;5(4):361-364.

107. Glover EI, Phillips SM. Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy. Curr Opin Clin Nutr Metab Care. 2010;13(6):630-634.

108. Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? J Cachexia Sarcopenia Muscle. 2012.

109. Gould DW, Lahart I, Carmichael AR, Koutedakis Y, Metsios GS. Cancer cachexia prevention via physical exercise: molecular mechanisms. J Cachexia Sarcopenia Muscle. 2013;4(2):111-124.

110. Lira FS, Rosa JC, Zanchi NE, Yamashita AS, Lopes RD, Lopes AC, et al. Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. Cell Biochem Funct. 2009;27(2):71-75.

111. Penna F, Busquets S, Pin F, Toledo M, Baccino FM, Lopez-Soriano FJ, et al. Combined approach to counteract experimental cancer cachexia: eicosapentaenoic acid and training exercise. J Cachex Sarcopenia Muscle. 2011;2(2):95-104.

112. Vogiatzis I, Simoes DC, Stratakos G, Kourepini E, Terzis G, Manta P, et al. Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. Eur Respir J. 2010;36(2):301-310.

113. Vogiatzis I, Stratakos G, Simoes DC, Terzis G, Georgiadou O, Roussos C, et al. Effects of rehabilitative exercise on peripheral muscle TNFalpha, IL-6, IGF-I and MyoD expression in patients with COPD. Thorax. 2007;62(11):950-956.

114. Adamopoulos S, Coats AJ, Brunotte F, Arnolda L, Meyer T, Thompson CH, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. Journal of the American College of Cardiology [Internet]. 1993; (5):[1101-1106 pp.]. Available from:

http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/004/CN-00092004/frame.html.

115. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008;67(3):253-256.

116. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv. 2010;4(2):87-100.

117. Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, Harris SR. Effects of exercise intervention on persons with metastatic cancer: a systematic review. Physiother Can. 2009;61(3):141-153.

118. Oldervoll LM, Loge JH, Paltiel H, Vidvei U, Oredalen E, Frantzen TL, et al. Physical Exercise for Cancer Patients with Advanced Disease: A Randomized Controlled Trial. The Oncologist 2011;Also reported in conference: EAPC 2010 Glasgow United Kingdom. Conference Start: 20100610 Conference End: 20100612. Conference Publication: (var.pagings). 24 (4 SUPPL. 1).

119. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Hjermstad MJ, et al. Are palliative cancer patients willing and able to participate in a physical exercise program? PalliatSupportCare. 2005;3(4):281-287.

120. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. J Sci Med Sport. 2009;12(4):428-434.

121. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-1426.

122. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the Exercise Guidelines for Cancer Survivors. J Support Oncol. 2012.

123. O'Donovan G, Blazevich AJ, Boreham C, Cooper AR, Crank H, Ekelund U, et al. The ABC of Physical Activity for Health: a consensus statement from the British Association of Sport and Exercise Sciences. J Sports Sci. 2010;28(6):573-591.

124. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, et al. A structured exercise program for patients with advanced non-small cell lung cancer. J Thorac Oncol. 2009;4(5):595-601.

125. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Wiken AN, et al. The effect of a physical exercise program in palliative care: A phase II study. Journal of Pain and Symptom Management. 2006;31(5):421-430.

126. Lowe SS, Watanabe SMS, Courneya KSK. Physical activity as a supportive care intervention in palliative cancer patients: a systematic review. The Journal of supportive oncology. 2009;7(1):27-34.

127. Hjermstad MJ, Lie HC, Caraceni A, Currow DC, Fainsinger RL, Gundersen OE, et al. Computer-based symptom assessment is feasible in patients with advanced cancer: results from an international multicenter study, the EPCRC-CSA. J Pain Symptom Manage. 2012;44(5):639-654.

128. Seaby L, Torrance G. Reliability of a physiotherapy functional assessment used in a rehabilitation setting. Physiotherapy Canada. 1989;41(5):264-271.

129. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34(2):119-126.

130. Scrimgeour CM, Rollo MM, Mudambo SM, Handley LL, Prosser SJ. A simplified method for deuterium/hydrogen isotope ratio measurements on water samples of biological origin. Biol Mass Spectrom. 1993;22(7):383-387.

131. Prosser SJ, Brookes ST, Linton A, Preston T. Rapid, automated analysis of 13C and 18O of CO2 in gas samples by continuous-flow, isotope ratio mass spectrometry. Biol Mass Spectrom. 1991;20(11):724-730.

132. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325-331.

133. Nicholson MJ, Holton J, Bradley AP, Beatty PC, Campbell IT. The performance of a variable-flow indirect calorimeter. Physiol Meas. 1996;17(1):43-55.

134. International Classification of Diseases (ICD-10): World Health Organisation (WHO); [cited 2014 28/03]. Available from: http://www.who.int/classification/icd/en.

135. Lieffers JR, Baracos VE, Winget M, Fassbender K. A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer. 2011;117(9):1957-1965.

136. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980;45(8):2220-2224.

137. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

138. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996;32a(7):1135-1141.

139. Schaafsma J, Osoba D. The Karnofsky Performance Status Scale re-examined: a cross-validation with the EORTC-C30. QualLife Res. 1994;3(6):413-424.

140. Karnofsky DAB, J.H. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM, editor. Evaluation of Chemotherapeutic Agents: ColombiaUniversity Press; 1949. p. 196.

141. Stromgren AS, Goldschmidt D, Groenvold M, Petersen MA, Jensen PT, Pedersen L, et al. Self-assessment in cancer patients referred to palliative care: a study of feasibility and symptom epidemiology. Cancer. 2002;94(2):512-520.

142. Knobel H, Loge JH, Brenne E, Fayers P, Hjermstad MJ, Kaasa S. The validity of EORTC QLQ-C30 fatigue scale in advanced cancer patients and cancer survivors. PalliatMed. 2003;17(8):664-672.

143. Elmqvist MA, Jordhoy MS, Bjordal K, Kaasa S, Jannert M. Health-related quality of life during the last three months of life in patients with advanced cancer. Support Care Cancer. 2009;17(2):191-198.

144. Solheim TS, Blum D, Fayers PM, Hjermstad MJ, Stene GB, Strasser F, et al. Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: Three peas in a pod? - analysis from a multicenter cross sectional study. Acta Oncol. 2013.

145. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Prado CMM, et al. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. Clinical nutrition (Edinburgh, Scotland). 2012.

146. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer. 2013.

147. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.

148. Levine J, Melanson EL, Westerterp KR, Hill JO. Measurement of the components of nonexercise activity thermogenesis. Am J Physiol Endocrinol Metab. 2001;281(4):E670-675.

149. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care. 2009;3(4):269-275.

150. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010;91(4):1133S-1137S.

151. Gronberg BH, Sørhaug, S., Hjelde, H. H., Stene G.B., Amundsen, T., editor Variation in health-related quality of life (HRQoL) during chemotherapy for advanced non-small cell lung cancer. 2013 ASCO Annual Meeting; 2013 2013; Chicago, Illinois, USA: J Clin Oncol 31, 2013 (suppl; abstr 9562).

152. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002;20(21):4285-4291.

153. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176-181.

154. Ryan CG, Grant PM, Tigbe WW, Granat MH. The validity and reliability of a novel activity monitor as a measure of walking. BrJSports Med. 2006;40(9):779-784.

155. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound ObstetGynecol. 2003;22(1):85-93.

156. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-1012.

157. Hemingway P, Brereton, N. . What is a systematic review? What is? series [Internet]. 2009 17.10.2010.

158. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-415.

159. Cohen J. Statistical power analysis for the behavioural sciences. 2nd ed. Hillsdale, New Jersey: Laurence Erlbaum Associates, Inc.; 1988. 19-74 p.

160. Durlak JA. How to select, calculate, and interpret effect sizes. J Pediatr Psychol. 2009;34(9):917-928.

161. Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ. 2009;339:b3410.

162. Battaglini C, Bottaro M, Dennehy C, Rae L, Shields E, Kirk D, et al. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. Sao Paulo Med J. 2007;125(1):22-28.

163. Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant. 2010;45(2):355-362.

164. Baumann FT, Zopf EM, Nykamp E, Kraut L, Schule K, Elter T, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. Eur J Haematol. 2011;87(2):148-156.

165. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. Cancer Nursing. 2003;26 (5):410-419.

166. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25(28):4396-4404.

167. Cunningham BA, Morris G, Cheney CL, Buergel N, Aker SN, Lenssen P. Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1986;10(6):558-563.

168. Demark-Wahnefried W, Case LD, Blackwell K, Marcom PK, Kraus W, Aziz N, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. Clinical Breast Cancer. 2008;8 (1):70-79.

169. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. Bone Marrow Transplantation. 2009;43 (9):725-737.

170. Monga U, Garber SL, Thornby J, Vallbona C, Kerrigan AJ, Monga TN, et al. Exercise Prevents Fatigue and Improves Quality of Life in Prostate Cancer Patients Undergoing Radiotherapy. Archives of Physical Medicine and Rehabilitation. 2007;88 (11):1416-1422.

171. Mustian KM, Peppone L, Darling TV, Palesh O, Heckler CE, Morrow GR. A 4-week home-based aerobic and resistance exercise program during radiation therapy: A pilot randomized clinical trial. Journal of Supportive Oncology. 2009;7 (5):158-167.

172. Schwartz AL, Winters-Stone K. Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women. Physician and Sportsmedicine. 2009;37 (3):62-67.

173. Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum. 2007;34(3):627-633.

174. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. Journal of Clinical Oncology. 2009;27 (3):344-351.

175. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. Blood. 2011;117(9):2604-2613.

176. Laake P, Hjartåker, A., Thelle, D.S. Epidemiologiske og kliniske forskningsmetoder. . Oslo, Norway: Gyldendal Akademisk; 2007. 551 p.

177. Newman TB, Browner, W.S., Cummings, C.R., Hulley, S.B. . Designing Cross-sectional and Case-control Studies In: Hulley SB, editor. Designing clinical research. 3rd ed. Philadelhpia, USA Lippincott, Williams and Wilkins 2007. p. 109-126.

178. Jordhoy MS, Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. Palliat Med. 1999;13(4):299-310.

179. Thadhani R, Tonelli M. Cohort Studies: Marching Forward. Clinical Journal of the American Society of Nephrology. 2006;1(5):1117-1123.

180. Fyllingen EH, Oldervoll LM, Loge JH, Hjermstad MJ, Haugen DF, Sigurdardottir KR, et al. Computer-based assessment of symptoms and mobility in palliative care: feasibility and challenges. J Pain Symptom Manage. 2009;38(6):827-836.

181. Cummings CR, Newman, T.B., Hulley, S.B. . Designing a cohort study. In: Hulley SB, editor. Designing clinical research. 3rd ed. Philadelhpia, USA Lippincott, Williams and Wilkins 2007. p. 109-126.

182. Dijkstra BB, Kamsma YB, Zijlstra WW. Detection of gait and postures using a miniaturised triaxial accelerometer-based system: accuracy in community-dwelling older adults. Age and Ageing. 2010;39(2):259-262.

183. Storti KL, Pettee KK, Brach JS, Talkowski JB, Richardson CR, Kriska AM. Gait speed and step-count monitor accuracy in community-dwelling older adults. MedSciSports Exerc. 2008;40(1):59-64.

184. Dijkstra B, Zijlstra W, Scherder E, Kamsma Y. Detection of walking periods and number of steps in older adults and patients with Parkinson's disease: accuracy of a pedometer and an accelerometry-based method. Age Ageing. 2008;37(4):436-441.

185. Esliger DW, Probert A, Gorber SC, Bryan S, Laviolette M, Tremblay MS. Validity of the Actical accelerometer step-count function. MedSciSports Exerc. 2007;39(7):1200-1204.

186. Ramstrand N. Validation of a patient activity monitor to quantify ambulatory activity in an amputee population. Prosthetics and orthotics international. 2007;31(2):157-166.

187. Hanneman SK. Design, analysis, and interpretation of method-comparison studies. AACN Adv Crit Care. 2008;19(2):223-234.

188. Weber MA, Krakowski-Roosen H, Schroder L, Kinscherf R, Krix M, Kopp-Schneider A, et al. Morphology, metabolism, microcirculation, and strength of skeletal muscles in cancer-related cachexia. Acta Oncol. 2009;48(1):116-124.

189. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-423.

190. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.

191. Arvidsson D, Slinde F, Nordenson A, Larsson S, Hulthen L. Validity of the ActiReg system in assessing energy requirement in chronic obstructive pulmonary disease patients. Clin Nutr. 2006;25(1):68-74.

192. Hustvedt BE, Svendsen M, Lovo A, Ellegard L, Hallen J, Tonstad S. Validation of ActiReg to measure physical activity and energy expenditure against doubly labelled water in obese persons. Br J Nutr. 2008;100(1):219-226.

193. Copland L, Liedman B, Rothenberg E, Ellegard L, Hustvedt BE, Bosaeus I. Validity of the ActiReg system and a physical activity interview in assessing total energy expenditure in long-term survivors after total gastrectomy. Clin Nutr. 2008;27(6):842-848.

194. Gardner AW, Poehlman ET. Assessment of free-living daily physical activity in older claudicants: validation against the doubly labeled water technique. J Gerontol A Biol Sci Med Sci. 1998;53(4):M275-280.

195. Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage. 2007;33(6):676-685.

196. Maddocks M, Jones LW, Wilcock A. Immunological and hormonal effects of exercise: implications for cancer cachexia. Curr Opin Support Palliat Care. 2013;7(4):376-382.

197. Solheim TS, Fayers PM, Fladvad T, Tan B, Skorpen F, Fearon K, et al. Is there a genetic cause of appetite loss?-an explorative study in 1,853 cancer patients. J Cachexia Sarcopenia Muscle. 2012;3(3):191-198.

198. Partridge M, Fallon M, Bray C, McMillan D, Brown D, Laird B. Prognostication in advanced cancer: a study examining an inflammation-based score. J Pain Symptom Manage. 2012;44(2):161-167.

Paper I

21. Gentleman RC, Carey VJ, Bates DM et al. Bioconductor: open software development for computational biology and bioinformatics. Genome Biol 2004; 5: R80.
22. Porzelius C, Binder H, Schumacher M. Parallelized prediction error estimation for evaluation of high-dimensional models. Bioinformatics 2009; 25: 827–829.
23. Yasrebi H. SurvJamda: an R package to predict patients' survival and risk assessment using joint analysis of microarray gene expression data. Bioinformatics 2011; 27: 1168–1169.
24. Schröder MS, Culhane AC, Quackenbush J et al. Survcomp: an R/Bioconductor package for performance assessment and comparison of survival models. Bioinformatics 2011; 27: 3206–3208.
25. Winter SC, Buffa FM, Silva P et al. Relation of a hypoxia metagene derived from head and neck cancer to prognosis of multiple cancers. Cancer Res 2007; 67: 3441–3449.
26. Eschrich SA, Pramana J, Zhang H et al. A gene expression model of intrinsic tumor radiosensitivity: prediction of response and prognosis after chemoradiation. Int J Radiat Oncol Biol Phys 2009; 75: 489–496.
27. Jung SH. Samples size calculation for microarray studies with survival endpoints. J Comput Sci Syst Biol 2013; 6: 177–181.
28. Slebos RJ, Yi Y, Ely K et al. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. Clin Cancer Res 2006; 12: 701–709.
29. Resnick RM, Cornelissen MT, Wright DK et al. Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers. J Natl Cancer Inst 1990; 82: 1477–1484.
30. Yang X, Regan K, Huang Y et al. Single sample expression-anchored mechanisms predict survival in head and neck cancer. PLoS Comput Biol 2012; 8: e1002350.
31. Edén P, Ritz C, Rose C et al. "Good Old" clinical markers have similar power in breast cancer prognosis as microarray gene expression profilers. Eur J Cancer 2004; 40: 1837–1841.
32. Sorlie T, Tibshirani R, Parker J et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100: 8418–8423.
33. Pramana J, Van den Brekel MW, van Velthuysen ML et al. Gene expression profiling to predict outcome after chemoradiation in head and neck cancer. Int J Radiat Oncol Biol Phys 2007; 69: 1544–1552.
34. Micheel CM, Nass SJ, Omenn GS, Editors; Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials; Board on Health Care Services; Board on Health Sciences Policy; Institute of Medicine; Evolution of translational OMICS: lessons learned and the path forward. (2012) The National Academies Press (Washington, D.C.)
35. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. PLoS Med 2012; 9: e1001216.

Annals of Oncology 25: 1635–1642, 2014
doi:10.1093/annonc/mdu086
Published online 20 February 2014

Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model—a study based on data from an international multicentre project (EPCRC-CSA)

D. Blum[1,2*], G. B. Stene[1,2,3,†], T. S. Solheim[1,2], P. Fayers[1,4], M. J. Hjermstad[1,5], V. E. Baracos[6], K. Fearon[7], F. Strasser[1,8] & S. Kaasa[1,2], on behalf of Euro-Impact

[1]European Palliative Care Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim; [2]Cancer Clinic, St Olavs Hospital, Trondheim University Hospital, Trondheim; [3]Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [4]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK; [5]Department of Oncology, Regional Centre for Excellence in Palliative Care, Oslo University Hospital, Ullevål, Oslo, Norway; [6]Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Alberta, Canada; [7]Clinical and Surgical Sciences (Surgery), University of Edinburgh, Royal Infirmary, Edinburgh, UK; [8]Department of Internal Medicine and Palliative Center Cantonal Hospital, Oncological Palliative Medicine, Oncology, St Gallen, Switzerland

Received 24 October 2013; revised 11 February 2014; accepted 17 February 2014

Background: Weight loss limits cancer therapy, quality of life and survival. Common diagnostic criteria and a framework for a classification system for cancer cachexia were recently agreed upon by international consensus. Specific assessment domains (stores, intake, catabolism and function) were proposed. The aim of this study is to validate this diagnostic criteria (two groups: model 1) and examine a four-group (model 2) classification system regarding these domains as well as survival.

*Correspondence to: David Blum, European Palliative Research Center, Department of Cancer Research and Molecular Medicine, NTNU, Faculty of Medicine, Trondheim N-7491, Norway. Tel: +47-728-26486; Fax: +47-728-26486; E-mail: david.blum@ntnu.no

†BD and SGB have contributed equally to this manuscript and are to be considered as joint first authors.

Patients and methods: Data from an international patient sample with advanced cancer (*N* = 1070) were analysed. In model 1, the diagnostic criteria for cancer cachexia [weight loss/body mass index (BMI)] were used. Model 2 classified patients into four groups 0-III, according to weight loss/BMI as a framework for cachexia stages. The cachexia domains, survival and sociodemographic/medical variables were compared across models.

Results: Eight hundred and sixty-one patients were included. Model 1 consisted of 399 cachectic and 462 non-cachectic patients. Cachectic patients had significantly higher levels of inflammation, lower nutritional intake and performance status and shorter survival. In model 2, differences were not consistent; appetite loss did not differ between group III and IV, and performance status not between group 0 and I. Survival was shorter in group II and III compared with other groups. By adding other cachexia domains to the model, survival differences were demonstrated.

Conclusion: The diagnostic criteria based on weight loss and BMI distinguish between cachectic and non-cachectic patients concerning all domains (intake, catabolism and function) and is associated with survival. In order to guide cachexia treatment a four-group classification model needs additional domains to discriminate between cachexia stages.

Key words: cancer, cachexia, classification, validation

introduction

Cachexia affects 60%–80% of all advanced cancer patients [1], and its consequences are devastating as it decreases physical function and quality of life, and shortens survival [2]. Cancer cachexia is a complex condition that is not yet fully understood and there is no standard treatment available [3].

Traditionally, patients with a weight loss of more than 5% of pre-illness stable weight have been considered to have some degree of cachexia, but other cut-offs have also been used (e.g. >10%, 2%) [4]. A three-factor model incorporating weight loss (≥10%), low food intake (1500 kcal/day) and systemic inflammation (C-reactive protein ≥10 mg/l) was tested by Fearon et al. in 170 advanced cancer patients [5]. In this study, all three factors had to be applied in order to identify patients with both adverse function and shortened survival.

Recently, an international panel of cachexia experts initiated a formal consensus process to agree on a common definition and a framework for the development of a new classification system for cancer cachexia [6]. Weight loss, body mass index (BMI) and levels of muscle mass (sarcopenia) forms the basis of this consensus definition. Additionally, information about anorexia or reduced food intake, catabolic drive, muscle strength as well as physical, social and psychological function were proposed as important domains for a cancer cachexia classification system. It was furthermore agreed that cancer cachexia is to be considered a trajectory and can be classified into the stages, pre-cachexia, cachexia and refractory cachexia.

Staging of cancer cachexia is of importance in guiding treatment decisions and inclusions into clinical trials. Both ends of the cancer cachexia trajectory must be recognized. For instance treatments to prevent or delay the development of cancer cachexia should be initiated early in the trajectory, and thus a clear distinction of the pre-cachexia is needed. In refractory cachexia where the tumour is no longer responding to anticancer treatment and the life expectancy is short, the primary focus should be symptom management and general care according to end of life care guidelines.

These stages were not accurately defined and how these domains should be assessed and operationalized in a classification system remains unclear.

The overall aim of this study was to contribute to the development of a new classification system for cancer cachexia by examining two classification models based on information on weight loss and BMI: (i) a two-group model validating the diagnostic criteria and (ii) a four-group model as a preliminary framework for classifying cachexia into stages. The research questions asked were as follows:

- Is a four-group model better than a two-group model in terms of classifying patients into different stages of cachexia?
- How can factors representing the other key cancer cachexia domains (intake, catabolism and function) contribute to the classification?

materials and methods

patients and study design

Patients were recruited from an international multicentre study initiated by the European Palliative Care Research Collaborative (EPCRC) [7]. A cross-sectional data collection was conducted from October 2008 until December 2009 in palliative care in-and out-patient units, hospices and general oncology and medical wards in several European countries (Norway, UK, Austria, Germany, Switzerland, Italy, Canada and Australia). Patients were eligible if they were aged ≥18 years and had an incurable metastatic or locally advanced cancer diagnosis. Patients not able to complete assessments due to physical or cognitive impairment or language problems were excluded. The ethical authorities in all participating centres approved the study protocol, and all patients gave their written informed consent.

data collection

Data were collected on touch-sensitive computers (HP Compaq TC4200 1200 tablet PCs made by Hewlett-Packard Development Company L.D.). Details on the lay-out and specifications for the computerized assessment have been presented by the EPCRC previously [8]. Data collection consisted of two parts: one to be completed by the study coordinators and the other part to be completed by the patients. A research assistant was available and provided help as necessary. All data were entered by tapping directly on the computer screen with an electronic pen.

assessments

Demographic information (age, gender, CRP and date of death), cancer diagnosis (ICD-10), stage of disease (locally advanced versus metastatic), performance status [9] and current oncological treatment (chemotherapy

or not) was collected from the patients' medical records by the study coordinators.

Assessments of symptoms were performed using Edmonton Symptom Assessment System (ESAS) [10] which includes nine numerical ratings scales, scoring 0 (no problem) to 10 (worst possible problem), for the symptoms pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being and shortness of breath.

Information about stature (weight, height), weight loss last 6 months (in kg) and food intake past month (unchanged, changed or less than usual) was provided by the patients using questions from the Scored Patient-Generated Subjective Global Assessment (PG-SGA) [11].

two-group classification model (model 1)

Patients were classified into two groups based on criteria from the international consensus [6]. Cachexia was weight loss >5% the past 6 months OR any degree of weight loss >2% the last 6 months + BMI <20 kg/m^2. Patients above or below these cut-offs were grouped as: cachexia and no cachexia.

four-group classification model (model 2)

As a preliminary framework for the staging system for cancer cachexia proposed by the international consensus, a four-group model based on information about weight loss and BMI was used in this analysis. In this model, patients were classified into four weight loss groups (0–III) according to the following criteria:

'No cachexia (group 0)': weight change (± 1 kg) or weight gain
'Pre-cachexia (group I)': weight loss >1 kg, but <5%
'Cachexia (group II)': weight loss >5% the last 6 months, or weight loss >2% the last 6 month + BMI <20 kg/m^2
'Refractory cachexia (group III)': weight loss >15% last 6 months + BMI <23 kg/m^2 OR weight loss >20% last 6 months + BMI <27 kg/m^2.

To further explore the consensus framework definition of pre-cachexia, a weight loss model adding information from the cachexia domains catabolism (CRP < or >10) and intake (appetite ESAS >3) was tested in terms of survival (model 3).

statistical analysis

Model 1 (two groups) was tested by group-wise comparison of cachectic versus non-cachectic patients with regards to items representing cachexia domains as well as a range of demographic and medical information. For continuous variables, an independent sample *t*-test was applied and a χ^2 test for categorical variables. In model 2 (four groups), comparisons using a one-way analysis of variance (ANOVA), or a non-parametric equivalent (Kruskal–Wallis test). Ninety-five percent confidence intervals (95% CIs) and *P*-values are presented.

To explore the relationship between cachexia domains and classification model (model 2), candidate items that differed between the groups in the univariate analysis were entered into a multivariate logistic regression by forced entry, and the no cachexia group (group 0) acted as the reference group.

Univariate survival analysis was performed using the Kaplan–Meier method and Cox regression (log-rank tests) to compare survival curves for both models (model 1 and model 2) and for the pre-cachexia model (model 3). In this analysis, survival was defined as time between date of clinical assessment and death. Patients alive on 1 January 2011 were treated as censored.

results

The EPCRC-CSA study included 1070 patients. Nineteen patients were excluded either because they withdrew consent ($n = 4$) or for technical failure ($n = 15$). Patients with missing data on body weight ($n = 86$) and survival ($n = 104$) were also excluded from the present study.

In total, 861 patients were subject to the final analyses. Mean age for all included patients was 62 years, 53% were males and the mean performance status was 71.7. BMI was 24.2 kg/m^2 and the average weight loss last six months was 3.9 kg. The most frequent diagnosis was cancer of the digestive organs (28%), followed by breast cancer (17%) and cancer of the respiratory organs (16%). The majority of patients suffered from metastatic disease and more than half of the patients were hospitalized (56%).

two-group classification (model 1)

In model 1, 399 patients were classified as cachectic, while 462 patients were non-cachectic. The cachectic patients had a mean BMI 23.0 kg/m^2 and an average weight loss 9.8 kg, while the non-cachectic had a mean BMI of 25.3 kg/m^2 and an average weight gain 1.1 kg. A separate analysis for criteria WL >5% showed that by this criterion alone, 388 patients were classified as cachectic. Ninety-nine patients were classified as cachectic by the other diagnostic criteria WL >2% + BMI <20 kg/m^2. There was an overlap between these two criteria of 88 patients, leaving only 11 that were not classified by both.

