Doktoravhandlinger ved NTNU, 2019:334

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NTNU
Kunnskap for en bedre verden

Doktoravhandling

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ISBN 978-82-326-4264-9 (trykt utg.)
ISBN 978-82-326-4265-6 (elektr. utg.)
ISSN 1503-8181

NTNU

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Trykket av NTNU Grafisk senter

Forekomst, tidlig diagnostikk og klassifikasjon av kreftrelatert kakeksi

Kreftrelatert kakeksi kjennetegnes av vekttap, muskelsvinn, nedsatt appetitt og redusert fysisk funksjonsevne. Kakeksi fører til dårlig livskvalitet og økt risiko for tidlig død. Inntil ganske nylig har man ikke hatt en omforent vitenskapelig definisjon av tilstanden. Sikre tall på utbredelsen av kakeksi fins derfor ikke. Man mangler også sikre tegn på tidlige faser av tilstanden, og den erkjennes derfor oftest først sent i forløpet. Muligheten til å klassifisere kakeksi i tidlig og sen fase har betydning for tilpasning av behandling til den enkelte pasient. Målet med denne avhandlingen er derfor å øke kunnskapen om utbredelsen av kreftrelatert kakeksi, og å bidra til en bedre klassifisering av tilstanden.

For å oppnå dette har vi brukt data fra to studier. Den ene er en tverrsnittsstudie gjennomført ved sykehus i Helse Midt-Norge, og den andre er en stor internasjonal studie hvor pasienter med kreft har vært fulgt over tid.

Vi har vist at kakeksi er utbredt blant kreftpasienter; 51% av innlagte pasienter og 22% av polikliniske pasienter hadde tilstanden. Pasienter med kreft i mage-tarmsystemet eller i lunge hadde økt risiko for kakeksi. Vi påviste også at pasienter med kakeksi følte at tilstanden fikk for lite oppmerksomhet når de var i kontakt med helsevesenet. Dette samsvarer med andre studier på området. Videre har vi vist at enkle markører som vekttap og kroppsmasseindeks effektivt kan klassifisere pasienter med ulik grad av symptomer på kakeksi, og til en viss grad kan forutsi hvem som har økt risiko for å utvikle tilstanden. Dersom man i tillegg vektlegger informasjon om pasientens krefttype, appetitt og andre sykdommer styrker dette muligheten til å forutsi hvem som utvikler kakeksi. Denne informasjonen kan brukes til å velge ut hvilke pasienter som bør følges nøye med tanke på å iverksette tiltak for å motvirke utvikling av kakeksi.

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Biveiledere: Førstelektor Barry Laird og professor Stein Kaasa

Finansiering: Samarbeidsorganet Helse Midt-Norge RHF og NTNU og European Palliative Care Research Centre/Kreftforeningen

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i palliativ medisin. Disputas finner sted i Auditorium MTA, Medisinsk Teknisk Forskningssenter, Fredag 15. november 2019, kl. 12.15.

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Acknowledgements

The scientific work of this thesis has been carried out at the European Palliative Care Research Centre (PRC) at the Department of Clinical and Molecular Medicine in collaboration with the Cancer Clinic at St. Olavs hospital – Trondheim university hospital. The first half of this work was funded by PRC through a grant from the Norwegian Cancer Society, and the latter half was funded by a grant from the Liaison committee between the Regional Health Authority of Central-Norway and NTNU.

Gratitude is in order to people who has been important to me during this project. First, I would like to thank the patients who offered some of their, in many cases, limited time to participate in the studies that this thesis builds on. Without their willingness to contribute to the gain of new knowledge in the field of palliative and cancer care, this work would not have been possible.

Warm thanks go to my supervisor, Tora S. Solheim for guidance along the path to this PhD. Thank you for always being up to date with my work, for always responding quickly to my inquiries, and for patience when progress at times has been slow due to clinical work or family obligations.

Thanks also to my co-supervisors; to Barry Laird for providing support and constructive feedback and always keeping in touch although the physical distance between us has been far, and to Stein Kaasa for initially offering me the opportunity to embark on this project and for providing valuable scientific insight along the way.

Thanks to the co-authors of the three papers which constitutes the basis of this thesis. Your contributions helped improve the manuscripts and were much appreciated. An especial thanks to Cinzia Brunelli and Peter Fayers for valuable assistance with the statistical analyses.

Thanks to friends and colleagues both in the research group of Cancer and Palliative care and at the Cancer Clinic. Thanks to Ragnhild Green Helgås for her continuous effort to bring the research group closer together, and for answering each of my

(probably) thousand questions. Thanks also to Are Kristensen, who started his PhD-studies at the same time as I did and has been a good friend and a valuable discussion partner through the years.

Thanks to my parents and siblings for always supporting me through school and education. And finally, thank you to the four most important persons in my life, my wife, Cecilie, for being my best friend and support through this work, and our three children, Elias, Marli and Guro.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
aPG-SGA	Abridged Patient-generated Subjective Global Assessment
BMI	Body mass index
CASCO	Cachexia Score
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
EAPC	European Association of Palliative Care
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EPCCS	European Palliative Care Cancer Symptom study
FDG-PET	18-fluorodeoxyglucose positron emission tomography
GAD-2	Generalized Anxiety Disorder 2-item scale
Hgb	Hemoglobin
IL	Interleukin
KPS	Karnofsky performance status
PHQ-4	Patient Health Questionnaire 4-item scale
PRC	European Palliative Care Research Center
REE	Resting energy expenditure
TNF	Tumor necrosis factor
TNM	Tumor, Nodulus, Metastasis classification system
WLGS	Weight loss grading system

Summary in English

Cancer cachexia is characterized by loss of muscle mass accompanied by a variable loss of fat mass. It leads to a decline in physical function and quality of life, and an increase in psychological distress and mortality. The pathophysiology is complex and characterized by a negative protein and energy balance mediated by inflammation and neuroendocrine changes. Anorexia and lack of exercise contributes to the decay. Estimates of cancer cachexia prevalence vary between 30-85% depending on how it is defined, and the population examined. There is no established treatment of cancer cachexia, and nutrition therapy alone will not fully reverse the condition. Several different pharmacological agents have been tested, but so far, no drug has been licensed.

An important barrier against progress in cachexia management has been the absence of a consensus definition, and thus, a common perception of what cachexia is. In the clinical setting, cachexia has most often been recognized by its historical phenotype of severe weight loss and poor physical function and as such not recognized until late in its development. This may have compounded the lack of awareness among health care professionals to the development of cachexia.

Criteria for the diagnosis of cachexia in studies have varied; often based on weight loss in varying degrees, but other characteristics of cachexia such as markers of appetite loss and the systemic inflammatory response have also been used. This heterogeneity has made comparison of research results challenging, and the differing estimates of prevalence have led to uncertainty as to the impact and extent of cachexia in the cancer population.

Progress was made in 2011 when an international consensus definition incorporating diagnostic criteria for cancer cachexia was published. Fundamental to this was a framework for the classification of the trajectory of cancer cachexia through the stages of ‘pre-cachexia’, ‘cachexia’ and ‘refractory cachexia’. Cachexia is present if 6 months’ weight loss is >5%, or if the patient either has a body mass index <20 kg/m2 or is

sarcopenic, and 6 months' weight loss >2%. Pre-cachexia is a stage of early metabolic change and appetite loss, and refractory cachexia a stage of variable degree of cachexia, but where the cancer disease is pro-catabolic and no longer responsive to anti-cancer therapy. The ability to classify patients according to where they are in the trajectory may help stratify treatment. To illustrate, where a patient with pre-cachexia or cachexia might be susceptible to treatment aiming to delay or reverse cachexia, such treatment would seem futile in a patient with refractory cachexia. Instead, treatment aiming to provide optimal symptom relief would be more appropriate.

Although the consensus definition and classification framework was an important starting point, it was acknowledged that further research was necessary to find objective and reliable criteria for the cachexia stages. Moreover, it was necessary to establish an accurate estimate of cancer cachexia prevalence based on the new definition to better understand the extent of the condition.

To this end, the overall aim of the thesis was to gain new knowledge of the prevalence of cancer cachexia and contribute to a better classification system to allow for optimal selection of anti-cachexia treatment for each individual patient in the future.

The aims pertaining to paper I were to estimate prevalence of cancer cachexia in an unselected population as well as in cohorts based on demographical and clinical characteristics, and to evaluate patient-perceived importance of clinical attention to cachexia. A cross-sectional study was conducted in patients with cancer at three centers in the Regional Health Authority of Central-Norway. Fifty-one percent (95%CI 40-63) of inpatients and 22% (95%CI 17-27) of outpatients had cachexia. Prevalence varied significantly with cancer type and was higher in patients with gastrointestinal (OR 4.4 [95%CI 2.0-9.6]) and lung cancer (OR 5.5 [95%CI 2.0-15.1]) compared to patients with hematologic cancer. Twenty percent of inpatients and 15% of outpatients wanted more clinical attention to cachexia. Having cachexia ($p=0.02$), symptoms of a mood disorder ($p=0.05$) or being male ($p<0.01$) were factors significantly associated with a need for more attention.

The aims pertaining to paper II were to confirm the survival prognostic validity of the Weight loss grading system (WLGS), a potential classification system of cancer cachexia; evaluate its relationship with established cachexia characteristics and to explore its ability to predict cachexia progression. An analysis of an international cohort of patients with incurable cancer (European Palliative Care Cancer Symptom study, EPCCS) was conducted. The WLGS significantly predicted survival ($p<0.001$), and the addition of measurements of performance status ($p<0.001$), appetite ($p=0.005$), physical ($p<0.001$) and emotional functioning ($p=0.004$) to this model significantly improved the prognostic accuracy. The WLGS was associated with increased severity of all evaluated cachexia characteristics ($p<0.001$), and patients with weight loss grade 2 were more likely to have cachexia progression than patients with weight loss grade 0 and 1 (descriptive analysis only).

The aims pertaining to paper III were to identify predictors of cachexia development and to create and evaluate a predictive model of cancer cachexia based on these predictors. Patients included in the EPCCS cohort that had not developed cachexia at baseline were included in this analysis. Early weight loss ($p<0.001$), cancer type ($p<0.01$), appetite loss ($p=0.04$) and chronic obstructive pulmonary disease ($p=0.04$) predicted development of cancer cachexia. A five-level model based on these predictors was created where each level was associated with an increasing risk of cachexia development. The accuracy of the model in patients remaining in the study after three months was 76%.

Norsk sammendrag

Kreftrelatert kakeksi kjennetegnes ved tap av muskelmasse ledsaget av et variabelt tap av fettvev. Det fører til tap av fysisk funksjonsevne og livskvalitet, psykisk ubehag og økt risiko for død. Patofysiologien er sammensatt og kjennetegnes av en negativ protein- og energibalanse som stimuleres av inflammasjon og nevroendokrine endringer. Tap av appetitt og nedsatt fysisk aktivitet bidrar til den negative utviklingen. Estimater for forekomst av kakeksi varierer mellom 30-85% og avhenger av hvordan kakeksi defineres og i hvilken befolkningsgruppe man undersøker forekomsten. Det fins ingen etablert behandling av kreftrelatert kakeksi, og ernæring alene vil ikke kunne snu tilstanden. Flere forskjellige medisiner har vært prøvd ut, men så langt har ingen fått markedsføringstillatelse til bruk mot kakeksi.

Et viktig hinder på veien mot en bedre behandling av kakeksi har vært fraværet av en omforent definisjon av tilstanden, og følgelig en felles oppfatning av hva tilstanden er. I klinisk sammenheng har tilstanden ofte blitt diagnostisert basert på en utdatert oppfatning av at kakeksi først og fremst kjennetegnes av alvorlig vekttap, og nedsatt fysisk funksjonsevne. Dette har medført at kakeksi ofte ikke erkjennes før utviklingen av tilstanden har kommet svært langt, og dette kan ha bidratt til mangel på oppmerksomhet blant helsepersonell rundt utvikling av kakeksi.

Diagnostiske kriterier for kakeksi i vitenskapelige studier har variert. Ofte har de vært basert på varierende grad av vekttap, men andre kjennetegn på kakeksi, som manglende appetitt eller systemisk inflammasjon har også vært brukt. Det manglende samsvaret mellom definisjonene har gjort det vanskelig å sammenlikne resultatene fra de ulike studiene, og varierende estimater for forekomsten av kakeksi har ført til usikkerhet vedrørende reell utbredelse og betydning av tilstanden.

Det var et framskritt da det i 2011 ble publisert en definisjon og diagnostiske kriterier for kreftrelatert kakeksi basert på internasjonal konsensus. Denne publikasjonen foreslo samtidig en skisse for hvordan en klassifikasjon av kakeksi burde være. Tre stadier ble foreslått: 'pre-kakeksi', 'kakeksi' og 'refraktær kakeksi'. Kakeksi foreligger

hvis vekttap siste 6 måneder >5%, eller ved lav kroppsmasseindeks (<20 kg/m2) eller lav muskelmasse dersom vekttap siste 6 måneder >2%. Pre-kakeksi er et stadium hvor det foreligger tidlige tegn til metabolske forandringer og nedsatt appetitt, og refraktær kakeksi er et stadium med varierende alvorlighetsgrad av kakeksi, men hvor den underliggende kreftsykdommen er i en katabolsk fase og ikke lenger responderer på tumorrettet behandling. Muligheten til å klassifisere pasientene etter hvor de befinner seg i forløpet av kakeksiutviklingen, kan bidra til at behandlingen i større grad kan tilpasses den enkelte. For eksempel, vil en pasient med pre-kakeksi kanskje være mottakelig for behandling som kan forsinke eller reversere utviklingen av kakeksi, mens dette antagelig ville være nytteløst hos en pasient med refraktær kakeksi, som heller burde få symptomlindrende behandling.

Selv om konsensusdefinisjonen og klassifikasjonen var en viktig begynnelse, var det nødvendig med mer forskning for å komme fram til objektive og robuste kriterier for alle stadiene av kakeksi. Det var også viktig å komme fram til et presist estimat for forekomsten av kakeksi basert på den nye definisjonen, for å forstå omfanget av tilstanden.

Følgelig, var hensikten med denne avhandlingen å oppnå økt kunnskap om prevalensen av kreftrelatert kakeksi og å bidra til et forbedret klassifikasjonssystem for å bedre kunne tilby tilpasset behandling til hver enkelt pasient.

Formålet med artikkel I var å estimere forekomsten av kreftrelatert kakeksi i en uselektert populasjon så vel som i kohorter basert på demografiske eller sykdomsmessige fellestrekk. Videre ønsket man å undersøke pasientens oppfatning av nødvendigheten av helsepersonells oppmerksomhet mot kakeksi. Det ble gjennomført en tverrsnitts-studie på pasienter med kreft ved tre sykehus i Helse Midt-Norge. 51% (95%KI 40-63) av inneliggende pasienter og 22% (95%KI 17-27) av polikliniske pasienter hadde kakeksi. Forekomsten varierte signifikant med krefttype og var høyere hos pasienter med gastrointestinal kreft (OR 4,4 [95%KI 2,0-9,6]) og lungekreft (OR 5,5 [95%KI 2,0-15,1]) sammenlignet med pasienter med hematologisk kreft. 20% av

inneliggende pasienter og 15% av polikliniske pasienter ønsket mer oppmerksomhet fra helsepersonell rettet mot kakeksi. Kakeksi ($p=0,02$), symptomer på affektiv lidelse ($p=0,05$) og hankjønn ($p<0,01$) var faktorer som var assosiert med et ønske om mer oppmerksomhet mot kakeksi.

Formålet med artikkel II var å bekrefte den prognostiske verdien av Vekttapsgraderingssystemet (VTGS), et potensielt klassifikasjonssystem for kreftrelatert kakeksi; undersøke sammenhengen mellom VTGS og etablerte kjennetegn på kakeksi, og å undersøke om WLGS kan brukes til å predikere utvikling av kakeksi. Analysene ble gjort på en internasjonal kohort bestående av pasienter med uhelbredelig kreft (European Palliative Care Cancer Symptom study, EPCCS). VTGS prognostiserte signifikant overlevelse ($p<0,001$), og det ble vist at tillegg av målinger av objektiv funksjonsstatus ($p<0,001$), appetitt ($p=0,005$) og pasientrapportert fysisk ($p<0,001$) og emosjonell funksjonsevne ($p=0,004$) til denne modellen signifikant økte evnen til å prognostisere overlevelse. VTGS var forbundet med økt alvorlighetsgrad av alle undersøkte kjennetegn på kakeksi ($p<0,001$), og pasienter med vekttap grad 2 hadde høyere sannsynlighet for å utvikle kakeksi enn pasienter med vekttap grad 0 og 1 (deskriptive analyser).

Formålet med artikkel III var å identifisere prediktive faktorer for utvikling av kakeksi, og å utvikle og evaluere en prediktiv modell for utvikling av kreftrelatert kakeksi. Pasienter uten kakeksi fra EPCCS-kohorten ble inkludert i analysen. Tidlig vekttap ($p<0,001$), krefttype ($p<0,01$), nedsatt appetitt ($p=0,04$) og kronisk obstruktiv lungesykdom ($p=0,04$) predikerte utvikling av kakeksi. En modell med fem nivåer ble utviklet hvor hvert av nivåene medførte gradvis økende risiko for kakeksiutvikling. Nøyaktigheten av modellen målt på pasienter som fortsatt var med i studien etter tre måneder var 76%.

List of papers

Paper I

A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer.

Vagnildhaug OM, Balstad TR, Almberg SS, Brunelli C, Knudsen AK, Kaasa S, Thronæs M, Laird B, Solheim TS.

Support Care Cancer. 2018 Jun;26(6):1871-1880.

Paper II

The applicability of a weight loss grading system in cancer cachexia: a longitudinal analysis.

Vagnildhaug OM, Blum D, Wilcock A, Fayers P, Strasser F, Baracos VE, Hjermstad MJ, Kaasa S, Laird B & Solheim TS on behalf of the European Palliative Care Cancer Symptom study group.

J Cachexia Sarcopenia Muscle. 2017 Oct;8(5):789-797.

Paper III

A prospective study examining cachexia predictors in patients with incurable cancer.

Vagnildhaug OM, Brunelli C, Hjermstad MJ, Strasser F, Baracos V, Wilcock A, Nabal M, Kaasa S, Laird B, Solheim TS.

BMC Palliative Care. 2019 Jun;18

1 Background

1.1 Cancer

Cancer is a multitude of different diseases which can affect virtually every organ in the body and has a common set of hallmarks such as uncontrolled cell proliferation and ability to invade neighbouring normal tissue and metastasize to distant organs [1]. Cancer is, together with cardiovascular disease, a leading cause of death globally [2]. There were 14.1 million new cases and 8.2 million deaths globally from cancer in 2012, and an estimated 32.6 million people were living with cancer (within five years of diagnosis) [3]. In Norway there were 33,564 new cases (2017), 10,994 deaths from cancer (2016) and 100,567 were living with cancer (within five years of diagnosis) as of December 31st 2017 [4]. Both in Norway and globally, the cancer incidence is increasing, mostly due to population growth and ageing [2, 4]. This will probably lead to an increase in demand for oncologic and palliative care services in years to come.

1.2 Palliative care

The World Health Organization (WHO) defines palliative care as follows:

> "*Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."* [5]

WHO further underlines that palliative care provides relief from symptoms, enhances quality of life and is applicable during early illness, in conjunction with other therapies. The latter is important because palliative care in cancer has traditionally been offered to patients with advanced disease and short life expectancy. This is illustrated in traditional cancer care where patients are referred from oncologic units to palliative care units when oncologic treatment options have failed or seem futile. As a result, symptoms may often be far advanced and difficult to treat. This paradigm is now changing. There is evidence that specialized palliative care early in the cancer trajectory improves quality of life, satisfaction with care, prognostic awareness and

survival and reduces time spent in institutions, symptom burden and depression [6-12]. Thus, early integration of palliative and oncologic care is now advocated to achieve better symptom control and to improve deliverance of anti-cancer treatment [13-15] (Figure 1). A prerequisite for both prevention and optimal treatment of symptoms is the ability to recognize early stages of its development and to classify each symptom correctly. Cachexia is a case in point in that respect.