Characteristics for the two groups in model 1 are shown in Table 1. In the cachectic patients, there were more males than females (59% versus 41%; $P < 0.01$). In cachectic patients, the most prevalent diagnosis was cancer of the digestive (30%) and respiratory (18%) organs. There were more in-patients among the cachectic patients (53% versus 47%, $P < 0.001$).

When comparing cachectic versus non-cachectic patients on items representative of the key cachexia domains, higher levels of CRP (44.8 versus 29.6 ml/g; $P < 0.001$) and appetite loss (3.9 versus 2.6; $P < 0.001$) and reduced food intake (58.6% versus 29.8%, $P < 0.001$) was observed for cachectic patients. Cachectic patients had lower scores on KPS than the non-cachectic patients (68.3 versus 74.5, $P < 0.001$).

four-group classification (model 2)

As shown in Table 2, 147 patients were classified into pre-cachexia group (mean BMI 25.1 kg/m^2 and WL 2.4 kg), 305 into cachexia group (mean BMI 23.8 kg/m^2 and WL 7.9 kg) and 86 patients into refractory cachexia group (mean BMI 19.9 kg/m^2 and WL 16.8 kg). Three hundred twenty-three patients were classified into no cachexia group (mean BMI 25.4 kg/m^2 and weight gain of 2.8 kg).

Serum concentrations of CRP (catabolism domain) were similar in patients in the no cachexia and the pre-cachexia group (30.3 and 29.3 ml/g, respectively) and were significantly higher in the cachexia group (40.6 ml/g) and the refractory cachexia group (60.6 ml/g, $P < 0.001$).

The proportion of patients reporting a reduced food intake (eating less than usual) was significantly higher in pre-cachexia, cachexia and refractory cachexia groups (48%, 56% and 47%)

Table 1. Two-group classification model (model 1)

Variables	Groups in model 1			All patients in study
	No cachexia: no weight loss or low BMI	Cachexia: weight loss and low BMI	*P*-value*	
Number of patients	462	399		861
Age, mean (95% CI), years	62 (61–63)	62 (61–63)	0.850	62 (61–63)
Number of female within group (%)	235 (59)	166 (41)	0.07	401 (47)
Performance status				
Karnofsky score (KPS), mean (95% CI)	74.5 (73.1–76.0)	68.3 (66.7–70.0)	0.001	71.7 (70.6–72.2)
Current medical situation, number (%)				
In-patient	226 (47)	254 (53)	<0.001	480 (56)
Outpatient	236 (62)	145 (38)	<0.001	381 (44)
Diagnosis, number of yes within group (%)				
Cancer of the head	13 (48)	14 (52)		27 (3)
Cancer of the digestive organs	123 (51)	119 (49)		242 (28)
Cancer of the respiratory organs	65 (48)	71 (52)		136 (16)
Malignant bone tumours	3 (100)	0		3 (0)
Skin cancer including malignant melanoma	18 (51)	17 (49)		35 (4)
Malignant connective and soft tissue tumours	17 (57)	13 (43)		30 (4)
Breast cancer	95 (65)	51 (35)		146 (17)
Gynaecological cancer	14 (64)	8 (36)		22 (3)
Cancer of male genital organs	46 (49)	47 (51)		93 (11)
Urinary cancer	25 (51)	24 (49)		49 (6)
Tumours of the CNS	11 (79)	3 (21)		14 (2)
Malignant endocrine tumours	1 (17)	5 (83)		6 (1)
Secondary an ill-defined malignant tumours	13 (59)	9 (41)		22 (3)
Leukaemia and lymphomas	17 (55)	14 (45)		31 (4)
Multiple primary cancers	1 (25)	(3 (75)		4 (1)
Current status of disease, number (%)				
Advanced, non-metastatic	74 (58)	54 (42)	0.500	128 (15)
Metastatic	388 (53)	345 (47)	0.307	733 (85)
Current oncology treatment: number of yes within group (%)				
Radiotherapy	86 (47)	98 (53)	0.034	184 (21)
Chemotherapy	247 (60)	166 (40)	0.001	413 (48)
Serum concentrations, mean (95% CI)[a]				
CRP	29.6 (24.1–35.2)	44.8 (38.0–51.6)	0.001	36.9 (32.5–41.3)
Haemoglobin	12.1 (11.9–12.3)	11.6 (11.4–11.8)	0.001	11.9 (11.7–12.0)
Albumin	38.0 (37.3–38.6)	35.1 (34.4–35.7)	0.001	36.7 (36.1–37.1)
Food intake, number of yes within group (%)				
Unchanged	275 (69)	125 (31)	<0.001	400 (46)
More than usual	58 (64)	33 (36)	0.089	91 (11)
Less than usual	129 (35)	241 (65)	<0.001	370 (43)
Symptoms, mean (95% CI)				
Pain	1.9 (1.7–2.1)	2.4 (2.2–2.6)	0.001	2.1 (2.0–2.3)
Fatigue	3.3 (3.1–3.5)	4.1 (3.8–4.3)	0.001	3.6 (3.5–3.8)
Nausea	0.9 (0.8–1.1)	1.3 (1.1–1.6)	0.004	1.1 (1.0–1.3)
Depression	1.8 (1.6–2.0)	2.0 (1.8–2.3)	0.090	1.9 (1.7–2.1)
Anxiety	2.0 (1.8–2.2)	2.2 (1.9–2.4))	0.200	2.1 (1.9–2.2)
Drowsiness	3.1 (2.9–3.3)	3.6 (3.4–3.8)	0.001	3.3 (3.2–3.5)
Appetite	2.6 (2.3–2.8)	3.9 (3.6–4.2)	0.001	3.2 (3.0–3.4)
Feeling of well-being	3.1 (2.9–3.3)	3.7 (3.5–3.9)	0.001	3.4 (3.2–3.5)
Shortness of breath	1.8 (1.6–2.0)	2.0 (1.8–2.3)	0.200	1.9 (1.7–2.1)

The table shows descriptive data on demographics, medical information and items representing key cachexia domains. Data are presented as means and 95% confidence intervals (95% CIs) for continuous variables and as frequencies (*n*) and proportions (%) for categorical variables.

[a]CRP ($n = 628$), haemoglobin($n = 737$), albumin ($n = 671$).

*In comparison to the two groups in the statistical analysis, an independent *t*-test was applied for continuous variables and for categorical variables, a χ^2 test.

Table 2. Four-group classification model (model 2) based on weight loss and BMI

Variables	No cachexia (Group 0)	Pre-cachexia (Group I)	Cachexia (Group II)	Refractory cachexia (Group III)	*P*-value*
Number of patients	323	147	305	86	
Age, mean (95% CI), years	61 (59.3–62.1)	64 (62.0–66.0)	63 (61.5–64.0)	60 (57.3–62.4)	0.010
Number of female within group (%)	168 (52)	70 (48)	126 (41)	37 (43)	0.030
Performance status					
Karnofsky score (KPS), mean (95% CI)	74.7 (73.0–76.4)	75.0 (72.6–77.4)	68.2 (66.4–70.0)	66.8 (63.4–70.2)	<0.001
Current medical situation, number of yes within group (%)					
In-patient	158 (33)	78 (16)	184 (38)	60 (13)	<0.001
Out-patient	165 (43)	69 (18)	121 (32)	26 (7)	<0.001
Diagnosis, number of yes within group (%)					
Cancer of the head	9 (33)	4 (15)	14 (52)	0	
Cancer of the digestive organs	82 (34)	41 (17)	86 (36)	33 (14)	
Cancer of the respiratory organs	45 (33)	19 (14)	60 (44)	12 (9)	
Malignant bone tumours	2 (67)	1 (33)	0	0	
Skin cancer including malignant melanoma	13 (37)	5 (14)	13 (37)	4 (11)	
Malignant connective and soft tissue tumours	12 (40)	5 (17)	8 (27)	5 (17)	
Breast cancer	71 (49)	27 (19)	40 (27)	8 (6)	
Gynaecological cancer	11 (50)	4 (18)	3 (14)	4 (18)	
Cancer of male genital organs	32 (34)	17 (18)	37 (40)	7 (8)	
Urinary cancer	15 (31)	11 (22)	15 (31)	8 (16)	
Tumours of the CNS	7 (50)	4 (29)	2 (14)	1 (7)	
Malignant endocrine tumours	1 (17)	0	4 (67)	1 (17)	
Secondary an ill-defined malignant tumours	10 (46)	5 (28)	6 (27)	1 (5)	
Leukaemia and lymphomas	12 (39)	4 (13)	14 (45)	1 (3)	
Multiple primary cancers	1 (25)	0	2 (50)	1 (25)	
Current status of disease, number of yes within group (%)					
Advanced, non-metastatic	48 (38)	25 (19)	43 (34)	12 (9)	<0.001
Metastatic	275 (37)	122 (17)	262 (36)	74 (10)	<0.001
Current oncology treatment, number of yes within group (%)					
Radiotherapy	57 (31)	34 (18)	76 (41)	17 (9)	0.036
Chemotherapy	167 (40)	79 (19)	139 (34)	28 (7)	0.074
Serum concentrations, mean (95% CI)[a]					
CRP	30.3 (23.5–37.1)	29.3 (21.2–37.3)	40.6 (33.7–47.5)	60.6 (2.9–78.4)	<0.001
Haemoglobin	12.1 (11.3–12.9)	12.0 (11.7–12.3)	11.7 (11.5–11.9)	11.0 (10.6–11.5)	<0.001
Albumin	38.4 (37.6–39.2)	37.6 (36.7–38.6)	35.5 (34.8–36.2)	32.9 (31.4–34.4)	<0.001
Food intake, number of yes within group (%)					
Unchanged	206 (52)	68 (17)	106 (26)	20 (5)	<0.001
More than usual	48 (53)	9 (10)	27 (30)	7 (8)	0.010
Less than usual	69 (19)	70 (19)	172 (47)	59 (16)	<0.001
Symptoms, mean (95% CI)					
Pain	2.1 (1.8–2.3)	1.6 (1.3–1.9)	2.4 (2.1–2.7)	2.5 (2.0–3.0)	0.003
Fatigue	3.2 (2.9–3.5)	3.4 (3.1–3.8)	3.9 (3.6–4.2)	4.6 (4.1–5.2)	<0.001
Nausea	1.0 (0.8–1.2)	0.8 (0.6–1.1)	1.2 (1.0–1.5)	1.6 (1.1–2.2)	0.009
Depression	1.7 (1.5–1.9)	1.9 (1.5–2.3)	2.0 (1.8–2.3)	2.0 (1.5–2.5)	0.291
Anxiety	1.9 (1.7–2.1)	2.1 (1.7–2.5)	2.1 (1.8–2.4)	2.3 (1.8–2.9)	0.377
Drowsiness	3.0 (2.7–3.3)	3.2 (2.8–3.6)	3.6 (3.4–3.9)	3.7 (3.2–4.3)	0.006
Appetite	2.5 (2.2–2.8)	2.9 (2.4–3.4)	3.7 (3.3–4.0)	4.6 (3.9–5.2)	<0.001
Feeling of well-being	3.1 (2.9–3.4)	3.1 (2.7–3.5)	3.7 (3.4–3.9)	3.9 (3.4–3.5)	0.003
Shortness of breath	1.7 (1.5–2.0)	1.9 (1.6–2.3)	2.1 (1.8–2.4)	1.8 (1.3–2.3)	0.325

The table shows descriptive data on demographics, medical information and items representing key cachexia domains. Data are presented as means and 95% confidence intervals (95% CIs) for continuous variables and as frequencies (*n*) and proportions (%) for categorical variables.

[a]CRP ($n = 628$), hemoglobin ($n = 737$), albumin ($n = 671$).

*In comparison to the four groups in the statistical analysis, an analysis of variance (ANOVA) was applied for continuous variables and for categorical variables, a Kruskal–Wallis test.

compared with the no-cachexia group (22%; $P < 0.001$). Compared with the no-cachexia group, mean scores on appetite loss were significantly higher in the pre-cachexia group (2.9), cachexia group 2 (3.9) and the refractory cachexia group (4.6, $P < 0.001$) than in the non-cachexia group.

The mean performance status (KPS) was significantly lower in the cachexia group (68.2) and the refractory cachexia group (66.8) compared with scores in the no-cachexia and the pre-cachexia group (75.0; $P < 0.001$).

Results from the multivariate logistic regression of candidate items are presented in the appendix. Food intake (eating less than usual) was a significant item for all cachexia groups. Appetite loss was a significant item in terms of classifying refractory cachexia ($P < 0.05$). CRP was not a significant item for the classification into any of the three cachexia groups but a tendency could be seen for the refractory cachexia group ($P < 0.065$).

survival

The median overall survival for all patients was 207 days. In model 1, the median survival for patients classified as cachectic was shorter than for non-cachectic patients (139 versus 269 days; $P < 0.001$). There was no significant survival difference, between no cachexia and pre-cachexia (Figure 1).

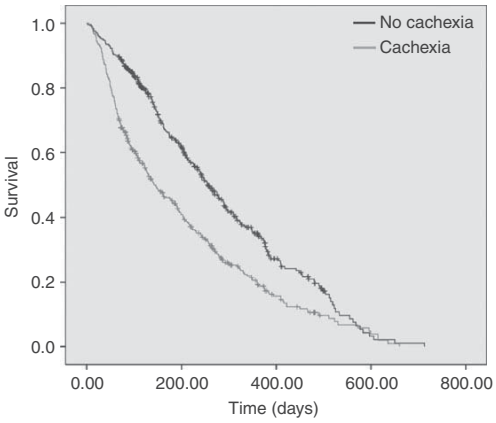
A definition of pre-cachexia in a model adding additional factors representing the cachexia domains (model 3) was tested. By adding CRP (>10 ml/g) and appetite loss (ESAS >3) to the <5% weight loss, the median survival was significantly shorter for patients with all three cachexia factors present compared with those with only 0%–5% weight loss (143 versus 377 days; $P < 0.001$).

discussion

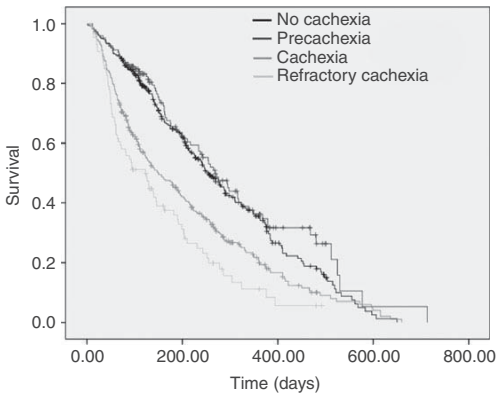
This study shows that patients with cachexia are clearly distinct from patients with no cachexia with regards to the key cachexia domains (stores, nutrition, catabolism and function) and survival (model 1). This underlines the legitimacy of the established diagnostic criteria for cancer cachexia based on weight loss/BMI. However using weight loss/BMI alone is not sufficient when classifying cancer cachexia from pre-cachexia to refractory cachexia (model 2).

In terms the cachexia characteristics, there appears to be little distinction between the no cachexia and pre-cachexia; this finding is also supported by the survival curves. Classification of pre-cachexia might be better based on additional items. A possible explanation for this is the inaccuracy of body weight measures and lack of information on sarcopenia. If only weight loss is taken into account, some patients suffering from slight muscle loss may be misclassified, because muscle loss can be masked due to fluid retention [12]. A measure of muscle loss by an objective method such as computed tomography, dual-energy X-ray, magnetic resonance imaging may be essential to specifically diagnose pre-cachexia but these methods have so far not been easily available in cancer clinics [13].

The refractory stage can be considered as cachexia with very poor prognosis, as it is the cancer disease that defines this stage. Unfortunately, there is no simple marker for tumour activity or



Overall 861; Number of censored = 281, survival (SE) 207d (10.6)
No cachexia: *n* = 462; dead 270; Survival (SE) 255d (14.5)
Cachexia: *n* = 399; dead 310; Survival (SE) 142f (14.1), *P < 0.001*
d = days



No cachexia: *n* = 323, dead = 194, survival (SE) = 255 (18.7)
Precachexia: *n* = 147, dead78, survival (SE) = 269d (24.0), *P = 0.204*
Cachexia: *n* = 305, dead = 239, survival (SE) = 150d (18.1), *P < 0.001*
Refractory: *n* = 86, dead = 69, survival (SE) = 123d (23.5), *P < 0.001*

Figure 1. Kaplan–Meyer survival plot for two-group (model 1) and four-group (model 2) classification models.

dynamics readily obtainable, which impedes an easily applicable classification in clinical practice.

Since the publication of the international consensus, two other proposals for classification of patients into cachexia stages have been made. The first, the Cachexia Score (CASCO) weights and sums five different factors: body weight and lean body mass loss; anorexia; inflammatory, immunological and metabolic disturbances; physical performance and quality of life [14]. A validation of the score is awaited. A barrier for the use in clinics may be the rarely available biochemical tests and missing cut-offs.

The clinical relevance of the consensus classification has been evaluated in 207 cancer patients by Vigano et al. [15]. In this

pilot study, patients were classified into the three stages by two independent researchers according to different combinations of clinical criteria and biological measurements. The final classification was mainly performed by subjective judgement, which is not easily replicated. Similar to the present study, pre-cachexia was not clearly distinctive but the other stages correlated with differences in patient-reported outcomes and survival. Both of these studies underline the importance of classification to guide treatment, but also the lack of simple indicators to classify patients into the stages. In clinical practice, it is important to have easily applicable measurements/assessments which allow bedside diagnostics.

A recent publication highlighted the association of cancer cachexia with symptoms, function, quality of life and survival in a cluster analysis. Prevalence of cachexia varied highly according to different definitions, which indicated once more the need for a classification with clear cut-offs [16].

limitations

A main limitation is that there was no measurement of muscle mass available. In the nutrition domain, the simple answer of 'eating less than usual' was considered to be sufficiently precise to measure decreased nutritional intake, even though this PG-SGA question has not been validated for this comparison.

In the catabolism domain, CRP was used as the main item as it is the most robust biomarker for cachexia inflammation [4]. CRP is indeed a marker for systemic inflammation, but is neither specific for cancer, cachexia or for tumour activity as it can be influenced by other factors such as infections. Due to the inclusion criteria (computerized assessment), the population of the study is younger and fitter than the average cancer population.

conclusion

In a large international cohort of advanced cancer patients, weight loss and BMI clearly distinguish between non-cachectic and cachectic patients both with regards to all the available domains proposed by the international consensus and with survival. Exploring the possibility to classify patients into four groups representing cachexia stages, using weight loss and BMI only, provides some indication of a possible distinct refractory cachexia group. The pre-cachexia stage might be better defined by additional factors representing the cachexia domain, for instance CRP and appetite loss. A clear definition of pre-cachexia is needed, especially because this group is the target of intervention trials. The next steps in the validation of a cachexia classification should quantify additional factors and investigate the role of muscle mass measurement.

acknowledgements

We would like to thank all people involved in the European Palliative Care Research Collaborative (EPCRC) and EURO IMPACT, European Intersectorial and Multidisciplinary Palliative Care Research Training.

funding

EPCRC was funded by the European Union's 6th 274 Support Care Cancer (2010) 18:273–279 framework in 2006 EURO IMPACT is funded by the European Union Seventh Framework Programme (FP7/2007–2013, under grant agreement no [264697]).

disclosure

The authors have declared no conflicts of interest.

references

1. Baracos VE. Pitfalls in defining and quantifying cachexia. J Cachexia Sarcopenia Muscle 2011; 2: 71–73.
2. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle 2010; 1: 1–5.
3. Yavuzsen T, Davis MP, Walsh D et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol 2005; 23: 8500–8511.
4. Blum D, Omlin A, Baracos VE et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol 2011; 80: 114–144.
5. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006; 83: 1345–1350.
6. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12: 489–495.
7. Kaasa S, Loge JH, Fayers P et al. Symptom assessment in palliative care: a need for international collaboration. J Clin Oncol 2008; 26: 3867–3873.
8. Hjermstad MJ, Lie HC, Caraceni A et al. Computer-based symptom assessment is feasible in patients with advanced cancer: results from an International Multicenter Study, the EPCRC-CSA. J Pain Symptom Manage 2012; 44: 639–54.
9. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980; 45: 2220–2224.
10. Bruera E, Kuehn N, Miller MJ et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991; 7: 6–9.
11. Detsky AS, McLaughlin JR, Baker JP et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987; 11: 8–13.
12. Martin L, Birdsell L, Macdonald N et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013; 31: 1539–1547.
13. Strasser F. Diagnostic criteria of cachexia and their assessment: decreased muscle strength and fatigue. Curr Opin Clin Nutr Metab Care 2008; 11: 417–421.
14. Argiles JM, Lopez-Soriano FJ, Toledo M et al. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. J Cachexia Sarcopenia Muscle 2011; 2: 87–93.
15. Vigano A, Del Fabbro E, Bruera E et al. The cachexia clinic: from staging to managing nutritional and functional problems in advanced cancer patients. Crit Rev Oncog 2012; 17: 293–304.
16. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013; 21: 1569–77.

appendix 1

Table A1. Logistic regression for the four-group model (model 2)

Domains		Group I (pre-cachexia) B(SE)	Group I (pre-cachexia) e^B	Group II (cachexia) B(SE)	Group II (cachexia) e^B	Group III (refractory cachexia) B(SE)	Group III (refractory cachexia) e^B
	Intercept	−1.33 (0.86)		0.87 (0.65)		−2.16* (1.07)	
Catabolism							
	C-reactive protein mg/l	−0.16 (0.20)	0.9	0.07 (0.17)	1.1	0.48 (0.26)	1.6
Nutrition							
	Food intake: eating less than usual	1.33** (0.46)	3.8	1.15** (0.34)	3.1	1.44* (0.59)	4.2
Nutition							
	ESAS appetite	−0.02 (0.05)	1.0	0.07 (0.04)	1.1	0.12* (0.06)	1.1
Function							
	ESAS fatigue	−0.01 (0.06)	1.0	0.05 (0.05)	1.1	0.12 (0.07)	0.9
	ESAS feeling of well-being	−0.12 (0.07)	0.9	−0.05 (0.05)	1.0	−0.14 (0.08)	1.0
Function							
	Karnofsky Performance Status	0.01 (0.01)	1.0	−0.02** (0.01)	1.0	−0.01 (0.01)	1.0

[a]Group 0 (no cachexia) is the reference category.
*$P < 0.05$, **$P < 0.01$.

appendix 2

The European Palliative Care Research Collaborative (EPCRC) was funded by the European Union's 6th274 Support Care Cancer (2010) 18:273–279 framework in 2006.

EURO IMPACT, European Intersectorial and Multidisciplinary Palliative Care Research Training, is funded by the European Union Seventh Framework Programme (FP7/2007–2013, under grant agreement no. [264697]).

collaborators

Van den Block Lieve[a], Meeussen Koen[a], Brearley Sarah[e], Caraceni Augusto[g], Cohen Joachim[a], Costantini Massimo[h], Francke Anneke[b], Harding Richard[c,d], Higginson Irene J[c,d], Kaasa Stein[f], Linden Karen[k], Miccinesi Guido[i], Onwuteaka-Philipsen Bregje[b], Pardon Koen[a], Pasman Roeline[b], Pautex Sophie[j], Payne Sheila[e], Deliens Luc[a,b]

EURO IMPACT aims to develop a multidisciplinary, multiprofessional and inter-sectorial educational and research training framework for palliative care research in Europe. EURO IMPACT is coordinated by Luc Deliens and Lieve Van den Block of the [a]End-of-Life Care Research Group, Ghent University and Vrije Universiteit Brussel, Brussels, Belgium. Other partners are [b]VU University Medical Center, EMGO Institute for health and care research, Amsterdam, the Netherlands; [c]King's College London, Cicely Saunders Institute, London, [d]Cicely Saunders International, London, and [e]International Observatory on End-of-Life Care, Lancaster University, Lancaster, UKingdom; [f]Norwegian University of Science and Technology, and [g]EAPC Research Network, [h]Trondheim, Norway; Regional Palliative Care Network, IRCCS AOU San Martino-IST, Genoa, and [i]Cancer Research and Prevention Institute, Florence, Italy; [j]EUGMS European Union Geriatric Medicine Society, Geneva, Switzerland; Springer Science and Business Media, Houten, the Netherlands.

Paper II

Clinical Nutrition 30 (2011) 812–821

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Patient-focused endpoints in advanced cancer: Criterion-based validation of accelerometer-based activity monitoring

Richard J.E. Skipworth [a,h], Guro B. Stene [b,c,h], Max Dahele [d], Paul O. Hendry [a], Alexandra C. Small [e], David Blum [f], Stein Kaasa [b], Peter Trottenberg [g], Lukas Radbruch [g], Florian Strasser [f], Tom Preston [e], Kenneth C.H. Fearon [a], Jorunn L. Helbostad [c,*] on behalf of the European Palliative Care Research Collaborative (EPCRC)

[a] Clinical and Surgical Sciences (Surgery), University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, United Kingdom
[b] Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, N-7491 Trondheim, Norway
[c] Department of Neuroscience, Norwegian University of Science and Technology, N-7489 Trondheim, Norway
[d] Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
[e] Stable Isotope Biochemistry Laboratory, Scottish Universities Environmental Research Center, The University of Glasgow, East Kilbride G75 0QF, United Kingdom
[f] Section Oncology, Department of Internal Medicine & Palliative Care Centre, Cantonal Hospital, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland
[g] Klinik für Palliativmedizin, Universitätsklinikum Aachen, Pauwelstr. 30, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Received 2 November 2010
Accepted 26 May 2011

Keywords:
Cancer
Physical activity
Accelerometer-based activity monitoring
Energy expenditure
Criterion-based validity

SUMMARY

Background & aims: Objective assessment of daily physical activity (PA) by body-worn accelerometers offers potential as a novel endpoint in the clinical management of advanced cancer patients. This study aimed to assess criterion-based validity of an accelerometer-based activity monitoring system (AM-system), ActivPAL™, using two different methods.
Methods: Advanced cancer in patients and outpatients (Karnofsky Performance Status (KPS) 40–100). ActivPAL™ measurements were validated against (i) observations and (ii) energy expenditure (EE) measured by 2-week doubly-labelled water (DLW) protocol.
Results: Absolute errors for mean time spent in different body positions (<0.1%) and number of transfers (0%) were low. Step count error was significantly higher in patients with KPS 40–60 (non-self caring) compared to KPS 70–100 (self-caring) (33 vs. 24%, $p = 0.006$). Post-hoc mathematical analysis demonstrated that absolute errors for the mean energy expenditure of activity (EEA) (1.4%) and mean total EE (0.4%) were low, but agreement was also low.
Conclusions: AM-systems provide valid estimates of body positions and transfers, but not step count, especially in non-self caring patients. ActivPAL™ can derive estimates of EE but there is considerable variability in results, which is consistent, in part, with the inaccuracy in step count. Further studies are required to assess the validity of different endpoints derived from AM-systems in advanced cancer patients.

1. Introduction

Patients with advanced cancer often report a significant decline in physical functioning (PF) that has a major impact on quality of life (QoL). Such loss of QoL may be more pronounced in patients with cachexia, a complex metabolic condition characterized by progressive muscle wasting, associated with excess morbidity and mortality.[1] When developing palliative therapies focused either on the tumor or its systemic effects, one challenge is to use patient-focused outcomes that are 'fit for purpose' and relate clinically to PF and QoL during everyday situations.

In routine practice or clinical trials, PF is measured by healthcare provider instruments such as the Karnofsky Performance Status[2] or The Eastern Cooperative Oncology Group (ECOG) score, which are of diagnostic value but lack responsiveness to change following disease progression and interventions. Physical activity (PA) as an indicator of PF is traditionally assessed by self-report. However, such tools are subjective, correspond only loosely with objectively

Abbreviations: AM – system, accelerometer-based activity monitoring systems; PA, physical activity; KPS, Karnofsky performance status; PF, physical function; EE, Energy Expenditure; EPCRC, European Palliative Care Research Collaborative.

* Corresponding author. Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway. Tel.: +47 725 75554, 0047 93032547(Cell).
E-mail address: jorunn.helbostad@ntnu.no (J.L. Helbostad).
[h] These two authors contributed equally to this work.

0261-5614/$ – see front matter
doi:10.1016/j.clnu.2011.05.010

measured activity, and may fail to recognise activity characteristic of frail populations.[3]

Recently, objective measurement of daily PA has been proposed as a useful tool for the evaluation of outcomes of medical interventions in cancer.[4] Crucially, it has been shown that PA variables correlate with QoL scores in advanced cancer patients,[5] and that PA can be improved by nutriceutical intervention in cachectic pancreatic cancer patients.[6] However, gold-standard PA assessments (e.g. stable isotope studies) can be complex, patient-intense, and expensive, and often provide limited detail regarding different PA behaviors.

In contrast, modern accelerometer-based activity monitoring systems (AM-systems) potentially offer a patient-friendly methodology of long-term PA assessment, which can be easily used in both the clinical and free-living environments.[4] AM-systems can estimate energy expenditure (EE) based on the amplitude and frequency of acceleration signals or on recognized activities.[7] Accurate identification of postures and transfers in healthy young adults,[8] older adults[9] and persons with minor functional limitations[10,11] by AM-systems has been demonstrated. AM-systems have also been trialled for the objective assessment of PA in cancer patients undergoing palliative chemotherapy.[5] However, recognition of PA from acceleration signals may be potentially more challenging in frail patients who walk slowly and have a cautious movement pattern.[12]

The present study is part of the EU-funded European Palliative Care Research Collaborative (EPCRC) with an objective to develop a computer-based assessment- and decision-making tool, where information on subjective symptoms, PF and biological data are combined in order to support clinicians in deciding optimal patient treatment.[13] The objective of the present study was to assess whether a small, lightweight AM system (ActivPAL™) could be used as an objective measure of daily PA in advanced cancer patients, and EE in both advanced cancer outpatients and healthy adults. Validation studies of ActivPAL™ have been performed previously, with regard to step count, postures and transitions, in hospital in patients (stroke patients, patients with hip fractures, and the elderly,[14] community-dwelling older adults,[15] sedentary overweight adults[16] and younger healthy adults,[8,17,18] but not in cancer patients. Furthermore, although attempts have been made to validate some aspects of ActivPAL-derived estimates of EE in healthy females aged 15–25 years,[19] no studies have been performed to validate calorific estimates in either healthy adults or cancer patients. Therefore, the specific aims of the present project were to test the criterion-based validity of ActivPAL™ with regard to (i) step count, number of transitions and time spent upright against video observations (video study) in advanced cancer patients and (ii) EE against doubly-labelled water (DLW) and indirect calorimetry (DLW study) in a pilot evaluation of advanced cancer patients and healthy adults.

2. Materials and methods

2.1. Subjects

For the video study, in-patients and out-patients with advanced cancer were recruited from Norway ($n = 29$), Germany ($n = 6$) and Switzerland ($n = 14$). Participants were stratified according to KPS (40–60 or 70–100) to ensure that the sample represented a wide spectrum of PF. Patients with KPS 40–60 require physical assistance with everyday activities (non-self caring) while patients with KPS 70–100 are regarded as self caring.

For the DLW study, a sample consisting of out-patients with advanced oesophago-gastric cancer ($n = 7$, KPS 80–100), and healthy subjects ($n = 10$ assessments in 9 subjects, KPS = 100), were included. Deliberate effort was taken to recruit individuals across a wide spectrum of PA, from advanced cancer patients to sedentary office workers to competitive athletes, as one of the key aims of future intervention studies will be to drive the PA of cancer patients from the frail end of the spectrum back into the range of healthy subjects.

Inclusion criteria for both studies were age >18yrs and ability to comply with study requirements. Exclusion criteria were physical handicap, severe co-morbidity or metastases that grossly impaired mobility, or inability to complete the study protocols. Participants in the video study were also excluded retrospectively if video recording or ActivPAL data were of insufficient quality for analysis. Participants in the DLW study had not had surgery, radiotherapy, or chemotherapy during the previous month, and were weight-stable. They were excluded retrospectively if they did not complete at least 7 days of ActivPAL™ data during the 2-week DLW protocol. Height and weight were measured to the nearest 0.1 cm and 0.1 kg respectively, with the patient wearing light clothing without shoes.

2.2. Accelerometer-based activity monitoring

ActivPAL™ (dimensions: 35x53x7 mm; mass: 20 g; PAL Technologies Ltd, Glasgow, UK) uses an uni-axial accelerometer sampling at 10 Hz to produce signals reflecting thigh inclination and movement. A USB interface docking station connects the monitor to a Windows-based computer and software package that classifies positions and activities into 3 categories: lying or sitting, standing and stepping. Acceleration signals exceeding particular peak acceleration amplitudes are registered as steps. Cadence and number of steps taken describes the intensity and volume of activity. The software assigns each activity an estimated energy cost in metabolic equivalents (METs),[20] representing the ratio of the active to resting metabolic rate, which are then summated over the assessment period to derive a value in MET.hours (hrs) that reflects overall free-living EE. One MET is equivalent to 1 kcal/kg of body weight/hour (basal metabolic rate). Lying or sitting is assigned an energy cost of 1.25METs, quiet standing 1.4METs and walking at 120steps/min 4METs. EE of stepping is scaled linearly according to the equation: EE (in MET.hrs) = (1.4d) + (4–1.4) × (c/120) × d, where c = cadence (steps/min), and d = activity duration (hrs).

In both studies, an ActivPAL™ monitor was attached to the subject's right leg approximately at the anterior mid-thigh with adhesive dressings. For the video study, a second ActivPAL™ attached to the mid-sternum was used in order to distinguish between lying and sitting. Subjects were allowed to remove ActivPAL™ during water-related activities.

2.3. Video study

A two-dimensional digital video camcorder (Sony Handycam DCR-HC96) was used to record activities measured by ActivPAL™. The camcorder clock was synchronised with ActivPAL™ before each trial. Testing lasted 30 mins and was performed in a hospital ward setting with a walking length of at least 6 m. Table 1 gives an overview of the two test series of activities used in the study. Series I included 10 standardised activities selected from physical test batteries developed for use in old and frail persons performed in a controlled environment.[21,22] Series II included 10 free-living activities intended to mimic everyday life situations in the home environment,[10,11] and each participant completed 3 randomly selected activities. Participants were offered support or use of a walking aid if required. Each forward movement of the foot in the upright position recorded by video was counted as a step. Walking speed (m/sec) was calculated for walking trials.

Table 1
Video study. Overview of tasks included in test series I and II.

Test series I		Test series II	
1.1	Turning to the right side in bed	2.1	Prepare and consume drink of choice
1.2	Turning to the left side in bed	2.2	Put on duvet cover and pillowcases
1.3	Transferring from lying in bed to sitting on edge of bed	2.3	Clean a mirror
1.4	Transferring from sitting on edge of bed to lying in bed	2.4[a]	Watch television
1.5	Sitting in chair for 20 s	2.5	Wash and dry dishes
1.6	Raising from a chair with handrails	2.6[a]	Read newspaper
1.7	Sitting down in a chair with handrails	2.7[a]	Make telephone call
1.8	Walk slowly as if you were strolling around	2.8	Wash and dry hands
1.9	Walk as you normally would do	2.9[a]	Write letter/list
1.10	Walk as fast as you safely can walk	2.10	Prepare and eat sandwich/biscuit

[a] Open-ended task lasting from 2 to 9 min.

2.4. DLW study

2.4.1. Measurement of resting energy expenditure (REE)

Following an overnight fast, patients attended at 08:00. Patients rested in a supine position for at least 30 min before undergoing indirect calorimetry using a ventilated hood technique (GEM; NutrEn Technology Ltd, Lancashire, UK).[23] This system provides measurements of VO_2 and VCO_2, which have an error of less than 2.3%.[24] Measurements were performed for at least 30 min. The measurements performed in the last 20 min were averaged to calculate REE using the Weir equation.[25] Predicted values for REE were derived from the equations of Schofield.[26]

2.4.2. Calculation of total energy expenditure (TEE)

The precision of Total Body Water (TBW) analysis was 0.11 kg (SD). TEE errors estimated by the re-sampling procedure averaged 3.1% (76.43 kcal/day, SD = 28.66). Tracer elimination rate was normal ($k_O/k_H = 1.289$, SD = 0.051) and average ^2H:^{18}O distribution volume or pool space ratio was 1.0294 (SD = 0.0123). LBM was calculated by assuming a hydration factor of 0.732.[27] EE of activity (EEA) was calculated from the formula EEA = TEE-REE. This definition of EEA includes dietary-induced and non-exercise activity thermogenesis.[28] Physical activity level (PAL) was calculated from the formula: PAL = TEE/REE.

2.4.3. Preparation of DLW

$^2H-H_2O$ and $^{18}O-H_2O$ doses were made from a common stock for the whole study which was optimized for a body weight of 70 kg (kg) and assuming 40 kg TBW. Doses were prepared from 10% $^{18}O-H_2O$ and 100% $^2H-H_2O$ to give an initial enrichment of 125 parts per million excess in body water. Five kg dose stock was prepared and this was aliquoted into 125 ml leak proof wide neck polypropylene bottles (#2105-0004, Nalgene, NY, USA) and stored at −20OC until required. Each dose was weighed to 4 decimal places. All were within 1% of a target weight of 48 g. No weight loss on freezer storage was observed. The final aliquot (or incomplete dose) was used to prepare a 500-fold gravimetric dilution (0.1 g in 50 g, weighed to 4 decimal places) with tap water. Aliquots of this 'diluted dose' and the local tap water were retained for analysis.

2.4.4. DLW protocol

On day 0, the subject collected their second urine sample of the day and poured an aliquot into a 30 ml universal container and recorded the time. The doubly-labelled water was then consumed by the patient. Thereafter, the bottle that had contained the labeled water was rinsed with tap water and then the contents drunk to ensure that all labeled water had been ingested. The time and date of ingesting the dose and unique code on the dose bottle were recorded. On days 1, 2, 3, 7, 12, 13 and 14, part of the second urine sample of the day was transferred to a 30 ml universal container and the time and date were recorded. Urine samples were frozen at −20 °C prior to analysis.

2.4.5. ^2H analysis of urine samples

Samples were prepared according to the method of Scrimgeour et al.[29] Urine samples were thawed completely, shaken and centrifuged at 1000 g for 5 min. Samples were prepared in duplicate. Urine (300 ml) was pipetted into 10 ml Exetainer gas testing vials (Labco, High Wycombe, Berks); polythene inserts (~200 ml, #8-NPWP, Chromacol, Welwyn Garden City, Herts) containing platinum catalyst (platinum 5% on alumina powder, 325 surface area >250 $m^2\ g^{-1}$, Sigma Aldrich, Gillingham, Dorset) were added to each vial, taking care not to wet the catalyst. Reference samples (0 and 300 ppm excess ^2H) were prepared and analysed with each batch. Exetainer vials were placed on a 220-tube manifold fitted with a dual concentric needle to automatically gas each tube in turn. Each tube was over gassed with a 100 ml min^{-1} flow of 20% hydrogen in helium, for 40 s (Air Products Special Gases, Crewe). Tubes were left at room temperature for a minimum of 48 h prior to analysis to allow sample water vapour to equilibrate with hydrogen gas. The abundance of deuterium in hydrogen gas was measured using a continuous flow isotope ratio mass spectrometer (CF-IRMS, Hydra, SerCon, Crewe, UK)[30] with reference to working water standards which had been calibrated against international standards. To ensure temperature stability, tubes were equilibrated beside this instrument within an air-conditioned instrument laboratory. The abundance of ^2H in patient samples was calculated with reference to the known abundance of the reference samples. Additional water samples were included in each sample batch for quality control purposes. Deuterium abundance of the independent quality control samples was typically within 1 ppm of the accepted value.

2.4.6. ^{18}O analysis of urine samples

Samples were prepared for ^{18}O analysis according to the method of Prosser et al.[31] After deuterium analysis, the samples were again placed on the 220-tube manifold fitted with a dual concentric needle to automatically gas each tube in turn. Each tube was over gassed with a 100 ml min^{-1} flow of 3% carbon dioxide in nitrogen, for 40s (Air Products Special Gases, Crewe). Reference samples (0 and 150 ppm excess ^{18}O) were prepared and analysed with each batch. Samples were left to equilibrate for 24 h at ambient temperature. The abundance of ^{18}O in the gas phase was measured by CF-IRMS (AP2003 IRMS, IsoPrime, Manchester, UK). To ensure temperature stability, tubes were equilibrated beside this instrument within an air-conditioned instrument laboratory. The abundance of ^{18}O in patients' samples was calculated with reference to the known abundance of the reference samples. Additional water samples were included in each sample batch for quality control purposes. ^{18}O abundance of the independent quality control samples was typically within 0.5 ppm of the accepted value.

2.4.7. Calculation of TEE

For DLW protocol, 'multipoint' calculations were used to derive turnover rates and initial enrichments of each isotope, to estimate CO_2 production and TBW, respectively. Schoeller's equation for estimating TEE was used in the form given by Goran et al.[32] A re-sampling procedure was used to estimate the errors in (TBW) and TEE measurement.[33] The precision of TBW analysis was 0.16 kg with

^{18}O (s.d.) and 0.18 kg with ^{2}H. TEE errors estimated by the re-sampling procedure averaged 4.8% (0.32 (s.d. 0.17) MJ day^{-1}). Tracer elimination rate was normal ($k_O/k_H = 1.279$, s.d. 0.071 and the average ^{2}H: ^{18}O distribution volume or pool space ratio was 1.0316 (s.d. 0.055). Predicted values for TEE were derived from predicted REE values [26]multiplied by 1.5. This prediction derives from the lifestyle category defined as 'Seated work with no option of moving around and little or no strenuous activity' given a PAL range of 1.4–1.5.[34] Values for lean body mass (LBM) and fat mass were also derived from DLW data. To derive 'ActivPAL TEE', total number of METs per day was multiplied by subject's weight.

Calculation of PAL: PAL was calculated from the formula PAL = TEE/REE. A PAL of 1.5 for healthy sedentary adults was derived from the work of Black and collegues.[34]

2.4.8. Calculation of energy expenditure of activity (EEA)

EEA was calculated from the formula EEA = TEE-REE. This definition of EEA includes dietary-induced thermo genesis and non-exercise activity thermo genesis.[28] To derive ActivPAL 'EEA METs per day', the number of METs recorded for non-activity (i.e. $1.25 \times 24 = 30$METs per day) was subtracted from the total number of METs per day.

2.5. Data analysis

2.5.1. Video study

Video data were analysed at each study site, and secondly by the study coordinator, blinded to ActivPAL™ data. ActivPAL™ data were converted into second-by-second outputs by manufacturer's software, and identification of relevant sequences was performed in a custom-made Mat Lab program. Test Series I included walking at 3 different speeds (slow, preferred and fast). Data from all 3 speeds were analysed.

2.5.2. DLW study

'TEE_{MET}' was defined as the average MET.hrs/day measured by ActivPAL™ over a recording period. To derive 'EEA_{MET}', the number of MET.hrs awarded for non-activity (24MET.hrs/day) was subtracted from TEE_{MET}. METs are measured in kcal/kg/hr and thus, to allow comparison between DLW and ActivPAL™, data were reduced to kcal/kg/hr by dividing DLW and indirect calorimetry data (expressed as kcal/day) by 24 × body weight whereas ActivPAL™ data (expressed in MET.hrs/day) was simply divided by 24. EE values expressed in kcal/kg/hr are identified in the current manuscript by.[1]

2.5.3. Statistics

Analyses were performed using Statistical Package for Social Sciences (Chicago, IL, USA). Demographics were presented as means, SD and ranges, and dichotomous variables as absolute numbers and percentages. Data were compared between patients with KPS 70–100 and KPS 40–60 in order to analyse differences between self-caring and non-self-caring populations. Differences between groups were determined using Student's Independent Sample *t*-test. Statistical significance was set at $p < 0.05$ level using exact, two-sided *p*-values. Bland–Altman plots with 95% limits of agreement (LOA) and absolute percentage errors were used to assess agreement between methods expressed in absolute units. Bi-variate relationships were assessed by Pearson's product moment correlation (*r*). Post-hoc mathematical modelling was used to assess the relationship between DLW and ActivPAL™-derived estimates of EE. Linear regression models were used to determine the contribution of independent PA variables on dependent EE variables.

2.6. Ethics

Written informed consent was obtained from all subjects. Ethical approval was granted by local regional ethics committees at the study sites and the Norwegian Social Science Data service (NSD). Procedures were in accordance with International Committee for Harmonization, Good Clinical Practices and the Helsinki Declaration.

3. Results

3.1. Video study

3.1.1. Subjects

Forty-five patients with advanced cancer (predominantly aero-digestive 56%, urogenital 18% and breast 13%) were recruited (Table 2), all of which performed Test Series I, and 29 of which performed Test Series II.

Patient KPS ranged from 40–100 with a mean of 63.5 (SD = 16.0). Twenty-four patients had KPS scores of 40–60 (mean = 51.7, SD = 8) and could thus be identified as patients requiring physical assistance with everyday activities (non-self caring). The reminding 21 patients had KPS scores of 70–100 (mean = 77.6, SD = 9) and could thus be identified as patients who are self caring.

In total, 133 walking trials were completed with a mean walking speed of 0.59 m/s (SD = 0.24, range = 0.19–1.50). Participants with KPS 40–60 walked with lower speed compared to those with KPS 70–100 (mean = 0.48, SD = 0.2, range = 0.19–1.0 versus mean = 0.67, SD = 0.2, range = 0.50–1.0; $p > 0.001$).

3.1.2. Time spent in body postures (Test series I and II)

The systematic measurement error for ActivPAL™ compared with video for time spent in different postures was <0.1sec (Table 3).

3.1.3. Transfers between body postures (Test series I)

Number of transfers showed 100% agreement between ActivPAL™ and video.

Table 2
Video study: Patient characteristics at entry. Values are mean (SD and range) unless otherwise stated.

	All ($n = 45$)		KPS[a] 40–60 ($n = 24$)		KPS 70–100 ($n = 21$)	
Age (years)	64.8	(12.5, 28–86)	62.5	(13.9, 28–84)	67.5	(10.5, 47–86)
Sex: Number of females (%)	23	(51.1)	9	(37.5)	14	(67.5)
Body weight: (kilograms):	63.5	(14.4, 36–105)	63.5	(13.9, 36–105)	63.6	(15.2, 36–95)
BMI[b]	22.2	(4.3, 12.2–32.4)	21.7	(4.4, 12.2–32.4)	22.9	(4.3, 15.4–32.1)
Habitual walking speed (m/s)	0.57	(0.19, 0.19–1.0)	0.48	(0.18, 0.19–1.0)	0.67	(0.15, 0.5–1.0)
Use of walking aid: Number of yes (%)	14	(31.1)	14	(58.3)	0	0

[a] KPS = Karnofsky Performance Status.
[b] BMI = Body Mass Index.

Table 3
Video study: time spent (seconds) in body postures for all patients. Values are mean (SD and range) unless otherwise stated.

	Video	ActivPAL	Absolute Error (%)	S_w[b]
Test series I ($n = 45$)				
Lying[a] ($n = 36$)	12.2 (4.8, 4–25)	12.2 (4. 8, 3.9–25)	0.1	0.06
Sitting	20.0 (0, 2–20)	20.0 (0.1, 19.9–20.1)	0.1	0.05
Upright (standing and walking)	36.1 (13.2, 21–86)	36.1 (13.2, 21,1–86.1)	0.1	0.05
Test series II ($n = 29$)				
Sedentary (lying and sitting)	98.6 (139.7, 0–455)	98.7 (139.7, 0–455)	0.0	0.00
Upright (standing and walking)	28.6 (36.1, 0–211)	28.6 (36.3, 0–211)	0.1	0.12

[a] Nine registrations were excluded from analysis because patients elevated their upper body during lying and turning in bed, and thus movements were registered by the chest ActivPAL™ as sitting.
[b] Within subject standard deviation (seconds).

3.1.4. Step count (Test series I)

Mean step count for the total of all 6 m walking trials were 14.7 (SD = 3.1, range = 9–27) by video and 10.2 (SD = 3.7, range = 0–22) by ActivPAL™ with a mean difference of 4.5 (SD 4.1, LOA -3.6 to 12.6), giving an absolute error of 28.6% (Fig. 1).

In patients with KPS 40–60, mean step count was 15.6 (SD = 3.4, range = 9–27) by video and 10.2 (SD = 4.7, range = 0–22) by ActivPAL™, giving a mean difference of 5.4 steps (SD = 4.9; 95% LOA = −4.2, 14.9) or an absolute error of 32.9%. For patients with KPS 70–100, mean step count was 13.6 (SD = 2.3, range = 9–20) by video and 10.1 (SD = 2.0, range = 4–16) by ActivPAL™, giving a mean difference of 3.5 steps (SD = 2.5; 95% LOA = −1.8, 8.6) or an absolute error of 24.1%. Step count error by ActivPAL™ was significantly higher in patients with KPS 40–60 compared with patients with KPS 70–100 ($p = 0.006$).

A correlation between walking speed and difference in step count between video and ActivPAL™ was $r = -0.51$; $p < 0.01$, indicating that agreement between methods became poorer as walking speed decreased (Fig. 2).

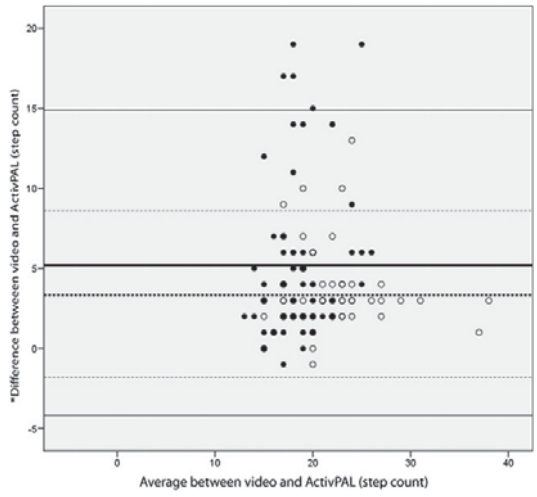


Fig. 1. Video study: Bland–Altman plot of agreement between video step count and ActivPAL™ step count. Filled circles represent patients with KPS 40–60 (non-self caring) and open circles KPS 70–100 (self caring). Solid lines represent the mean difference and 95% LOA for patients with KPS 40–60. Dotted lines represent the mean difference and 95% LOA for patients with KPS 70–100. KPS = Karnofsky Performance Status.

3.2. DLW study

3.2.1. Subjects

One cancer patient and one healthy subject were excluded because they did not complete 7 days of ActivPAL™ completion. Therefore, 15 assessments were included (6 cancer patients and 9 assessments in 8 healthy subjects). Cancer patients did not differ from the healthy subjects in LBM or fat mass (Table 4). As expected, when assessed by DLW, cancer patients exhibited lower mean TEE (2321 kcal/day vs. 3202 kcal/day; $p = 0.044$) and EEA (742 kcal/day vs. 1609 kcal/day; $p = 0.036$) compared with healthy subjects.

3.2.2. REE

When expressed in relation to body weight, average measured REE^I for the entire study cohort was 0.84 kcal/kg/hr (SD = 0.12, range = 0.63–1.14). This value equates to the EE of 1MET (as measured by ActivPAL™) and differs from the hypothesized value of 1 kcal/kg/hr. Predicted REE was derived by multiplication of 0.84 kcal/kg/hr by 24 × body weight (Table 5). A Bland–Altman plot of the agreement between predicted REE (mean = 1587 kcal/day, SD = 259, range = 1160–2054) and measured REE (mean = 1614 kcal/day, SD = 168, range = 1280–1885) demonstrated a mean difference of 27 kcal/day (SD = 218; 95%LOA = −400,454) or absolute error of 1.7%.

3.2.3. EEA

Median length of ActivPAL™ monitoring was 14 days (range = 7–14 days). On regression analysis, step count accounted for 80.0% of the variation in EEA^I_{DLW} (in kcal/kg/hr) ($p < 0.001$). However, the relationship between time spent upright and EEA^I_{DLW} was less strong ($r^2 = 0.52$).

Values of EEA^I_{DLW} were higher than values of EEA^I_{MET} (Fig. 3). These two variables expressed a non-linear relationship with

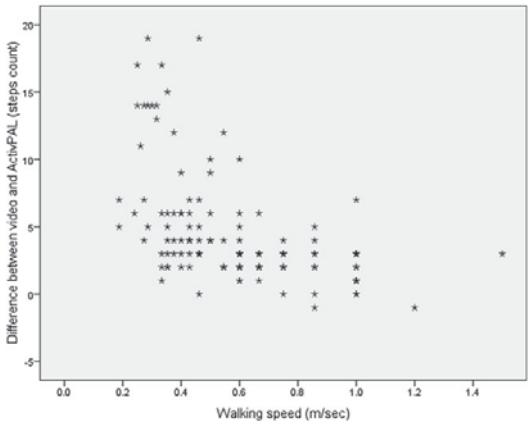


Fig. 2. Video study: Difference in step count (number of steps) between the ActivPAL™ and the video observation plotted against the walking speed (meter per second) for all walking trials ($n = 133$).