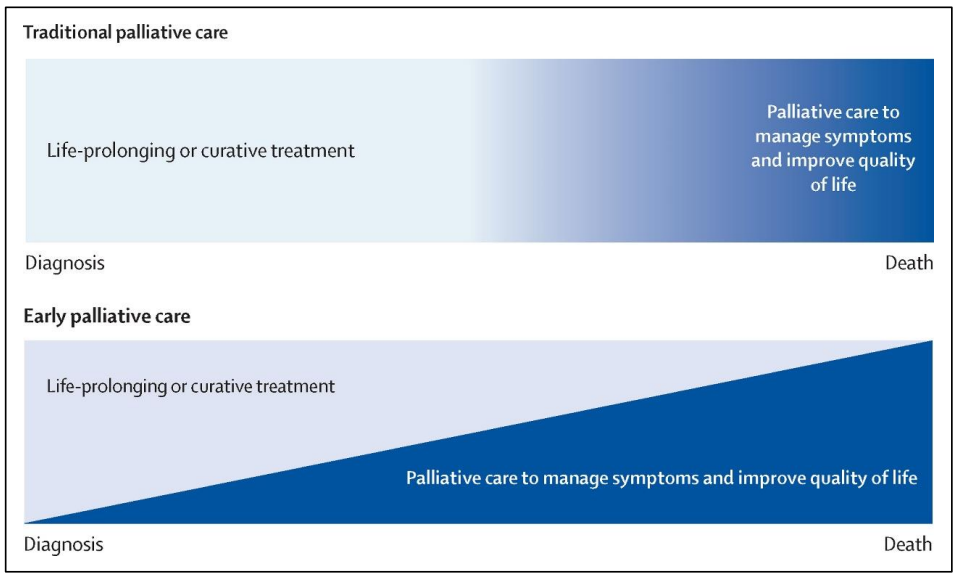

Figure 1 Traditional versus early palliative care. (Reprinted from The Lancet Oncology, 19(11), Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E et al., Integration of oncology and palliative care: a Lancet Oncology Commission, e588-e653, Copyright (2018), with permission from Elsevier)

1.3 Cachexia

The word cachexia derives from Greek 'kakos' 'hexos', which translates into bad condition [16]. Cachexia is a syndrome characterized by weight loss, loss of appetite and functional impairment, and may accompany many chronic diseases, such as congestive heart failure, chronic obstructive pulmonary disease (COPD), kidney failure, chronic infectious disease, acquired immunodeficiency syndrome (AIDS), arthritis and cancer [17]. Although there are common characteristics in the pathophysiology [18], prevalence and mortality of cachexia vary depending on underlying disease [17]. Mortality seem to be especially high in patients with cancer, estimated to 20-80% in

one year [17]. Patients with cancer cachexia also tolerate anti-cancer treatment less well [19, 20].

Patients and their loved ones often suffer from severe psychological distress due to the uncontrollable weight loss and lack of desire to eat [21-23]. Lack of attention to cachexia from health care personnel may contribute to increased anxiety, confusion and concern both for patients and their relatives [24]. Still, it is reported that some health care professionals avoid talking to patients and families about cachexia due to lack of treatment options, and fear of increasing patients' distress by asking questions about untreatable conditions [25]. Lack of awareness to cachexia was also indicated by another study, which identified 275 oncologic societies on the Internet, of which only 10 provided web-based guidelines for cachexia management [26].

1.3.1 Cachexia definition

Severe cachexia is often easily recognized by extensive weight loss and fat and muscle tissue wasting, and the syndrome has always been well known to clinicians. This is illustrated by its description in sources dating back to the age of Hippocrates: "The flesh is consumed and becomes water; […]the shoulders, clavicles, chest and thighs melt away" [27]. Still, it is only in the past decade that the research community has been able to agree upon a concise definition of cachexia [28]. Historically, several different definitions have been used in clinical studies, and although most of them have been based on degree of weight loss, cut-offs and developmental time for weight loss have varied (2%, 5%, 10% or 20% weight loss , over 2 months, 6 months or compared with premorbid body weight) [29]. Some definitions have also incorporated other characteristics of cachexia, such as altered body composition, appetite loss, dietary intake or fatigue [29]. Although some definitions have been validated in the sense that they were shown to identify patients with symptoms and signs of cachexia [30, 31], the heterogeneity of definitions have left research results incomparable and hindered advancement of cachexia research and development of effective treatments.

1.3.1.1 Generic definition

To address the problem of the multitude of cachexia definitions, scientists and clinicians with experience in the field of cachexia assembled to agree upon *one* definition, which was published in 2008 [28]:

> *"Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity"* [28]

To aid clinicians and scientists in identifying cachexia, the group also agreed on a set of diagnostic criteria to accompany the definition:

- Weight loss of more than 5% in 12 months; and at least 3 of the 5 following items
    - Decreased muscle strength (lowest tertile)
    - Fatigue
    - Anorexia (eg. total caloric intake < 20 kcal/kg or poor appetite)
    - Low fat-free mass index (eg. mid upper arm muscle circumference < 10^{th} percentile)
    - Abnormal biochemistry
        - Increased inflammatory markers (CRP > 5.0 mg/L, IL-6 > 4.0 pg/mL)
        - Anemia (Hgb < 12g/dL)
        - Low serum albumin (< 3.2 g/dL)

1.3.1.2 Cancer cachexia definition

The definition and diagnostic criteria are generic in the sense that they are valid for cachexia resulting from *any* underlying disease. However, it has been questioned whether some of the criteria are sufficiently specific to accurately diagnose *cancer* cachexia [29]. In particular, fatigue and anemia are frequent symptoms of cancer that in many cases are not caused by cachexia but could be directly related to anti-cancer treatment. This established the need for a cancer specific definition. Bozzetti and Mariani [30] proposed that cachexia should be diagnosed by weight loss ≥ 10% and further subdivided as either asymptomatic or symptomatic cachexia based on the presence of anorexia, fatigue or early satiation. These criteria identified patients with worse performance status and risk of nutrition-related morbidity. Fearon et al. [31] suggested the following diagnostic criteria of cachexia: weight loss (≥ 10%), low food intake (≤ 1500 kcal/day) and systemic inflammation (CRP ≥ 10 mg/L). They demonstrated that these criteria identified patients with both adverse function and prognosis, and in that respect was superior to a definition solely based on weight loss. Again, there was a need for unity in defining cancer cachexia, and a Delphi process was conducted among leading experts in clinical cancer cachexia research. Consensus was reached on the following definition, which was published in 2011:

> *"Cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."* [32]

Cancer specific diagnostic criteria were based on weight loss and body composition [32]:

- Weight loss >5% over past 6 months (in absence of simple starvation); or
- Body mass index (BMI) <20 kg/m^2 and any degree of weight loss >2%; or

- Appendicular skeletal muscle index consistent with sarcopenia and any degree of weight loss >2%

The publication of the consensus definition provided a platform for further research to validate the definition against established characteristics of cachexia. Such characteristics had previously been identified in a systematic review of measurements, or items, used to describe involuntary weight loss in the literature between 1976 and 2007 [33]. Expert focus groups categorized the items into domains, each describing separate aspects of cachexia. These domains were adopted with only minor alterations when the consensus paper later published the key characteristics by which cachexia was to be assessed [32]:

- Anorexia and reduced food intake (e.g. caloric intake, appetite loss, other nutritional impact symptoms)
- Catabolic drivers (e.g. markers of inflammation, responsiveness to anti-cancer therapy)
- Muscle mass and strength (e.g. CT, DEXA, hand grip strength)
- Functional and psychosocial effects (e.g. physical functioning, activity meter, patient reported outcomes).

Using these domains and items as markers of cachexia, three publications have validated the consensus definition [34-36]. LeBlanc et al. [35] prospectively evaluated patients with non-small cell lung cancer and found that patients fulfilling the cachexia diagnostic criteria had low performance status and poor quality of life compared to patients without cachexia. During follow-up, patients with cachexia also had a more negative development of hand grip strength and six-minute walking distance. Wallengren et al. [36] found that patients with cancer undergoing palliative care and meeting the cachexia criteria had more adverse quality of life, higher symptom burden and shorter survival.

Blum et al. [34] adapted the cachexia diagnostic criteria by omitting measurements of muscle mass and only using the first two criteria (weight loss and BMI). They validated

these adapted criteria in patients with advanced cancer by demonstrating that patients with cachexia had higher levels of CRP, less appetite and lower food intake.

Blum's definition has the advantage of being simpler and thus, clinically more applicable. However, it must be highlighted that definitions to date have a reliance on patient recalled weight loss which is often subjective and may be inaccurate. Therefore, the inclusion of objective parameters such as measurement of lean body mass and the systemic inflammatory response has been advocated.

1.3.1.3 Sarcopenia

Sarcopenia is an element in the international cancer cachexia consensus from 2011 [32]. The definition of sarcopenia was recently revised and is now defined as low muscle strength, and the diagnosis is confirmed by measurements of low muscle mass or quality [37]. Sarcopenia is divided into primary sarcopenia, which results from ageing, and secondary sarcopenia, which results from causes other than, or in addition to, ageing [38]. An example of the latter is sarcopenia following cachexia. In effect, sarcopenia is often seen in cachexia, however most cases of sarcopenia are not caused by cachexia. Earlier the diagnosis was primarily based on muscle mass rather than muscle strength [38], hence, the requirement of muscle mass measurements in the international cancer cachexia consensus [32].

While the first two criteria (weight loss and BMI) of the three-factor definition of the international cancer cachexia consensus [32] are easily evaluated in clinical practice, the criteria related to sarcopenia is somewhat more challenging to assess.

Firstly, no clear consensus exists as to which method of muscle mass measurement is to be preferred [32, 37, 39]. One of the following methods are appropriate for this purpose: Dual-energy x-ray absorptiometry (DEXA) [40] or bioelectrical impedance [41], which both measure lean (fat-free) body mass, or estimation of muscle area of the mid upper arm [42]or at the level of L3 [43] – measured by anthropometry or computed tomography (CT), respectively. The choice of method has clear consequences for the resulting prevalence of sarcopenia, which varied from 13% (mid

upper arm muscle area) to 93% (bioelectrical impedance) in one study [44]. Secondly, muscle mass is correlated with body size [45], and there are several ways to adjust for this (divide by height^2, BMI or weight), but no general recommendation is provided [37]. Finally, to be able to set sarcopenia diagnostic cut-offs for the various methods of muscle mass measurements, normative data for the studied population are needed, and this is not always available [37].

1.3.2 Cachexia classification

Cachexia is probably not a single entity but evolves through several stages; from minor signs of anorexia and metabolic alterations, to severe weight loss and impaired physical function [46]. It is likely that the opportunity to intervene diminishes with the progression of cachexia. This is supported by a study showing that there is less potential to regain muscle mass as a patient enters his or hers final 90 days of life [47]. Thus, to manage cachexia properly it is instrumental to classify the condition correctly so that stages of cachexia responsive to treatment can be identified. Acknowledging this, a framework for cancer cachexia classification was published along with the international consensus from 2011 [32]. Cachexia was classified as a trajectory of three different stages: Pre-cachexia, cachexia and refractory cachexia (Figure 2). As described above, the 'cachexia' stage is identified by specific diagnostic criteria, whereas for the other two stages, only suggestive characteristics were presented. Pre-cachexia was described as a stage where cachexia is not yet established, but where early signs, such as anorexia and metabolic changes, are present. Refractory cachexia was described as a stage where cachexia is established, and where the cancer disease has become resistant to anti-cancer treatment. Patients in this stage are characterized by low performance status and short expected survival. The intention was that more exact criteria of pre-cachexia and refractory cachexia were going to be determined by future research. The ability to classify patients in this matter would enable the selection of patients to optimal treatment strategies. Patients with pre-cachexia should receive treatment with the aim of delaying or preventing cachexia, while patients with refractory cachexia should be spared of futile attempts to reverse

cachexia, and instead receive treatment with attention to best possible symptom relief.

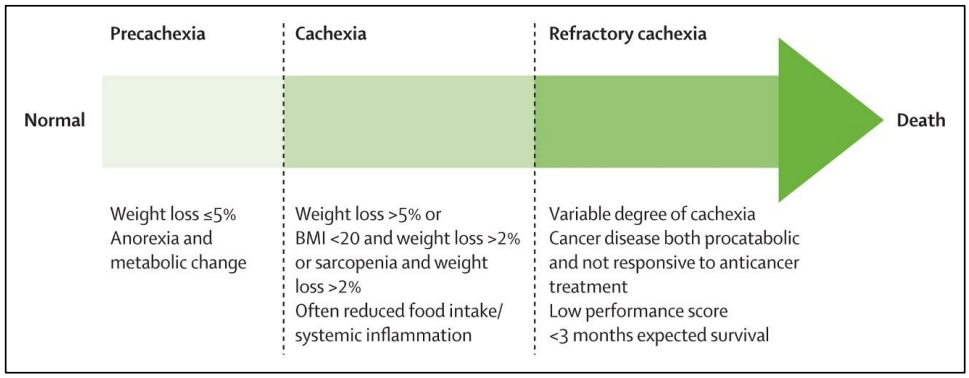

Figure 2 The framework for cachexia classification according to Fearon et al. The cachexia trajectory is classified into three stages, pre-cachexia, cachexia and refractory cachexia. Note that only the cachexia-stage has precise diagnostic criteria, while the other two stages only are described by general characteristics. (Reprinted from The Lancet Oncology, 12(5), Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al., Definition and classification of cancer cachexia: an international consensus, 489-95, Copyright (2011), with permission from Elsevier)

Several studies have been published with the purpose of identifying possible criteria for a classification system modelled after the consensus framework (Table 1) [34, 48-51]. All these studies suggest criteria *a priori* and then attempt to validate the criteria against selected outcomes from the cachexia domains in a cross-sectional study design or against overall survival. Blum et al. [34] performed a study using only anthropometric data (weight loss and BMI) to classify patients. Although there was an overall tendency of worsening in performance status, appetite loss, CRP and survival associated with advanced stages of cachexia, there was little distinction between patients classified as having pre-cachexia and either no cachexia on one side, or cachexia on the other. The authors thus concluded that weight loss and BMI alone is not enough to classify cachexia into several stages. Zhou et al. [52] assessed performance status, appetite loss and biochemistry in addition to anthropometric data to classify patients and demonstrated good discrepancy between all stages in most outcomes, including quality of life, symptoms and survival. The downside of using several items to classify cachexia is that the complexity of the classification system

increases, thus limiting the usability in the clinical setting. An example is the Cachexia Score (CASCO) classification system by Argiles et al. [48], which is very comprehensive and assesses in total 51 different items to classify cachexia. Except for survival analysis, none of the presented studies used longitudinal data to evaluate the trajectory of cachexia or to evaluate if patients with pre-cachexia are at greater risk of developing cachexia compared to patients without cachexia.

Table 1 Studies with the aim of identifying criteria for cancer cachexia classification modelled after the international consensus framework from 2011

Author, year	Study design, cancer type and stage, number included	Classification parameters	Classification system (No cachexia (NC) is present when neither PC, C or RC are applicable)			Outcome (NC – PC – C – RC)
			Pre-cachexia (PC)	Cachexia (C)	Refractory cachexia (RC)	
Van der Meij, 2012 [49]	Cross-sectional + survival analysis NSCLC stage III n=40	WL, anorexia, CRP, FFM index	WL 0-5% + Energy intake < 70% of TEE or <84kJ/kg or appetite < 5 cm VAS + CRP > 8	WL > 5% or WL > 2% and BMI <20 or FFM-index< 5th percentile + Energy intake < 70% of TEE or <84kJ/kg or appetite < 5 cm VAS + CRP > 8	Cachexia + Karnofsky < 50 + Cancer disease pro-catabolic and unresponsive to anti-cancer treatment + Expected survival < 3 months	No patients with RC. Overall differences in QoL[a] (62 – 57 – 35), and mean CRP (30 – 40 – 92), but no difference in physical functioning[a] (76 – 69 – 64). No between stage comparisons. Shorter survival in C (HR 2.93), but not in PC (HR 0.78), compared to NC.
Blum, 2014 [34]	Cross-sectional + survival analysis Locally advanced and metastatic cancer of any type n=861	WL, BMI	1 kg <WL< 5%	WL > 5% or WL>2%+BMI<20	WL>15%+BMI<23 or WL>20%+BMI<27	Mean CRP higher (30 – 29 – 41 – 61) and mean KPS lower (75 – 75 – 68 – 67) in C and RC. Food intake[b] lower in PC, C and RC (21% – 48% – 56% – 69%).

						No between group comparisons. Shorter median survival in C and RC (255 – 269 – 150 – 123)
Vigano, 2016 [50]	Cross-sectional + survival analysis Any type of cancer stage III and IV n=297	A Abnormal biochemistry[c] B Decreased food intake (aPG-SGA box 2 score ≥ 1) C WL < 5% D WL > 5% G Decreased functioning (aPG-SGA box 4 > 2)	A+B or A+C or B+C or A+B+C	A+D or B+D or A+B+D or	A+D+G G + Alb <25 B+D+G A+B+D+G	Median fatigue[d] higher in C and RC (3.5 – 4 – 5 – 7), RC higher than C. Median appetite[d] loss higher in PC, C and RC (0 – 3 – 5 – 7), no difference between C and RC. Differences in body composition in males (various indexes), but not in females. Survival worse in RC and better in NC, no difference between PC and C (median survival not reported).
Argiles, 2017 [48]	Cross-sectional/case-control	WL/lean body mass (0-40 pts.)	15-28 pts.	29-46 pts.	>46 pts.	Good discrimination between patients with cancer (32.54) and healthy controls

	Any type and stage of cancer/healthy controls n=281	Abnormal biochemistry (0-20 pts.) Physical performance (0-15 pts.) Anorexia (0-15 pts.) QoL (0-10 pts.) (All domains assessed with a 51-item questionnaire)				(8.72). Correlation coefficient between classification and oncologist subjective assessment of cachexia severity 0.4. Between classification and ECOG PS 0.3.
Zhou, 2018 [52]	Cross-sectional + survival analysis Any type of cancer stage III and IV n= 259	WL (0-3 pts.) SARC-F (0-3 pts.) ECOG (0-2 pts.) Appetite loss (0-2 pts.) Abnormal biochemistry (0-2 pts.)	3-4 pts.	5-8 pts.	9-12 pts.	Male SMI lower in RC and C (59 – 49 – 45 – 43), No difference between C and RC. Female SMI lower in C and RC (45 – 43 – 38 – 35), no difference between C and RC, but RC lower than PC. QoL[e] lower in PC, C and RC (36– 32 – 26 – 19), and PC, C and RC different from each other. Survival worse in PC, C and RC.

Abbreviations: NSCLC, non-small cell lung cancer; WL, weight loss; CRP, C-reactive protein; FFM, fat-free mass; TEE, total energy expenditure; VAS, visual analogue scale; BMI, body mass index; QoL, quality of life; HR, hazard ratio; KPS, Karnofsky performance status; aPG-SGA, abridged patient generated subjective global assessment; SMI, skeletal muscle index;

[a]European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
[b]Percentage reporting food intake less than usual the last month. [c]CRP>10 mg/mL, white blood cells > 11 000/L, albumin < 32 g/L, hemoglobin < 120 g/L (men) < 110 g/L (women) [d]Edmonton Symptom Assessment Scale [e]Functional Assessment of Anorexia Cachexia Therapy – Anorexia Cachexia Subscale

1.3.2.1 The Weight loss grading system

In addition to describing the *trajectory* of cachexia development – from pre-cachexia, via cachexia, to refractory cachexia, the international consensus also stated that *severity* of cachexia is proportional with magnitude of weight loss, and inversely proportional with BMI [32]. Based on this, Martin *et al.* [53] suggested a five-stage classification system of weight loss severity, termed the Weight loss grading system (WLGS). The classification criteria were based on increments of weight loss and decrements of BMI in combination, as shown in Figure 3. They validated the WLGS with survival as outcome. Little or no weight loss and high BMI was associated with longer survival, while the opposite was associated with shorter survival. However, the relationship with the cachexia domains described in the international consensus [32] was not evaluated. For the WLGS to be fully applicable as a cachexia classification system, it is important that it not only predicts survival, but also associates with other cachexia domains [32].