Table 4
DLW study: demographics and nutritional status of the study subjects. Values are mean (SDs and range).

	M:F	Age (yrs)	Height (m)	Weight (kg)	BMI[a] (kg/m^2)	LBM[b] (%)	Fat mass (%)	KPS
Whole Cohort (n = 15 assessments in 14 subjects)	12:2	43(19, 25–76)	1.75 (0.06, 1.66–1.84)	80.0 (12.8, 57.5–101.8)	26.2 (4.2, 20.4–33.5)	70.1 (9.4, 52.1–84.3)	29.9 (9.4, 15.7–47.9)	95 (8, 80–100)
Cancer Patients[c] (n = 6)	6:0	65* (7, 59–76)	1.72 (0.07, 1.65–1.82)	86.0 (11.5, 69.4–101.8)	29.0** (3.6, 25.3–33.5)	65.5 (5.3, 57.4–73.0)	34.5 (5.3, 26.6–42.6)	87* (8, 80–100)
Healthy Subjects (n = 9 assessments in 8 subjects)	6:2	28 (2, 25–31)	1.77 (0.06, 1.68–1.84)	76.0 (12.6, 57.5–94.6)	24.3 (3.5, 20.4–30.7)	73.2 (10.5, 52.1–84.3)	26.8 (10.5, 15.7–47.9)	100 (0, 100–100)

[a] BMI = body mass index.
[b] LBM = lean body mass.
[c] Letters in superscript demonstrate statistical difference from healthy subjects on independent *t*-test. * = $p < 0.001$; ** = $p < 0.05$.

Table 5
DLW study: Physical Activity Level (PAL) and Energy Expenditure (EE) of the study subjects. Values are means (SD and range).

	Indirect Calorimetry		Doubly Labelled Water			ActivPAL				
	Measured REE[a] (kcal)	Predicted REE (kcal)	TEE_{DLW} (kcal)	[b]EEA_{DLW} (kcal)	PAL_{DLW}	EEA_{METs} (MET[c].hrs)	$EEA_{ActivPAL}$ (kcal)	TEE[d]$_{METs}$ (MET.hrs)	$TEE_{ActivPAL}$ (kcal)	PAL[e]$_{ActivPAL}$
Whole Cohort	1592	1614	2849	1262	1.80	9.8	1245	33.8	2859	1.82
	(168, 1280–1885)	(259, 1160–2054)	(849, 2017–5309)	(807, 374–3424)	(0.47, 1.21–2.82)	(1.8, 7.4–13.8)	(825, 486–3334)	(1.8, 31.4–37.8)	(787, 2129–5045)	(0.62, 1.26–3.43)
Cancer Patients	1579	1736	2321**	742**	1.48**	8.3*	701**	32.3[a]	2436	1.41**
(n = 6)[f]	(104, 1465–1770)	(233, 1400–2054)	(347, 2017–2795)	(374, 374–1275)	(0.25, 1.21–1.84)	(0.8, 7.4–9.4)	(235, 486–1133)	(0.8, 31.4–33.4)	(343, 2143–2985)	(0.14, 1.26–1.61)
Healthy Subjects	1602	1533	3202	1609	2.01	10.7	1607	34.7	3140	2.09
(n = 9)	(211, 1280–1885)	(255, 1160–1909)	(915, 2478–5309)	(845, 615–3424)	(0.46, 1.33–2.82)	(1.7, 8.9–13.8)	(887, 873–3334)	(1.7, 32.9–37.8)	(888, 2129–5045)	(0.67, 1.50–3.43)

[a] REE = resting energy expenditure.
[b] EEA = energy expenditure of activity.
[c] METs = metabolic equivalents.
[d] TEE = total energy expenditure.
[e] PAL = physical activity level.
[f] Letters in superscript demonstrate statistical difference from healthy subjects on independent *t*-test. * = $p < 0.001$; ** = $p < 0.05$.

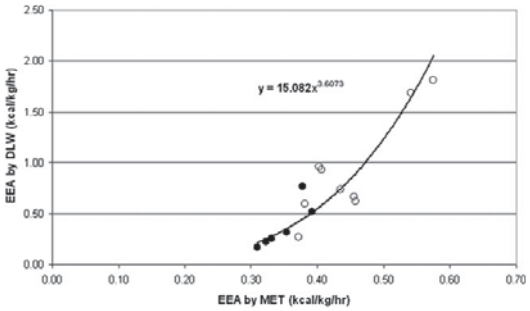


Fig. 3. DLW study: Scatter plot of EEA^{l}_{MET} versus EEA^{l}_{DLW} ($r^2 = 0.80$). Filled circles represent cancer patients whereas open circles represent healthy subjects. DLW = doubly labelled water; EEA = energy expenditure of activity; MET = metabolic equivalent.

equation: $EEA^{l}_{DLW} = 15.08EEA^{l}_{MET}{}^{3.61}$ ($r^2 = 0.80$) (Fig. 3). Thus, a validated estimate of EEA (in kcal/day) was derived using the equation: $EEA_{ActivPAL} = 24 \text{ x weight x } 15.08EEA^{l}_{MET}{}^{3.61}$

This equation was transposed further to use the primary EE output of ActivPAL™, namely TEE_{MET}: $EEA_{ActivPAL} = 362 \text{ x weight x } ((TEE_{MET}\text{-}24)/24)^{3.61}$

A Bland–Altman plot of the agreement between $EEA_{ActivPAL}$ (mean = 1244 kcal/day, SD = 825, range = 486–3334) and EEA_{DLW} (mean = 1262 kcal/day, SD = 807, range = 374–3424) demonstrated a mean difference of −18 kcal/day (SD = 347; 95% LOA = −699,663) or absolute error of 1.4% (Fig. 4).

Furthermore, as $TEE^{l} = REE^{l}+EEA^{l}$, a validated estimate of TEE (in kcal/day) was derived using the equation: $TEE_{ActivPAL} = 24 \text{ x weight x } [0.84+ (15.08 \text{ x } ((TEE_{MET}\text{-}24)/24)^{3.61}]$.

A Bland–Altman plot of the agreement between $TEE_{ActivPAL}$ (mean = 2859 kcal/day, SD = 787, range = 2129–5045) and TEE_{DLW} (mean = 2849 kcal/day, SD = 849, range = 2017–5309) demonstrated a mean difference of 9 kcal/day (SD = 411; 95% LOA = −796,814) or absolute error of 0.4%. No obvious relationship was observed between TEE_{DLW} and the difference in TEE between the two methods as values were scattered evenly about the mean.

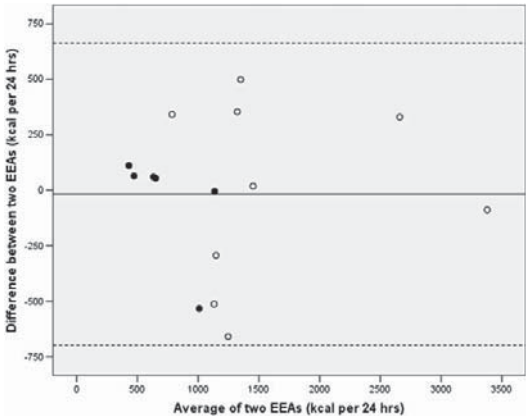


Fig. 4. DLW study: Bland–Altman plot of agreement between $EEA_{ActivPAL}$ and EEA_{DLW}. *Y* axis defined by calculation: $EEA_{ActivPAL}$ - EEA_{DLW}. Solid line represents the mean difference and dotted lines represent 95% limits of agreement (+/− 2SD). Filled circles represent cancer patients whereas open circles represent healthy subjects. DLW = doubly labelled water; EEA = energy expenditure of activity.

In a regression model, $EEA_{ActivPAL}$ accounted for 85.1% of the variation in TEE_{DLW} ($p < 0.001$), whereas predicted REE was not a significant determinant.

4. Discussion

This study represents the first attempt to validate an AM system in patients with advanced cancer. It demonstrates that ActivPAL™ can provide valid estimates of body postures and transfers in advanced cancer patients with KPS 40–100. Furthermore, post-hoc mathematical modeling can reduce percentage errors in the assessment of EEA in healthy subjects and advanced cancer patients with KPS 80–100 compared to the ActivPAL algorithm, although overall agreement between ActivPAL™ and DLW was also low.

The video study showed a very small measurement error (<0.1%) for the AM monitor in the registration of time spent in different body postures and the number of sit-to-stand transfers. These findings correspond with other validation studies of ActivPAL™[8,14,15,18] and suggest that time in different body positions and numbers of transitions between positions are reliable outcomes from the AM monitor, even in frail persons.

However, step count in patients with KPS 40–60 and KPS 70–100 demonstrated absolute errors of 32.9% and 24.1, respectively. This may be explained by a slow absolute gait speed; 0.48 m/s in patients with KPS 40–60 and 0.67 m/s in patients with KPS 70–100. Slow gait speed gives low acceleration amplitudes that may fail to be detected by the software system as steps.[14,19] Inspection of the raw ActivPAL™ acceleration data confirmed that steps had been registered by the monitor but were left unrecognised following software calculations. Similar high step count errors have also been demonstrated in slow walkers (<0.8 m/s) when using other AM-systems[12,35–37]and cumulatively, these observations suggest that, at the present time, algorithms imbedded in AM soft wares may not be sophisticated enough to detect steps in frail and slow walkers. Furthermore, it has been shown that the reliability of ActivPAL™ is less for self-paced floor walking compared with treadmill walking and stair walking in healthy adults.[38] The present data also highlight the potential difficulties of validating PA outcome measures in "mixed" populations. The video study aimed to recruit patients across a range of KPS, and yet by doing this, it has been shown that the quality of the validation of step count as an outcome varies significantly between self-caring (KPS 70–100) and non-self-caring (KPS 40–60) populations.

The inaccuracies in ActivPAL™-derived measures of step count may also be explained by the short walking distance used in the video study (6 m). Short walking sequences give atypical gait characteristics with low acceleration amplitudes during start and stop, and this may have contributed to the high step count errors observed.[39] Still, for clinical purposes, short walking distances are more likely to be representative of the daily PA of advanced cancer patients in their home environment.

The preliminary DLW results show that, although ActivPAL™ demonstrates inaccuracy when measuring step count during short walking distances, post-hoc mathematical modeling can be used to provide valid mean assessments of EE in free-living healthy individuals and non-hospitalized patients with cancer (KPS 80–100). However, despite valid mean assessments, ActivPAL™-derived assessments demonstrated wide variability compared with DLW-derived measurements, thus limiting their current applicability as outcome measures in intervention trials. For measured variables, mean difference between the two methodologies was small; mean bias in TEE between ActivPAL™ and DLW was only 9 kcal/day, whereas the mean bias in EEA between the two methodologies was an underestimation by ActivPAL™ of 18 kcal/day. The results of the present study show either similar or superior mean agreement

between ActivPAL™ and DLW compared with other studies.[40–43] However, to derive these small measurements of mean error, retrospective mathematical correction was required. Thus, further studies are required to validate these measurements.

Furthermore, despite small mean errors, within-subject variability was high. For example, when considering EEA, the mean measured EEA_{DLW} across the entire DLW study cohort was 1262 kcal/day and yet the 95%LOA between the two methodologies was approximately +/−700 kcal/day i.e. a potential variability of 55%. This high degree of variability would render the conclusions of any intervention study using EEA as an outcome measure very difficult to interpret, particularly as the DLW study included cancer patients with KPS scores of 80–100, the target population of future intervention studies. (Patients with KPS scores ≤70 would likely be considered too frail to be offered palliative therapeutic interventions, such as chemotherapy). Avoiding mixed study populations by repeating the DLW study in larger, "pure" cohorts of cancer patients or healthy subjects might demonstrate differing degrees of variability within subgroups. However, within the context of the current pilot study, dividing the DLW study cohort into cancer patients and healthy subjects would not appear to be of benefit.

Sources of error that may have introduced disagreement between methods in the DLW study would have included under-report of steps during slow walking.[14,19] However, in the present study, under-reporting of step count is unlikely to be the sole reason, as there were no obvious linear relationships between gold standard-derived measures of EE and disagreement between methodologies. In previous studies using ActivPAL™ in community-dwelling older adults (mean age 79 years), principal components analysis demonstrated that 80% of the variance in PA scores was described by walking behavior (39%), sedentary behaviour (24.3%) and postural transitions (16.7%).[44] Thus, patient behaviour not registered by the ActivPAL may affect the validity of PA outcome measures. Furthermore, regression analysis demonstrated age and BMI to be significant predictors of physical behaviour.[44] Therefore, increasing patient age and worsening nutritional depletion, both factors associated with frailty in advanced cancer, might influence PA outcome validity.

Consistent with previous studies,[6] cancer patients exhibited lower mean TEE and EEA than healthy subjects. However, inter-subject variation in nutritional status or basal metabolic rate is unlikely to explain these observed differences in TEE or EEA, as cancer patients and healthy subjects did not differ significantly with regards to weight, LBM, and measured REE. Therefore, reduced TEE and EEA in cancer patients is presumably a result of increased fatigue and lower performance, rather than severe cachexia. Recently, much interest has focused on the concept of 'pre-cachexia' (cancer –related anorexia and systemic inflammation in the absence of significant weight loss), and the fact that any systematic approach to the treatment of cachexia requires early identification of patients at risk and institution of prophylactic measures to attenuate the progression of disease, prior to the development of significant weight loss.[45] In the 'pre-cachectic' phase, many patients are more likely to be physically active than later in the disease trajectory, and thus the accuracy of PA outcomes measured by AM systems might be at their highest.

The best-fit relationship between ActivPAL™- and DLW-derived estimates of EEA appeared to be curvi-linear, rather than linear. The reason behind this observation is unclear, but the most likely explanation would appear to be an underestimation of METs during higher intensity activities, a phenomenon witnessed previously in the ActivPAL™ meter.[19] An alternative explanation might be differences in upper limb activity between subjects. ActivPAL™ only records thigh activity and thus the relatively smaller contributions of arm activity to TEE and EEA are not assessed. The non-linear (power) relationship between EEA^{l}_{MET} and EEA^{l}_{DLW} could thus be explained by a proportionally larger contribution of upper limb activity to EEA in fitter, more active individuals. However, it is worth noting that Bland–Altman plots did not demonstrate any significant variations in bias by ActivPAL™ at extremes of TEE and EEA.

The present study did not aim to assess the validity of different outcomes from the AM monitor, and therefore questions remain regarding the best way to utilise PA outcome measures in future intervention studies. The type of PA measure that may be the most sensitive to change following anti-cancer/anti-cachexia intervention, is yet to be identified. However, the study does suggests that time spent upright may be an accurate outcome measure that can be utilised in patient with a wide range of PF. Step count and EEA showed less accuracy, but it could be argued that these measures provide valuable additional information, including intensity of PA, in self caring populations (KPS 70–100). Both ActivPAL™-derived step count and/or time spent upright have been used with success as both outcome measures and measures of compliance following exercise training interventions in patients with heart failure[46] and stroke[15] and neuromuscular electrical stimulation on the quadriceps in patients with non-small cell lung cancer.[47] Time spent upright also correlated negatively with symptoms of psychological distress in patients with chronic low back pain.[48] Future clinical trials may need to assess different outcomes from AM-systems initially in order to stratify their relevant importance in patients with advanced cancer.

In conclusion, although AM-systems promise the possibility of patient-focused outcomes for clinical trials and the clinical management of patients with advanced cancer, at present, some outcomes such as step count and EE cannot be used with accuracy in frail populations. However, ActivPAL™ is accurate at assessing body positions and transfers across functional levels. Further prospective studies with larger cohorts with a wide spectrum of PA are required to improve our understanding of the relationship between patient demographics, behavior and PA, and to assess the validity of different endpoints and different AM-systems in advanced cancer patients.

Conference presentation

Skipworth RJE, Stene GB, Hendry PO, Dahele M, Small AC, Blum D, Kaasa S, Trottenberg P, Radbruch L, Strasser F, Preston T, Fearon KCH, Helbostad JL. Patient-focused endpoints for clinical trials: criterion-based validation of accelerometer-based activity monitoring in advanced cancer. *Palliative Medicine* 2010 June; 24(4) (Suppl): S63–S64. (Poster presentation at the 11th EAPC congress in Glasgow June 7th 10th 2010).

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgements

This study is part for the Work Package 2.3. Assessment and classification of cachexia in the the European Palliative Care Research Collaborative (EPRCR) and is funded by the European Commission's Sixth Framework Programme (contract no LSHC-CT-2006-037777) with the overall aim to improve treatment of pain, depression and fatigue through translation research.

Core scientific group/work package leaders: Stein Kaasa (project coordinator), Frank

Skorpen, Marianne Jensen Hjermstad, and Jon Håvard Loge, Norwegian University of Science and Technology (NTNU); Geoffrey Hanks, University of Bristol; Augusto Caraceni and Franco De

Conno, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Irene Higginson, King's College London; Florian Strasser, Cantonal Hospital St. Gallen; Lukas Radbruch, RWTH Aachen University; Kenneth Fearon, University of Edinburgh; Hellmut Samonigg, Medical University of Graz; Ketil Bø, Trollhetta AS, Norway; Irene Rech- Weichselbraun, Bender MedSystems GmbH, Austria; Odd Erik Gundersen, Verdande, Technology AS, Norway. *Scientific advisory group:* Neil Aaronson, The Netherlands Cancer

Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St. George's University of London; Mari Lloyd-Williams, University of Liverpool.

Project management: Stein Kaasa, Ola Dale, and Dagny F. Haugen, NTNU.

Statement of authorship: RJES and GBS contributed equally to this piece of work and are both listed as first authors. RJES carried out the DLW study and data analyses and drafted the manuscript and GBS carried out the video study and data analyses and drafted the manuscript. POH, MD, ACS, TP and KCHF were all involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data in the DLW study. DB, FS, SK, PT, LR and JLH were all involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data in the video study. SK is the principal investigator of the EPCRC. KCHF was the principal investigator of the DLW study. JLH was the principal investigator of the video study. All authors were involved in writing the manuscript and revising it critically for important intellectual content.

References

1. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–9.
2. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;**45**:2220–4.
3. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act* 2008;**5**:56.
4. Mantovani G, Madeddu C, Serpe R. Improvement of physical activity as an alternative objective variable to measure treatment effects of anticachexia therapy in cancer patients. *Curr Opin Support Palliat Care* 2010;**4**:259–65.
5. Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. *J Pain Symptom Manage* 2007;**33**:676–85.
6. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer* 2004;**90**:996–1002.
7. Chen KY, Bassett Jr DR. The technology of accelerometry-based activity monitors: current and future. *Med Sci Sports Exerc* 2005;**37**:S490–500.
8. Grant PM, Ryan CG, Tigbe WW, Granat MH. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. *Br J Sports Med* 2006;**40**:992–7.
9. Grant PM, Dall PM, Mitchell SL, Granat MH. Activity-monitor accuracy in measuring step number and cadence in community-dwelling older adults. *J Aging Phys Act* 2008;**16**:201–14.
10. Bussmann HB. Validity and reliability of measurements obtained with an "activity monitor" in people with and without a transtibial amputation. *Phys Ther* 1998;**78**:989–98.
11. van den Berg-Emons HJ, Bussmann JB, Balk AH, Stam HJ. Validity of ambulatory accelerometry to quantify physical activity in heart failure. *Scand J Rehabil Med* 2000;**32**:187–92.
12. Storti KL, Pettee KK, Brach JS, Talkowski JB, Richardson CR, Kriska AM. Gait speed and step-count monitor accuracy in community-dwelling older adults. *Med Sci Sports Exerc* 2008;**40**:59–64.
13. Kaasa S, Loge JH, Fayers P, Caraceni A, Strasser F, Hjermstad MJ, et al. Symptom assessment in palliative care: a need for international collaboration. *J Clin Oncol* 2008;**26**:3867–73.
14. Taraldsen K, Askim T, Sletvold O, Einarsen EK, Bjastad KG, Indredavik B, et al. Evaluation of a body-worn sensor system to measure physical activity in older people with impaired function. *Phys Ther* 2011;**91**:277–85.
15. Grant PM, Granat MH, Thow MK, Maclaren WM. Analyzing free-living physical activity of older adults in different environments using body-worn activity monitors. *J Aging Phys Act* 2010;**18**:171–84.
16. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson P. Validation of Wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc*; 2011.
17. Ryan CG, Grant PM, Tigbe WW, Granat MH. The validity and reliability of a novel activity monitor as a measure of walking. *Br J Sports Med* 2006;**40**:779–84.
18. Maddocks MM, Petrou AA, Skipper LL, Wilcock AA. Validity of three accelerometers during treadmill walking and motor vehicle travel. *Br J Sports Med*; 2008.
19. Harrington DM, Welk GJ, Donnelly AE. Validation of MET estimates and step measurement using the ActivPAL physical activity logger. *J Sports Sci* 2011;**29**:627–33.
20. Ainsworth BE. Comparison of three methods for measuring the time spent in physical activity. *Med science sports Exercise* 2000;**32**:S457–64.
21. Seaby L, Torrance G. Reliability of a physiotherapy functional assessment used in a rehabilitation setting. *Physiother Can* 1989;**41**:264–71.
22. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc* 1986;**34**:119–26.
23. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. *Ann Surg* 1994;**219**:325–31.
24. Nicholson MJ, Holton J, Bradley AP, Beatty PC, Campbell IT. The performance of a variable-flow indirect calorimeter. *Physiol Meas* 1996;**17**:43–55.
25. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949;**109**:1–9.
26. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985;**39**(Suppl. 1):5–41.
27. Pace Nr EN. Studies on body composition lll. The body water and chemically combined nitrogen content in relation to fat content. *J Biol Chem* 1945;**158**:685–91.
28. Levine J, Melanson EL, Westerterp KR, Hill JO. Measurement of the components of nonexercise activity thermogenesis. *Am J Physiol Endocrinol Metab* 2001;**281**: E670–5.
29. Scrimgeour CM, Rollo MM, Mudambo SM, Handley LL, Prosser SJ. A simplified method for deuterium/hydrogen isotope ratio measurements on water samples of biological origin. *Biol Mass Spectrom* 1993;**22**:383–7.
30. Prosser SJ, Scrimgeour CM. High-precision determination of 2H/1H in H2 and H2O by continuous-flow isotope ratio mass spectrometry. *Anal Chem* 1995;**67**:1992–7.
31. Prosser SJ, Brookes ST, Linton A, Preston T. Rapid, automated analysis of 13C and 18O of CO2 in gas samples by continuous-flow, isotope ratio mass spectrometry. *Biol Mass Spectrom* 1991;**20**:724–30.
32. Goran MI, Poehiman ET, Danforth E. Experimental reliability of the doubly labeled water technique. *Am J Physiol Endocrinol Metab*; 1994:E510–5.
33. Wolfe RR. *Radioactive and stable isotope Tracers in Biomedicine*. New York: Wiley; 1992.
34. Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr* 1996;**50**:72–92.
35. Dijkstra B, Zijlstra W, Scherder E, Kamsma Y. Detection of walking periods and number of steps in older adults and patients with Parkinson's disease: accuracy of a pedometer and an accelerometry-based method. *Age Ageing* 2008; **37**:436–41.
36. Esliger DW, Probert A, Gorber SC, Bryan S, Laviolette M, Tremblay MS. Validity of the Actical accelerometer step-count function. *Med Sci Sports Exerc* 2007;**39**:1200–4.
37. Ramstrand N. Validation of a patient activity monitor to quantify ambulatory activity in an amputee population. *Prosthetics Orthotics International* 2007;**31**:157–66.
38. Dahlgren G, Carlsson D, Moorhead A, Hager-Ross C, McDonough SM. Test-retest reliability of step counts with the ActivPAL device in common daily activities. *Gait Posture* 2010;**32**:386–90.
39. Dijkstra BB, Kamsma YB, Zijlstra WW. Detection of gait and postures using a miniaturised triaxial accelerometer-based system: accuracy in community-dwelling older adults. *Age and Ageing* 2010;**39**:259–62.
40. Arvidsson D, Slinde F, Nordenson A, Larsson S, Hulthen L. Validity of the ActiReg system in assessing energy requirement in chronic obstructive pulmonary disease patients. *Clin Nutr* 2006;**25**:68–74.
41. Hustvedt BE, Svendsen M, Lovo A, Ellegard L, Hallen J, Tonstad S. Validation of ActiReg to measure physical activity and energy expenditure against doubly labelled water in obese persons. *Br J Nutr* 2008;**100**:219–26.
42. Copland L, Liedman B, Rothenberg E, Ellegard L, Hustvedt BE, Bosaeus I. Validity of the ActiReg system and a physical activity interview in assessing total energy expenditure in long-term survivors after total gastrectomy. *Clin Nutr* 2008;**27**:842–8.
43. Gardner AW, Poehlman ET. Assessment of free-living daily physical activity in older claudicants: validation against the doubly labeled water technique. *J Gerontol A Biol Sci Med Sci* 1998;**53**:M275–80.
44. Lord S, Chastin SF, McInnes L, Little L, Briggs P, Rochester L. Exploring patterns of daily physical and sedentary behaviour in community-dwelling older adults. *Age Ageing* 2011;**40**:205–10.
45. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics. *Clin Nutr* 2010;**29**:154–9.

46. Cowie A, Thow MK, Granat MH, Mitchell SL. A comparison of home and hospital-based exercise training in heart failure: immediate and long-term effects upon physical activity level. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:158–66.
47. Maddocks M, Lewis M, Chauhan A, Manderson C, Hocknell J, Wilcock A. Randomized controlled pilot study of neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer. *J Pain Symptom Manage* 2009;**38**:950–6.
48. Ryan CG, Gray HG, Newton M, Granat MH. The relationship between psychological distress and free-living physical activity in individuals with chronic low back pain. *Man Ther* 2010;**15**:185–9.