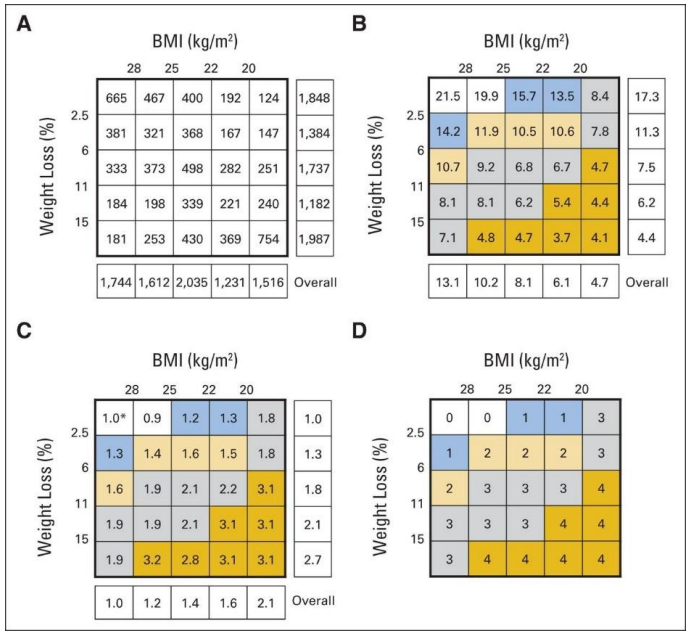

Figure 3 The Weight loss grading system. Increments of weight loss and decrements of BMI combined in in a 5x5 matrix with 25 resulting categories. Sample size, median overall survival and unadjusted hazard ratios for each category are presented in panel A, B and C, respectively. The difference in colors represent significant differences in median overall survival and hazard ratios ($p < 0.05$). The weight loss grades are presented in panel D and result from categories with similar survival. (Martin, L et al: J Clin Oncol 33(1), 2015:90-99. Reprinted with permission. ©2015 American Society of Clinical Oncology. All rights reserved.)

1.3.3 Cancer cachexia prevalence

Knowledge about prevalence of diseases or conditions is important in health care planning. For cachexia, prevalence affects planning of palliative care services, such as nutritional interventions, physiotherapy and numbers of hospital beds, nurses, doctors and more. It is also likely that familiarity with prevalence will affect health care workers' alertness to a condition [54]. Knowing that certain patient groups are susceptible to cachexia may increase vigilance and keep health care workers on the lookout for early signs and symptoms of the condition.

Prevalence depends on several factors, such as population in which it is estimated, choice of diagnostic criteria and methods of measurement of the criteria. There has been great variability in reported estimates of cancer cachexia, and figures have varied

from 30% to 85% [36, 55-57]. Some of the variability can be explained by differences in populations under study. In cancer cachexia, the type of cancer is determining for the prevalence as demonstrated by Sun *et al*. [58]. Overall, they found a prevalence of 36% in a population of mixed, advanced cancer types. However, cachexia was more prevalent in pancreatic cancer (89%) and gastric cancer (77%), and less prevalent in breast cancer (3%) and lymphoma (0%).

As explained previously, the diagnostic criteria for cachexia have varied, and this has likely also affected published prevalence estimates. In a study by Wallengren et al. [36], prevalence varied between 12% using Fearon's definition from 2006 [31]and 85% using the international consensus definition from 2011 [32].

A study examining the consequences of using different methods of measuring muscle mass in patients with advanced cancer found that the prevalence of low muscle mass was 13% using mid upper arm muscle area, 59% using CT-scan and 93% using bioelectrical impedance analysis [44]. However, this had only minor impact on the prevalence of cachexia which was 37%, 43% and 48%, respectively. The reason for this relatively little variation in cachexia prevalence was that most patients (68%, 75% and 89%, respectively) already were diagnosed with cachexia due to the weight loss criterion (weight loss > 5%) [44].

1.3.4 Cancer cachexia pathophysiology

The pathophysiology of cancer cachexia is not fully understood; however, the knowledge is increasing. Cancer cachexia is caused by a variable combination of lowered energy intake and altered metabolism leading to increased energy consumption and muscle and fat tissue breakdown [32]. Systemic inflammation is believed to play an important role, and mediators of cachexia derived from tumor or host include the cytokines tumor necrosis factor-alpha (TNF-alpha) and Interleukin-6 (IL-6) [59-64]. In vitro, TNF-alpha inhibits differentiation of both adipocytes and skeletal myocytes through activation of NF-kappaB [61, 63], however it is unclear if levels are elevated in patients with cancer cachexia, and the role could be more of the

facilitating kind, rather than a direct effect on cachexia development [60]. IL-6 levels correlate with weight loss and reduced survival [62, 64]. IL-6 induces synthesis of acute phase proteins in the liver [62] at the cost of muscle protein synthesis [60] and is also directly involved in muscle protein degradation in animals [59]. Other cytokines, like IL-1, amplify secretion of IL-6 and contribute to a sustained inflammatory process [60]. Further down the reaction cascade, myostatin and activin A are ligands binding to the ActRII receptor and inhibit muscular hypertrophy in the normal state [65-67]. Evidence of increased activity and/or serum levels in both animals and humans with cancer suggest a role in cancer cachexia development [68, 69].

Inflammation also affects the endocrine system via the hypothalamus and the pro-opiomelanocortin system with unfavorable effects on appetite and nutritional intake [70]. Other hormonal changes are also believed to influence cachexia. Advanced cancer affects the pituitary gland to selectively cause activation of the adrenal axis while it suppresses the gonadal axis [70]. Glucocorticoids are well known to cause muscle wasting [60] and might be acting through upregulation of MuRF1 and MAFbx [71]. Low testosterone levels cause muscle breakdown, although the molecular mechanisms behind this are not clear [72]. Patients with cancer also often have increased insulin resistance, which impairs anabolism after food intake [73].

The body's total energy expenditure consists of its resting energy expenditure (REE), diet-induced energy expenditure and activity-induced energy expenditure. In sedentary people, the REE amounts to about 70% of the total energy expenditure [74]. Increased REE, or hypermetabolism, is seen in about 50% of cancer patients [75], however it seems to vary according to tumor type. While patients with pancreatic and lung cancer seem to have elevated REE, patients with gastric and colorectal cancer may have normal levels [76, 77]. Elevated REE may be associated with elevated CRP and weight loss [76, 78], although other studies do not show this association [79]. Several mechanisms of increased resting energy expenditure are proposed. Malignant tumors have an increased glucose uptake, glycolysis activity and lactate production, also known as the Warburg effect [80]. Lactate is later converted back to glucose in the

liver through the Cori cycle with resulting net consumption of energy. Another suggested mechanism is the uncoupling of energy substrate oxidation and synthesis of adenosine triphosfate in the mitochondria occurring in brown adipose tissue [60]. The result is futile burn of energy, released as heat. Brown adipose tissue is usually present in newborn and children, however, the use of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with cancer as well as healthy persons has revealed that brown adipose tissue occurs also in adults [81]. There are reports suggesting that cancer induces browning of white adipose tissue, and thereby increasing resting energy expenditure [82].

Ultimately, muscle protein breakdown occurs through the ubiquitin-proteasome system or by autophagy [83]. In the ubiquitin-proteasome system, ubiquitin molecules bind to the muscle proteins and facilitates degradation by the 26S proteasome. Autophagy is a process where organelles and macromolecules are degraded intracellularly by inclusion in autophagosomes which subsequently fusion with lysosomes.

1.3.5 Cancer cachexia treatment

The complexity of the cachexia pathophysiology and the lack of success of unimodal treatment strategies supports a multimodal strategy for the treatment of cancer cachexia [84]. The evidence for this is limited but growing [85-87]. Guidelines suggest that multimodal treatment should be composed of nutritional therapy, physical exercise and pharmacological treatment [88].

According to the guidelines, all patients should be screened for nutritional risk, further classified and receive dietary counselling and treatment as needed. This may increase energy intake, body weight and possibly quality of life, but results are inconsistent [89-91]. Artificial nutrition is recommended if dietary advice and oral nutritional supplements are insufficient. In that case, enteral nutrition should be preferred, and parenteral nutrition should be reserved for patients that do not benefit from enteral administration [88].

Physical exercise is recommended to maintain muscle mass and physical function in patients with cancer [88]. Aerobic and resistance exercise can improve aerobic capacity and muscle strength [92, 93], and moderate to small effects on fatigue and quality of life are also observed [93-95]. However, the majority of studies are performed on patients with early stage breast or prostate cancer, and little data exist on patients with advanced stage cancer [92]. Still, exercise seem safe and well-tolerated also in these patients, and individually adapted exercise programs to avoid a sedentary lifestyle are probably beneficial [88, 96, 97].

Cachexia is caused by metabolic changes resulting from tumor, host or the interaction between the two [60], and although inactivity and lack of nutrients probably contributes to the development of the condition, nutrition and exercise treatment by itself will not be effective in fully reversing cachexia. Thus, to significantly improve the negative protein- and energy balance in cachexia, it is believed that pharmacological intervention is necessary. Agents targeting different aspects of the cachexia pathophysiology, such as inflammation, reduced anabolism and appetite loss have been tested [98-100]. In 2005 Yavuzsen *et al.* [101] published a systematic review of pharmacological treatments of cancer cachexia and concluded that only corticosteroids and progestins had documented effects against cachexia. Corticosteroids improve appetite, fatigue and well-being [101, 102], and progestins improve appetite and weight, but not fat-free body mass [101, 103]. Potentially serious side effects such as muscle wasting, infections and thromboembolism limit the use of these two agents, and they are primarily recommended for patients with advanced cancer [88]. Several new agents have been tested in recent years, and an updated systematic review of new pharmacological treatments in the period 2004-2018 highlights the effects of enobosarm and anamorelin [104]. Enobosarm is a selective androgen receptor modulator, which showed promising results in a phase 2 study with an increase in lean body mass of 1.5 kg vs. 0.02 kg in the placebo group, and an increase in mean stair climb power [98]. However, in two phase 3 studies, which are yet unpublished, results failed to ascertain the effect on function as only one of the

studies was able to demonstrate an improvement in stair climb power [105]. Anamorelin is a ghrelin-analogue, which in two phase 3 studies showed an improvement in lean body mass of 0.99 kg and 0.65 kg vs. a reduction of 0.47 kg and 0.98 kg in the respective placebo arms [100, 106]. However, there was no difference in hand grip strength, which was the functional endpoint in both studies. Marginal improvement of lean body mass, and lack of effect on functional endpoints are the reasons why these two agents have been denied approval by the U.S. Food and Drug Agency [107] and by the European Medicines Agency [108].

Failure to demonstrate effect on clinically relevant functional endpoints by unimodal pharmacological intervention studies has encouraged further research on multimodal therapy, and a study investigating the effect of nutrition, physical exercise and anti-inflammatory treatment on cachexia is ongoing [109].

2 Aim of the thesis

The overall aim of the thesis was to gain new knowledge of the prevalence of cancer cachexia and contribute to a better classification system to allow for optimal selection of anti-cachexia treatment for each individual patient in the future.

The following research questions were posed:

Paper I:

1. What is the prevalence of cancer cachexia in an unselected population of patients with cancer?
2. Which demographic and clinical factors are associated with cancer cachexia prevalence, and what is the prevalence in the subgroups defined by these factors?
3. Which demographical and clinical factors are associated with patient-perceived need of increased clinical attention to weight loss and nutrition

Paper II:

1. Can prognostic utility of the Weight loss grading system (WLGS), which has been proposed as a potential classification system of cancer cachexia, be confirmed in a population of patients with incurable cancer?
2. Can specific cachexia parameters (e.g. appetite loss) contribute to the prognostic ability of the Weight loss grading system?
3. Does the Weight loss grading system have validity as a classification system of cancer cachexia?
4. Is the Weight loss grading system predictive of cachexia progression?

Paper III:

1. Which demographical and clinical factors are independent predictors of cachexia development?

2. Which combinations and cut-offs of these predictors most optimally predict cachexia development?
3. What is the accuracy of cachexia predictions using the resulting model?

3 Materials and methods

3.1 Patients and study design

Data from two studies were used in this thesis, the Symptom Prevalence Study and the European Palliative Care Cancer Symptom Study (EPCCS). An overview of the studies is presented in Table 2.

Table 2 Overview of study designs and populations

Paper	Study name	Study design	Population	Amenable to analysis	Number of patients (total/analyzed)
I	Symptom prevalence study	Cross-sectional study Regional (Central-Norway) Three centers	Cancer (all stages and types, also follow-up), COPD or heart failure Adult patients	Active cancer (not follow-up) and non-missing data on weight loss and BMI	553/386
II	European Palliative Care Cancer Symptom Study (EPCCS)	Longitudinal, prospective observational study International (Europe, Canada, Australia) 30 centres	Incurable cancer (all types and stages) Under care of a palliative care facility Adult patients	Non-missing data on weight loss and BMI at baseline and for at least one follow-up visit	1739/1406
III				Patients without cachexia at baseline, else as in paper II	1739/628

Abbreviations: COPD, chronic obstructive pulmonary disease;

3.1.1 The symptom prevalence study

Paper I was based on a cross-sectional study conducted among in- and outpatients at three sites: St. Olavs Hospital – Trondheim University Hospital, Ålesund Hospital and Øya community hospital, all within the Central Norway Regional Health Authority, serving a total population of 700,000. The overall aim was to quantify severity and prevalence of pain, cachexia and mood disorder in patients with cancer, heart failure

and chronic obstructive pulmonary disease (COPD). Eligible patients had cancer (including patients with potentially cured cancer but still in follow-up), COPD or heart failure, were aged >18 years, were able to read and write Norwegian and had sufficient cognitive function to complete assessments. To minimize possible influence of temporary post-operative symptoms (nausea, pain etc.), patients who had had surgery in the preceding 24 hours to inclusion were excluded. All inpatients with cancer at departments of surgery, internal medicine and medical and radiation oncology at all three study sites were screened and approached on predefined days in September 2013. At the same time, in- and outpatients with COPD or heart failure were recruited from the department of internal medicine at St. Olavs hospital and Øya community hospital. Outpatients with cancer were recruited from the department of medical and radiation oncology at St Olav's Hospital in January 2014. As different primary tumor types cluster on specific days of the week, the recruitment of outpatients was spread out over 10 predefined days (such that each weekday was represented twice) to avoid selection bias. A total of 553 patients were included. For the preplanned analysis in paper I, only patients with active cancer (not in follow-up after potentially curative treatment) and with non-missing data on weight loss and body mass index (BMI) were analyzed.

3.1.2 The European Palliative Care Cancer Symptom Study (EPCCS)

Paper II and III were based on the European Palliative Care Cancer Symptom study (EPCCS) [110], which was a longitudinal, prospective, observational study conducted by the European Palliative Care Research Centre (PRC) and the European Association for Palliative Care (EAPC) Research Network. Between April 2011 and October 2013, 1739 patients from 30 centres across Europe (27), Canada (2) and Australia (1) were included. The overall aim of the EPCCS study was to improve the understanding of symptom development, and how these symptoms may best be assessed and classified in order to improve symptom management [110]. Eligible patients were ≥18 years of age; with incurable cancer and were under care of a palliative care facility. For the

analyses in paper II and III, patients with non-missing data on weight loss and BMI at baseline and for at least one follow-up visit were included.

3.2 Assessments

3.2.1 Anthropometric data and cachexia

Current body weight and height were reported by the patients in paper I and measured by study personnel in paper II and III. Historic weight loss in the 6 months prior to inclusion was patient reported in all three papers. In paper II and III, which is based on longitudinal data, weight loss at follow up visits was computed by adding 1) measured weight loss relative to baseline weight and 2) patient reported weight loss at inclusion.

The diagnosis of cachexia was based on the consensus diagnostic criteria published in 2011 [32] except for measurement of muscle mass:

- Weight loss >5% since 6 months prior to inclusion; or
- BMI <20 kg/m^2 and any degree of weight loss >2% since 6 months prior to inclusion

This simplification of the consensus definition has been validated by Blum et al. [34] and results in a minor underestimation of cachexia prevalence [44]. It was chosen because measurements of muscle mass were not available in the dataset.

3.2.2 aPG-SGA

The abridged Patient Generated Subjective Global Assessment (aPG-SGA) was used in paper I to assess weight loss and nutritional risk. It is a four-part questionnaire, which assesses the following axes of cachexia [111]:

- Weight loss history
- Food intake
- Symptoms that affects nutritional intake (Nutritional Impact Symptoms)
- Performance status.

aPG-SGA is exclusively based on patient-reported statements and is an abridged version of PG-SGA [112], which encompasses both patient-reported statements and clinical examination by health care personnel. aPG-SGA is simpler and less resource demanding in clinical studies, but still correlates well with PG-SGA [113]. It is also associated with unfavourable symptoms and clinical findings of cachexia [111].

3.2.3 EORTC QLQ C15-PAL

The European Organization for Research and Treatment of Cancer Palliative Core Quality of Life Questionnaire (EORTC QLQ-C15-PAL) was used in paper II and III to assess quality of life. It is a 15-item questionnaire covering the following functional and symptom scales relevant to palliative care: physical functioning, emotional functioning, fatigue, pain, nausea, lack of appetite, shortness of breath, constipation, sleeping difficulties and overall quality of life [114]. Each of these scales are based on the patient's answers to questions such as "Do you have any trouble taking a short walk outside of the house?" or "Have you lacked appetite?", and where the answering options are "Not at all", "A little", "Quite a bit" and "Very Much" (Except for overall quality of life which is scored on a numerical rating scale ranging from 1 [worst] to 7 [best]). The answer options correspond to a score of 1-4 and are linearly converted to a score of 0-100 for each scale, which can be based on one or several questions [114]. For the two functional scales and overall quality of life, 100 represents high functioning/quality of life, while for the seven symptom scales, 100 represents high symptom load. EORTC QLQ-C15-PAL is an adaptation of EORTC QLQ-C30 [115], which is a generic quality of life questionnaire in cancer. According to Osoba *et al.* [116], a difference in scores of more than 20 on the 0-100 scale of EORTC QLQ-C30 is considered a large difference, a difference of 10-20 a medium difference, and 5-10 a small, but still clinically significant difference. These cut-offs were used in paper II when evaluating the clinical significance of differences in quality of life between patients of different weight loss grade.

3.2.4 Performance status

Performance status is one of the most important prognostic and predictive factors of oncology and have great utility in oncologic practice. It is based on the physician's assessment of the patient through history taking and clinical examination, and scored from 0 (worst) to 100 (best) in increments of 10 (Karnofsky) or from 0 (best) to 5 (worst) (ECOG) [117, 118]. It is one of the strongest prognostic factors of survival in cancer [119], and it is used to guide treatment initiation, dosage and termination of chemotherapy, targeted therapy and radiotherapy. It is a mandatory assessment in nearly all clinical trials in oncology and part of the EAPC basic dataset of descriptors of palliative care patients [120].

Cachexia leads to lowered performance status and functional impairment through progressive loss of muscle mass and function [32]. Performance status is therefore an important factor in the assessment of cachexia. The Karnofsky performance status was used in paper II and III, while patients in paper I was assessed with either Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status. To harmonize the scores in paper I, performance status was reclassified into three groups corresponding to ECOG 0-1, ECOG 2 and ECOG 3-4 based on a previously published algorithm [121].

3.2.5 PHQ-4

The Patient Health Questionnaire for Depression and Anxiety (PHQ-4) is a 4-item questionnaire for screening of symptoms of mood disorder [122]. It is a combination of the two 2-item questionnaires PHQ-2 [123] and Generalized Anxiety Disorder scale (GAD-2) [124], which screens for symptoms of depression and anxiety, respectively. Each question is answered using a 4-point Likert-scale scored from 0 to 3. Thus, the possible total score ranges from 0 to 12. A score of 3 or greater on either the depression or anxiety subscale is considered indicative of the respective disorders, while the total score complements the subscales and is an overall measure of symptom burden, impairment and disability due to mood disorder [122].

3.2.6 Chalder fatigue scale

The Chalder fatigue scale was originally developed to measure symptoms of chronic fatigue syndrome [125], but have later been revised and is now a valid measurement of fatigue in several clinical populations as well as in the general population [126, 127]. It has not been validated in a cancer population, but have in spite of this been recommended for use in patients with cancer [128]. The full questionnaire consists of 11 questions answered on a 4-point Likert scale scored from 0 to 3. The questions span two dimensions of fatigue; item 1-7 concerns physical fatigue, whereas item 8-11 relates to psychological fatigue, and scores can be reported separately or in total [129]. The physical subscale was applied in paper I to measure fatigue that could relate to lowered muscle mass in patients with cachexia.

3.2.7 Brief pain inventory

The brief pain inventory is a questionnaire originally developed for a cancer population and assesses intensity of pain and consequences of pain in daily living [130].The initial question on presence of pain (yes/no) in the Brief Pain inventory [131] was used in paper I to identify patients with pain.

3.2.8 Study specific assessments

In paper I, a study specific question was used to assess if patients had an unmet need of attention to weight loss and nutrition. The question was (translated from Norwegian): “Serious illness can cause many different ailments. Is there something you could wish that your doctor had focused more or less on?” The patients were then presented a list of different ailments, of which nutrition/weight loss was one item, and pain, nausea, depression and anxiety were the other ailments. For each ailment, patients were asked to choose between the following answer options on a Likert-type scale: “A lot less focus”, “Less focus”, “Sufficient as it is”, “More focus” or “A lot more focus”.

3.3 Statistical analysis

Stata v. 13.1 (StataCorp, College Station, Texas, USA) was used for the statistical analyses of paper I and III, while IBM SPSS Statistics v. 21 (IBM, Armonk, New York, USA) was used in paper II. Unless stated otherwise, a two-sided significance level of 0.05 was used.

3.3.1 Paper I

Prevalence of cachexia was estimated in total, and for subgroups based on demographic, and disease related characteristics (age, gender, cancer type, tumour spread, oncologic treatment and treatment intent). Due to differences in recruitment between the in- and outpatient samples, prevalence was reported separately for in- and outpatients in all instances to avoid selection bias. Univariable and multivariable logistic regression was used to determine associations between prevalence and the subgroups listed above. Proportion of patients expressing an unmet need of attention to weight loss and nutrition was evaluated by dichotomizing the answer options for the study specific question: “A lot less focus”, “Less focus” and “Sufficient as it is” was regarded as not having an unmet need, and “More focus” or “A lot more focus” was regarded has having an unmet need of attention to weight loss and nutrition. The proportion was reported both for the total sample and was stratified based on whether patients had cachexia or not. Linear regression was used to determine associations between need for attention and demographical factors, disease and treatment specific factors as well as cachexia, food intake, pain, fatigue and symptoms of mood disorder.

3.3.2 Paper II

To evaluate prognostic validity of the weight loss grading system (WLGS), Kaplan-Meier plots were drawn, and Cox Proportional hazards’ method was used with the WLGS as independent variable. Adjustments for possible covariates as age, sex, cancer type and tumour spread were made. To evaluate if items from the cachexia domains improved prognostic ability – appetite loss, dietary intake, performance status, fatigue, physical functioning and emotional functioning were added to the Cox model in a forward

stepwise manner. To evaluate if a worsening in weight loss grade was associated with a worsening in any of the cachexia items above, the mean of each item was plotted against the WLGS. To confirm statistical significance, analysis of variance was used with the WLGS as grouping variable, and a post-hoc linear test for trend was applied to confirm a linear relationship. For items with non-normal distributions, non-parametric analogues were used. To explore if the WLGS predicted progression of cachexia, a comparison of the proportions of patients progressing from their baseline weight loss grade to a more severe grade was conducted. Due to attrition, a sensitivity analysis was performed replacing missing values for weight loss grade with minimum and maximum attainable values. As the sensitivity analysis revealed a risk for attrition bias, single imputations using an iterative estimation and maximization (EM) algorithm with auxiliary variables sex, height, body weight, weight loss and appetite loss were performed.

3.3.3 Paper III

To identify predictors of cachexia development, time to cachexia development was used as outcome in Cox proportional hazards' regression. Potential predictors where identified in univariable analysis and predictors with a p-value < 0.2 were included in the multivariable analysis. Predictors which where non-significant in the multivariable analysis where removed one by one until the model consisted of only significant predictors. Interaction between remaining predictors where checked and included in the model if significant. The significant independent predictors were all included in a classification and regression tree analysis to identify which combinations and cut-offs of the predictors that optimally classified patients into levels of different risk of cachexia development. A Kaplan-Meier plot was constructed to illustrate time to cachexia development for each risk level, and Receiver Operating Characteristic curve analysis, calibration plot and Harrell's C-statistic was used to assess accuracy of the risk level model in a subset of patients still in the study after 3 months.

3.4 Ethics

Both the Symptom Prevalence Study and the EPCCS study were conducted in accordance with the principles of the Helsinki Declaration of 1964 and its amendments [132]. The studies were approved by the regional ethics committees at each study site (in Norway: The symptom prevalence study: REK Midt 2013/896 and EPCCS: REK Midt 2010/2945), and all participating patients had to provide written informed consent.

Authorship was awarded and funding and conflicts of interest were reported in keeping with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" [133].

4 Results and summary of papers

A summary of patient characteristics is presented in Table 3.

Table 3 Characteristics of patients included in final analysis and patients excluded due to missing data on weight loss or BMI

	Paper I		Paper II		Paper III	
	Incl.	Miss.	Incl.	Miss.	Incl.	Miss.[a]
N	386	40	1406	333	628	425[b]
Median age (IQR)	65 (16)	69 (12)	66 (17)	70 (16)	65 (17)	69 (17)
Gender f(%)						
Female	172 (45)	25 (63)	705 (50)	166 (50)	359 (57)	208 (49)
Male	214 (55)	15 (38)	700 (50)	166 (50)	269 (43)	216 (51)
Cancer type f(%)						
Gastrointestinal	85 (22)	12 (30)	418 (30)	110 (33)	139 (22)	141 (34)
Urological/male genitalia	79 (20)	5 (13)	160 (11)	48 (14)	68 (11)	61 (15)
Haematological	70 (18)	4 (10)	38 (3)	9 (3)	13 (2)	11 (3)
Lung	25 (6)	2 (5)	282 (20)	63 (19)	125 (20)	70 (17)
Breast	76 (20)	10 (25)	252 (18)	35 (11)	171 (27)	45 (11)
Gynaecological	4 (1)	1 (3)	82 (6)	21 (6)	36 (6)	25 (6)
Other	47 (12)	6 (15)	174 (12)	47 (14)	75 (12)	64 (15)
Performance status[c]						
ECOG PS 0-1 f(%)	302 (78)	26 (65)	517 (37)	56 (17)	312 (50)	95 (23)
ECOG PS 2 f(%)	62 (16)	9 (23)	625 (45)	139 (43)	257 (41)	169 (41)
ECOG PS 3-4 f(%)	22 (6)	5 (13)	261 (19)	126 (39)	59 (9)	150 (36)
Mean weight loss (6 months) [%] (SD)	2.6 (7.1)	-	5.9 (7.5)	-	0.5 (1.2)	-
Mean BMI [kg/m2] (SD)	25.6 (4.3)	-	24 (4.9)	-	25.5 (4.5)	-

Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviations; BMI, body mass index

[a]The 686 patients excluded due to cachexia at baseline are not counted [b]216 missing at baseline and 209 missing at follow-up [c]Karnofsky performance status has been converted to ECOG PS in patients from paper II and III, and in some patients from paper I.

4.1 Paper I

Background: Estimates of cachexia prevalence vary due to use of different definitions and selected patient samples. Accurate estimates of prevalence are important for planning of health care services and may improve recognition of the condition. Even if cachexia in many situations is not treatable, several studies have pointed to the psychological consequences patients and their next of kin suffer if cachexia is not

acknowledged by health care personnel [24, 134]. Following the international consensus definition of cancer cachexia in 2011 [32], there is now a need to establish estimates of prevalence.

Aim: The primary aim of the present study was to assess the prevalence of cachexia in an unselected cancer population. A secondary aim was to assess patient-perceived need of attention to cachexia.

Methods: A cross-sectional study in hospital patients was undertaken. Key inclusion criteria were age >18 years, cancer diagnosis, and no surgery the preceding 24 hours. Data on demographics, disease, performance status, symptoms, cachexia and patients' perceived need of attention to weight loss and nutrition were registered. Cachexia was defined as weight loss >5% past six months prior to inclusion, or body mass index (BMI) < 20 kg/m^2 if weight loss >2%.

Results: 386 patients were included in the analysis. Median age was 65 years (IQR 56-72), 214(55%) were male, 302(78%) had a performance status of 0-1 (Eastern Cooperative Oncology Group) and 308 (80%) were outpatients. Prevalence of cachexia was 51% (95%CI 40-63) in inpatients and 22% (95%CI 17-27) in outpatients. Prevalence was significantly higher in patients with lung cancer (OR 6.3 [95%CI 2.3 -17.2]) and gastrointestinal cancer (OR 4.1 [95% CI 1.9-8.8]) compared to patients with hematological cancer. Prevalence was also significantly higher in patients with palliative treatment intent (OR 1.6 [95%CI 1.0 -2.6]). There was no significant difference between patients with metastatic disease (OR 1.3 [95%CI 0.8-2.0]) and localized disease, or between male (OR 1.3 [95%CI 0.9 – 2.1]) and female. After multivariable analysis, only cancer type and provision of care (inpatient/outpatient) significantly affected prevalence of cachexia. 20% of inpatients and 15% of outpatients wanted more attention to weight loss and nutrition. For patients with cachexia this proportion increased to 37% in inpatients and 33% in outpatients. Apart from cachexia ($p<0.001$), symptoms of mood disorder ($p<0.001$) and male gender ($p<0.01$) were independently associated with increased need of attention.

Conclusion: Cachexia is a common condition among cancer patients and is especially prevalent in patients with gastrointestinal and lung cancer. Surprisingly, the difference in prevalence between localized and metastatic cancer is small. Clinical attention to the condition is an unmet need in one third of patients with cachexia.

4.2 Paper II

Background: A weight loss grading system (WLGS) classifying the severity of weight loss in patients with cancer based on historic weight loss and current BMI has been published [53]. The WLGS has been proposed as a tool for prognostication of survival. However, the WLGS has not been evaluated as a cancer cachexia classification system.

Aim: To examine if the WLGS is applicable as a classification system of cancer cachexia by 1) confirming its prognostic validity and explore if items from the cachexia domains can improve prognostic ability of survival, 2) evaluating concurrent validity to cachexia domains and 3) exploring its ability to predict cachexia progression.

Methods: An international, prospective observational study of patients with incurable cancer was conducted. For each patient, weight loss grade was scored 0-4. Weight loss grade 0 represents a high BMI with limited weight loss, progressing through to weight loss grade 4, representing low BMI and a high degree of weight loss. Survival analyses were used to confirm prognostic validity. Cox regression was used to evaluate if the addition of cachexia domains to the WLGS improved prognostic accuracy. Analyses of variance were used to evaluate the relationship between the WLGS and cachexia domains (anorexia, dietary intake, Karnofsky performance status [KPS], physical and emotional functioning). Predictive ability of cachexia progression was assessed by estimating proportion of patients progressing to a more advanced weight loss grade.

Results: 1406 patients were analyzed (median age 66 years; 50% female, 63% KPS ≤70). The overall effect of the WLGS on prognosis of survival was significant as expressed by change in -2 log likelihood ($p<0.001$) and persisted after adjustment for age, sex, cancer type and stage ($p<0.001$). Median survival decreased across the weight loss grades, ranging from 407 days (95%CI 312-502) – weight loss grade 0, to

119 days (95%CI 93-145) – weight loss grade 4. This confirmed the result in the primary study of the WLGS [53]. When KPS, appetite, physical and emotional functioning was added to the survival model, the prognostic accuracy of the WLGS improved. When evaluating the relationship between cachexia domains and the WLGS, all cachexia domains significantly deteriorated with increasing weight loss grade. Deterioration was greatest for dietary intake, with a difference corresponding to 0.87 standard deviations between weight loss grade 0 and 4. Likelihood of cachexia progression was greater in patients with weight loss grade 2 (39%) than with weight loss grade 0 (19%) or 1 (22%).

Conclusion: The WLGS is associated with survival and cachexia domains. Adding the following items from the cachexia domains to the WLGS improves prognostic accuracy: KPS, appetite, physical and emotional functioning. The likelihood of cachexia progression is greater with weight loss grade 2 compared to weight loss grade 0 or 1.

4.3 Paper III

Background: Several new drugs have been evaluated in clinical trials in recent years [104], but none have so far received approval for the treatment of cancer cachexia. One reason for this might be that they have not been used at the optimal time point or in patients truly at risk of developing cachexia. A predictive model of cachexia development would help identify those at greatest risk for early therapeutic intervention.

Aim: The aims of this study were to identify predictors of cachexia development and to create and evaluate accuracy of a predictive model based on these predictors.

Methods: A secondary analysis of a prospective observational study was conducted. Patients who received palliative care due to incurable cancer and did not have cachexia at baseline, were amenable to the analysis. Cachexia was defined as weight loss >5% (6 months) or weight loss >2% and body mass index<20kg/m^2. Clinical and demographic markers were evaluated as possible predictors with Cox analysis. A classification and regression tree analysis was used to create a model based on optimal combinations and cut-offs of significant predictors for cachexia development, and

accuracy was evaluated with a calibration plot, c-statistic and receiver operating characteristic curve analysis.

Results: Six-hundred-twenty-eight patients were included in the analysis. Median age was 65 years (IQR 17), 359(57%) were female and median Karnofsky performance status was 70(IQR 10). Median follow-up was 109 days (IQR 108), and 159(25%) patients developed cachexia. Initial weight loss, cancer type, appetite and chronic obstructive pulmonary disease (COPD) were significant independent predictors ($p \leq 0.04$) of cachexia development. A five-level model was created with each level associated with an increasing risk of cachexia development. For level 1-patients (weight loss <3%, breast or hematologic cancer and no or little appetite loss), median time to cachexia development was not reached, while level 5-patients (weight loss 3-5%) had a median time to cachexia development of 51 days. The estimated risk of cachexia development fitted well with the observed risk in the dataset, however ability to discriminate between a randomly selected pair of patients that did and did not develop cachexia after three months was only 76%.

Conclusion: Initial weight loss, cancer type, appetite loss and COPD are identified as important predictors of cancer cachexia. These predictors can be used to construct a clinically applicable five-level predictive model of cancer cachexia.

5 Discussion

5.1 Main findings

In paper I, it is confirmed that cachexia is a prevalent condition, especially in hospitalized patients (51%), but also in a considerable number of outpatients (22%). The prevalence is highly dependent on type of cancer, being more prevalent in gastrointestinal cancers and lung cancers, and less prevalent in breast cancer. Our findings suggest a lesser dependency of prevalence on tumor spread. Furthermore, a considerable number of patients suffering from cachexia feel that too little of their physicians' attention is given to the issues of weight loss and nutrition. In paper II, it is confirmed that the Weight loss grading system (WLGS), grading the severity of weight loss based on the patients' concurrent body mass index (BMI), is prognostic of survival in patients with incurable cancer. The prognostic precision of this grading system was improved by using information on performance status, physical and emotional functioning, and appetite. Furthermore, the validity of this grading system as a classification system for cancer cachexia was verified based on a demonstrated association between the WLGS and severity of several characteristics related to the cachexia phenotype. To some extent, the WLGS also predicts who will have cachexia progression, as patients with weight loss grade 2 were more likely to progress than patients with weight loss grade 0 or 1. In paper III, it is demonstrated that information on cancer type, appetite loss and comorbidity with chronic obstructive pulmonary disease (COPD) increases the accuracy of cachexia classification when added to information on early weight loss, and a model for prediction of cachexia development based on these predictors was constructed.

For more than a decade it has been argued that it is essential for successful management of cachexia to start treatment already in the developmental phase of the condition. Hence, the term pre-cachexia [32, 46]. Early detection of cancer cachexia necessitates an awareness to the condition and knowledge about its prevalence [54]. In diagnostics, prevalence is also fundamental for understanding how test accuracy (sensitivity and specificity) affects post-test likelihood of a condition [135]. A high

prevalence (pre-test likelihood), as compared to a low prevalence, will increase the probability of the condition following a positive test, even though the test accuracy stays the same in both scenarios. The same test will thus have different predictive ability depending on which clinical setting, or population, it is applied to. Thus, estimates of cachexia prevalence in different patient groups is an important prerequisite when evaluating diagnostic tests for cachexia.

Prevalence has been reported in several previous publications [36, 56-58], and the only consistency seem to be that the estimates are varying. Explanation for this are of course the variance in definitions of cancer cachexia being used and the case mix of the investigated populations. In paper I, we found that the prevalence varies strongly with type of cancer and with level of care (inpatients vs. outpatients). Although a cross-sectional study does not allow for inferences on causation, it is likely that certain cancer types to a greater degree causes cachexia, and this is confirmed in paper III. Regarding the association between cachexia and level of care, this can be explained by the fact that patients with cachexia generally are in a poorer state and require more comprehensive care. Thus, cachexia prevalence will always be dependent of the types of cancer in a population and the setting in which cachexia prevalence is measured. However, studies of this kind are often done in single or a few institutions [36, 58], and the overall prevalence reported thus only reflect the kinds of patients who are seen in that institution. To increase external validity, one should at least report the composition of cancer types and the number of inpatients and outpatients. Preferably, prevalence should be reported for each subgroup. To find a meaningful estimate of overall cancer cachexia prevalence, a large epidemiological survey in patients with cancer is needed. Such a study is justified by the impression left by paper I, and others [17, 36, 58], that cachexia is highly prevalent and causes significant distress to many patients with cancer. A precise estimate of overall cachexia prevalence would help planning for better cancer care, both for patients in hospitals and in the community.

Health care personnel's awareness to cachexia has been questioned in a previous study [25], and several qualitative studies report that progressive weight loss is of

great concern to patients with cancer and their next of kin [21, 136-138]. Lack of attention to weight loss seem to increase the concern they are experiencing [24]. We have shown that one third of patients with cachexia have an unmet need for attention to their weight loss and related therapies. Our result was comparable to a later questionnaire-based study in Japanese patients in a palliative care setting where 53% of patients with cachexia vs. 33% of patients without cachexia had a self-perceived need for nutritional support [139]. One can conclude that cachexia is a source of great concern, and patients suffering from cachexia are very much aware of the severity of their condition. This underlines the need for integration of palliative and oncological care as cancer cachexia is prevalent, not only late in the cancer trajectory, but also at diagnosis and during active anti-cancer treatment [19]. Knowing that cachexia may greatly affect tolerance to chemotherapy and overall prognosis [20, 140], it is imperative that cachexia as well as other symptoms is acknowledged and managed. Introducing the patient-centered approach, characteristic of palliative care, into the tumor-centered mindset of oncological care could facilitate the future management of cancer cachexia and improve overall cancer care [141].