Paper III

Acta Oncologica, 2014; Early Online: 1–9

informa
healthcare

ORIGINAL ARTICLE

Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer

GURO B. STENE[1,2,3], JORUNN L. HELBOSTAD[3,4], TORE AMUNDSEN[5,6], SVEINUNG SØRHAUG[1,5], HARALD HJELDE[5], STEIN KAASA[1,2] & BJØRN H. GRØNBERG[1,2]

[1]*European Palliative Care Research Centre, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology NTNU, Trondheim, Norway,* [2]*The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway,* [3]*Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology NTNU, Trondheim, Norway,* [4]*Department of Clinical Services, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway,* [5]*Department of Thoracic Medicine, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway and* [6]*Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology NTNU, Trondheim, Norway*

ABSTRACT

Background. Sarcopenia is a defining feature of cancer cachexia associated with physical decline, poor quality of life and poor prognosis. Thus, maintaining muscle mass is an important aim of cachexia treatment. Many patients at risk for developing cachexia or with cachexia experience side effects of chemotherapy that might aggravate the development of cachexia. However, achieving tumor control might reverse the catabolic processes causing cachexia. There is limited knowledge about muscle mass changes during chemotherapy or whether changes in muscle mass are associated with response to chemotherapy.

Patients and methods. In this pilot study, patients with advanced non-small cell lung cancer (NSCLC) receiving three courses of palliative chemotherapy were analyzed. Muscle mass was measured as skeletal muscle cross sectional area (SMCA) at the level of the third lumbar vertebrae using CT images taken before and after chemotherapy.

Results. In total 35 patients, 48% women, mean age 67 years (range 56–86), participated; 83% had stage IV disease and 71% were sarcopenic at baseline. Mean reduction in SMCA from pre- to post-chemotherapy was 4.6 cm^2 (CI 95% −7.3–−1.9; $p < 0.002$), corresponding to a 1.4 kg loss of whole body muscle mass. Sixteen patients remained stable or gained SMCA. Of these, 14 (56%) responded to chemotherapy, while two progressed ($p = 0.071$). Maintaining or gaining SMCA resulted in longer median overall survival (loss: 5.8 months, stable/gain: 10.7 months; $p = 0.073$). Stage of disease ($p = 0.003$), treatment regimen ($p = 0.023$), response to chemotherapy ($p = 0.007$) and SMCA change ($p = 0.040$), but not sarcopenia at baseline, were significant prognostic factors in the multivariate survival analyses.

Conclusion. Almost half of the patients had stable or increased muscle mass during chemotherapy without receiving any cachexia treatment. Nearly all of these patients responded to the chemotherapy. Increase in muscle mass, but not sarcopenia at baseline, was a significant prognostic factor.

Cancer cachexia is a common feature of advanced cancer, and has been estimated to be the main cause of death in 20% of cancer patients [1]. The syndrome is characterized by anorexia, reduced food intake, metabolic changes, weight loss, low body mass index and/or low skeletal muscle mass (sarcopenia) [2,3]. Recent studies show that sarcopenia is frequent in advanced cancer, and is associated with physical decline, reduced quality of life, increased chemotherapy toxicity and shorter survival time [4–8].

Muscle mass can be assessed from CT images and has been proposed as an important entry criteria and outcome for clinical trials of cachexia therapy [9]. Studies using CT image analysis to measure

Correspondence: G. B. Stene, Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Faculty of Medicine, Trondheim, 7491, Norway. Tel: +47 482 26799. E-mail: guro.b.stene@ntnu.no

(Received 19 May 2014; accepted 3 August 2014)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2014.953259

muscle mass, have revealed a loss of muscle mass during anti-cancer therapy in patients with various advanced cancers [7,10–14], but some of them also show that patients might gain muscle mass [7,13,14]. Catabolic processes, such as inflammation (associated with high C-reactive protein and low albumin values [15]), abnormal metabolism and reduced caloric intake due to the underlying malignancy are considered to be main causes of muscle loss [14]. Thus, it has been proposed that successful treatment of the underlying malignancy can reduce or even reverse the catabolic effects on the muscle mass [7].

Although it has been shown that chemotherapy might improve quality of life and survival in advanced cancer patients [16], there is still limited knowledge about changes in muscle mass during chemotherapy in patients with advanced cancer, and whether changes in muscle mass are associated with response to the treatment.

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related deaths. Nearly all patients develop advanced, incurable disease for which palliative chemotherapy is the recommended therapy. The prevalence of sarcopenia is high (40–60%) and higher than in most other types of cancer [4]. Thus, in this study of patients with advanced NSCLC receiving three cycles of platinum-based chemotherapy, the primary aim was to explore changes in muscle mass assessed by CT images taken before and after chemotherapy in order to answer the following research questions:

1. Does skeletal muscle mass change during palliative chemotherapy?
2. Are there any associations between changes in muscle mass and response to chemotherapy?

As a secondary aim, we explored whether change muscle is an independent prognostic factor for survival.

Methods

This pilot observational cohort study used data from a randomized study comparing quality of life during chemotherapy with two different regimens for advanced NSCLC [17]. Main eligibility criteria were written informed consent, age ≥ 18 years, WHO performance status score (PS) 0–2, and stage IIIB–IV NSCLC eligible for palliative chemotherapy [17]. Patients were randomized to receive either carboplatin AUC = 5 (Calvert's formula) day 1 plus vinorelbine 25 mg/m^2 day 1 & 8 or carboplatin AUC = 5 (Calvert's) day 1 plus gemcitabine 1000 mg/m^2 day 1 & 8 every three weeks. Three courses were planned for all patients.

Patients who received at least one course of chemotherapy and had a CT scan before and after chemotherapy were included in the present study. The study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway.

Imaging and assessment of skeletal muscle mass

CT scans were taken within two weeks before chemotherapy commenced and within three weeks after the last course of chemotherapy was administered. Median time between the CT scans was 88 days (SD 22; range 43–122).

Muscle mass was measured as total SMCA using CT-images at the third lumbar vertebra level (L3) and expressed in cm^2 [18]. The Slice O' Matic v 4.3 by Tomovision, Canada software was used for image analysis. One image (with a maximum slice thickness of 5 mm) was selected for each patient. During anatomical land marking, the first image at L3 with both vertebral transverse processes clearly visible, were used in the analysis. Radio density of the skeletal muscle was calculated by use of Hounsfield Units, with thresholds from -29 to $+150$ [18].

Change in SMCA was dichotomized according to change from pre-to post-chemotherapy: 1) patients with $>2\%$ loss of SMCA; and 2) all other patients. The cut-offs were defined according to the previously reported measurement error of 2% for CT image analysis at the L3 vertebral level [19], equivalent to a change of whole body skeletal muscle mass of ≥ 1 kg [20]. Whole body muscle mass in kilogram was calculated from the SMCA, as described by Mourtzakis et al. [19]. Thresholds for classifying sarcopenia at baseline were based on previously reported cut-off values; SMCA normalized for stature (height, m^2) ≤ 38, 5 cm^2/m^2 for women and ≤ 52, 4 cm^2/m^2 for men [21].

Other assessments

Stage of disease was assessed at baseline according to the TNM v7.0 [22]. Response to chemotherapy was assessed by comparing the post-treatment CT scans with pre-treatment images and was classified according to the RECIST-criteria v1.1 as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [23]. Toxicity was classified and graded according to the CTCAE 3.0 [24]. Weight loss (kg) the last three months before start of chemotherapy was assessed by patients' self-report. Values of C-reactive protein (CRP) and albumin were collected from hospital medical records. Patients reported health-related quality of life (HRQoL) at pre-treatment and three weeks after the last course of chemotherapy by the European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaires C30 and LC 13 [25].

Data analysis and statistical analysis

Descriptive data is presented as means and standard deviations (SD) for continuous variables and proportions and percentages for categorical variables. χ^2 and Fisher's exact tests were used for group-comparisons in categorical variables, and for the purpose of statistical analysis variables were dichotomized. Thus, patients with a CR, PR or SD were categorized as having *disease-control*, and those with progressive disease as having *progression*.

Survival time was defined as time from inclusion in the study until death and was estimated using the Kaplan-Meier method. The log-rank test was used for uni-variate survival analysis and the Cox proportional hazard method for multivariate survival analysis, adjusting for established prognostic factors in advanced NSCLC (PS, stage of disease, gender, tumor response, patient-reported global quality of life and appetite loss at baseline; and weight loss), CRP- and albumin-values at baseline, sarcopenia at baseline, body mass index and treatment [5,26].

Results

Patient characteristics

From August 2009 to May 2010, 54 patients were enrolled in the main study. Of these, 35 patients were eligible for inclusion in the present study. Reasons for exclusion were discontinuation from the main trial or death (n = 10), or no CT scans at the L3 vertebral level both before and after chemotherapy (n = 9).

Patients characteristics are shown in Table I. Median age was 66 (range 55–86) years, 18 (51%) were men, 29 (83%) had stage IV disease, 4 (11%) had PS 0 and 29 (83%) had PS 1. Mean body weight was 71.5 kg (SD 14.4); 2 (6%) were underweight (BMI < 18.5 kg/m^2), 17 (49%) had normal weight (BMI 18.5–24.9 kg/m^2), 13 (37%) were overweight (BMI 25.0–29.9 kg/m^2), and three (9%) were obese (BMI > 30.0 kg/m^2). Mean weight loss during the three months prior to chemotherapy was 3.4 (SD 4.5) kg, 21 (60%) had < 5% loss of body weight, eight (26%) between 5% and 10%, and five (14%) more than 10%. Twenty-six (74%) patients, 12 women and 14 men, were sarcopenic at baseline.

Changes in skeletal muscle mass

Mean SMCA reduced in the total cohort from 121.9 cm^2 to 117.4 cm^2 from pre- to post chemotherapy (mean change 4.6 cm^2, CI 95% −7.3–−1.9; $p < 0.002$), corresponding to a reduction of whole body muscle mass of 1.4 kg (CI 95% 0.6–2.2) [19]. Nineteen (54%) had a reduction in SMCA, with a mean

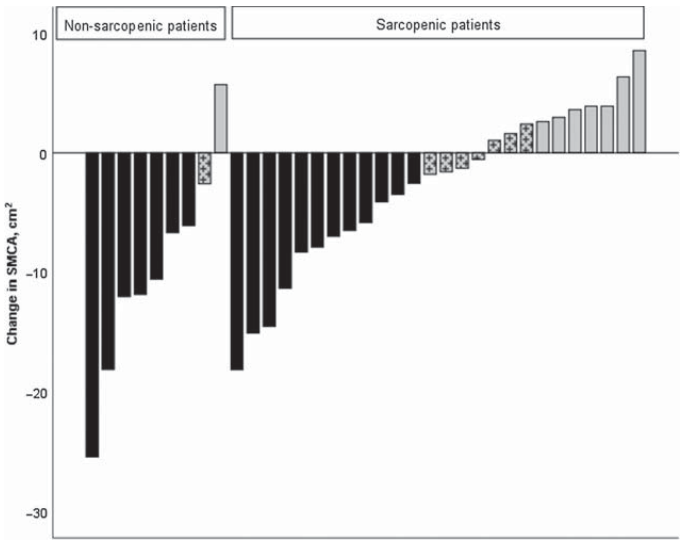


Figure 1. Change in skeletal muscle cross sectional area in patients according to sarcopenia. Individual changes in skeletal muscle cross sectional area (SMCA) from pre- to post-chemotherapy (Y-axis) according to sarcopenia at baseline, measured in cm^2. Negative values indicate loss in muscle mass. Thresholds for sarcopenia were based on previously reported cut-off values for the skeletal muscle index, which were SMCA/body height 2; ≤ 38.5 cm^2/m^2 for women and ≤ 52.4 cm^2/m^2 for men [20]. Non-sarcopenic patients (n=9) are shown in the bars to the left, and sarcopenic (n=26) in the bars to the right. Black bars are SMCA Loss, Dotted grey bars are SMCA Stable and Light grey bars are SMCA Gain.

decrease of 10.3 cm^2 (CI 95% −13.1–−7.4; $p < 0.001$). Sixteen patients (46%) had stable or increased SMCA, with a mean increase of 2.2 cm^2 (CI 95% 0.5–3.9; $p = 0.016$). Figure 1 shows that amongst patients who were sarcopenic at baseline, 14/26 (54%) had stable or increased muscle mass, whereas among non-sarcopenic patients, the corresponding numbers were 2/9 (22%) ($p = 0.104$).

Associations between response to chemotherapy, laboratory values, changes in skeletal muscle mass and changes in HRQoL

A total of 25 patients (71%) had disease-control following chemotherapy (response or stable disease), while 10 patients (29%) progressed (Table II). Among those with disease-control, 14/25 (56%) maintained or gained SMCA, whereas 2/10 (20%) of those who progressed gained muscle mass ($p = 0.071$). Descriptive data of changes in SMCA from pre- to post-chemotherapy depending on response to the chemotherapy are illustrated in Figure 2.

CRP or albumin levels at the start of chemotherapy were not significantly associated with change in muscle mass. Among patients with a CRP ≥ 10 ml/g, there were 14 patients who maintained or gained SMCA and 12 who lost SMCA ($p = 0.101$). For albumin, the proportions with low values (< 36 m/l) were 6/14 and 4/12 before and after chemotherapy, respectively ($p = 0.283$).

Patients who maintained or gained SMCA, had an increase in physical function, with a change in mean scores from 65.7 (SD 22.2) to 66.2 (SD 20.2) points; for reduced appetite loss, the mean score changed from 19.0 (SD 25.2) to 14.3 (SD 31.3),

Table 1. Baseline characteristics.

		All patients n = 35		$SMCA_{Gain/stable}$ n = 16		$SMCA_{Loss}$ n = 19	
Age, years	*mean, SD*	67.1	6.8	66.0	4.1	68.0	8.4
Gender							
Female	*n, (%)*	17	49	7	44	10	53
Male		18	51	9	56	9	47
Stage of cancer[1]	*n, %*						
IIIB		6	17	3	19	3	16
IV		29	83	13	81	16	84
Performance status[2]							
0	*n, %*	4	11	1	6	3	16
1		29	83	14	88	15	79
2		2	6	1	6	1	5
Height, m	*mean, SD*	1.70	20.1	1.72	7.7	1.71	8.7
Weight, kg	*mean, SD*	71.5	14.4	72.2	12.9	70.8	15.7
BMI, kg/m^2[2,3]	*mean, SD*	24.2	4.2	24.2	3.9	24.2	4.5
Underweight < 18.5	*n, %*	2	6	1	6	1	5
Normal 18.5–24.9		17	49	7	44	10	53
Overweight 25–29.9		13	37	7	4	6	32
Obese ≥ 30		3	9	1	6	2	11
WL, 3 months pre-study (kg)	*mean, SD*	3.4	4.5	5.0	5.8	1.9	2.3
< 5%	*n, %*	21	60	9	56	13	68
5–10%		9	26	3	19	5	26
> 10%		5	14	4	25	1	5
C-reactive protein (ml/g)	*mean, SD*	43.3	46.0	44.5	35.1	42.3	54.4
< 10	*n, %*	9	26	2	12	7	37
≥ 10		26	74	14	88	12	63
Albumin (m/l)	*mean, SD*	38.2	4.3	37.3	3.8	39	4.6
< 36	*n, %*	25	71	10	62	15	79
≥ 36		10	29	6	38	4	21
Skeletal muscle cross sectional area (cm^2)	*mean, SD*	121.9	30.8	124.9	32.2	119.3	30.2
Skeletal muscle index (cm^2/m^2)		41.1	9.0	41.0	7.6	40.8	9.6
LBM, kg		42.6	9.2	43.5	9.7	41.8	9.0
Sarcopenic at study entry[4]	*n, %*	26	74	14	88	12	63
Not-sarcopenic		9	26	2	12	7	36

[1]TNM-classification; [2]European Collaborative Oncology Group; [3]n = 29; [4]Thresholds for sarcopenia were based on previously reported cut-off values for the skeletal muscle index, which was SMCA/body $height^2 \leq 38$, 5 cm^2/m^2 for women and > 52, 4 cm^2/m^2 for men [20].
BMI, body mass index; LBM, lean body mass; SMCA, skeletal muscle cross sectional area; WL, weight loss.

Table II. Courses of chemotherapy, response evaluation and toxicity.

	All patients n = 35	$SMCA_{Gain/stable}$ n = 16	$SMCA_{Loss}$ n = 19
	n	*n*	*n*
Chemotherapy regimen			
Carboplatin	35	16	19
Vinorelbine	13	4	9
Gemcitabine	22	12	10
Courses of chemotherapy			
1A	35	16	19
1B	30	13	17
2A	34	16	18
2B	32	14	18
3A	32	16	16
3B	30	14	16
Dose reductions			
1B	5	0	5
2A	17	6	11
2B	20	9	11
3A	23	10	13
3B	24	10	14
Treatment response[1]			
Complete or partial response	13	8	5
Stable disease	12	6	6
Progressive disease	10	8	2
Hematological grade 3–4 toxicity[2]			
Anemia	0	0	0
Neutropenia	28	13	15
Trombocytopenia	13	5	8
Non-hematological grade 3–4 toxicity[2]			
Neutropenic infection	3	1	2
Infection without neutropenia	3	1	2
Lung embolism	1	0	1

[1]RECIST version 1.1; [2] CTCAE v. 3.0.
SMCA, skeletal muscle cross sectional area.

while those with disease progression had a decline in physical function [mean score changed from 65.3 (SD 28.8) to 61.8 (SD 27.7) and increase in appetite loss (mean score changed from 20.0 (SD 27.6) to 22.2 (SD 32.5)].

Toxicity

Neutropenia (n = 28) and thrombocytopenia (n = 13) were the most common grade 3–4 toxicities (Table II). Those who were sarcopenic at baseline did not experience more toxicity from the chemotherapy. There were no significant differences in grade 3–4 toxicity between patients who maintained/gained or those who lost SMCA.

Survival

In the uni-variate analysis, stage of disease (IIIB: 18.6 months vs. IV: 7.4 months; $p = 0.034$), treatment response (disease-control: 10.7 months vs. progression: 4.1 months; $p < 0.001$) and appetite loss (no appetite loss: 10.7 months vs. appetite loss: 6.7 months; $p = 0.022$) were significant prognostic factors for survival (Table III). There was a trend towards shorter survival for patients who lost SMCA compared to patients with stable or gained SMCA (5.8 vs. 10.7 months, $p = 0.073$). Sarcopenia at baseline was not a significant prognostic factor (non-sarcopenic: 7.9 vs. sarcopenic 7.5 months; $p = 0.490$).

Stage of disease ($p = 0.003$), treatment regimen ($p = 0.023$), response to treatment ($p = 0.007$) and stable/gain in SMCA ($p = 0.040$) were significant prognostic factors in the multivariate survival analysis.

Discussion

In this exploratory pilot study of patients with advanced NSCLC we found a mean reduction in muscle mass of 1.4 kg during nine weeks of first-line platinum-doublet chemotherapy. There were large variations in changes of SMCA corresponding to changes in whole body muscle mass from −7.6 to + 2.6 kg. Furthermore, there was a trend towards less loss of muscle mass among those with disease control compared with the patients who progressed

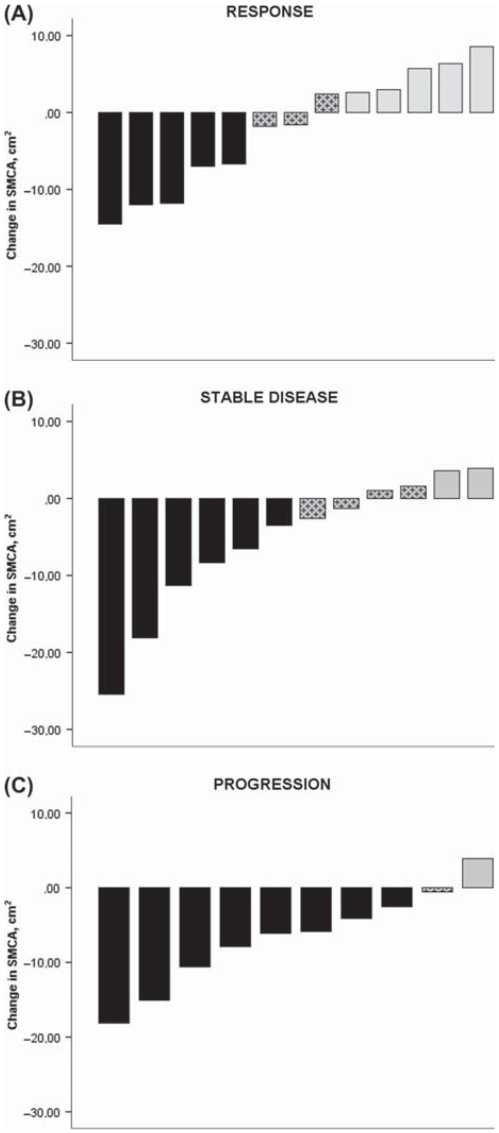


Figure 2. Change in skeletal muscle cross sectional area in patients according to response to treatment. (Includes Figure A, B and C). Individual changes in skeletal muscle cross sectional area (SMCA) from pre- to post-chemotherapy (Y-axis) according to response to treatment, measured in cm^2. Negative values indicate loss in muscle mass. Black bars are SMCA Loss, Dotted gray bars are SMCA Stable and Light gray bars are SMCA Gain.

during the chemotherapy. Despite the absence of specific cachexia therapy (e.g. nutritional support, anti-inflammatory medication or physical exercise), 46% of patients had a stable or increased muscle mass following chemotherapy. These patients also had a slight improvement in self-reported physical function and appetite, and significantly longer survival compared to other patients. The response rate to chemotherapy was similar as in other studies of NSCLC [27], and established prognostic factors in advanced NSCLC (stage of disease, loss of appetite and response to treatment) but not sarcopenia pre-chemotherapy were significant prognostic factors for time to death.

Maintained or gained muscle mass during cytotoxic chemotherapy has to our knowledge only been demonstrated in one other study. In that study, patients with various types of advanced cancer were included [7]. Similar to our study, large variations in changes of muscle mass during systemic therapy have been found in other studies of NSCLC [10] and advanced pancreatic cancer [11,13]. In the study by Murphy et al, NSCLC patients lost 1.1 kg of skeletal muscle over the duration of chemotherapy, but the mean change in muscle mass ranged from a loss of −6. 9 kg/100 days to a gain of + 1.6 kg/100 days [10]. In both studies of advanced pancreatic cancer patients, muscle loss was predominant, but Tan et al. showed that 14% of the patients had a mean muscle gain of 7.9 ± 14.4%/100 days [13], and in the study by Dalal et al., 34% of the patients gained muscle mass [11].

None of these studies did however investigate whether changes in muscle mass were associated with response to the systemic therapy. Nevertheless, a link between gain in muscle mass and stable disease has been proposed by Prado et al. [7]. They found that 15% of patient with advanced cancer gained muscle mass and nearly 50% remained stable over the clinical course of cancer disease. Patients with large gains in muscle mass had better response to treatment, ate well and had good symptom control, whereas those who lost muscle mass, had progressive disease and a short survival [7]. In our study, we found that almost all of those who maintained or increased muscle mass had stable disease or responded to the chemotherapy. Thus, it appears that the chemotherapy might suppress the catabolic processes driving muscle breakdown in those who respond to the treatment – since no specific interventions aiming at preventing or reversing cachexia was administered (e.g. anti-inflammatory medication, nutritional support or physical exercise). It is noteworthy that our patients received a relatively short chemotherapy regimen.

It should be acknowledged that there are multiple causes of muscle loss in advanced cancer. In addition to the catabolic effects on the muscle caused by the underlying malignancy and cachexia, advanced cancer patients often have a reduced caloric intake and are physically inactive, which

Table III. Uni- and multivariate survival analysis.

			Uni-variate analysis				Multivariate analysis		
	n	n events (deaths)	Median survival (months)	HR	95% CI	p–value	HR	95% CI	p–value
Gender									
Men[a]	*18*	13	7.9	1.4	0.6–2.9	*0.422*	1.0	0.4–2.3	*0.909*
Women	*17*	15	7.2						
Performance status[1]									
0[a]	*4*	3	8.5	1.8	0.5–6.3	*0.347*	2.5	0.3–19.5	*0.398*
1	*31*	25	7.5						
Stage of cancer[2]									
IIIB[a]	*6*	3	18.6	3.5	1.0–11.9	*0.045*	11.1	2.3–54.0	*0.003*
IV	*29*	25	7.4						
Treatment regime									
Gemcitabine[a]	*22*	17	9.2	1.6	0.8–3.5	*0.203*	4.2	1.2–14.4	*0.023*
Vinorelbin	*13*	11	7.0						
Treatment response[3]									
Disease control[a]	*25*	18	10.7	5.3	2.2–12.8	*< 0.001*	4.8	1.6–15.0	*0.007*
Progression	*10*	10	4.1						
BMI									
≥ 25 kg/m^2[a]	*16*	11	7.4	0.6	0.3–1.6	*0.196*	0.8	0.7–2.6	*0.721*
< 25 kg/m^2	*19*	17	8.5						
WL 3 months pre-study									
< 5%[a]	*21*	16	7.5	0.7	0.4–1.7	*0.534*	0.4	0.2–1.1	*0.084*
≥ 5%	*14*	12	7.9						
C-reactive protein									
< 10 ml/g[a]	*9*	7	7.0	0.9	0.4–2.3	*0.905*	0.8	0.2–3.1	*0.761*
≥ 10 ml/g	*26*	21	7.9						
Albumin									
< 36 m/l[a]	*25*	19	8.5	1.5	0.7–3.4	*0.299*	3.5	0.9–13.1	*0.069*
≥ 36 m/l	*10*	9	7.2						
Baseline sarcopenia[4]									
No[a]	*9*	6	7.9	1.4	0.6–3.4	*0.492*	2.1	0.5–9.2	*0.330*
Yes	*26*	22	7.5						
SMCA change[5]									
Stable or gain[a]	*16*	12	10.7	2.0	0.9–4.2	*0.078*	3.6	1.1–12.5	*0.040*
Loss	*19*	16	5.8						
Global QoL[6]									
High QoL (score ≥ 65)[a]	*15*	12	9.2	1.2	0.6–2.6	*0.594*	0.8	0.3–2.3	*0.687*
Low QoL (score < 65)	*20*	16	6.7						
Appetite loss[6]									
No (score 0)[a]	*20*	14	10.7	2.4	1.1–5.1	*0.025*	2.5	0.8–7.7	*0.115*
Yes (score 1–3)	*15*	14	6.2						

[a]Reference category. [1]European Collaborative Oncology Group; [2]TNM-classification; [3]RECIST version 1.1; [4]Thresholds for sarcopenia were based on previously reported cut-off points for the skeletal muscle index, which was SMCA/body height^2 ≤ 38, 5 cm^2/m^2 for women and ≤ 52, 4 cm^2/m^2 for men; [5]Change in SMCA from pre- to post chemotherapy; [6]Items extracted from the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30).
BMI, body mass index; QoL, quality of life; SMCA, skeletal muscle cross sectional area; WL, weight loss.

adds to the muscle loss. In addition, nausea, vomiting and loss of appetite are well-known side effects of chemotherapy that might negatively influence energy intake and activity levels and thus contribute to aggravate loss of muscle mass. These side effects are frequently reported among patients receiving the regimens administered in our study. There were no differences in grade 3–4 toxicity between those with stable/increased or those who lost muscle mass among our patients.

We are aware of three other studies in patients with advanced pancreatic cancer investigating whether change in muscle mass during the course of cancer treatment as a prognostic factor for survival [11–13]. Unlike our study, neither of these studies demonstrated a statistically significant difference in survival

related to change in muscle mass, possibly due to small sample sizes. Another likely explanation could be that methods for assessing muscle mass in these studies were different from the methods we used. We used previously reported cut-off values in the assessment of sarcopenia and for calculating longitudinal changes in muscle mass during chemotherapy. Still, the diversity of methods makes comparison between studies challenging and future studies should therefore address cut-offs for this outcome.

Our finding, that sarcopenia at baseline was not a significant prognostic factor for survival is not in line with previous studies conducted in larger cohorts of advanced cancer patients. The short expected survival of patients with advanced NSCLC and the high proportion of sarcopenic patients in our study (>70%) are possible explanations. An association between sarcopenia and chemotherapy toxicity has been observed previously [8]; the finding were however not replicated in our study cohort.

The main limitation of our study was the small sample size, limiting the power of the survival analyses. However, the sample is, in our opinion, large enough to demonstrate that more knowledge is needed before the role of assessing muscle mass in advanced cancer patients can be established – as a prognostic factor as well as in research on classification and treatment of cachexia. Another limitation is the use of cut-off levels for the definition of sarcopenia – there might be differences in body composition between countries. In case, this might influence the survival analyses, but not the analyses of changes in muscle mass.

Conclusion and suggestions for future research

In this exploratory study of patients with advanced NSCLC, we found large individual variations in changes in muscle mass during palliative chemotherapy. We observed that many patients had an increase in muscle mass without receiving any additional cachexia therapy and that many of these patients were sarcopenic before starting chemotherapy. There was also a trend towards more gain in muscle mass among patients who had disease control following chemotherapy, suggesting that response to cancer treatment is essential for controlling or reversing cancer cachexia. The finding that change in SMCA was a significant prognostic factor for survival, suggest that response to cancer therapy and changes in SMCA, and not only muscle mass measured before starting chemotherapy, should be assessed in future studies on prognosis of cancer cachexia. Furthermore, use of SMCA as an endpoint in studies of cancer cachexia should be used with caution and need careful consideration until more is known about changes in muscle mass in patients undergoing anti-cancer therapy.

Key message

Sarcopenia or loss of skeletal muscle mass has recently been proposed as a key clinical feature of cachexia. Assessment of skeletal muscle mass on CT images might be used to classify cachexia and to evaluate the effect of interventions aiming at controlling or reversing cachexia. However, little is known about the nature and magnitude of changes in muscle mass in cancer patient during the course of their disease – or during cancer therapy. In our pilot study of patients with advanced non-small cell lung cancer, nearly 50% of the patients had stable or increased muscle mass during chemotherapy without receiving any cachexia treatment. Almost all of these patients responded to the chemotherapy – suggesting that tumour control is essential for successfully treating cachexia. Furthermore, change in muscle mass during treatment and not sarcopenia presenting at baseline, was a significant prognostic factor for survival. More studies about longitudinal changes in skeletal muscle mass in cancer patients – and the correlation with response to cancer therapy – are needed before the role of sarcopenia in advanced cancer and the value in cachexia research can be established.

Acknowledgements

The European Centre for Palliative Care Research and the Department of Cancer Research and Molecular Medicine, NTNU. This work is part of a PhD degree supported by Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: Facts and numbers. J Cachexia Sarcopenia Muscle 2010;1:1–5.
[2] Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: A new definition. Clin Nutr 2008;27:793–9.
[3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95.
[4] Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell

lung cancer: A contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr 2010;91:1133S–7S.
[5] Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31:1539–47.
[6] Parsons HA, Baracos VE, Dhillon N, Hong DS, Kurzrock R. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. PLoS One 2012;7:e29330.
[7] Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: Do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr [Internet]. [cited 2013 Aug 21]. Available from: http://ajcn.nutrition.org/content/98/4/1012.full.pdf.
[8] Antoun S, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. Curr Opin Support Palliat Care 2013;7:383–9.
[9] Baracos V, Caserotti P, Earthman CP, Fields D, Gallagher D, Hall KD, et al. Advances in the science and application of body composition measurement. J Parenter Enteral Nutr 2012;36:96–107.
[10] Murphy RA, Mourtzakis M, Chu QS, Reiman T, Mazurak VC. Skeletal muscle depletion is associated with reduced plasma (n-3) fatty acids in non-small cell lung cancer patients. J Nutr 2010;140:1602–6.
[11] Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: A pilot study. J Pain Symptom Manage 2012;44:181–91.
[12] Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, et al. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: The relationship with diabetes and anaemia. Br J Nutr 2013;109 :302–12.
[13] Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15:6973–9.
[14] Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: Contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr 2009;89:1173–9.
[15] Scott HR, McMillan DC, Forrest LM, Brown DJ, McArdle CS, Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer 2002;87:264–7.
[16] Mannion E, Gilmartin JJ, Donnellan P, Keane M, Waldron D. Effect of chemotherapy on quality of life in patients with non-small cell lung cancer. Support Care Cancer 2014;22:1417–28.
[17] Gronberg BH, Sørhaug S, Hjelde HH, Stene GB, Amundsen T, editor. Variation in health-related quality of life (HRQoL) during chemotherapy for advanced non-small cell lung cancer. 2013 ASCO Annual Meeting; 2013; Chicago, Illinois, USA. J Clin Oncol 2013;31(Suppl; abstr 9562).
[18] Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care 2009;3:269–75.
[19] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997–1006.
[20] Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8.
[21] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. Lancet Oncol 2008;9:629–35.
[22] Sobin LHG, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, 7th ed. Wiley-Blackwell; Oxford. 2009.
[23] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[24] Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
[25] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[26] Gronberg BH, Sundstrom S, Kaasa S, Bremnes RM, Flotten O, Amundsen T, et al. Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy. Eur J Cancer 2010;46:2225–34.
[27] Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002;20:4285–91.

Paper IV

ELSEVIER

Critical Reviews in Oncology/Hematology 88 (2013) 573–593

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Effect of physical exercise on muscle mass and strength in cancer patients during treatment—A systematic review

G.B. Stene [a,b,e,*], J.L. Helbostad [b,c], T.R. Balstad [a,d], I.I. Riphagen [d], S. Kaasa [a,e], L.M. Oldervoll [f,g]

[a] *European Palliative Care Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway*
[b] *Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway*
[c] *Clinic for Clinical Services, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway*
[d] *Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway*
[e] *Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway*
[f] *Centre for Health Promotion HiST/NTNU, Department of Social Work and Health Science, Faculty of Social Sciences and Technology Management, Norwegian University of Science and Technology (NTNU), Trondheim, Norway*
[g] *Røros Rehabilitation, LHL Health, Røros, Norway*

Accepted 4 July 2013

Contents

* Corresponding author at: European Palliative Care Research Centre (PRC), Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Bevegelsessenteret, 4th Floor East, St. Olavs Hospital, N-7006 Trondheim, Norway. Tel.: +47 72571574/48226799.
E-mail address: guro.b.stene@ntnu.no (G.B. Stene).

1040-8428/$ – see front matter
http://dx.doi.org/10.1016/j.critrevonc.2013.07.001

Abstract

Cancer treatment and its side effects may cause muscle wasting. Physical exercise has the potential to increase muscle mass and strength and to improve physical function in cancer patients undergoing treatment. A systematic review was conducted to study the effect of physical exercise (aerobic, resistance or a combination of both) on muscle mass and strength in cancer patients with different type and stage of cancer disease. Electronic searches were performed up to January 11th 2012, identifying 16 randomised controlled trials for final data synthesis. The studies demonstrated that aerobic and resistance exercise improves upper and lower body muscle strength more than usual care. Few studies have assessed the effect of exercise on muscle mass. Most studies were performed in patients with early stage breast or prostate cancer. Evidence on the effect of physical exercise on muscle strength and mass in cancer patients with advanced disease is lacking. More exercise studies in patients with advanced cancer and at risk of cancer cachexia are warranted.

Keywords: Physical exercise; Cancer; Muscle mass; Muscle strength; Cachexia

1. Introduction

Cancer patients are faced with a range of disease- and treatment-related effects that might alter metabolism, food intake and body composition and cause significant physical and psychosocial impairment. Physical exercise has in general a positive impact on many biological processes such as energy expenditure, insulin resistance, inflammation and most body organs and tissues. In cancer patients, there is evidence that physical exercise contributes to reduce fatigue [1], improves quality of life [2,3] and relieves many of the adverse side-effects experienced both during and after treatment [4,5].

Physical exercise is defined as an activity that is planned, structured, repetitive and purposeful, with the aim to improve or maintain one or more components of physical fitness, i.e. endurance, muscular strength and body composition [6]. According to national and international physical activity recommendations, 150 min of weekly moderate intensity aerobic exercise, or alternatively 75 min of high-intensity exercise, are required to promote and maintain health in adults. Additionally, muscle-strengthening exercise is recommended to be performed twice weekly [7].

In principle, the same activity recommendations apply to patients with cancer [8]. However, a range of factors beyond those usually encountered when providing exercise advice in healthy populations must be considered, especially in patients who are undergoing cancer treatment or experience adverse side-effects of treatment [9,10]. Physical exercise is considered to be well-tolerated, feasible and safe during and following cancer treatment [5,11] and even cancer patients with advanced stages of disease are willing to engage in physical exercise [12]. Thus, based on current knowledge, it is considered clinically sound to advise most cancer patient to perform physical exercise.

Cancer cachexia is "a multifactorial condition characterised by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" [13]. As much as 60–80% of patients with advanced cancer, depending on diagnosis, develop this condition and at present there are few efficient therapeutic options [14]. Loss of muscle mass and strength is one of several factors that is associated with involuntary weight loss in cancer cachexia [15]. Physical exercise may be of particular importance for cancer patients with advanced disease in a pre-cachectic or cachectic stage because of its potential effects on muscle mass and strength [16]. Experimental trials have demonstrated possible anti-inflammatory effects of exercise in cachectic mice [17] as well as partial rescue of muscle mass and strength in tumour-bearing mice when exercise was combined with eicosapentiaenoic acid [18]. Furthermore, a small number of clinical studies have demonstrated the contribution of exercise to reduce or delay cachexia in patients with chronic diseases other than cancer [19,20]. Previous reviews on effects of physical exercise in patients with cachexia have been narrative and not specific to cancer patients [21,22], or have mainly discussed biological and pathophysiological effects of exercise on cachexia-related muscle wasting [23,24].

Primarily, our idea for a systematic review was to examine the scientific evidence of effects of physical exercise on muscle mass and strength in cancer patients in a pre-cachectic or cachectic stage. Our first systematic search, per January 2012, did not identity controlled studies to answer this question, and therefore we re-defined our aims to include a wider group of cancer patients. We consider it appropriate to guide further clinical studies in patients with advanced cancer by extrapolating data from general cancer.

The overall aim of this systematic review was to evaluate the scientific evidence of effect of physical exercise on muscle mass and strength in patients with cancer. The following research questions were formulated:

1. What type of physical exercise intervention, i.e. aerobic, resistance or combined aerobic and resistance exercise, is most effective at improving muscle mass and strength?
2. Is the effect on muscle mass and strength consistent between different cancer patient cohorts with different diagnoses and stage of disease?

2. Methods

2.1. Search strategy and selection criteria

Electronic searches were performed on January 11th 2012 in PubMed (National Library of Medicine), Pedro (Centre for Evidence-Based Physiotherapy), Embase (Elsevier through OvidSP, edition 1980–2012, week 1) and Cochrane Central Registry of Controlled Trials (CENTRAL) through the Cochrane Library (John Wiley and Sons Ltd.), edition 2011 October, issue 4 of 4. Additionally, the bibliographies of included studies and relevant systematic reviews were reviewed.

The searches consisted of combinations of controlled terminology and free-text terms expressing the concepts; (1) physical exercise, (2) cancer and (3) muscle mass and strength (including terms such as cachexia, anorexia, malnutrition, wasting, and asthenia), and were adapted to each database (PubMed search details in Table 1).

To be eligible for inclusion, studies must have (1) a randomised controlled trial design, (2) include patients aged 18 years or more with a confirmed cancer diagnosis and who were about to start or undergoing active cancer treatment at trial entry, (3) physical exercise had to be repetitive (more than once), consist of aerobic[1] or strength exercise[2] or a combination of both, and be delivered either as a single intervention or as part of a multimodal approach and finally (4) published in a peer reviewed journals and written in English language.

2.2. Trial selection and data extraction

All identified records were screened for duplicates and irrelevant titles by the first author (GBS) and one of the co-authors (IIR). Remaining abstracts were screened by two reviewers (GBS, LMO) and subsequently full-text papers were reviewed independently in pairs of reviewers (GBS, LMO, TRB, JLH). In both instances, cases of disagreement about eligibility between two reviewers warranted a third reviewer's opinion.

Eligible studies were then submitted to data extraction using a custom made pre-piloted electronic form using a Microsoft Office Excel 2010 software spread sheet. Data on study design, participants, interventions, outcome measures, results and conclusions were extracted independently by two reviewers. Disagreements on final inclusion and exclusion were resolved by consensus by two of the authors (GBS, LMO).

[1] The use of oxygen is adequate to meet energy demands during exercise via aerobic metabolism, e.g. low or moderate intensity running, cycling, etc.

[2] The use of resistance against gravity or elastic tension to muscular contraction in order to build the strength, anaerobic endurance and size of muscles.

2.3. Assessment of study limitations

All included studies were subject to an assessment of study quality performed independently by two reviewers. The assessment was based on the criteria for "risk of bias" within the GRADE system for rating quality of evidence [25]. These criteria are: randomisation procedures, allocation concealment, blinding, power-estimation, loss to follow-up, intention-to-treat analysis and selective end-point reporting. Study limitations for each trial were summarised in a table and described in the text.

2.4. Data synthesis

In the included trials treatment effects for each of the two or more groups are presented as differences in change between the groups. In order to compare effects across studies and outcomes (muscle strength and muscle mass) effect sizes were calculated according to Cohen's method [26]. Standardised mean difference (SMD) was calculated based on descriptive data (mean and standard deviation) at post-intervention and sample sizes for each trial. The formula for SMD is: mean values for experimental group minus mean values for control group divided by the pooled[3] standard deviation [27]. The SMD and the 95% confidence intervals are presented in the text. According to Cohen's "rule of thumb" a SMD of 0.2–0.5 is considered small to moderate, 0.51–0.8 moderate to large and greater than 0.8 large [26].

3. Results

3.1. Search results and selection of studies

The database searches retrieved 1321 records which were reduced to 405 after removal of duplicates and exclusion of irrelevant records by title. After screening of abstracts, 76 records were found to meet the inclusion criteria. Furthermore, nine records were identified by manual searches, giving 85 full text publications to be screened for eligibility. Out of these, 67 papers did not meet the selection criteria and were excluded. Thus, data extraction was performed on 18 papers. Two of the papers were publications based on the same study and were excluded [28,29], leaving 16 trials for final synthesis. Fig. 1 shows the outcome of the search process and selection of studies.

Ten trials compared one physical exercise regime against usual care (UC). Of these, three trials used aerobic exercise (AE) alone [30–32], while seven trials used AE and resistance exercise (RE) in a combined intervention (CAE) [33–39]. Four trials compared AE or RE against UC [40,41,42,43]. One trial compared two different RE interventions (three

[3] Pooled standard deviation is calculated using the formula: square root of SD for experimental group^2 + SD of control group^2 divided by 2.

Table 1
Search strategy in PubMed.

#8	#7 AND English [la]
#7	(#1 OR #2) AND #3 AND #4 NOT (#5 OR #6)
#6	Child[ti] OR children[ti] OR paediatric[ti] OR paediatric[ti] OR ((child[mesh] OR infant[mesh] OR adolescent[mesh]) NOT adult[mesh])
#5	case reports[pt] OR case study[ti] OR case report[ti] OR comment[pt] OR letter[pt] OR news[pt]
#4	"Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh:noexp] OR exercise[tiab] OR exercises[tiab] OR Gymnastics[mesh] OR gymnastics[tiab] OR "Hydrotherapy"[Mesh:noexp] OR hydrotherapy[tiab] OR "physical activity"[tiab] OR pilates[tiab] OR "Swimming"[Mesh] OR swimming[tiab] OR training[tiab] OR Walking[mesh] OR walking[tiab]
#3	Neoplasms [MeSH] OR cancer[tiab] OR "Palliative Care"[Mesh] OR palliative[tiab] OR palliation[tiab]
#2	("Muscle Strength"[Mesh:noexp] OR "muscle strength"[tiab] OR "muscular strength"[tiab] OR "muscular endurance"[tiab] OR "muscle mass" [tiab] OR "muscle function"[tiab] OR "muscle functions"[tiab] OR "Physical endurance" [tw] OR "muscle capacity"[tiab] OR "muscle force"[tiab] OR ((muscle[tw] OR muscles[tw] OR muscular[tw]) AND ("body composition"[tw] OR anabolic[tiab] OR strengthening[tiab]))) AND ("Quality of Life" [Mesh] OR "quality of life" [tiab] OR Fatigue[Mesh] OR fatigue[tiab] OR catabolism[tiab] OR deterioration[tiab] OR deteriorated[tiab] OR depletion[tiab] OR decline[tiab] OR reduced[tiab] OR reduction[tiab] OR reductions[tiab] OR loss[tiab] OR decrease[tiab] OR decreasing[tiab])
#1	Anorexia[mesh] OR anorexia[tiab] OR anorectic[tiab] OR Asthenia[mesh] OR asthenia[tiab] OR asthenic[tiab] OR cachexia[tiab] OR cachectic[tiab] OR Emaciation[MeSH] OR emaciation[tiab] OR emaciated[tiab] OR Malnutrition [Mesh] OR malnutrition[tiab] OR "muscle wasting"[tiab] OR "muscular wasting"[tiab] OR "Muscle Weakness"[Mesh] OR "muscle weakness"[tiab] OR "muscular weakness"[tiab] OR "Muscular atrophy" [MeSH] OR "muscle atrophy" [tiab] OR "muscular atrophy" [tiab] OR "Muscle, Skeletal/physiopathology"[Mesh:noexp] OR "Muscle, Skeletal/pathology"[Mesh:noexp] OR "Muscle, Skeletal/physiology"[Mesh:noexp] OR Muscles/pathology[Mesh:noexp] OR Muscles/physiopathology[Mesh:noexp] OR Muscles/physiology[Mesh:noexp] OR sarcopenia[tiab] OR "Wasting syndrome" [MeSH:noexp] OR "wasting syndrome" [tiab]

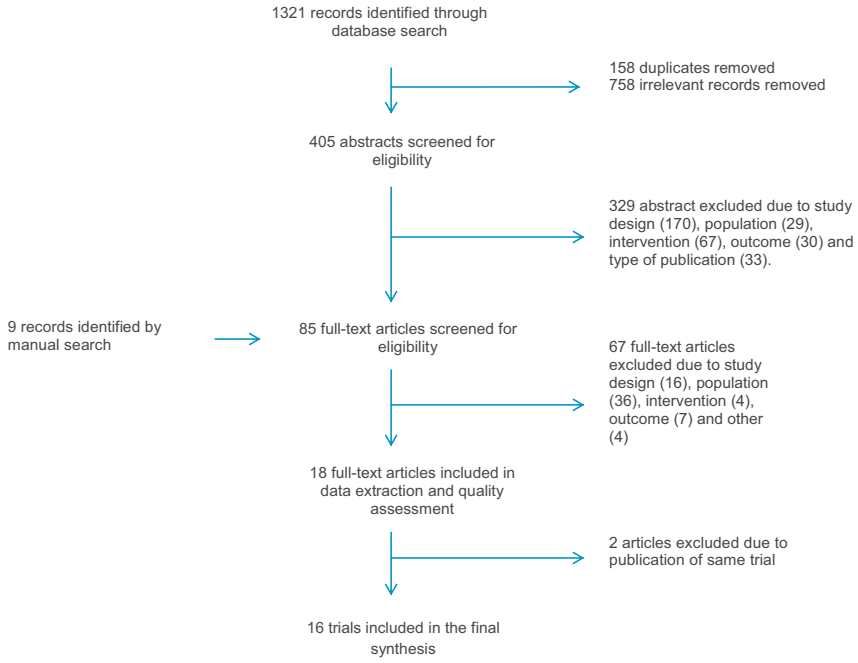


Fig. 1. Flow chart over literature selection and reason for exclusion.

or five days per week) against usual care [44]. One trial compared RE alone or RE together with a low fat vegetable diet (RE-LFVD) against UC. All groups in this trial were on a calcium-rich diet [45]. Details of the content of the physical exercise programmes are provided in Table 2.

3.2. Study limitations (risk of bias)

The quality assessment of the included trials is provided in Table 5.

Nine trials described methods used for random allocation. Six trials used concealed allocation [34–37,40,43,44]. The

Table 2
Description of type and content of physical exercise in the included studies.

Study	Delivery	Duration and frequency	Resistance exercise			Aerobic exercise			Additional exercise
			Mode of exercise	Dose: number of reps × sets	Intensity % of 1RM	Mode of exercise	Dose: Minutes per session	Intensity % o HR_{max}	Type
Adamsen et al. [33]	Combined AE and RE exercise, supervised, group in hospital	6 weeks–3 days per week	Exercise performed on stationary machines incl. leg press, chest press, pull down	5–8 × 3	85–95	Interval training on stationary bikes	15	60–100	Relaxation, body awareness, massage
Battaglini et al. [34]	Combined AE and RE exercise, supervised, group in hospital	15 weeks–2 days per week	8–12 exercises for large muscle groups performed on stationary machines or using dumb bells, elastic bands, therapeutic balls	6–12 × 2–3	40–60	Treadmill/ergometer cycle	6–12	40–60	Flexibility exercises
Baumann et al. [30]	Aerobic exercise, individually supervised in hospital	8 weeks–7 days per week	None			Cycle ergometer	10–20	80	Activities of daily living training
Coleman et al. [35]	Combined AE and RE, self-directed, in the patients home	26 weeks–(frequency not reported)	Exercise stretch bands with variable resistance for LL (chair stand, knee flexion/extension) and UL (biceps/triceps extension, upright row)	8 × 1–2	15–17 (RPE)	Fast speed walking (if relevant running or cycling)	18	12–15 (RPE)	Stretching
Courneya et al. [40]	Two exercise groups, either RE or AE, supervised, group in hospital	17 weeks–3 days per week	9 exercises for major muscle groups I whole body	8–12 × 2	60–70	Ergometer cycle, treadmill or elliptical trainer	15–20	60–80	None
Cunningham et al. [44]	Resistance exercise, individual supervised in hospital	4 weeks, two groups either 5 days or 3 days per week,	Exercises for whole body	15 reps (sets not reported)	Not reported	None			None
Demark-wahnefried et al. [45]	Resistance exercise, self-directed in the patients home	26 weeks–3 days per week	7 exercises using body weight resistance, elastic bands, ankle weights	Not reported	Not reported	None			Calcium rich diet with or without low fat vegetable diet
Jarden et al. [36]	Combined AE and RE exercise, supervised, group in hospital	4–6 weeks–5 days per week	Exercise for major muscle groups using free hand and ankle weights	10–12 × 1–2	Not reported	Stationary cycling	15–30	50–75	Relaxation + psycho-education
Mello et al. [31]	Aerobic exercise, individually supervised in hospital	6 weeks, 7 days per week	None			Treadmill walking	15–20	70	Flexibility exercises

Table 2 (*Continued*)

Study	Delivery	Duration and frequency	Resistance exercise			Aerobic exercise			Additional exercise
			Mode of exercise	Dose: number of reps × sets	Intensity % of 1RM	Mode of exercise	Dose: Minutes per session	Intensity % o HR_{max}	Type
Monga et al. [32]	Aerobic exercise, individual supervised in hospital	8 weeks–3 days per week	None			Treadmill walking	30	Not reported	None
Mustian et al. [37]	Combined AE and RE, self-directed in the patient home	4 weeks, 7 days per week	11 exercises for upper body using elastic bands	8–15 to 4–15 × 1	Not reported	Individually tailored walking	Not reported	60–70	None
Oldervoll et al. [38]	Combined exercise, supervised, group in hospital	8 weeks, 2 days per week	Circuit training (strength exercises for whole body)	Not reported	Not reported	Circuit training (stepping, stationary cycling)	30	Not reported	Stretching, relaxation
Schwartz et al. [42]	Two exercise groups, either RE or AE, self-directed in the patient home	26 weeks, 4 days per week	8 exercises for upper and lower body using resistance bands	8–10 × 2	Not reported	Activity of own choice (walking, jogging etc.)	15–30	Moderate	None
Schwartz et al. [41]	Two exercise groups, either RE or AE, self-directed in the patient home	52 weeks, 4 days per week	3–4 exercises for upper and lower body using resistance bands and free weights	12 × 3 or 18–20 × 2	Not reported	Activity of own choice (walking, jogging, dancing, etc.)	20–30	Moderate	None
Segal et al. [43]	Two exercise groups, either RE or AE, supervised, group in hospital	24 weeks, 3 days per week	10 exercises for major muscle groups in whole body	8–12 × 2	60–70	Cycle ergometer, treadmill or elliptical trainer	15–45	70–75	None
Wiskemann et al. [39]	Combined AE and RE, individually supervised (in hospital) and self-directed home (after discharge from hospital)	16 weeks, 5 days per week	3 exercise regimes; extremities only, whole body or bed bound with or without use of resistance bands	8–20 × 2–3	14–16(RPE)	Brisk walking, bicycling, treadmill walking, Nordic walking, jogging	20–40	12–14 (RPE)	None

Abbreviations: AE, aerobic exercise; RE, resistance exercise; UL, upper limb; LL, lower limb; RPE, rate of perceived exertion; max HR, maximal heart rate; 1RM, one repetition maximum.

majority of trials had small sample sizes; eight trials had less than 50 participants [30–32,34–37,44]. Four trials were feasibility trials [30,35,37,45].

Overall, the most frequent study limitation was lack of blinding of assessors. In only two trials blinding was applied [37,43]. Six trials had drop-out rates above >20% [30,31,35,38,39,44]. In case of three of these trials, it was not reported how missing data were dealt with [31,35,44]. Nine of the trials reported data analysis by using intention-to-treat principles [30,33,35–39,41,43].