The Swedish botanist Carl von Linnè, known as the founder of modern taxonomy, is often quoted: *"All real knowledge which we possess depends on methods by which we distinguish the similar form the dissimilar. The greater the number of natural distinctions this method comprehends the clearer becomes our idea of things." [142]* A prerequisite for modern medicine is the ability to recognize the different medical conditions and distinguish them from each other, so that we can develop and subsequently prescribe specific treatment to each condition. The International Statistical Classification of Diseases and Related Health Problems (ICD), currently in version 10 (version 11 in preparation), is perhaps the most widely used classification system for medical diagnoses [143]. Each disease can be further subdivided according to any number of different classifiers on several different levels (clinical, cellular or molecular). As an example, cancer is often classified according to the TNM-system (Tumor, Nodulous, Metastasis), which stages the cancer according to size of primary

tumor; presence, number and localization of lymph nodes and presence of metastases to distant organs [144]. TNM-stage is often mandatory to guide treatment decisions about surgery, radiotherapy, chemotherapy or palliative care. In addition, cancer can be classified according to pathological findings and, increasingly, molecular and genetic analyses to further tailor treatment.

In cancer cachexia, there has been an ongoing effort to classify the condition for the last decade. The international consensus from 2011 stated that cachexia should be classified according to both severity and trajectory [32], as described in the background section of this thesis. Particular attention has been devoted to identifying a pre-cachexia stage, as it is expected that preventive rather than therapeutic measures against cachexia will be more efficacious [46]. Given that cachexia ensues when weight loss exceeds 5 % in 6 months (or 2% if BMI is less than 20 kg/m^2), pre-cachexia obviously exists somewhere below this cut-off. Other than that, the international consensus published in 2011 stated no specific criteria for its diagnosis but suggested that it be characterized by metabolic change and/or appetite loss [32]. A common prerequisite of later studies attempting to establish diagnostic criteria for pre-cachexia seems to be that patients with pre-cachexia must differ in cachexia symptom severity, physical performance and quality of life from patients classified as non-cachectic as well as from patients classified with cachexia [34, 48-50, 52]. I.e. they must do significantly worse than patients without cachexia but do better than patients with cachexia. This is reasonable if the goal is to identify patients with some symptoms of cachexia without having cachexia. “Mild cachexia” could perhaps be a more appropriate term as it reflects that the identified criteria relate more to severity of cachexia rather than the trajectory of cachexia. Although we demonstrate in paper II that severity and trajectory are related, it has not been investigated in previous studies (Table 1) if patients with pre-cachexia actually have a greater risk of progressing to cachexia [34, 48-50, 52].

The term *pre-cachexia* indicates a condition that precedes cachexia, implying that these patients have an increased risk of developing cachexia with time. If the criteria

define a population that have such an increased risk of developing cachexia, the patients may or may not differ from patients with no cachexia in terms of symptoms, quality of life etc. The criteria defining pre-cachexia may be based on symptoms, clinical findings or biomarkers associated with cachexia, although in the case of weight loss, the diagnostic cut-off may of course not supersede the diagnostic cut-off of cachexia. In paper II and paper III, we show that weight loss and weight loss grade *is* an important predictor of cachexia development, and probably should be included as one diagnostic criterion of pre-cachexia. This is consistent with the considerations of most researchers in the field, as many of the published pre-cachexia models include weight loss as one diagnostic criterion (Table 1). Given that the diagnosis of cachexia mainly is based on weight loss, it might not seem surprising that minor weight loss is a predictor. However, it should be remembered that the cachexia diagnostic cut-off of 5 % is a small cut-off, only 3.75 kg in a person weighing 75 kg. Any weight loss less than that, for example 1 or 2 kg, is practically within the normal day to day variation of a human being and need not be an initial sign of progressive weight loss. In fact, our results support this by showing that weight loss becomes increasingly important as a predictor when it supersedes 3%. In patients with weight loss less than 3%, other predictors, such as cancer type and appetite loss, become important.

As shown in previous work as well as in paper I, cancer type is associated with cancer cachexia prevalence [19, 58]. Following from this, and that occurrence of cancer always precedes the occurrence of cachexia, a logical assumption would be that cancer type predicts the development of cancer cachexia. Indeed, this is confirmed in paper III, showing that patients with pancreatic and gastric cancer have an increased risk of cachexia development, while a diagnosis of breast or hematologic cancer seem to reduce risk of cachexia. To our knowledge, cancer type have never been suggested as marker of pre-cachexia in any previously published classification system [34, 48-50, 52], and the reason for this might be that these studies have not evaluated cachexia prediction, as per the discussion above. However, some studies evaluating early intervention against cachexia have used cancer type as a selection criterion [86, 145],

presumably to select patients with an increased risk of cachexia development and/or progression, and thereby increasing the likelihood of demonstrating an effect.

Paper III shows that appetite loss is another predictor of cachexia and is an especially important predictor in the group of patients without weight loss or high-risk cancer type (pancreatic or gastric cancer). In this group, patients with considerable appetite loss have approximately two times the risk of developing cachexia compared to patients with little or no appetite loss. Appetite loss was suggested by the consensus paper as a clinical marker of pre-cachexia [32] due to its role in the cachexia pathophysiology [70, 146], and most of the classification systems published to date have adopted this and use appetite loss as a classifier [48, 49, 52].

The fourth predictor identified by paper III is COPD comorbidity in patients with cancer. COPD is, independently of cancer, associated with cachexia [147], and it is therefore reasonable that COPD comorbidity in cancer result in an increased risk of cachexia development. However, the other comorbidities evaluated in paper III (heart disease, renal disease or arthritis) did not predict cachexia, although also these are associated with cachexia [17, 148, 149]. In the case of arthritis, the reason might be that the estimated prevalence of cachexia is less than in COPD, 2% vs 5% [17], and that a weaker association between arthritis in cancer patients and cachexia development might have gone undetected. Regarding the remaining two comorbidities that were evaluated in paper III, heart disease and renal disease, any disease in the respective organs were queried, and no specification as to the occurrence of *chronic heart failure* or *end-stage renal disease*, was made. This might have weakened a possible association with cachexia development as it is predominantly these two conditions within their respective organs that are known to be associated with cachexia, with prevalence estimates of 8% and 25% in chronic heart failure and end-stage renal disease, respectively [17, 148, 149].

Using classification and regression tree analysis to find the most optimal combinations and cut-offs of these four predictors to classify risk of cachexia development, a model with five levels of increasing risk of cachexia was presented in paper III (Figure 4).

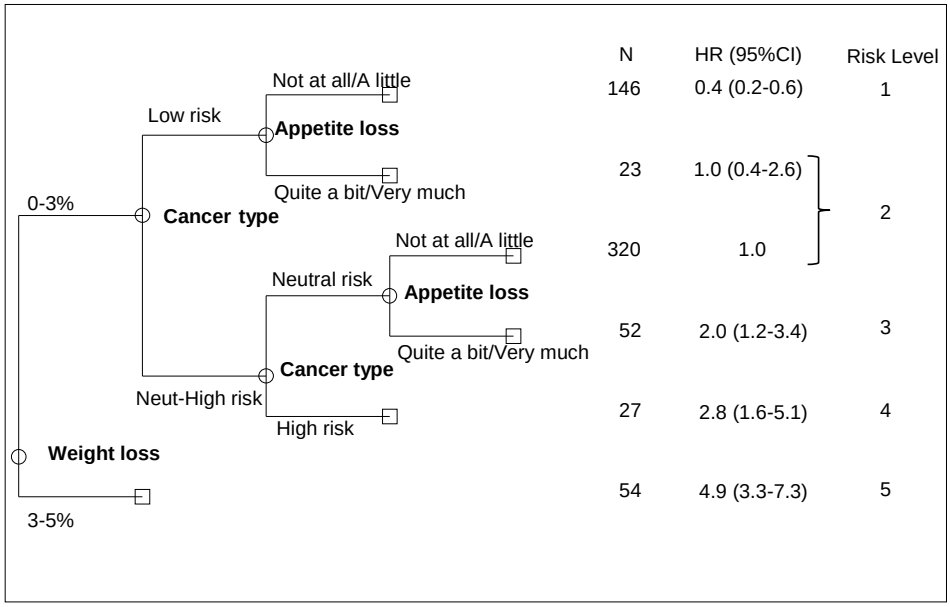

Figure 4 A classification and regression tree model of risk of cachexia development. Adjacent branches with similar hazard ratios were combined, resulting in a five-level classification system of increasing risk of cachexia development. Low risk cancer – breast and hematologic cancers. High risk cancers – Pancreatic and gastric cancers. Neutral risk cancer – all other cancers.

A diagnostic test for pre-cachexia could be extracted from this model by interpreting this model as a scale and choose a scale cut-off where sensitivity and specificity for predicting the future development of cachexia both are high. Next, one would have to use the criteria defining that level, and all levels above, as a test for pre-cachexia. For example, choosing a cut-off between level 2 and 3 would imply that every patient with level 3, 4 or 5 have pre-cachexia. Hence, the criteria for having pre-cachexia would be to fulfill at least one of the following criteria:

- Neutral risk cancer (all cancers but breast, hematologic, gastric or pancreatic) and quite a bit/very much appetite loss
- High risk cancer (pancreatic or gastric)

- Weight loss exceeding 3%

The sensitivity of this test in terms of predicting cachexia 3 months ahead in time would be as low as 47%, meaning that many patients that actually develops cachexia in that time frame, go undiagnosed (many false negatives) [135]. The specificity, however, is acceptable with 88%, meaning that most patients that are diagnosed with pre-cachexia, will actually go on to develop cachexia (few false positives) [135]. Choosing an alternative cut-off between 1 and 2 would imply that every patient with level 2, 3, 4 or 5 have pre-cachexia, i.e. fulfilling at least one of the following criteria:

- Low risk cancer (breast or hematologic) and quite a bit/very much appetite loss
- Neutral or high-risk cancer (all other cancers)
- Weight loss exceeding 3%

This would result in a high sensitivity of 95%, while the specificity would be only 35%, meaning that most patients who actually will develop cachexia, are detected, but many patients who will not develop cachexia are also classified as having pre-cachexia.

Hence, no diagnostic test of pre-cachexia can be derived from this five-level risk model that both have a high sensitivity and high specificity. This is reflected in the overall model accuracy of only 76%. Thus, this thesis cannot claim to present the definitive diagnostic test for pre-cachexia, but the resulting model *can* identify some patients that have a high risk of developing cachexia, and some patients that are less likely to develop cachexia based on a few, simple and easily accessible clinical markers.

5.2 Methodological considerations

5.2.1 Study design

The two studies in this thesis have different designs. While they are both observational studies, the Symptom Prevalence study (Paper I) is a cross-sectional study and the EPCCS (Paper 2 and 3) is a prospective, longitudinal study.

From a practical point of view, a cross-sectional study design is an effective way to gather large datasets in a short period of time. In the Symptom Prevalence study, we were able to approach most eligible patients in the predefined period of recruitment, ensuring a representative sample of a considerable size. However, a cross-sectional study design has several limitations. One of these is the ability only to estimate prevalence, and not incidence of conditions. Prevalence is not only dependent on the number of new cases of a condition, but also on the duration of the condition (for example time until death from a condition) [150]. Conditions with shorter durations are less likely to be represented in cross-sectional studies. Since cachexia is a condition that shortens life expectancy [19], the percentage of patients with cachexia at a single instance in time (prevalence) will more likely be lower than the percentage of patients that will develop cachexia during the course of their cancer disease (incidence). Thus, to treat prevalence as an approximation for incidence, for example when evaluating a newly diagnosed cancer patient's probability of developing cachexia, would lead to an underestimation. Cross-sectional designs also only permit measurements in a single instance of time. Inferences about possible predictors of a future outcome (e.g. cachexia) are thus problematic. Even though a possible predictor is associated with the outcome, we cannot know if the predictor was present before the outcome, as long as the measurements of both predictor and outcome were performed simultaneously. An exception is when a predictor is known to be constant over time. This is illustrated in paper I, where we know that a patient's cancer type is constant, and do not shift with time. With the demonstrated association between cancer type and cachexia, one can thus argue that cancer type predicts cachexia. Another disadvantage with cross-sectional designs is that measurements of exposures in the past must be based on patient records or patients' recollection. Both is problematic, and this will be discussed in more detail below. As the primary aim of paper I was to evaluate prevalence of cancer cachexia, a cross-sectional design was appropriate.

Longitudinal studies do not have as many limitations as cross-sectional studies as they allow for measurements of predictors initially and the subsequent observation for

outcomes over time. Longitudinal studies, however, are more resource demanding, and take longer time to undertake. Another problem with carrying out longitudinal studies, especially in patients in poor condition, is the attrition inherent to this study design [151]. This will be discussed in more detail below. The aims of paper II and III partly regarded evaluation of predictive markers, and a longitudinal study design was therefore required.

5.2.2 Recruitment

About 350 patients was estimated to be included in the Symptom Prevalence study, and 2-3000 in the EPCCS. In neither study, sample size calculations were performed. The reason for this, according to the respective protocols, was that the studies were not testing one specific hypothesis, and as such, calculation of sample size was not possible. The estimated number of patients was therefore based on previous experience with similar studies. The resulting numbers of 553 and 1739 offered sufficient precision in most analyses performed in this thesis, with one important exception. In the Symptom Prevalence study, too few inpatients were recruited (78 included in final analysis). This had a negative impact on the precision of prevalence estimates in this group. This number could have been increased by running a second round of recruitment among inpatients. However, it was not foreseen that prevalence for in- and outpatients had to be reported separately (see discussion below).

Selection bias is a systematic error which stems from procedures used to recruit patients, or from factors influencing who participates in studies [150]. The consequence of selection bias is that the study sample is not representative of the underlying population. Thus, inferences based on the study sample might not be transferrable to the entire population. To counteract selection bias in the Symptom Prevalence study, one approached most eligible patients attending the participating centers. This was possible due to the cross-sectional design and the limited period of recruitment. Furthermore, it was made sure that recruitment of outpatients was equally weighted on all weekdays (Monday to Friday) because different cancer types cluster on specific days of the week. However, due to limited resources, outpatients

were only recruited from the *oncology* outpatient clinic, whereas inpatients were recruited from *all* departments treating patients with cancer (departments of oncology, surgery, internal medicine, gynecology and head and neck). Consequently, many patients with certain types of cancer are underrepresented, or not represented at all in the outpatient group. For example, treatment of lung cancer is a shared responsibility between the department of oncology and the department of internal medicine, and for this reason, a limited number of patients with lung cancer attends the oncology outpatient clinic. Furthermore, surgical oncological patients are not seen at all at the oncology outpatient clinic. The recruitment of outpatients is therefore biased compared to the recruitment of inpatients, and for this reason, estimates of cachexia prevalence were reported separately for these two groups.

The oligo-center design of the symptom prevalence study is another source of selection bias, which affect the external validity of the results. At the centers where the study was performed, there has been a shift from predominantly inpatient cancer treatment to outpatient treatment over the past 10-20 years. Inpatient treatment is now primarily reserved for patients in need of emergency care, extensive surgery or intensive chemotherapy. The organization of patient care probably varies throughout the world, and consequently the characteristics of in- and outpatients might not be the same everywhere. Thus, the validity of the study elsewhere depends largely on local organization.

Finally, a source of selection bias in both the Symptom Prevalence study and the EPCCS, may be that patients in poor physical condition may decline participation because they find it too strenuous. Thus, the patients participating might on average be healthier than the population which the study recruits from. This is clearly a problem when the aim of both studies is to evaluate symptom burden in the underlying population, as the patients with more symptoms often are those in poorest physical condition.

5.2.3 Measurements

Information bias is the common term for systematic errors regarding the information reported by or about the patients in a study, and recall bias is information bias related to patients' recollection when asked about possible exposures in the past [150]. This is particularly a problem in cross-sectional analyses, like in paper I and partly in paper II. Recall bias can be non-differential and differential. Non-differential bias occurs when erroneous information is not related to the outcome, whereas differential bias occurs when erroneous information is more likely to be reported depending on the outcome [150]. For example, weight loss grade is the main outcome in paper II, and appetite loss is an explanatory variable in a cross-sectional analysis of associations between weight loss grade and several cachexia items. It might be that patients with weight loss are more prone to acknowledge that they suffer from appetite loss than patients without any sign of weight loss, simply because patients suffering from weight loss have been dwelling by the possible causes of their condition. This would be an example of differential recall bias, and the consequence can be that an association between appetite loss and weight loss grade becomes stronger than it is. The same argument can be made for several other patient reported variables in the same analysis, such as dietary intake, fatigue or physical function. Longitudinal analyses mitigate this effect, as in paper III, where patients are asked about their appetite *before* cachexia becomes evident.

Information about patients' current weight and height was patient reported in paper I. A review of the literature has shown that this is not as accurate as objective measurements and results in an underestimation of weight and overestimation of height [152]. However, the same review states that the inaccuracy is greatest in patients being overweight or obese. In a study of 488 patients undergoing preoperative screening for malnutrition (25% had cancer), there was a high concordance between self-reported and measured weight and height [153]. The mean difference in weight and height was -1.3 kg (95%CI -5.8 – +3.2) and +1.0 cm (95%CI -4.2 – +6.1), and the intraclass correlation coefficient was 0.99 and 0.97, respectively. Self-

reported weight, height, BMI and weight loss had high sensitivity and specificity for the diagnosis of malnutrition, 0.97 and 0.98, respectively.

No adjustments for ethnicity were made when using BMI to diagnose cachexia. The international consensus definition does not suggest such adjustments [32], but this might be appropriate since normal range of BMI can vary according to ethnicity [56].

Weight loss history was patient reported in all three papers as there rarely are recorded standardized data on weight prior to study inclusion. This also reflects the situation in the clinical setting when seeing a patient for the first time – weight loss history is something we ask the patient about.

In paper I, a study-specific, not previously validated question was used to assess the need for clinical attention to cachexia. The problem with non-validated measurements is that one cannot be certain that they measure what we want to measure. One problem with the question might have been that it only asked about *the physician's* focus on nutrition and weight loss. This might have underestimated the attention given to nutrition and weight loss by other health care workers. Another problem might be the choice to interpret the statement "wish for more focus" as representing an "unmet need". The former statement could merely indicate an interest or curiosity about the subject, and not something that is necessary for the patient to feel acknowledged. However, we are not aware that there are any validated questions measuring clinical attention to cachexia, and given the psychosocial consequences of lack of attention from health care workers [24], we felt that the analysis was important and included it as an exploratory part of paper I.

Aside from potentially inaccurate measurements, there are also measurements altogether lacking from this thesis. Objective measures of muscle or fat mass were not available in the Symptom Prevalence Study or in the EPCCS. Effect on weight change by accumulation of third space fluids or shifts between fat and muscle mass could therefore not be assessed. Low muscle mass is, besides low BMI and weight loss > 5%, one of the criteria for cachexia according to the international consensus definition

[32], and therefore an adapted definition, using only weight loss and BMI, had to be used. This may have resulted in an underestimation of cachexia in our studies. The magnitude of such an underestimation has been reported by Blauwhoff-Buskermolen et al. [44] to be between 11% and 32%, depending on modality of muscle mass measurement. Nevertheless, the definition used is also validated [34], and while weight loss and BMI are regularly registered in clinical practice, the assessment of muscle mass necessitates supplementary tests (computed tomography, bioelectrical impedance analysis etc.), which not always are available. Thus, the definition used in this study can also be said to be clinically more applicable.

Markers of systemic inflammation were not available in either study. Although the EPCCS study allowed for registration of incidental C-reactive protein (CRP) measurements performed within three days before inclusion, only 64 non-missing values in 628 patients were available. This was too few values to enable statistical inferences. Systemic inflammation is very interesting because it is considered a driver of cancer cachexia [6], and markers of inflammation could potentially be important in diagnosing or predicting cachexia. Consequently, markers of systemic inflammation could have increased the accuracy of the cachexia predictive model presented in paper III, and this should be explored in future studies.