The majority of trials described one primary outcome, which was muscle mass or muscle strength in only two trials [31,34].

3.3. Outcome measurements

Six trials used muscle mass as an outcome. Two trials measured muscle mass as Lean body Mass (LBM) using a Skinfold Calliper, in which one expressed LBM in percentage [34] and the other as arm muscle area (mm^2) [44]. Two trials measured LBM, expressed as kilograms, using Dual X-ray Absorptiometry [40,45]. One trial measured LBM in kilograms by using Air Displacement Plethysmography [35]. Finally, one trial measured skeletal muscle mass (kg) using Bioelectrical Impedance Analysis [37].

Fourteen trials had muscle strength as an outcome. Estimations of one repetition maximum (1RM) for upper and lower body strength were most frequently used [33–36,40–43]. Chest press (involving major muscles of the chest, shoulders and triceps), seated row (involving the Lattisimus Dorsi and the Rhomboid muscles, predominantly) and leg extension (involving all major leg muscle groups such as Quadriceps, Hamstrings and Gluteus maximum), were most commonly used. Maximum isometric strength was measured in four trials [30,31,36,39], grip strength by dynamometry in two trials [37,38], and a functional test to assess leg strength in one trial [32]. Except for the functional strength test (sit-to-stand measured in seconds), all trials reported muscle strength in kilograms or Newton (1 kg equals 9.81 N).

3.4. Effects on muscle mass

Detailed results on muscle mass are presented in Table 3. Two trials reported better effect on muscle mass for patients randomised to CAE compared with UC. In Battaglini and colleagues [34], the CAE group (exercise three days per week for six weeks) had an increase in mean lean body mass (LBM) compared to patients in the UC group (3.1% ↑ versus 0.2% ↓; $p = 0.004$). In Coleman and colleagues [35], the CAE group (exercise two days per week for eight weeks) had an increase in mean LBM while the UC group lost LBM (0.4% ↑ versus 0.4% ↓; $p < 0.01$).

In a study by Courneya and colleagues [40], both AE and RE groups exercised three days per week for 17 weeks. Patients in the RE group demonstrated significantly better effect on LBM than patients in the AE group (1.0 kg ↑ versus 0.5 kg ↑; $p = 0.004$) and UC (1.0 kg ↑ versus 0.2 kg ↓; $p = 0.015$). No statistically significant differences in change in LBM between AE and UC were found.

No effects were reported in the trials by Cunningham and colleagues [44], comparing two RE groups exercising three or five days per week with UC, the study by Mustian and colleagues [37] comparing a CAE group exercising seven days a week for four weeks with UC, or in the trial by Demark-Wahnefried and colleagues [45]. In the Denmark-Wahnefried trial, patients were allocated either to RE five days a week for 26 weeks, RE five days a week for 26 weeks + LFVD or UC (no RE or LFVD). All three-study groups were on a calcium-rich diet.

Effect sizes could be calculated for two studies using Dual Energy X-ray Analysis (DEXA) as outcome measure for muscle mass. In the study by Courneya and colleagues [40] the post-treatment effect on muscle mass was better for RE than UC however the effect was small (SMD = 0.22; CI −0.1 to 0.6). There was no additional effect of AE compared with UC. In the study by Demark-Wahnefried et al. [45], effect on muscle mass at post-treatment were better in the UC group (no RE or LFVD) compared with both RE groups; RE only (SMD = 0. 27; CI −2.9 to 2.2) and RE–LFVD (SMD = 0.36; CI −2.8 to 2.3).

3.5. Effect on muscle strength

Details on results on muscle strength are provided in Table 4. Four trials reported statistically significant differences in change between groups on muscle strength for CAE compared with usual care (UC): these studies included Jarden and colleagues [36] (five days per week for 4–6 weeks) for 1RM chest press (2.6 kg ↑ versus 8.7 kg ↓; $p < 0.001$) and 1RM leg extension (3 kg ↑ versus 17.2 kg ↓; $p = 0.0003$); Adamsen and colleagues (3 days per week for six weeks) for chest press (7.3 kg ↑ versus 0.5 kg ↓; $p < 0.0001$), pull down (7.6 kg ↑ versus 0.8 kg ↑; $p < 0.0001$) and leg press (31.6 kg ↑ versus 2.8 kg ↑); Battaglini and colleagues for total upper and body muscle strength (2.4 kg ↑ versus 12.6 kg ↓; $p < 0.05$), and Oldervoll and colleagues for grip strength (1.1 kg ↑ versus 1.3 kg ↓; $p < 0.05$). No statistically significant group differences in change in muscle strength were reported by Mustian and colleagues [37]; Coleman and colleagues [35] and Wiskemann and colleagues [39].

Three trials reported that RE was better than UC in improving muscle strength. In Courneya and colleagues [40], patients in the RE group exercised three days per week for 17 weeks (chest press: 3.3 kg ↑ versus 1.5 kg ↑; $p < 0.001$ and leg press: 8.2 kg ↑ versus 1.4 kg ↑; $p = 0.001$). In a trial by Segal and colleagues [43], patients in the RE group exercised three days a week for 24 weeks (chest press: 10.9 kg ↑ versus 2.5 kg ↓; $p < 0.001$ and leg press 25.6 kg ↑ versus 0.4 kg ↑; $p < 0.001$). In the two trials by Schwartz et al. [41,42], better effects for RE than UC was only reported in the most recent study [41] for 1RM overhead press (1.3 kg ↑ versus 0.9 kg ↓; $p < 0.05$), seated row (31.7 kg ↑ versus 1.4 kg ↓;

Table 3
Results from studies on the outcome muscle mass.

Studies	Study population characteristics	Design/intervention	Data collection points	Outcomes	Results
Battaglini et al. [34] USA	20 patients, mean age 56.6 years, with breast cancer post-surgery and starting chemotherapy	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (no exercise)	1. Post-surgery (week 4) 2. End of intervention (week 21)	Relative lean body mass (%) measured by Lange Skinfold Calliper	Experimental group increased muscle mass by 3.1% ($\Delta 7.1 \pm 3.4$–74.1 ± 2.9) compared to control who reduced by 0.2% ($\Delta 69.1 \pm 4.2$–68.9 ± 4.1). The change within groups (time effect) was not statistically significant for either group ($p = 0.82$) Interaction effect between groups were statistically significant at end of intervention ($p = 0.004$)
Coleman et al. [35] USA	24 patients, mean age 55 years, with multiple myeloma undergoing a tandem HSCT and conditioning chemotherapy/total body irradiation Half of the patients (in both groups) were given Thalidomide (anti-nausea and sedative drug)	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (encouragement to remain active and walk 20 min at least 3 times per week)	1. Before transplant (week 1) 2. After transplant (week 12)	Lean body mass (kg), measured by Air Displacement Plethysmography[a]	Experimental group increased muscle mass by 0.4 kg per month compared to control who reduced by 0.44 kg per month. Average difference of 0.84 kg per month between groups (rate of change in muscle mass) was statistically different ($p < 0.01$)
Courneya et al. [40] Canada	242 patients, mean age 49.2 years, breast cancer stage I–IIIA, beginning adjuvant chemotherapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: – Usual care (no exercise)	1. Before chemotherapy (week 0) 2. After chemotherapy (week 17 ± 4 weeks)	Total LBM (kg) measured by Dual X-ray Absorptiometry (DEXA)	Exp. group (resistance) had a larger increase in muscle mass – 1.0 kg ($\Delta 40.3 \pm 4.6$–41.3 ± 4.9) compared to exp. group (aerobic) who increased by 0.5 kg ($\Delta 40.3 \pm 4.8$–40.9 ± 5.1). The control group reduced muscle mass by 0.2 kg ($\Delta 40.8 \pm 5.3$–40.9 ± 5.6) Muscle mass was superior in the exp. group (resistance) compared to control group ($p = 0.015$).
Cunningham et al. [44] USA	30 patients, mean age 26 years, with acute leukaemia undergoing allogeneic HSCT and high dose chemotherapy/total body irradiation	Experimental group: a. Resistance exercise 3 days per week b. Resistance exercise 5 days per week Control group: – Usual care (no exercise)	1. Day of transplant (baseline) 2. 35th day after transplant (post-test)	Arm muscle area (mm^2) measured by Lange Skinfold Calliper[b]	Exp. group (resistance ex. 5 days per week) increased muscle mass more ($\Delta 4.0\%$) than the exp. groups (resistance ex. 3 days per week)–1.5% increase Control group reduced muscle mass by 5.7%. No statistically significant change within groups over time There were no statistically significant differences in change in muscle mass between groups

Table 3 (*Continued*)

Studies	Study population characteristics	Design/intervention	Data collection points	Outcomes	Results
Demark-wahnefried et al. [45] USA	90 patients, mean age 42 years, with breast cancer stage I-IIIA undergoing adjuvant chemotherapy/radiotherapy + hormone therapy	Experimental group: a. Resistance + calcium rich diet b. Resistance + Low Fat Diet + Calcium rich diet Control group: – Calcium rich diet	1. Baseline 2. 6 months	Total lean body mass (kg) measured by Dual X-ray Absorptiometry (DEXA)	Control group (CA only) increased muscle mass by 0.7 kg (Δ42.5 ± 6.6–43.2 ± 7.4) compared to both experimental groups who reduced muscle mass: R + CA reduced by 0.4 kg (Δ41.1 ± 7.1–40.6 ± 7.1) and R+ LFVD + CA reduced by 0.3 kg (Δ41.6 ± 5.6–41.3 ± 7.0) No statistically significant differences over time within groups
Mustian et al. [37]	38 patients, mean age 60 years, with breast cancer (71%) and prostate cancer (29%) undergoing radiotherapy	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (no exercise)	1. Baseline 2. Post-intervention (week 4)	Skeletal muscle mass (kg) measured by Bioelectrical Impedance Analysis	Experimental group (combined AE and RE) Increased muscle mass by 0.06 kg (Δ24.5 ± 8.8–25.5 ± 9.0, while control group reduced by 0.2 kg (Δ23.6 ± 5.6–23.4 ± 5.4) No statistically significant differences in muscle mass between groups at post-treatment

[a] Reported as change baseline – post-transplant/number of months participated in study.
[b] Change reported as percent of admission values (median (range)).

$p < 0.05$) and for leg extension (21.1 kg ↑ versus 1.8 kg ↑; $p < 0.05$).

Better effects of AE than UC on muscle strength was reported in five studies; Baumann and colleagues [30] for mean isometric quadriceps muscle strength (10% ↓ versus 24% ↓; $p = 0.002$); Monga and colleagues [32] for time to complete a five repetition sit to stand test (1.3 s ↓ versus 0.4 s ↑; $p < 0.001$); Segal and colleagues [43] for 8RM chest press (1.3 kg ↑ versus 2.5 kg ↓; $p = 0.006$); Schwartz and colleagues [42] for 1RM seated row (1.5 kg ↑ versus 0.1 kg ↓; $p = 0.02$) and 1RM leg extension (14.6 kg ↑ versus 4.6 kg ↑; $p = 0.001$). A more recent trial by Schwartz and colleagues from 2009 [41] confirmed previous findings for 1RM overhead press (4.2 kg ↑ versus 0.9 kg ↓; $p < 0.05$); 1RM seated row (7.7 kg ↑ versus 1.4 kg ↓; $p < 0.05$) and 1RM leg extension (33.6 kg ↑ versus 1.8 kg ↑; $p < 0.05$).). No statistically significant differences between AE and UC in change in muscle strength were reported by Mello and colleagues [31].

The effect sizes calculated for seven trials with comparable outcomes for upper and lower body muscle strength are illustrated in Fig. 2. For AE, moderate to large effect sizes were found in the two trials by Schwartz and colleagues [41,42] for overhead press (SMD 0.7; CI −0.8 to 12.2 and SMD 0.5; CI 0.0–1.0); seated row (SMD 0.8; CI 0.3–1.5 and SMD 0.8; CI 0.3–1.3) and leg extension (SMD 0.3; CI −0.3 to 8.8 and SMD 1.0; CI 0.6–1.6). Equally, in the same two trials, effect sizes in favour of RE compared to UC were large for seated row (SMD 0.8; CI 0.3–1.8 and 0.9; CI = 0.4 to 0.8) and leg extension (SMD 0.8; CI 0.3–1.2 in Schwartz and Winters-Stone [41] only) but small for overhead press (SMD 0.2; CI −0.4 to 0.8 and 0.2; CI −0.3 to 0.7) leg extension in Schwartz and colleagues [42] (SMD 0.2; CI −0.4 to 0.8).

Effect sizes in favour of AE compared to UC were small in two trials by Courneya and colleagues [40] and Segal and colleagues [43] for the outcomes chest press (SMD 0.0; CI −0.3 to 0.3 and SMD 0.2; CI −0.3 to 0.6) and leg extension (SMD 0.1; CI −0.3 to 0.4 and 0.2; CI −0.3 to 0.6). In comparison, effect sizes were moderate to large in the trials by Courneya and Segal when comparing RE with UC for chest press (SMD 0.8; CI 0.5–1.1 and SMD 0.6; CI 0.1–1.0) and for leg extension (SMD 0.4; CI 0.1–0.7 and SMD 0.3; CI 0.1–0.8).

Effect sizes were moderate to small both for upper and lower body strength in favour of CAE compared with UC in three trials [33,36,39]. Effect sizes were largest in the study by Jarden and colleagues [36] for both leg extension (SMD 1.7; CI −3.5 to 6.9) and chest press (0.8; CI −5.5 to 7.1). More moderate effects were found by Adamsen and colleagues [33] for leg extension (0.5; CI 0.3–0.8) and chest press (0.3; CI 0.1–0.6) and by Wiskemann and colleagues [39] for isometric strength in upper body (SMD 0.2; CI −0.3 to 0.6) and lower body (SMD 0.3; CI −0.1 to 0.8).

For grip strength (not illustrated in Fig. 2) effect sizes were small in favour of CAE versus UC (SMD = 0.23; CI −0.5 to 0.1) [38].

Table 4
Result from studies on the outcome muscle strength.

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Adamsen et al. [33]	269 patients, mean age 47 years, with 21 different diagnoses (solid tumours), mainly breast cancer (44%), bowel cancer (13%) + haematological malignancies (10%) Including both early and advanced stage cancer patients (no formal staging system used to report stage)	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (no exercise)	1. Baseline 2. End of study (week 6)	1RM (kg) leg press, chest press, pull-down	Exp. group: – Leg press increase 31.6 kg ($\Delta 100.8 \pm 30.6$–132.4 ± 42.3) – Chest press increase 7.3 kg ($\Delta(37.9 \pm 15.6$–$45.2 \pm 17.9)$ – Pull down increase 7.6 kg ($\Delta 39.6 \pm 14$–47.2 ± 14.4) Control group: – Leg press increase 2.8 kg ($\Delta 107.6 \pm 33.3$–110.4 ± 36) – Chest press decrease 0.5 kg ($\Delta 40.2 \pm 39.7 \pm 17.2$–$39.7 \pm 17.2$) – Pull down increase by 0.8 kg ($\Delta 42 \pm 16.3$–42.8 ± 16.1) At post-treatment, statistically significant improvements in muscle strength was found in favour of the exp. group versus control group for: – Leg press: mean difference 29.7 (95% CI 23.4–34.9); $p < 0.0001$ – Chest press 7.5 (95% CI 5.6–9.4); $p < 0.0001$ – Pull-down 6.4 (95% CI 4.5–8.3); $p < 0.0001$
Battaglini et al. [34]	20 patients, mean age 56.6 years, with breast cancer post-surgery and starting chemotherapy	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (no exercise)	1. Post-surgery (week 4) 2. End of intervention (week 21)	Predicted RM (kg) by submaximal muscle endurance protocol	Exp. group increase muscle strength by 25.9 kg ($\Delta 269.8 \pm 12.8$–295.6 ± 22.7) Control group reduced by 1.6 kg ($\Delta 262.5 \pm 40.9$–260.9 ± 38.8) At post-treatment, statistically significant improvements in muscle strength was found in favour of the exp. group versus control group ($p = 0.025$)
Baumann et al. [30]	64 patients, mean age 45 years, with mixed haematological malignancies (mainly acute and chronic leukaemia) undergoing autologous/allogeneic HSCT + high dose chemotherapy/TB)	Experimental group: – Aerobic exercise Control group: – Low intensity exercise (passive and active mobilisation, coordination, stretching)	1. Hospital admission (day 0) 2. After discharge (mean duration of hospitalization 41 days)	Maximal isometric strength quadriceps (Newton) measured by Digimax-2000 load cell	Both groups decreased muscle strength; exp. group 10% ($\Delta 439$–395) and control by 24% ($\Delta 448$–342) At post-treatment, there was a statistical significant difference between groups in favour of exp. group ($p = 0.002$)

Table 4 (*Continued*)

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Coleman et al. [35]	24 patients, mean age 55 years, with multiple myeloma undergoing a tandem HSCT and conditioning chemotherapy/total body irradiation Half of the patients (in both groups) were given Thalidomide (anti-nausea and sedative drug),	Experimental group: – Combined aerobic and resistance exercise Control group: – Usual care (encouragement to remain active and walk 20 min at least 3 times per week)	1. Before transplant (week 1) 2. After transplant (week 12)	1RM (Newton) * specification of muscle group not reported	Exp. group Increased muscle strength by 2.4 kg, while control group reduced by 12.6 kg No statistically significant differences between groups at post-test
Courneya et al. [40]	242 patients, mean age 49.2 years, breast cancer stage I-IIIA, beginning adjuvant chemotherapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: – Usual care (no exercise)	1. Before chemotherapy (week 0) 2. After chemotherapy (week 17 ± 4 weeks)	Estimated 1RM by sub-maximal testing: 8RM chest press and leg extension (kg)	All groups increased muscle strength for: Chest press: – Aerobic 2.6 kg (Δ22.1 ± 7.5–24.4 ± 7.5) – Resistance 3.3 kg (Δ23.2 ± 7.2–31.9 ± 10.8) – Control 1.5 kg (Δ22.8 ± 8.9–24.6 ± 7.8) Leg extension: – Aerobic 8.8 kg (Δ24.8 ± 12.5–28.2 ± 14.2) – Resistance 8.2 kg (Δ24.4 ± 11.2–32.8 ± 12 ± 6) – Control 1.4 kg (25.6 ± 12.6–27.1 ± 14.1) At post-test, there was a statistically significant difference between groups in favour of resistance exercise versus control for chest press (mean difference 7.7 kg; $p = 0.001$) and leg extension (mean difference 6.8 kg; $p = 0.001$) There were no statistically significant difference between the groups aerobic and control

Table 4 (*Continued*)

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Jarden et al. [36]	34 patients, mean age 39 years, with mixed haematological malignancies (mainly acute and chronic leukaemia) undergoing allogeneic HSCT + high dose chemotherapy/TBI	Experimental group – Combined aerobic and resistance exercise Control group: – Usual care (offered standard care in terms of physiotherapy)	1. Baseline 2. Post–intervention (week 12)	1RM chest press; leg press (kg) Isometric right elbow and right knee flexion (Newton)	Chest press – Exp. group 2.4% increase ($\Delta 50.6 \pm 21.8$–53.2 ± 22.1) – Control 20.5% decrease ($\Delta 47.1 \pm 16.7$–38.4 ± 14.6); $p < 0.0001$ Leg extension – Exp. group 2.4% increase ($\Delta 63.6 \pm 18$–66.6 ± 17.8) – Control 25.1% decrease ($\Delta 56.6 \pm 19.7$–39.4 ± 12.6); $p = 0.0003$ Elbow flexion: – Exp. group 4.8% increase ($\Delta 2.34 \pm 0.9$–2.49 ± 0.9) – Control 20% decease ($\Delta 2.5 \pm 0.9$–1.9 ± 0.5); $p = 0.0009$ Knee extension – Exp. group 2.2% increase ($\Delta 4.0 \pm 1.5$–4.1 ± 1.6) – Control 20.1% decrease ($\Delta 3.9 \pm 1.5$–3.1 ± 1.2); $p < 0.0001$ Statistical significant differences between groups in change in muscle strength was found in favour of exp. group versus control group for chest press ($p < 0.001$), leg extension ($p = 0.0003$), elbow flexion ($p = 0.0009$) and knee extension ($p < 0.0001$)
Mello et al. [31]	32 patients, mean age 30.2 years with mixed haematological malignancies undergoing allogeneic HSCT + high dose chemotherapy/TBI,	Experimental group: – Aerobic exercise Control group: – No exercise	1. Pre-transplant (week 0) 2. Discharge from hospital (week 6)	Max isometric strength (Newton) measured by strain-gauge dynamometer for dominant and non-dominant muscles in the upper body (shoulder, elbow) and lower body (hip, knee and ankle)	In exp. group, there were no statistically significant changes in upper body muscle strength but for control group, muscle strength was significantly reduced in all muscle groups, except dominant elbow extensors For lower body muscle strength, significant reductions were found for the exp. group in dominant ($p = 0.033$) and non-dominant ($p = 0.0001$) knee flexors The control group significantly reduced lower body muscle strength in knee flexors ($p < 0.01$), ankle flexors ($p < 0.01$) There were statically significant differences between groups at post-test in favour of exp. group versus control group for non-dominant hip-flexors ($p < 0.01$)

Table 4 (*Continued*)

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Monga et al. [32]	30 patients, mean age 68 years with first time diagnosis of localised prostate cancer (stage not reported) undergoing radiotherapy	Experimental group: – Aerobic exercise Control group: – Standard care (no exercise)	1. Pre-radiotherapy (week 0) 2. Post–radiotherapy (week 8)	Time to complete 5 times sit to stand, measured in seconds	Exp. group improved by reducing time to complete test with 1.3 s ($\Delta 12.6 \pm 2.3$–11.3 ± 1.9) while the control used 0.4 s longer time to complete test ($\Delta 10.8 \pm 1.6$–11.3 ± 1.6) At post-test there was a statistically significant difference between groups in change in time to complete test in favour of exp. group versus control of 1.7 s ($p = 0.000$)
Mustian et al. [37]	38 patients, mean age 60 years, with breast cancer (71%) and prostate cancer (29%) undergoing radiotherapy	Experimental group: – Combined aerobic and resistance exercise Control group – No exercise	1. Baseline 2. Post–intervention (week 4)	Grip strength (kg) measured by dynamometry	Both groups reduced muscle strength, in exp. group by 0.5 kg ($\Delta 26.0 \pm 2.1$–25.5 ± 7.3) and control by 0.8 kg ($\Delta 24.9 \pm 7.9$–24.1 ± 8.7) There were no statistically significant differences in muscle strength between groups at post intervention,
Oldervoll et al. [38]	231 patients, mean age 62 years, with advanced incurable stage Iv cancer (stage IV), mainly gastrointestinal tract, breast, lung, urological undergoing palliative chemotherapy/radiotherapy hormone therapy/targeted therapy	Exp, group: – Combined aerobic and resistance exercise Control group: – Usual care (no exercise)	1. Baseline (week 0) 2. End of intervention (week 8)	Grip strength (kg) measured by dynamometry	Exp. group increased grip strength from 26.4 ± 0.9 to 27.5 ± 1.0 while control group reduced from 29.6 ± 0.9 to 28.3 ± 1.0 At post–test, statistically significant between group effects were found in favour of exp. group versus control group (estimated mean difference 2.0; CI 95% 0.4–3.5; $p = 0.01$)

Table 4 (*Continued*)

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Schwartz et al. [42]	66 patients, mean age 50 years, with stage stage I-III breast cancer undergoing adjuvant chemo/radiotherapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: – Usual care (no exercise)	1. Baseline (week 0) 2. End of study (week 26)	1RM (kg) overhead press, seated row, leg extension	Overhead press: – Aerobic increase (Δ12.2 ± 5.9–13.7 ± 6.4) – Resistance increase (Δ9.5 ± 6.9 2–10.8 ± 5.1) – Control reduce (Δ9.6 ± 4.5 2–9.5 ± 4.1) Seated row: – Aerobic increase (Δ32.3 ± 12.1–40.1 ± 13.6) – Resistance increase (Δ32.7 ± 12.5–38.1 ± 8.6) – Control increase (Δ30.5 ± 10.8–30.7 ± 9.1) Leg extension: – Aerobic increase (Δ64 ± 26–78.6 ± 30.5) – Resistance increase (Δ60.4 ± 31.8–75.3 ± 34.5) – Control increase (Δ65.9 ± 27.7–70.5 ± 28.1) There was a statistically significant difference between groups in favour exp. group (aerobic) versus control for overhead press ($p = 0.02$) and leg extension ($p = 0.01$) No statistically significant differences between exp. groups (resistance) versus control group were found
Schwartz et al. [41]	101patients, mean age 48 years, mainly stage I-III breast cancer (76%) and colon (13%), lymphoma (11%) undergoing chemotherapy + steroids	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: – Usual care (no exercise)	1. Baseline 2. End of intervention (week 52)	1RM (kg) overhead press, seated row, leg extension	Overhead press: – Aerobic increase (Δ24.9 ± 13.6–29.1 ± 13.7) – Resistance increase (Δ24.1 ± 13.6–25.4 ± 13.6) – Control reduce (Δ22.7 ± 9.9–23.6 ± 10.4) Seated row: – Aerobic increase (Δ35.8 ± 14.9–43.5 ± 12.7) – Resistance increase (Δ36.7 ± 15.8–44.9 ± 13.2) – Control reduce (Δ33.6 ± 17.1–32.2 ± 15.8) Leg extension: – Aerobic increase (Δ74.4 ± 32.2–108.0 ± 29.5) – Resistance increase (Δ74.8 ± 34.8–98.9 ± 30.8) – Control reduce (Δ73.9 ± 35.8–76.2 ± 29.5) Statistical significant between group differences in favour of both exp. groups (aerobic and resistance) versus control were found for all muscle strength outcomes ($p < 0.05$)

Table 4 (*Continued*)

Studies	Study population characteristics	Study design/intervention	Data collection points	Outcomes	Results
Segal et al. [43]	121 patients, mean age 66 years, with stage I-III prostate cancer undergoing radiotherapy with or without androgen suppression therapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: – Usual care (no exercise)	1. Baseline (week 0) 2. Post-test (week 24)	Estimated 1RM by sub-maximal testing: 8RM chest press and leg extension (kg)	Chest press: – Aerobic 1.3 kg increase (Δ53.4 ± 12.1–54.9 ± 13) – Resistance 10.9 kg increase (Δ49.5 ± 11.1–60.8 ± 14) – Control 2.5 kg decrease (Δ55.2 ± 13.3–52.9 ± 14.6) Leg extension: – Aerobic 4.4 kg increase (Δ126.6 ± 55.8–128 ± 60.9) – Resistance 25.6 kg increase (Δ104.6 ± 37.7–134.1 ± 41.6) – Control 0.4 kg increase (Δ117.3 ± 53.5–119.2 ± 55.9) Statistically significant differences in muscle strength between groups were found in favour of: – Exp. group (resistance) versus control group for chest press (mean difference 13.7 kg; $p < 0.001$) and leg extension (mean difference 25.1 kg; $p < 0.001$) – Exp. group (aerobic) versus control for chest press (mean difference 4 kg; $p < 0.006$)
Wiskemann et al. [39]	105 patients, mean age 49 years, with mixed haematological malignancies (mainly acute and chronic leukaemia) undergoing allogeneic HSCT + high dose chemotherapy/TBI	Experimental group: – Combined aerobic and resistance exercise Control group: – No exercise, but not discouraged to be physically active	1. Pre-transplant 2. End of intervention (6–8 weeks after discharge)	Isometric upper and lower body strength (kg)	Muscle strength was reduced in both exp. group (upper body Δ155.5 ± 50.6–132.3 ± 36.8 and lower body Δ192.2 ± 65.9–167.8 ± 49.5) and in the control group (upper body Δ154.5 ± 51 to124.9 ± 46.2 and lower body Δ188.7 ± 61.9–149.3 ± 58.7), but no statistically different changes in muscle strength over time was found for either group, Between-group comparison was not reported

Based on sum score for all tests: leg extension, seated leg curl, lateral pull down, seated chest press.
Results: numbers are mean difference, and in brackets, pre- and post intervention values (mean ± SD).

Table 5
Assessment of study limitations ("risk of bias") according to GRADE.[a]

Study	Randomisation	Allocation concealment	Blinding of outcome assessor	Adherence to intention-to-treat principle	Other limitations
Adamsen et al. [33]	Yes – computer generated numbers	No	No	Yes–participants with missing data included as MR	Heterogeneous sample in terms of diagnosis and stage
Battaglini et al. [34]	Yes – drawing of random numbers by the patient	Yes – sealed envelopes	Not stated	Not stated (no drop-out)	Inclusion criteria not described Small sample size
Baumann et al. [30]	Yes–no detail	Not stated	Not stated	Yes–no details	Pilot study–small sample size Loss to follow up 23.5%
Courneya et al. [40]	Yes – computer generated numbers	Yes – external site	Not stated	Yes – participants with missing data included as MR	
Coleman et al. [35]	Yes, drawing of random numbers by the patient	Yes – sealed envelopes	Not stated	Not stated	Pilot study – small sample size Loss to follow up 42%
Cunningham et al. [44]	Yes – computer generated	Yes–no details	Not stated	Not stated	Loss to follow up 20%
Demark-wahnefried et al. [45]	Yes – stratified block randomisation	Not stated	Not stated	Not stated	Pilot study
Jarden 2009	Yes -computer generated–stratified by age and gender	Yes	Not stated	Yes – participants with missing data included as MR	Small sample size
Mello et al. [31]	Yes–no detail	Not stated	Not stated	Not stated	Small sample size Loss to follow up 44%
Monga et al. [32]	Yes–no detail	Not stated	Not stated	Not stated	Small sample size
Mustian et al. [37]	Yes–no detail	Yes–no details	Blinded	Yes–patients analysed according to allocated group	Pilot study–small sample size
Oldervoll et al. [38]	Yes – block randomisation	Not stated	Not stated	Yes – participants with missing data included as MR	Loss to follow up 29%
Schwartz et al. [42]	Yes–no detail	Not stated	Not stated	Not stated	
Schwartz et al. [41]	Yes–no detail	Not stated	Not stated	Yes–no details	Multiple end-points
Segal et al. [43]	Yes – computer generated	Yes	Blinded	Yes–no details	
Wiskemann et al. [39]	Yes–no detail	Not stated	Not stated	Yes–no details	Between group comparison not reported Loss to follow up 23%

[a] For details on criteria, see Guyatt et al. [25].

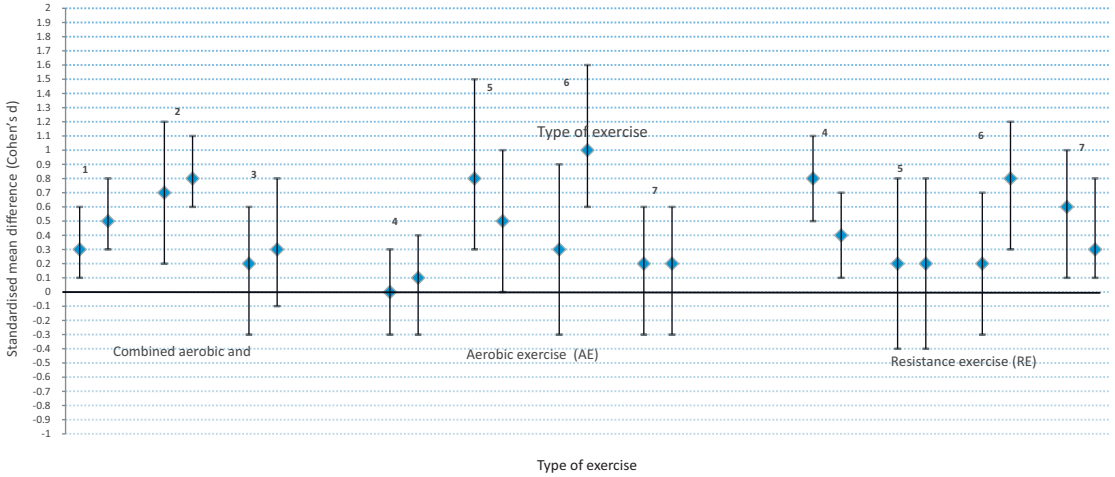


Fig. 2. Effect sizes for muscle strength, measured in kilograms, for physical exercise including (a) combined aerobic and strength exercise, (b) aerobic exercise alone and (c) strength exercise alone. The bars illustrate the standardised mean difference (dots) and the upper and lower 95% confidence intervals for each outcome (upper body and lower body strength measured as kilograms) in the presented studies ($n = 7$)*. Effect sizes above zero represent the magnitude of the effect in favour of physical exercise compared to treatment as usual. Effect sizes < 0.2 are interpreted as small; 0.2–0.5 small to moderate; 0.51–0.8 moderate to large; >0.8 large. *Out of 12 studies measuring muscle strength, 7 studies using repetition maximum or isometric testing is reported in figure. 4 studies measuring muscle strength as a sum score for whole body, grip strength and functional sit to stand test, is not presented in the figure. One study did not provide calculable data for muscle strength.

3.6. Comparing effects across patient cohorts

The majority of trials were performed on stage I–III breast cancer patients undergoing adjuvant chemotherapy and prostate cancer patients receiving radiation therapy. A few trials included some other cancer diagnoses, such as bowel or colon cancer [32–34,37,40–43,45]. Six trials included patients with various haematological malignancies, mainly acute or chronic leukaemia or lymphomas, undergoing hematopoietic stem cell transplants (HSCT) [30,36,39,44]. Only one trial included patients with advanced stage IV cancer undergoing palliative cancer treatment. These patients were diagnosed with tumours in the gastro-intestinal tract, breast, lung or bladder [38].

Muscle mass was reported in only six trials, and except for two trials involving HSCT patients [35,44], these were conducted on patients with breast cancer or prostate cancer [34,37,40,45]. Overall, the tendency in these six trials was that the experimental groups (either AE, RE or CAE) maintained or modestly improved muscle mass from pre to post-test while the UC reduced muscle mass.

For muscle strength outcomes, moderate to large effects were demonstrated in the trials on breast and prostate cancer patients [33,34,40–43] and in trials on HSCT patients [30,35,36,39] but not in patients with advanced stage IV cancer [38], where effects on grip strength were small.

4. Discussion

4.1. Summary of results

In this systematic review of 16 trials with cancer patients during active treatment, both aerobic and resistance exercise, and a combination of these, improves upper and lower body muscle strength more than usual care. Muscle mass was reported in only six trials and shows a tendency towards an effect of physical exercise on maintaining muscle mass during treatment. There are some indications that resistance exercise (RE) is more effective than aerobic exercise (AE) both on muscle mass and strength, though the evidence is not very strong. Large effects on muscle strength were demonstrated across different patient cohorts. However, most trials involved patients with early stage cancer while only one trial was on patients with advanced cancer.

4.2. Effects of physical exercise

This review shows a possible effect of physical exercise on muscle mass during cancer treatment, as three trials reported significantly better effects of physical exercise compared to usual care [34,35,40]. The findings are in line with a systematic review and a meta-analysis by Speck et al. [5] based on five trials reporting muscle mass as outcome. This review concluded with small effects sizes in favour of different physical activity interventions compared with usual care in cancer

survivors. One of the trials by Demark-Wahnefried et al. [45] included in the present review reported negative findings for resistance training and low fat diet on LBM compared to usual care. The negative result can likely be explained by a higher non-adherence rate in the experimental groups. In summary, because of few exercise trials using muscle mass as outcome, most of them having methodological shortcomings, there is still too little evidence to draw a firm conclusion on the effect of physical exercise on muscle mass for patients undergoing cancer treatment.

The present review of 14 trials using muscle strength as outcome, demonstrated a positive effect of physical exercise compared to usual care. These findings are also in line with Speck and colleagues [5] who, based on eight trials, concluded with small to moderate effect of physical exercise on muscle strength.

From the review, as compared to UC, we found positive effects of exercise on muscle strength in favour of AE in five trials [30,32,41–43]; RE in three trials [40,41,43] and CAE in four trials [33,34,36,38]. Only two trials compared effects of AE and RE, and both reported significantly better effect of RE on change in muscle strength [40,43]. Furthermore, the study by Courneya and colleagues from 2007 [40] also found a significant effect in favour of RE compared to AE on muscle mass. Although the evidence is not very strong, the result could support the use of RE in future clinical trials.

4.3. Populations

The majority of trials in the present review included breast or prostate cancer patients. Only three trials included patient groups with other types of solid tumours, such as gastro-intestinal, bowel or lung cancer [33,38,42]. Possible explanations for this are that recruitment into exercise trials in very sick patients is challenging due to a high disease and symptom burden, side-effect of treatment, and gate-keeping from health personnel [46].

This review found six trials conducted in patients with haematological malignances undergoing hematopoietic stem cell transplant (HSCT) and high dose chemotherapy, and only one trial [38] conducted in cancer patients with advanced disease. Muscle wasting is a common symptom, reported in more than 60% of patients with advanced cancer [14] and patients with haematological malignancies undergoing stem cell transplants [47]. For both groups there is a need for treatment strategies that contribute to reduce side-effect of treatment, maintain muscle mass and strength in order to maintain quality of life, and prolong survival. Future exercise trials are therefore needed in cancer populations at high risk for developing cachexia.

Even if the search criteria were set to detect papers with patients prone to cachexia, the present review only identified one trial with advanced cancer patients. In this study, patients with advanced incurable cancer were randomised to eight weeks of CAE performed twice weekly in a supervised hospital setting, or to usual care. The increased grip strength in the CAE relative to UC supports previous uncontrolled trials in advanced cancer [48,49] on efficacy of exercise on muscle strength also in this population. In conclusion, the findings from our review support the effect of exercise on muscle strength in cancer patient undergoing curative treatment. The evidence is however sparse with regards to the effects in patients with advanced cancer.

4.4. Methodological quality of the included trials

Conclusions that can be drawn from any literature review are based on the quality of the trials included. Thus, identifying possible biases in the conducted trials are essential [25]. The included trials in the present review had some shortcomings: first, the trials varied considerably in terms of sample size. Eight trials had less than 50 participants [31,32,34–37,42,44], and only one of performed a sample size estimation [36]. Second, nine trials lacked or did not report use of concealed allocation [30–33,38,39,41,42,45]. Third, in most trials, the assessment and interventions was performed by the same persons.

4.5. Outcomes

Previous reviews on effects of physical exercise in patients with cachexia have been narrative and not been specific to cancer patients [21,22] or have mainly discussed biological and pathophysiological aspects of exercise on cachexia-related muscle wasting [23,24]. Existing systematic reviews and meta-analyses on the effects of physical exercise in cancer patients have evaluated multiple end-points both during and after anti-cancer treatment [5,50], and many have primarily focused on specific outcomes such as fatigue [1] and quality of life [3]. At present, no systematic review has primarily been designed to examine the effect of physical exercise on muscle mass and strength in cancer patients during active treatment. Considering that depletion of muscle mass is associated with more toxic side-effects, poor response of cancer treatment and short survival in advanced cancer populations, muscle mass as outcome should be of clinical interest. Furthermore, preventing loss of muscle mass and function during active cancer treatment may contribute to maintaining activities of daily living. In advanced cancer patients, reduction in daily physical activity is linked to impaired quality of life [51]. Further trials are needed to assess the effect of exercise on muscle mass and secondary on quality of life in these patients.

The scarcity of data on muscle mass is not exclusive to the trials relevant in this review. As shown in the systematic review by Blum and colleagues, the impact of cachexia on muscle mass, strength and physical function in general is not widely assessed [15].

Several factors are to be considered when using muscle mass as endpoint. Objective measurements of skeletal muscle mass require expensive equipment and experienced personnel that might not always be a feasible option in a clinical research

setting. In addition, the type and dose of exercise required to gain muscle mass remains unclear, making it difficult to interpret what are clinically relevant changes in muscle mass following exercise interventions. Further trials should also assess whether muscle strength can be used as a surrogate outcome for muscle mass in clinical trials in advanced cancer patients.

4.6. Study limitations

The search strategy in this systematic review was predefined and designed by a trained research librarian and performed in multiple biomedical and therapeutic databases in order to reduce publication bias. A large group of different search terms were used to represent muscle outcomes as well as cachexia however it was acknowledged that search terms for outcomes are not always represented in abstracts of indexing terms (i.e. Mesh). To account for this, additional manual searches were performed by the first author (GBS) in bibliographies of the 85 full-text articles.

Although we searched for trials of relevance for patients with cachexia, only one RCT conducted in patients with advanced stage cancer was detected. As only RCT's were included, two uncontrolled trials performed in patients with advanced lung cancer [48,49] were not described in our results. These trials showed improvement in muscle strength after eight weeks of CAE but none of these studies used muscle mass as outcome. Furthermore, an observational study of a multimodal rehabilitation intervention (nutrition, exercise and symptom management) involving cancer patients with advanced disease and significant anorexia/weight loss, was identified but not included [52]. After two months of intervention, patients who were still in the study increased their body weight and physical function, and reduced their symptom burden. This is the only study identified through the literature search that provides data concerning physical exercise in cancer cachexia. However, a few study protocols of ongoing trials were identified [53,54]; suggesting that the research focus in this field will increase in the time to come.

4.7. Conclusion and future directions

This systematic review provides evidence that both aerobic and resistance exercise or a combination of these, can contribute to improve muscle strength more than usual care in cancer patients during treatment. Whether these different types of exercise have specific effects remains unclear. Improvements in muscle mass were demonstrated in favour of resistance exercise; however the evidence was not strong. Few trials measured muscle mass and besides one large trial; the studies included a small number of patients. Although effects were similar across different patients cohorts included in this review, there was a predominance of trials conducted in patients with early stage cancer, and conclusions cannot be drawn with regard to advanced cancer populations. Future research in this field should include studies of effects of physical exercise on muscle mass in patients with advanced cancer and at risk of cancer cachexia.

Funding

The manuscript is conducted as part of a PhD Thesis funded by the joint research fund of the Regional Health Authorities of Middle Norway and the Norwegian University of Science and Technology in Trondheim.

Conflict of interest

The author(s) has no conflicts of interest associated with this manuscript.

Reviewer

Matthew Maddocks, Cicely Saunders Institute, London, United Kingdom.

Acknowledgements

Thanks to Tora Solheim, MD Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital/PhD student, *European Palliative Care Research Centre, Faculty of Medicine*, Norwegian University of Science and Technology, Trondheim, for valuable feedback on the manuscript and support throughout the writing process.

References

[1] Puetz TW, Herring MP. Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. American Journal of Preventive Medicine 2012;43(2):e1–24, http://dx.doi.org/10.1016/j.amepre.2012.04.027. PMID: 22813691.

[2] Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database of Systematic Reviews 2012;8:CD007566, http://dx.doi.org/10.1002/14651858.CD007566.pub2. PMID: 22895961.

[3] Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database of Systematic Reviews 2012;8:CD008465, http://dx.doi.org/10.1002/14651858.CD008465.pub2. PMID: 22895974.

[4] Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. Acta Oncologica 2011;50(2):167–78, http://dx.doi.org/10.3109/0284186X. 2010.529822. PMID: 21091401; PMCID: PMC3228995.

[5] Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. Journal of Cancer Survivorship:

Research and Practice 2010;4(2):87–100, http://dx.doi.org/10.1007/s11764-009-0110-5. PMID: 20052559.
[6] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports 1985;100(2):126–31.
[7] O'Donovan G, Blazevich AJ, Boreham C, et al. The ABC of physical activity for health: a consensus statement from the British Association of Sport and Exercise Sciences. Journal of Sports Science 2010;28(6):573–91, http://dx.doi.org/10.1080/02640411003671212. PMID: 20401789.
[8] Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine and Science in Sports and Exercise 2010;42(7):1409–26, http://dx.doi.org/10.1249/MSS.0b013e3181e0c112. PMID: 20559064.
[9] Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. Journal of Supportive Oncology 2012, http://dx.doi.org/10.1016/j.suponc.2012.02.001. PMID: 22579268.
[10] Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. Journal of Science and Medicine in Sport 2009;12(4):428–34, http://dx.doi.org/10.1016/j.jsams.2009.03.002. S1440-2440(09)00056-5 [pii]; PMID: 19428291.
[11] Lowe SS, Watanabe SMS, Courneya KSK. Physical activity as a supportive care intervention in palliative cancer patients: a systematic review. Journal of Supportive Oncology 2009;7(1):27–34.
[12] Oldervoll LM, Loge JH, Paltiel H, et al. Are palliative cancer patients willing and able to participate in a physical exercise program? Palliative & Supportive Care 2005;3(4):281–7.
[13] Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncology 2011;12(5):489–95, http://dx.doi.org/10.1016/S1470-2045(10)70218-7. PMID: 21296615.
[14] von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. Journal of Cachexia, Sarcopenia and Muscle 2010;1(1):1–5, http://dx.doi.org/10.1007/s13539-010-0002-6. PMID: 21475699; PMCID: PMC3060651.
[15] Blum D, Omlin A, Baracos VE, et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Critical Reviews in Oncology/Hematology 2011;80(1):114–44, http://dx.doi.org/10.1016/j.critrevonc.2010.10.004. PMID: 21216616.
[16] Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? Journal of Cachexia, Sarcopenia and Muscle 2012, http://dx.doi.org/10.1007/s13539-012-0067-5. PMID: 22565649.
[17] Lira FS, Rosa JC, Zanchi NE, et al. Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. Cell Biochemistry and Function 2009;27(2):71–5, http://dx.doi.org/10.1002/cbf.1540. PMID: 19226603.
[18] Penna F, Busquets S, Pin F, et al. Combined approach to counteract experimental cancer cachexia: eicosapentaenoic acid and training exercise. Journal of Cachexia, Sarcopenia and Muscle 2011;2(2):95–104, http://dx.doi.org/10.1007/s13539-011-0028-4. PMID: 21766055; PMCID: PMC3118004.
[19] Vogiatzis I, Simoes DC, Stratakos G, et al. Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. European Respiratory Journal 2010;36(2):301–10, http://dx.doi.org/10.1183/09031936.00112909, 09031936.00112909 [pii]; PMID: 20110400.
[20] Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis & Rheumatism 2009;61(12):1726–34, http://dx.doi.org/10.1002/art.24891. PMID: 19950325.
[21] Maddocks M, Murton AJ, Wilcock A. Improving muscle mass and function in cachexia: non-drug approaches. Current Opinion in Supportive and Palliative Care 2011;5(4):361–4, http://dx.doi.org/10.1097/SPC.0b013e32834bdde3. PMID: 21934503.
[22] Glover EI, Phillips SM. Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy. Current Opinion in Clinical Nutrition and Metabolic Care 2010;13(6):630–4, http://dx.doi.org/10.1097/MCO.0b013e32833f1ae5. PMID: 20829685.
[23] Al-Majid S, Waters H. The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. Biological Research for Nursing 2008;10(1):7–20. PMID: 18705151.
[24] Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. Journal of Cachexia, Sarcopenia and Muscle 2010;1(1):9–21, http://dx.doi.org/10.1007/s13539-010-0007-1. PMID: 21475693; PMCID: PMC3060644.
[25] Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). Journal of Clinical Epidemiology 2011;64(4):407–15, http://dx.doi.org/10.1016/j.jclinepi.2010.07.017. PMID: 21247734.
[26] Cohen J. Statistical power analysis for the behavioural sciences. 2nd ed. Hillsdale, NJ: Laurence Erlbaum Associates, Inc.; 1988. p. 19–74.
[27] Durlak JA. How to select, calculate, and interpret effect sizes. Journal of Pediatric Psychology 2009;34(9):917–28, http://dx.doi.org/10.1093/jpepsy/jsp004. PMID: 19223279.
[28] Jarden M, Hovgaard D, Boesen E, Quist M, Adamsen L. Pilot study of a multimodal intervention: mixed-type exercise and psychoeducation in patients undergoing allogeneic stem cell transplantation. Bone Marrow Transplantation 2007;40(8):793–800, http://dx.doi.org/10.1038/sj.bmt.1705807, 1705807 [pii]; PMID: 17704795.
[29] Baumann FT, Zopf EM, Nykamp E, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. European Journal of Haematology 2011;87(2):148–56, http://dx.doi.org/10.1111/j.1600-0609.2011.01640.x. PMID: 21545527.
[30] Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplantation 2010;45(2):355–62, http://dx.doi.org/10.1038/bmt.2009.163. PMID: 19597418.
[31] Mello M, Tanaka C, Dulley FL. Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplantation 2003;32(7):723–8. PMID: 2003414053.
[32] Monga U, Garber SL, Thornby J, et al. Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. Archives of Physical Medicine and Rehabilitation 2007;88(11):1416–22. PMID: 2007517460.
[33] Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. British Medical Journal 2009;339:b3410. PMID: 19826172; PMCID: PMC2762035.
[34] Battaglini C, Bottaro M, Dennehy C, et al. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. Sao Paulo Medical Journal 2007;125(1):22–8. PMID: 17505681.
[35] Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. Cancer Nursing 2003;26(5):410–9. PMID: 2003400931.
[36] Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. Bone Marrow Transplantation 2009;43(9):725–37. PMID: 2009228005.

[37] Mustian KM, Peppone L, Darling TV, Palesh O, Heckler CE, Morrow GR. A 4-week home-based aerobic and resistance exercise program during radiation therapy: a pilot randomized clinical trial. Journal of Supportive Oncology 2009;7(5):158–67. PMID: 2010027264.
[38] Oldervoll LM, Loge JH, Paltiel H, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 2011;16(11):1649–57. PMID: 70450349.
[39] Wiskemann J, Dreger P, Schwerdtfeger R, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. Blood 2011;117(9):2604–13, http://dx.doi.org/10.1182/blood-2010-09-306308. PMID: 21190995.
[40] Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Journal of Clinical Oncology 2007;25(28):4396–404, http://dx.doi.org/10.1200/jco.2006.08.2024. PMID: 17785708.
[41] Schwartz AL, Winters-Stone K. Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women. Physician and Sports Medicine 2009;37(3):62–7. PMID: 2010091592.
[42] Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum 2007;34(3):627–33, http://dx.doi.org/10.1188/07.ONF.627-633. R5848R482572562P [pii]; PMID: 17573321.
[43] Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. Journal of Clinical Oncology 2009;27(3):344–51. PMID: 2009038538.
[44] Cunningham BA, Morris G, Cheney CL, Buergel N, Aker SN, Lenssen P. Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 1986;10(6):558–63. PMID: 3098997.
[45] Demark-Wahnefried W, Case LD, Blackwell K, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. Clinical Breast Cancer 2008;8(1):70–9. PMID: 2008117208.
[46] Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 2005;14(7):1672–80, http://dx.doi.org/10.1158/1055-9965.EPI-04-0736. PMID: 16030100.
[47] van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. Physical Therapy 2012, http://dx.doi.org/10.2522/ptj.20120181. PMID: 23224217.
[48] Temel JS, Greer JA, Goldberg S, et al. A structured exercise program for patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology 2009;4(5):595–601, http://dx.doi.org/10.1097/JTO.0b013e31819d18e5. PMID: 19276834; PMCID: PMC2975103.
[49] Quist M, Rorth M, Langer S, et al. Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: a pilot study. Lung Cancer 2011, http://dx.doi.org/10.1016/j.lungcan.2011.07.006. PMID: 21816503.
[50] Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. British Medical Journal 2012;344:e70, http://dx.doi.org/10.1136/bmj.e70. PMID: 22294757; PMCID: PMC3269661.
[51] Lowe SS. Physical activity and palliative cancer care. Recent results in cancer research. Fortschritte der Krebsforschung Progres dans les recherches sur le cancer 2011;186:349–65, http://dx.doi.org/10.1007/978-3-642-04231-7_15. PMID: 21113772.
[52] Glare P, Jongs W, Zafiropoulos B. Establishing a cancer nutrition rehabilitation program (CNRP) for ambulatory patients attending an Australian cancer center. Support Care Cancer 2010, http://dx.doi.org/10.1007/s00520-010-0834-9. PMID: 20204419.
[53] Rogers ES, MacLeod RD, Stewart J, Bird SP, Keogh JW. A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), resistance training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients – ACCeRT study. BMC Cancer 2011;11:493, http://dx.doi.org/10.1186/1471-2407-11-493. PMID: 22111896; PMCID: PMC3252396.
[54] Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Current Opinion in Supportive and Palliative Care 2012;6(4):424–31, http://dx.doi.org/10.1097/SPC.0b013e328359b668. PMID: 23111703.

Biography

Guro Birgitte Stene (MSc Physiotherapy) is an experienced physiotherapist who has had a research position at the Faculty of Medicine, Norwegian University of Science and Technology (NTNU) since 2007. She is involved in clinical trials at the Cancer Clinic at St. Olav Hospital, Trondheim University Hospital, and in international research projects initiated by the European Association for Palliative Care Research Network (EAPC–RN) and the European Palliative Care Research Centre (PRC). She currently holds a position as a senior physiotherapist and researcher at the Cancer Clinic, Department of Education and Research, St.Olavs Hospital, Trondheim University Hospital, and is finalising an international PhD in Palliative Care Research at NTNU.