5.2.4 Missing data

Missing data occurs when there are no data value stored for a variable in an observation. Missing data is classified as follows [154]:

- Missing completely at random: Missingness is unrelated to any other variable in the dataset, and the subgroup with complete data can be interpreted as a randomly drawn sample from the complete study sample
- Missing at random: Missing data is not at random, however the reason for its missingness is not related to the outcome of interest in the study
- Missing not at random: The reason for missingness is related to the outcome of interest in the study

In this thesis, patient reported weight loss and measurements of BMI were central, and patients without these measurements at baseline could not be included in final analysis. In paper I, the proportion of patients with missing data were less than 10%, and the only difference in characteristics in the sample with missing data was the higher number of women. The reason for missingness thus seemed unrelated to the outcome of interest, cachexia. The data were considered to be missing at random or missing completely at random, and the number of missing was found to be at an acceptable level. Thus, risk of bias was assumed to be low. In paper II, the proportion of patients with missing baseline values was 19% (Table 3), and the patients with missing data were older, had poorer performance status, were to a greater degree hospitalized and had shorter time since diagnosis. It is quite possible that the reason for missingness was that patients were in such poor condition that measuring height and weight was skipped. If cachexia contributed to their poor condition, which is not unlikely, the data are missing not at random, and this might have introduced a bias in the reported effect sizes of paper II [154]. In paper III, which used the same dataset as paper II, measures were taken to remedy the relatively high number of missing baseline values. Patients with missing data for weight loss or BMI at baseline, but with complete data at first follow-up visit, were included, letting the observations at first follow up visit replace baseline visit. This was considered appropriate due to the open study design, which allowed inclusion of patients at any point in their disease trajectory, and because the exact same data were registered at baseline as at all subsequent visits. This reduced the proportion of patients with missing data at baseline from 19%, as reported in paper II, to 12% in paper III.

As is common in many studies in palliative care [151], the number of missing follow-up observations, also known as attrition, was high. The attrition for the EPCCS study was estimated in paper II, revealing that 18% was dead and 41% was lost to follow-up after three months. It is likely that a worsening in physical condition is among the reasons for patients dropping out. Since cachexia is associated with increased morbidity and mortality, it is possible that this is missing not at random, and a bias may have

resulted. To mitigate this effect, Cox proportional hazards method was used to let each patient contribute with his or her time on the study. In addition, for the longitudinal analysis in paper II, where the objective was to estimate the proportion of patients having progressive weight loss, imputations where performed, aiming to reduce the risk of bias [154].

5.2.5 Other aspects affecting external validity

The classification and regression tree methodology, which was applied in paper III, is a data mining procedure that provides intuitive results. However, it is criticised for creating models that are overfitted to the data, and thus reduces the external validity of the results. By only including significant factors from the Cox model this effect is reduced.

6 Conclusion

What is the overall prevalence of cancer cachexia in an unselected population of patients with cancer?

The prevalence of cachexia in inpatients with cancer was 51% (95%CI 40-63) and in outpatients 22% (95%CI 17-27), however the estimates must be viewed in light of the study's oligo-center design and that characteristics of in- and outpatients can vary depending on local organization.

Which demographic and clinical factors are associated with cancer cachexia prevalence, and what is the prevalence in the subgroups defined by these factors?

Prevalence was independently associated with provision of care (inpatient/outpatient status) and cancer type. Prevalence was highest in patients with gastrointestinal cancers (inpatients: 62% [38-82], outpatients: 42% [30-55]) and lung cancer (inpatients: 83% [52-98] outpatients: 36% [13-65]), and lowest in breast cancer (not assessable in inpatients, outpatients: 11% [5-20]). The accuracy of prevalence estimates in subgroups of inpatients was poor due to a small sample size.

Which demographical and clinical factors are associated with a patient-perceived need of increased clinical attention to weight loss and nutrition?

Cachexia, male gender and symptoms of mood disorder were factors independently associated with a patient-perceived need of increased clinical attention to weight loss and nutrition. One third of patients with cachexia wanted more attention to this topic.

Can the prognostic ability of a weight loss grading system (WLGS) be confirmed in a population of patients with incurable cancer?

The prognostic ability of the WLGS was confirmed.

Can items from the cachexia domains contribute to the prognostic ability of the WLGS?

Performance status, physical functioning, emotional functioning and appetite loss contributed to improved prognostic accuracy when added to the WLGS in a survival model.

Does the WLGS have validity as a classification system of cancer cachexia?

Concurrent validity of the WLGS measured against items from the cachexia domains was demonstrated.

Is the WLGS predictive of cachexia progression?

Patients with weight loss grade 2 were more likely to have cachexia progression than patients with grade 0 or 1.

Which demographical and clinical factors are independent predictors of cachexia development?

Initial weight loss, cancer type, appetite loss and comorbidity with chronic obstryctive pulmonary disease (COPD) independently predict development of cachexia.

Which combinations and cut-offs of these predictors most optimally predict cachexia development?

A model has been constructed for the optimal prediction of cachexia development. The model is based on initial weight loss (<3% vs. 3-5%), cancer type (low risk, neutral risk, high risk) and appetite loss (none/a little vs. quite a bit/very much). It classifies patients into five levels of increasing risk of cachexia development.

What is the accuracy of cachexia predictions using the resulting model?

Using the model to dichotomize patients into high probability (pre-cachexia) or low probability (no cachexia) of future cachexia development, the estimated accuracy of the model was 76%. No single cut-off had both high sensitivity and high specificity for cachexia development.

7 Future perspectives

Effective management of cachexia still represents an unmet need, and we must make progress on several different areas of cachexia research to achieve improvement. Regarding prevalence, we mostly have estimates in hospital-based populations – as is the case in paper I and in Sun *et al.* [58] – or even more selected populations as in Wallengren *et al.* [36]. Since patients with cachexia are more likely to need hospital services, there is reason to believe that the prevalence will be lower in a broader population. For a better understanding of the overall prevalence of cachexia, we thus need large community-based surveys. This is important considering that community health services also have responsibility for cancer care.

This thesis presents a model for prediction of cachexia development. However, the accuracy of the model is not very high, and future research should seek to improve the model. One obvious path forward is to follow-up on one of the limitations of this thesis, namely to examine the potential of inflammatory markers to improve prediction of cachexia development when added to the markers identified in paper III (initial weight loss, cancer type, appetite and COPD). To achieve this, new longitudinal studies sampling biological material as well as clinical and patient reported data are needed. To minimize the attrition often associated with studies in palliative care populations, it might be wise to limit the number of assessments to what is needed to answer a few, focused research questions [151]. Thereby the strain on the patients, who often are in poor condition, is reduced, and a higher proportion of patients might be likely to complete follow-up. In addition, studies need to apply adequate statistical methods to compensate for the missing data and attrition that inevitably will occur [155]. Furthermore, the results need to be validated, either as part of the primary study with a training/validation sample, or in subsequent studies.

Longitudinal studies also represent a good opportunity to study the fluctuation of inflammatory markers and weight loss over time, and thereby gain greater insight into the pathophysiology of cancer cachexia. A better understanding of the pathophysiology will possibly also affect the way we define cachexia in the future. A

recent publication from the Global Leadership Initiative on Malnutrition (GLIM) suggests that presence of systemic inflammation should be mandatory for a cachexia diagnosis [156]. This builds on the knowledge that inflammation is a driver of cancer cachexia, however it contradicts the previous perception that cachexia can also exist without inflammation [32]. As the international consensus definition from 2011 [32], the GLIM definition is based on consensus among experts in the field, and validation is necessary to ensure the clinical relevance

Effective treatment modalities of cachexia are key to improve management, and it is important that guidelines for the management of cancer cachexia are updated and implemented regularly based on developing evidence. Future intervention studies should continue to spring from gained insight into cachexia pathophysiology but should also stratify patients according to accurate cachexia risk models to evaluate if efficacy of treatments is better in patients in early stages of cachexia. Intervention studies should also be used to explore new predictive markers of treatment to allow patient subgroups with superior effect of the studied treatment to be identified. In turn, this will contribute to a continuous refinement of classification systems, improved understanding of pathophysiology and subsequently, further improvements in treatment.

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9 Appendix

APPENDIX 1: Case report forms of the Symptom prevalence study

APPENDIX 2: Case report forms of the EPCCS

APPENDIX 3: Paper I

APPENDIX 4: Paper II

APPENDIX 5: Paper III

APPENDIX 1:

Case report forms of the Symptom prevalence study

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

Dato for utfylling: ☐☐.☐☐.☐☐☐☐

Symptomprevalensstudien

1. Hoveddiagnose

☐ Kreft — Vennligst oppgi primær kreftdiagnose med kode

ICD-10 kode: C☐☐.☐

☐ Hjertesvikt — Vennligst oppgi hjertesviktdiagnose med kode, NYHA-klasse og ejeksjonsfraksjon:

ICD-10 kode: I☐☐.☐

☐ NYHA-klasse 1: Ingen symptomer i vanlig fysisk aktivitet.

☐ NYHA-klasse 2: Lett begrensning i vanlig fysisk aktivitet.

☐ NYHA-klasse 3: Markert begrensning i vanlig fysisk aktivitet.

☐ NYHA-klasse 4: Symptomer i hvile.

Ejeksjonsfraksjon (siste tilgjengelige måling). *Oppgi prosent eller ev kryss av for at ekkokardiografi ikke er foretatt*

Prosent ☐☐ %

☐ Ekkokardiografi ikke foretatt

☐ KOLS — Vennligst oppgi stadium (kjent fra tidligere spirometri):

☐ I Mild kols FEV1 ≥ 80 % av forventet verdi

☐ II Moderat kols 50 % ≤ FEV1 < 80 % av forventet verdi

☐ III Alvorlig kols 30 % ≤ FEV1 < 50 % av forventet verdi

☐ IV Svært alvorlig kols FEV1 < 30 % av forventet verdi

☐ Uspesifisert

☐ Annen — Vennligst oppgi ICD-10 klassifikasjon ☐☐☐.☐

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

2. Komorbiditet. Har pasienten annen sykdom i tillegg til diagnosen angitt i spørsmål 1? *Flere kryss mulig*

☐ Nei

☐ Kreft
☐ Hjerte-karsykdom
☐ Diabetes
☐ Nyresykdom
☐ Muskel/skjelettplager
☐ Psykisk lidelse
☐ KOLS
☐ Leversykdom

☐ Annet, spesifiser: _____

3. Årsak til kontakt med sykehus/sykehjem. *Flere kryss mulig*

☐ Rutinekontroll
☐ Utredning
☐ Planlagt behandling
☐ Optimalisering av symptombehandling
☐ Nedsatt allmenntilstand
☐ Hjemmesituasjon
☐ Smerter
☐ Depresjon
☐ Vekttap
☐ Tungpust
☐ Infeksjon

☐ Annet, spesifiser: _____

4. Kirurgi. Har pasienten gjennomgått kirurgi i forbindelse med dette sykehusbesøket?

☐ Ja ☐ Nei

Hvis JA, hvor mange dager siden operasjon? ☐☐

5. Karnofsky Performance Score

☐ 100% Normal. Ingen plager eller subjektive tegn på sykdom
☐ 90% Klarer normal aktivitet, sykdommen gir lite symptomer
☐ 80% Klarer med nød normal aktivitet. Sykdommen gir en del symptomer
☐ 70% Klarer seg selv, ute av stand til normal aktivitet eller aktivt arbeid
☐ 60% Trenger noe hjelp, men klarer stort sett å tilfredsstille egne behov
☐ 50% Trenger betydelig hjelp og trenger stadig medisinske tiltak
☐ 40% Ufør, trenger spesiell hjelp og omsorg
☐ 30% Helt ufør, men fare for død er ikke overhengende
☐ 20% Svært syk, understøttende behandling nødvendig
☐ 10% Moribund, dødsprosessen i rask frammarsj

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

6. Aktuell medikamentell behandling

Opioider ☐ Ja ☐ Nei

a. Varighet: ☐ < 3 dager ☐ < 14 dager ☐ > 14 dager

b. **Planlagt** opioid-behandling siste 24 timer:

Opioid	*Total døgndose*	*Enhet*	*Administrasjonsmåte*(kryss av)*					
			po	sc	td	iv	tm	annet
Morfin	☐☐☐☐	mg	☐	☐	☐	☐	☐	☐
Oksykodon	☐☐☐☐	mg	☐	☐	☐	☐	☐	☐
Fentanyl	☐☐☐☐	µg	☐	☐	☐	☐	☐	☐
Andre:	☐☐☐☐	☐	☐	☐	☐	☐	☐	☐

po: per oral, sc: subcutant, td: transdermalt, iv: intravenøst, tm: transmucosalt, annet: spesifiser i kommentarfelt

Ev kommentar, planlagt opioid-behandling siste 24 timer:

c. Opioider brukt mot **gjennombruddssmerte** siste 24 timer:

Opioid	*Total døgndose*	*Enhet*	*Administrasjonsmåte*(kryss av)*					
			po	sc	td	iv	tm	annet
Morfin	☐☐☐☐	mg	☐	☐	☐	☐	☐	☐
Oksykodon	☐☐☐☐	mg	☐	☐	☐	☐	☐	☐
Fentanyl	☐☐☐☐	µg	☐	☐	☐	☐	☐	☐
Andre:	☐☐☐☐	☐	☐	☐	☐	☐	☐	☐

po: per oral, sc: subcutant, td: transdermalt, iv: intravenøst, tm: transmucosalt, annet: spesifiser i kommentarfelt

Antall ganger spesifisert dose(r) er tatt, ev. andre kommentarer ang. opioider brukt mot gjennombruddssmerter siste 24 timer:

6. Aktuell medikamentell behandling forts.

☐ Analgetika – IKKE-opioider

☐ Anti-depressiva for depresjon. Hvis ja, varighet:
☐ < 3 dager ☐ < 14 dager ☐ > 14 dager

☐ Anti-depressiva for andre tilstander enn depresjon

☐ Kortikosteroider

☐ Anti-emetika

☐ Neuroleptika

☐ Sedativer/anxiolytika

☐ Laxantia

☐ Næringstilskudd med høyt proteininnhold

☐ Diuretika

☐ Hjertesviktmedikamenter
- ☐ ACE-hemmer
- ☐ Betablokker
- ☐ Angiotensin 2-reseptorantagonist
- ☐ Aldosteronantagonist
- ☐ Diuretika

☐ Beta-2-agonister

☐ Inhalasjonssteroider

☐ Annet:

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

De siste spørsmålene er kun aktuelle for pasienter som er på sykehuset pga kreft.

7. Sykdomsutbredelse i dag. Kun relevant for pasienter med kreft.

☐ Lokalisert /lokalavansert

☐ Metastatisk Metastaselokalisasjon: ☐ Skjelett ☐ Lunge ☐ Lever ☐ Hjerne ☐ Lymfeknuter ☐ Annet

8. Hva er behandlingsintensjonen nå? Kun relevant for pasienter med kreft.

☐ Kurativ ☐ Palliativ

9. Hvilken tumorrettet behandling får pasienten nå? Kun relevant for pasienter med kreft. *Flere kryss mulig*

☐ Kjemoterapi
☐ Strålebehandling
☐ Hormonbehandling
☐ Targeted therapy (monoklonale antistoff, TKA etc)
☐ Annen
☐ Behandlingspause (ikke avsluttet tumorrettet behandling)
☐ Ingen tumorrettet behandling

10. Hvilken tumorrettet behandling har pasienten fått i løpet av de *siste 4 uker*? Kun relevant for pasienter med kreft. *Flere kryss mulig*

☐ Kjemoterapi
☐ Strålebehandling Hvis ja, var det mot smertefull tilstand? ☐ Ja ☐ Nei
☐ Hormonbehandling
☐ Targeted therapy (monoklonale antistoff, TKA etc)
☐ Kirurgi
☐ Annen
☐ Behandlingspause (ikke avsluttet tumorrettet behandling)
☐ Ingen tumorrettet behandling

TUSEN TAKK FOR AT DU BESVARTE SPØRSMÅLENE!

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

Dato for utfylling: ☐☐.☐☐.☐☐☐☐

Symptomprevalensstudien

Kjære pasient
Takk for at du har sagt deg villig til å delta i vår undersøkelse som omhandler smerter og andre symptomer som kan følge av sykdom.
Vi ønsker at du fyller ut de påfølgende spørsmål etter beste evne.

Innledende spørsmål

1. Fødselsår ☐☐☐☐

2. Kjønn ☐ Kvinne ☐ Mann

3. Sivilstand ☐ Enslig (singel/enke/enkemann) ☐ Gift/samboer

4. Utdanning. Hva er din høyeste utdanning? ☐ ≤ 9 års skolegang
   ☐ 10-12 års skolegang
   ☐ Høyskole eller universitet ≤ 4 år
   ☐ Høyskole eller universitet > 4 år

5. Etnisk tilhørighet ☐ Norsk/Skandinavisk
   ☐ Vest-Europeisk / Nord Amerikansk/Oceania
   ☐ Sør-Amerikansk / Mellom-Amerikansk
   ☐ Øst-Europeisk
   ☐ Asiatisk
   ☐ Afrikansk

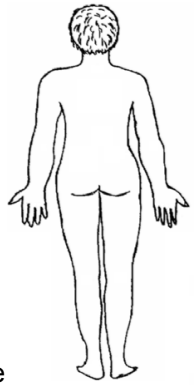
Smerter

6. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine). Har du i dag smerter av et annet slag enn slike dagligdagse smerter?

   ☐ Ja ☐ Nei Hvis NEI, gå videre til spørsmål 13

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

7. Vennligst skraver de områdene på kroppen hvor du har smerter. Marker med et kryss der du har mest vondt.



venstre høyre

høyre venstre

8. Vennligst marker det tallet som **best beskriver de <u>sterkeste</u> smertene du har hatt i løpet av de <u>siste 24 timer</u>**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Ingen smerte — Verst tenkelige smerter

9. Vennligst marker det tallet som **best angir hvor sterke smerter du har hatt i <u>gjennomsnitt i løpet av de siste 24 timer</u>**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Ingen smerter — Verst tenkelige smerte

10. I hvor stor grad har **behandling eller medisiner lindret smertene dine <u>de siste 24 timene</u>?** Vennligst marker det tallet som viser hvor stor smertelindring du har fått.

☐0% ☐10% ☐20% ☐30% ☐40% ☐50% ☐60% ☐70% ☐80% ☐90% ☐100%

Ingen lindring — Fullstendig lindring

11. Føles huden i det smertefulle området annerledes enn normalt; mer nummen eller mer følsom?

☐Ja ☐Nei Hvis NEI, gå videre til spørsmål 12

a. Føles smertene dine som rare, ubehagelige fornemmelser i huden? *Ord som prikking, kribling eller stikking kan beskrive denne følelsen*

☐ NEI - smertene mine føles egentlig ikke slik

☐ JA - jeg får disse fornemmelsene ganske ofte

b. Gjør smertene dine at huden i det vonde området ser annerledes ut enn normalt? *Ord som marmorert eller mer rødlig eller rosa farge kan kanskje beskrive dette utseende*

☐ NEI - smertene mine påvirker ikke hudens farge

☐ JA - jeg har merket at smertene får huden til å se annerledes ut enn normalt

c. Gjør smertene dine den affiserte huden unormalt følsomt for berøring? *Dette kan beskrives som ubehag når man stryker lett over huden eller smerter når man bruker trange klær*

☐ NEI - smertene mine gjør ikke huden unormalt følsom i dette området

☐ JA - huden virker unormalt følsom for berøring i dette området

d. Kommer smertene dine plutselig og i utbrudd uten noen bestemt grunn når du ikke beveger deg? *Ord som elektriske støt og anfallsvise smerter kan beskrive denne følelsen.*

☐ NEI - smertene mine føles egentlig ikke slik

☐ JA - jeg får disse fornemmelsene ganske ofte

e. Føles smertene dine som om hudtemperaturen i det smertefulle området har forandret seg unormalt? *Ord som varm og brennende kan beskrive denne følelsen*

☐ NEI -, jeg får egentlig ikke disse fornemmelsene

☐ JA- jeg får disse fornemmelsene ganske ofte

Gjennombruddssmerte *kan defineres som en kortvarig forverring av smerte. Det kan være en forverring av den vanlige, konstante smerten du alltid har (din konstante smerte) ELLER det kan være en smerte som er forskjellig fra din konstante smerte.*

12. Har du hatt **gjennombruddssmerter siste 24 timer**?

☐ Ja ☐ Nei Hvis nei, gå videre til spørsmål 13

a. **Hyppighet**. Omtrent hvor mange ganger i løpet av de siste 24 timer har du hatt denne **gjennombruddssmerten**? *Vennligst ta med alle episodene, uavhengig av om du tok medisin for dem eller ikke*.

Påfør antallet episoder her: ☐☐

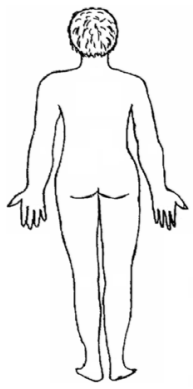
Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

b. **Smerteintensitet**. Når denne **gjennombruddssmerten er på det verste**, hvordan vil du beskrive smerten på en skala fra 0-10, der 0 er «ingen smerte» og 10 er «verst tenkelige smerte»? *Vennligst marker det tallet som best angir intensiteten av dine gjennombruddssmerter*

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Ingen smerter — Verst tenkelige smerte

c. **Lokalisering**. Hvor kjenner du denne gjennombruddssmerten? *Vennligst **marker hele området** der du kjenner denne smerten*



venstre høyre

høyre venstre

d. **Forhold til dine konstante smerter**. Er **gjennombruddssmerten** en kortvarig forverring av din konstante smerte eller er den en smerte som er forskjellig fra din konstante smerte?

☐ Kortvarig forverring av konstant smerte

☐ Forskjellig fra konstant smerte

☐ Usikker

e. **Forutsigbarhet**. Kan du forutsi når gjennombruddssmerten vil komme?

☐ Aldri ☐ Sjelden ☐ Av og til ☐ Ofte ☐ Alltid

f. **Årsaker.** Er det noe som utløser gjennombruddssmerten? *Kryss av for de alternativene som passer*

☐ Å bevege seg i sengen	☐ Å stå	☐ Å hoste
☐ Å ha avføring	☐ Å svelge	☐ Å berøre et område av huden
☐ Å gå	☐ Å sitte	☐ Å kaste opp
☐ Å late vannet	☐ Å spise	☐ Å puste

☐ Smerten kommer tilbake når virkningen av de faste smertestillende medisinene går ut

☐ Annet, vennligst beskriv: _____

_____

☐ Usikker

☐ Nei, det er ikke noe spesielt som utløser denne smerten

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

Spørsmålene under omhandler andre forhold og symptomer som kan være relevant ved sykdom.

13. **Vekt og høyde.**

a. Høyden min er ca. ☐☐☐.☐ cm

b. Jeg veier ca ☐☐☐.☐ kg

c. For 6 måneder siden veide jeg ☐☐☐.☐ kg

d. De siste to ukene har vekten min: *velg ett svaralternativ*

☐ Minsket ☐ Vært uforandret ☐ Økt

14. **Matinntak**

Sammenlignet med mitt normale, har matinntaket mitt siste måneden vært: *velg ett svaralternativ*

☐ Uendret

☐ Mer enn vanlig

☐ Mindre enn vanlig

Jeg spiser og drikker nå: *velg ett svaralternativ* (besvares bare hvis du spiser "Mindre enn vanlig")

☐ Vanlig mat, men mindre mengde enn vanlig

☐ Litt fast føde

☐ Kun flytende

☐ Kun næringsdrikker

☐ Veldig lite av alt

☐ Kun sondeernæring eller intravenøs ernæring

15. **Matinntak og symptomer**. De siste to ukene har jeg hatt følgende problem som har hindret meg fra å spise tilstrekkelig: *angi ett eller flere alternativer*

☐ Ingen problem
☐ Ingen appetitt, ikke lyst til å spise
☐ Kvalme
☐ Brekninger
☐ Forstoppelse
☐ Diaré
☐ Sår i munnen
☐ Munntørrhet
☐ Maten smaker annerledes eller ingenting
☐ Plaget av lukter
☐ Problemer med å svelge maten
☐ Blir fort mett
☐ Smerter
☐ Tungpust
☐ Slapphet
☐ Annet, vennligst spesifiser: _____

16. **Fysisk aktivitet**. Den siste måneden vil jeg beskrive aktiviteten min som: *velg ett alternativ*

- ☐ Normal, ingen begrensninger
- ☐ Ikke normal, men er oppe og er i noe aktivitet
- ☐ Ikke vært i form, men vært oppe mer enn halve dagen
- ☐ Vært i litt aktivitet, tilbringer det meste av dagen i sengen eller i en stol
- ☐ Ligget for det meste i sengen

17. **Fatigue**.
Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden. Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke om hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenligner deg med hvordan du følte deg sist du var bra.
Ett kryss på hver linje

	Mindre enn vanlig	Ikke mer enn vanlig	Mer enn vanlig	Mye mer enn vanlig
Har du problemer med at du føler deg sliten?	☐	☐	☐	☐
Trenger du mer hvile?	☐	☐	☐	☐
Føler du deg søvnig eller døsig?	☐	☐	☐	☐
Har du problemer med å komme i gang med ting?	☐	☐	☐	☐
Mangler du overskudd?	☐	☐	☐	☐
Har du redusert styrke i musklene dine?	☐	☐	☐	☐
Føler du deg svak?	☐	☐	☐	☐

18. **Tung pust og/eller brystsmerter.**
Begrenses din fysiske aktivitet av tung pust eller hjertekrampe (angina)?

- ☐ Ingen plager med tung pust eller hjertekrampe i hvile
- ☐ Noe begrensning av daglig fysisk aktivitet
- ☐ Betydelig begrensning av daglig fysisk aktivitet (påkledning, gange i lett motbakke)
- ☐ Tung pust eller hjertekrampe ved den minste aktivitet eller også i hvile

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

19. **Depresjon og/eller angst**
Hvor ofte har du vært plaget av ett eller flere av de følgende problemene i løpet av de siste 2 ukene?

	Ikke i det hele tatt	Noen dager	Mer enn halvparten av dagene	Nesten hver dag
Lite interesse for eller glede over å gjøre ting	☐	☐	☐	☐
Følt deg nedfor, deprimert eller fylt av håpløshet	☐	☐	☐	☐
Følt deg nervøs, engstelig eller veldig stresset	☐	☐	☐	☐
Ikke klart å slutte å bekymre deg eller kontrollere bekymringene dine	☐	☐	☐	☐

Dine ønsker i forbindelse med samtale med lege.

20. Alvorlig sykdom kan medføre mange forskjellige plager. Er det noe du kunne ønske at legen hadde fokusert mere eller mindre på?

	Mye mindre fokus	Mindre fokus	Passe som det er	Noe mer fokus	Mye mer fokus
Smerte	☐	☐	☐	☐	☐
Ernæring/vekttap	☐	☐	☐	☐	☐
Kvalme	☐	☐	☐	☐	☐
Depresjon	☐	☐	☐	☐	☐
Angst/uro	☐	☐	☐	☐	☐
Annet: _____	☐	☐	☐	☐	☐
Annet: _____	☐	☐	☐	☐	☐

Senter: ☐ Avd: ☐☐ Pas: ☐☐☐

21. Alvorlig sykdom påvirker mange aspekter ved livet. Er det noe du kunne ønske at legen i større eller mindre grad hadde vektlagt?

	Mye mindre fokus	Mindre fokus	Passe som det er	Noe mer fokus	Mye mer fokus
Mine sykdoms-relaterte plager (symptomer)	☐	☐	☐	☐	☐
Mine tanker og eventuelle bekymringer om fremtiden	☐	☐	☐	☐	☐
Min generelle trivsel og livsglede	☐	☐	☐	☐	☐
Forhold i hjemmet	☐	☐	☐	☐	☐
Annet: _____	☐	☐	☐	☐	☐
Annet: _____	☐	☐	☐	☐	☐

KOLS-pasienter skal i tillegg besvare CAT (COPD assessment test) *på eget skjema*

TUSEN TAKK FOR AT DU BESVARTE SPØRSMÅLENE!

Skjemaet er fylt ut av (sett ett kryss):

☐ Pasient
☐ Pårørende
☐ Helsepersonell
☐ Pasient med hjelp fra pårørende eller helsepersonell

APPENDIX 2:

Case report forms of the EPCCS

Patient number ☐☐ ☐ ☐☐☐

CRF Health Care personnel

European Palliative Care Cancer Symptom study (EPCCS)

A prospective data collection

Version: June 06, 2011, English

Patient number: ☐☐ ☐ ☐☐☐

Initials: ☐☐☐☐

Date of registration: ☐☐.☐☐.☐☐☐☐

Registration: ☐ First enrolment

☐ Subsequent enrolment

Patient number ☐☐ ☐ ☐☐☐

Minimum Data Set, Physician form

Patient variables

Born (year) ☐☐☐☐

Height(cm) ☐☐☐.☐

Current weight (kg) measured without heavy clothes and shoes ☐☐☐.☐

Any weight loss last 6 months? ☐ Yes ☐ No

If YES, ongoing weight loss last 1 or 2 months? ☐ Yes ☐ No

If YES, how many kg last 2 months? ☐☐☐.☐

If YES, how many kg last 6 months? ☐☐☐.☐

Medical condition

Principal cancer diagnosis (if more than one, register the diagnosis that is subject to current treatment / symptom alleviation)
(ICD-10 e.g. C50, if malignant neoplasm of breast) C☐☐

Additional diagnosis ☐ Heart disease ☐ Renal disease
☐ Arthritis ☐ Liver disease
☐ COPD ☐ Other

Time of the cancer diagnosis (if more than one, register the time for the diagnosis that is subject to current treatment / symptom alleviation) ☐☐ ☐☐☐☐ (mm yyyy)

Stage of disease, solid tumours ☐ Local ☐ Locally advanced ☐ Metastatic

Stage of disease, non-solid tumours ☐ Local ☐ Disseminated

Metastases ☐ Bone ☐ Liver ☐ Lung ☐ CNS ☐ Lymph nodes ☐ Other ☐ None

Current oncology treatment ☐ Chemotherapy
☐ Radiotherapy
☐ Hormonal therapy
☐ Other, anti-cancer treatment
☐ None

Patient number ☐☐ ☐ ☐☐☐

Place of care <u>TODAY</u> (tick one)

- ☐ Oncology department
- ☐ Hospital palliative care unit
- ☐ Other hospital department
- ☐ Hospice
- ☐ Nursing home
- ☐ Primary care setting/ Home

Provision of care <u>TODAY</u> (tick one)

- ☐ Inpatient
- ☐ Day care, outpatient
- ☐ Home

C-Reactive Protein (CRP) measured last 3 days ☐ Yes ☐ No

If, yes, please provide value (mg/l) ☐☐☐

Current Medication

Non-opioid analgesics	☐ Yes	☐ No
Opioids	☐ Yes	☐ No
Co-analgesics	☐ Yes	☐ No
Corticosteroids	☐ Yes	☐ No
Antidepressants for depression	☐ Yes	☐ No
Antidepressants for conditions other than depression	☐ Yes	☐ No
Antiemetics	☐ Yes	☐ No
Neuroleptics	☐ Yes	☐ No
Sedatives/anxiolytics	☐ Yes	☐ No
Stomach acid-suppressing drugs	☐ Yes	☐ No
Laxatives	☐ Yes	☐ No
Antibiotics	☐ Yes	☐ No
Diuretics	☐ Yes	☐ No
Heart medication/anti-hypertensives	☐ Yes	☐ No
Prokinetics (Metoclopramid, Domperidon)	☐ Yes	☐ No
Psychostimulants (e.g methylphenidate)	☐ Yes	☐ No
Oral nutritional supplements with high protein level	☐ Yes	☐ No
Antithrombotic agents (treatment or prophylactic)	☐ Yes	☐ No
Other	☐ Yes	☐ No

Patient number ☐☐ ☐ ☐☐☐

Karnofsky Performance Status Scale, KPS

Date completed: ☐☐.☐☐.20☐☐

	Per cent	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 his needs.
☐	**50%**	Requires considerable assistance and frequent medical care.
☐	**40%**	Disabled; requires special care and assistance.
☐	**30%**	Severly disabled; hospitalization is indicated although death not imminent.
☐	**20%**	Very sick; hospitalization necessary; active supportive treatment necessary.
☐	**10%**	Moribund; fatal processes progressing rapidly.
☐	**0%**	Dead.

Patient number ☐☐ ☐ ☐☐☐

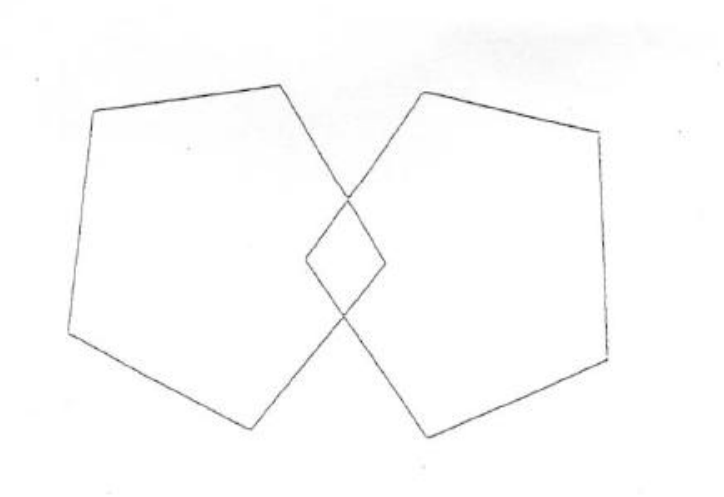
Mini-Mental State Examination (MMSE), short version

ORIENTATION	Score	Maximum score
What year is it?	☐	1
What is today's date?	☐	1
ABSTRACT THINKING		
Spell "world" backwards, 1 point for each correct.	☐	5
HIGHER CORTICAL FUNCTIONS		
Copy the design - below	☐	1

Patient number

Mini-Mental State Examination (MMSE), short version

Copy the design - below



Patient number ☐☐ ☐ ☐☐☐

Edmonton Classification System for Cancer Pain

For each of the following features, tick the response that is most appropriate, based on your clinical assessment of the patient.
If the patient does not have any pain (i.e. "No" under mechanism of pain), then no further assessment is required in relation to completion of the ECS-CP

1. Mechanism of Pain

☐ No No pain syndrome

☐ Nc Any nociceptive combination of visceral and/or bone or soft tissue pain

☐ Ne Neuropathic pain syndrome with or without any combination of nociceptive pain

☐ Nx Insufficient information to classify

2. Incident Pain

☐ Io No incident pain

☐ Ii Incident pain present

☐ Ix Insufficient information to classify

3. Psychological Distress

☐ Po No psychological distress

☐ Pp Psychological distress present

☐ Px Insufficient information to classify

4. Addictive Behavior

☐ Ao No addictive behavior

☐ Aa Addictive behavior present

☐ Ax Insufficient information to classify

5. Cognitive Function

☐ Co No impairment. Patient able to provide accurate present and past pain history unimpaired
☐ Ci Partial impairment. Sufficient impairment to affect patient's ability to provide accurate present and/or past pain history
☐ Cu Total impairment. Patient unresponsive, delirious or demented to the stage of being unable to provide any present and past pain history
☐ Cx Insufficient information to classify

Patient number ☐☐ ☐ ☐☐☐

CRF Patient

European Palliative Care Cancer Symptom study (EPCCS)

A prospective data collection

Version: June 06, 2011, English

Patient number: ☐☐ ☐ ☐☐☐

Initials: ☐☐☐☐

Date of registration: ☐☐.☐☐.☐☐☐☐

Registration: ☐ First enrolment

☐ Subsequent enrolment

Patient number ☐☐ ☐ ☐☐☐

Basic Data set, Patient form

Born (year) ☐☐☐☐

Sex ☐ Female ☐ Male

Present marital status (tick one)

☐ Single ☐ Widowed ☐ Divorced/separated ☐ Married/cohabiting

Highest completed education (tick one)

☐ ≤ 9 years of schooling
☐ 10-12 years of schooling
☐ College or university ≤ 4 years
☐ College or university > 4 years

Living situation (tick one)

☐ Alone
☐ With spouse/partner
☐ With spouse/partner and children
☐ With children
☐ With other adult(s)
☐ In an institution

Pain intensity 1

Patient number ☐☐ ☐ ☐☐☐

Please rate your pain by marking the one number that best describes your pain on the average in the last 24 hours.

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

No pain — Pain as bad as you can imagine

Pain intensity 2

Please rate your pain by marking the one number that best describes your pain at its worst in the last 24 hours.

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

No pain — Pain as bad as you can imagine

Neuropathic Pain

This question can tell us about the type of pain that you may be experiencing. This can help in deciding how best to treat it.

Does the skin in the painful area feel different from normal; more numb or more sensitive?

☐ Yes ☐ No

Breakthrough pain

Breakthrough pain can be defined as a brief flare-up of pain. It can be a flare-up of the usual, steady pain you always experience (your baseline pain) OR it can be a pain that is different from your baseline pain.

Have you had flare-ups of breakthrough pain in the last 24 hours? ☐ Yes ☐ No

Depression

Over the last 2 weeks, how often have you been bothered by:

1. Little interest or pleasure in doing things

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly every day

2. Feeling down, depressed, or hopeless

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly every day

Food intake

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

☐ Unchanged ☐ More than usual ☐ Less than usual

Only to be answered if "less than usual". I am now taking:

☐ Normal food but less than normal amount
☐ Little solid food
☐ Only liquids
☐ Only nutritional supplements
☐ Very little of anything
☐ Only tube feedings or only nutritional by vein

Patient number ☐☐ ☐ ☐☐☐

Edmonton Symptom Assessment System (revised version) (ESAS-r)

Date completed: ☐☐.☐☐.20☐☐

Please mark the number that best describes how you feel NOW:

No pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible pain
No tiredness (Tiredness=lack of energy)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible tiredness
No drowsiness (Drowsiness=feeling sleepy)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible drowsiness
No nausea	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible nausea
No lack of appetite	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible lack of appetite
No shortness of breath	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible shortness of breath
No depression (Depression=feeling sad)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible depression
No anxiety (Anxiety=feeling nervous)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible anxiety
Best wellbeing (Wellbeing=how you feel overall)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible wellbeing
No_____ Other problem (for example, constipation)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Worst possible

Patient number ☐☐ ☐ ☐☐☐

EORTC QLQ-C15 PAL

(Version 1)

Date: ☐☐.☐☐.☐☐☐☐

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

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble taking a short walk outside of the house?	☐	☐	☐	☐
2. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
3. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

During the past week:	Not at all	A little	Quite a bit	Very much
4. Were you short of breath?	☐	☐	☐	☐
5. Have you had pain?	☐	☐	☐	☐
6. Have you had trouble sleeping?	☐	☐	☐	☐
7. Have you felt weak?	☐	☐	☐	☐
8. Have you lacked appetite?	☐	☐	☐	☐
9. Have you felt nauseated?	☐	☐	☐	☐

Please go to the next page

Patient number ☐☐ ☐ ☐☐☐

During the past week:

	Not at all	A little	Quite a bit	Very much
10. Have you been constipated?	☐	☐	☐	☐
11. Were you tired?	☐	☐	☐	☐
12. Did pain interfere with your daily activities?	☐	☐	☐	☐
13. Did you feel tense?	☐	☐	☐	☐
14. Did you feel depressed?	☐	☐	☐	☐
15. Did you worry?	☐	☐	☐	☐
16. Did you feel irritable?	☐	☐	☐	☐

For the following question please tick the number between 1 and 7 that best applies to you.

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

☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐ **6** ☐ **7**

Very poor Excellent

Completed by (check one):

☐ Patient ☐ Health care professional caregiver

☐ Family caregiver ☐ Caregiver-assisted

APPENDIX 3:

Paper I

Paper 1

A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer.

https://doi.org/10.1007/s00520-017-4022-z
http://hdl.handle.net/11250/2476083

APPENDIX 4:

Paper II

ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2017; **8**: 789–797
Published online 18 June 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12220

The applicability of a weight loss grading system in cancer cachexia: a longitudinal analysis

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Abstract

Background A body mass index (BMI) adjusted weight loss grading system (WLGS) is related to survival in patients with cancer. The aim of this study was to examine the applicability of the WLGS by confirming its prognostic validity, evaluating its relationship to cachexia domains, and exploring its ability to predict cachexia progression.

Methods An international, prospective observational study of patients with incurable cancer was conducted. For each patient, weight loss grade was scored 0–4. Weight loss grade 0 represents a high BMI with limited weight loss, progressing through to weight loss grade 4 representing low BMI and a high degree of weight loss. Survival analyses were used to confirm prognostic validity. Analyses of variance were used to evaluate the relationship between the WLGS and cachexia domains [anorexia, dietary intake, Karnofsky performance status (KPS), and physical and emotional functioning]. Cox regression was used to evaluate if the addition of cachexia domains to the WLGS improved prognostic accuracy. Predictive ability of cachexia progression was assessed by estimating proportion of patients progressing to a more advanced weight loss grade.

Results One thousand four hundred six patients were analysed (median age 66 years; 50% female, 63% KPS $\leq$ 70). The overall effect of the WLGS on survival was significant as expressed by change in −2 log likelihood ($P < 0.001$) and persisted after adjustment for age, sex, and cancer type and stage ($P < 0.001$). Median survival decreased across the weight loss grades ranging from 407 days (95% CI 312–502)—weight loss grade 0 to 119 days (95% CI 93–145)—weight loss grade 4. All cachexia domains significantly deteriorated with increasing weight loss grade, and deterioration was greatest for dietary intake, with a difference corresponding to 0.87 standard deviations between weight loss grades 0 and 4. The addition of KPS, anorexia, and physical and emotional functioning improved the prognostic accuracy of the WLGS. Likelihood of cachexia progression was greater in patients with weight loss grade 2 (39%) than that with weight loss grade 0 (19%) or 1 (22%).

Conclusions The WLGS is related to survival, cachexia domains, and the likelihood of progression. Adding certain cachexia domains to the WLGS improves prognostic accuracy.

Keywords Neoplasms; Cachexia; Classification; Weight loss; Survival; Nutritional status

Received: 16 September 2016; Revised: 14 March 2017; Accepted: 4 May 2017
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Trial registration number ClinicalTrials.gov identifier: NCT01362816.
†Joint senior authors.

Introduction

Cancer cachexia was first described by Hippocrates as severe weight loss and a sign of impending death.[1] It is considered to be one of the most distressing aspects of advanced cancer, resulting in progressive functional impairment and psychological distress,[2,3] and it impedes the delivery of anticancer treatment.[4,5] About 80% of patients with advanced cancer experience weight loss,[6] which is a key component of cancer cachexia. Cachexia contributes to about 20% of cancer-related deaths.[6,7] Despite this, there has been relatively little research in this area, resulting in a failure to advance treatment and a therapeutic nihilism that cachexia is an inevitable and untreatable consequence of advanced cancer.[8]

One of the barriers to cachexia research has been the lack of an agreed definition and classification system. The latter is fundamental as cancer cachexia is not a single entity but a syndrome with various stages.[9] Various definitions have been used, resulting in heterogeneous research populations, making comparison of findings difficult.[10]

A major step in advancing the research agenda in cachexia was taken in 2011 when a consensus-based cachexia definition was published.[11] Cachexia was defined as a 'multifactorial syndrome characterized by an ongoing muscle loss (with or without fat loss) that cannot be fully reversed by nutritional support and leads to progressive functional impairment'.[11] Integral was the idea that cachexia is a progressive process from an early to a late stage, and the stages of pre-cachexia, cachexia, and refractory cachexia were proposed (Figure 1). Diagnostic criteria, based predominantly on weight loss and body mass index (BMI), were assigned to the cachexia stage, whereas for the other stages, only suggestive characteristics were presented. Further work was recommended to validate the definition and classification.

Another important step forward was made when Martin *et al.*[12] confirmed that severity of weight loss depends on the concurrent depletion of fat and muscle reserves. They showed that weight loss, adjusted for concurrent BMI, predicted survival; patients with a low degree of weight loss and a high BMI had the best prognosis, and those with a high degree of weight loss and a low BMI had the worst prognosis. By combining weight loss and BMI, they produced and validated a weight loss grading system (WLGS) ranging from 0 to 4, with each weight loss grade predicting survival independently of cancer type and stage, age, sex, and performance status.

The WLGS was not intended as a classification system of cancer cachexia. However, because weight loss is a key component of the syndrome, the WLGS could still potentially be used to classify cancer cachexia. In order to test this hypothesis, concurrent validity in relation to established cachexia domains needs to be demonstrated. Further, because cachexia is a trajectory from pre-cachexia to refractory cachexia, a classification system should be able to predict which patients are at risk of having cachexia progression. This is of particular interest early in the cachexia trajectory.

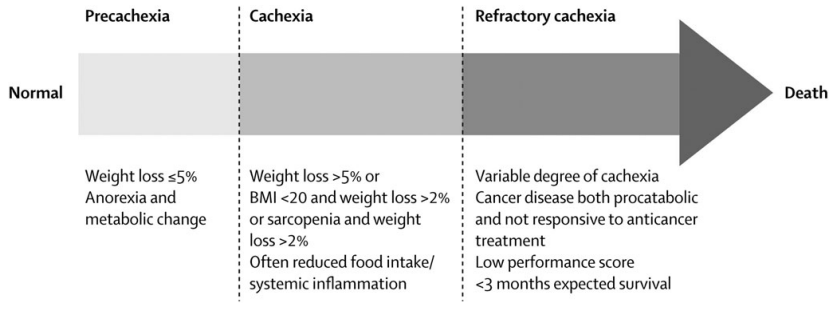
Thus, the present study had three aims: (i) to confirm the prognostic validity of the WLGS in an independent, prospective cohort of patients with incurable cancer; (ii) to evaluate the concurrent validity of the WLGS in relation to cachexia domains (anorexia, dietary intake, performance status, and physical and emotional functioning) and to explore if adding these domains to the WLGS improves prognostic accuracy; and (iii) to evaluate if the WLGS predicts cachexia progression.

Methods

Patients and study design

Between April 2011 and October 2013, 1739 patients from 30 centres across Europe (27), Canada (2), and Australia (1) were included in the European Palliative Care Cancer Symptom

Figure 1 Postulated stages of cachexia (Reprinted from The Lancet Oncology, 12(5), Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al., Definition and classification of cancer cachexia: an international consensus, 489–95, Copyright (2011), with permission from Elsevier).



study.[13] This was a prospective observational study by the European Palliative Care Research Centre (PRC) and the European Association for Palliative Care (EAPC) Research Network with the aim of improving the understanding of the development of symptoms and how these symptoms may best be assessed and classified in order to improve symptom management. Eligible patients met the following key criteria: ≥18 years of age, with incurable cancer, enrolled in a palliative care programme, and available for at least one follow-up registration. All patients provided written informed consent.

Data collection and weight loss grading

Patients were assessed at baseline and approximately every 4 weeks for at least three follow-up visits or until death. The following information was collected: patient demographics, height, current body weight, and patient-reported weight loss in the 6 months prior to inclusion. Weight loss at subsequent visits was computed by adding measured weight change to baseline-reported weight loss. BMI was recalculated at every visit based on current body weight. Weight loss grade was assessed and given a score of 0–4 by combining weight loss and BMI (Table 1).[12]

Table 2 includes the items from the Patient-Generated Subjective Global Assessment (PG-SGA)[14] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) C15 PAL[15] that were used to collect data pertaining to the cachexia domains for nutrition and functional and psychosocial effects. Both instruments are commonly used and well validated patient reported outcome measurements. The clinical meaning of PG-SGA scores is listed in Table 2. Regarding the EORTC-QLQ, a difference in score of ≥20 was considered a definite clinical significant difference, a difference in score of 10–20 was considered a moderate difference, and a difference in score of 5–10 was considered a small difference.[16] In addition, health care personnel-reported performance status (Karnofsky scale) was assessed due to its long standing importance in cancer prognostication.[17] The Karnofsky scale ranges from 0 (Dead) to 100 (normal, no complaints, and no evidence of disease).

Statistical considerations

To evaluate the prognostic validity of the WLGS, time to death or last known date to be alive was calculated and Kaplan–Meier curves were plotted for each grade. Hazard

Table 1. Grading of weight loss (0–4) based on percentage weight loss and current body mass index[12]

	Body mass index (kg/m^2)				
Weight loss (%)	≥28	25–27.9	22–24.9	20–21.9	<20
<2.5	0	0	1	1	3
2.5–5.9	1	2	2	2	3
6–10.9	2	3	3	3	4
11–14.9	3	3	3	4	4
≥15	3	4	4	4	4

Table 2. Cachexia domains assessed

Cachexia domain	Factors	Reported by	Instrument	Scale
Nutrition	Dietary intake	Patient	PG-SGA (food intake sub-score)[14]	0 points: unchanged or more than usual 1 point: normal food but less than normal amount (or nutrition by vein) 2 points: little solid food 3 points: only liquids or nutritional supplements 4 points: very little of anything
	Appetite loss	Patient	EORTC QLQ C15 PAL[15]	0–100[a]
Functional and psychosocial effects	Emotional functioning Physical functioning Fatigue	Patient	EORTC QLQ C15 PAL[15]	0–100[a]
	Performance status	Health care personnel	Karnofsky scale[17]	0–100[a]

Abbreviations: EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PG-SGA, Patient-Generated Subjective Global Assessment.
[a]For emotional functioning, physical functioning, and performance status, 100 is the best score, while for appetite loss and fatigue, 100 is the worst score.

ratios (HRs) were calculated by using Cox proportional hazard methods. Adjustments for possible differences in age, sex, and cancer type (digestive organ cancer, respiratory organ cancer, breast cancer, cancer of urinary tract and male genitalia, gynaecological cancer, haematological cancer, and others) and stage (local, locally advanced, or metastatic/disseminated) between weight loss grades were made. Adjustments for differences in performance status between grades were not performed as a worsening in this parameter is an expected consequence of cachexia progression.

To investigate the baseline differences between weight loss grades 0 and 4 in terms of severity of appetite loss, dietary intake, performance status, fatigue, and physical and emotional functioning, one-way analysis of variance was used. A linear test for trend was applied to confirm if severity increased with grade. Where normality could not be assumed, the non-parametric Kruskal–Wallis test and Jonckheere–Terpstra test were used instead. To illustrate the magnitude of change over the entire spectrum of the WLGS, absolute change in mean values between grade 0 and grade 4 was calculated. To rank which domain had the greatest relative change, the absolute change in mean values of each domain was divided by its standard deviation.

To examine if the cachexia domains improved the prognostic validity of the WLGS, a survival prediction model was built by using Cox proportional hazard methods. The general prognostic factors age, sex, and cancer type and stage were added first, and then a forward stepwise (likelihood ratio) method was used to add the cachexia domains (appetite loss, dietary intake, performance status, fatigue, and physical and emotional functioning) and the WLGS.

To assess the likelihood of progression of cachexia during follow-up, a longitudinal analysis was performed. Weight loss grade was assessed at every follow-up visit and the proportion of patients progressing to higher grades, improving to lower grades, or dying after 1, 2, and 3 months was calculated.

High attrition resulting in missing data was expected because of patient deterioration. Therefore, a sensitivity analysis replacing missing values with extreme values was performed to assess the robustness of the longitudinal analysis. This significantly altered the results (data not shown), and thus, for patients alive but unable to attend follow-up, imputations of likely values for missing data on body weight were performed by using the iterative estimation and maximization algorithm with auxiliary

Table 3. Baseline characteristics of the total population and by weight loss grade

	Total	Weight loss grade				
		0	1	2	3	4
n	1406	326	325	135	347	273
Median age [years] (IQR)	66 (57–74)	65 (56–73)	65 (56–74)	66 (60–74)	66 (56–74)	67 (58–75)
Sex						
Female	705 (50%)	173 (53%)	188 (58%)	61 (46%)	166 (48%)	117 (43%)
Male	700 (50%)	153 (47%)	137 (42%)	74 (54%)	181 (52%)	155 (57%)
KPS						
≤70	886 (63%)	175 (54%)	162 (50%)	86 (64%)	241 (70%)	222 (81%)
>70	517 (37%)	149 (46%)	163 (50%)	49 (36%)	105 (30%)	51 (19%)
Principal cancer diagnosis						
Cancer of the digestive organs	418 (30%)	71 (22%)	85 (26%)	45 (33%)	112 (32%)	105 (38%)
Cancer of the respiratory organs	282 (20%)	58 (18%)	63 (19%)	36 (27%)	70 (20%)	55 (20%)
Breast cancer	252 (18%)	87 (27%)	83 (26%)	22 (16%)	36 (10%)	24 (9%)
Other cancers	174 (12%)	33 (10%)	32 (10%)	10 (7%)	57 (16%)	42 (15%)
Urinary cancer or cancer of the male genitalia	160 (11%)	43 (13%)	38 (12%)	17 (13%)	40 (12%)	22 (8%)
Gynaecological cancer	82 (6%)	27 (8%)	18 (6%)	3 (2%)	16 (5%)	18 (7%)
Haematological cancer	38 (3%)	7 (2%)	6 (2%)	2 (1%)	16 (5%)	7 (3%)
Stage						
Local	61 (4%)	15 (5%)	17 (5%)	4 (3%)	18 (5%)	7 (3%)
Locally advanced	148 (11%)	36 (11%)	27 (8%)	12 (9%)	35 (10%)	38 (14%)
Metastatic	1190 (85%)	273 (84%)	279 (86%)	118 (88%)	293 (85%)	227 (83%)
Median time since diagnosis [months] (IQR)	19 (7–48)	25 (11–58)	23 (9–51)	17 (6–37)	14 (5–38)	14 (5–43)
Current oncologic treatment						
No treatment	560 (40%)	100 (31%)	97 (30%)	52 (39%)	171 (49%)	140 (51%)
Chemotherapy	625 (45%)	153 (47%)	179 (55%)	67 (50%)	129 (37%)	97 (36%)
Radiotherapy	74 (5%)	19 (6%)	17 (5%)	11 (8%)	15 (4%)	12 (4%)
Hormonal therapy	141 (10%)	48 (15%)	37 (11%)	9 (7%)	24 (7%)	23 (8%)
Other	83 (6%)	30 (9%)	18 (6%)	6 (4%)	20 (6%)	9 (3%)
Mean weight loss (6 months)[%] (SD)	5.9 (7.5)	0.1 (0.4)	0.4 (1.2)	5.3 (2.2)	8.0 (5.8)	16.9 (6.1)
BMI [kg/m^2] (SD)	24 (4.9)	29 (3.7)	24 (3.0)	26 (5.2)	23 (3.9)	20 (2.9)

Abbreviations: BMI, body mass index; IQR, interquartile range; KPS, Karnofsky performance status; SD, standard deviation.

variables sex, height, body weight, weight loss, and appetite loss. This was done in order to minimize potential bias that could arise by simply ignoring missing assessments. A moderate effect of imputations was observed, with the largest difference seen in patients with weight loss grade 2, where it led to a computational increase in risk of cachexia progression of 9 percentage points compared with the non-imputed dataset.

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 21, IBM Corp, Armonk, NY, USA.

Results

A total of 1406 patients had data available on BMI and weight loss at baseline; those who did not were excluded (n = 333). Patient characteristics are shown in Table 3. Median [IQR] age was 66 [57–74] years, 705 (50%) were female, and most were outpatients (1136, 81%) and had a KPS ≤70 (886, 63%). The 333 patients who were excluded were significantly older (median age 70 vs. 66), had a poorer performance status (KPS ≤ 70, 83% vs. 63%) and a shorter median time since diagnosis (13 vs. 19 months), and were more likely to be hospice or nursing home inpatients (25% vs. 6%).

Of the 1406 patients included, 574 (41%) patients completed 3 months of follow-up, while 259 (18%) died. A total of 573 (41%) were lost to follow-up: 239 (17%), 126 (9%), and 208 (15%) after the first, second, and third visits respectively. Although several patients were lost to follow-up after the baseline visit, survival data was still available for a total of 1327 patients.

Prognostic validity

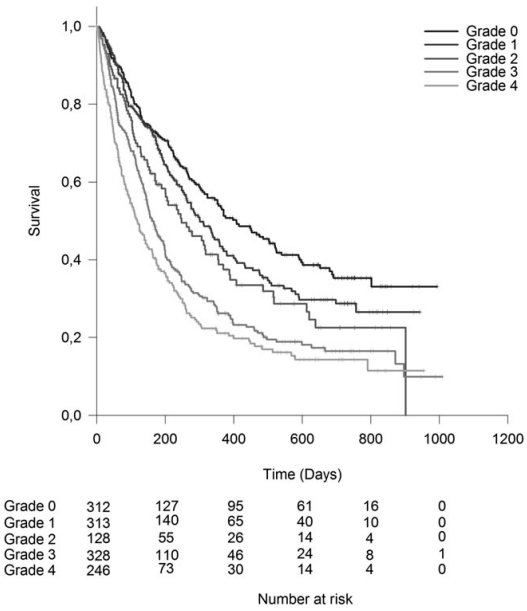
Survival worsened with increasing weight loss grade (Figure 2). The overall effect of the WLGS on survival was significant as expressed by change in −2 log likelihood (P < 0.001) and persisted after adjustment for age, sex, and cancer type and stage (P < 0.001).

Median (95% CI) survival ranged from 407 (312–502) days in weight loss grade 0 to 119 (93–145) days in weight loss grade 4 (Table 4). Adjusted HR ranged from 1.2 (P = 0.20) in weight loss grade 1 to 2.2 (P < 0.001) in weight loss grade 4 (Table 4).

Concurrent validity in relation to other cachexia domains and impact on prognostic accuracy

There was a worsening of all cachexia domains with increasing weight loss grade (P < 0.001) (Figure 3). Between grades 0 and 1, the severity of the cachexia domains was similar with overlapping confidence intervals.

Figure 2 Cumulative survival by weight loss grade.



The magnitude of the differences between grades 0 and 4 was greatest for food intake. The mean score worsened from 0.4 to 1.4 (0.87 SD), followed by appetite loss 18 to 48 (0.86 SD), fatigue 42 to 62 (0.69 SD), physical functioning 72 to 54 (0.64 SD), KPS 71 to 63 (0.46 SD), and emotional functioning 69 to 63 (0.29 SD).

When performance status (P < 0.001), physical functioning (P < 0.001), emotional functioning (P = 0.004), and appetite loss (P = 0.005) were added to the WLGS (P < 0.001), the accuracy of survival prediction improved. Of note was that the magnitude of improvement due to performance status (Karnofsky) or physical functioning (EORTC-QLQ C15 PAL) depended on which of the two factors were added first (data not shown). This indicates some collinearity between the two. However, they were both highly significant when present together, indicating some degree of independent contribution, so both were kept in the model.

Predicting the progression of cachexia

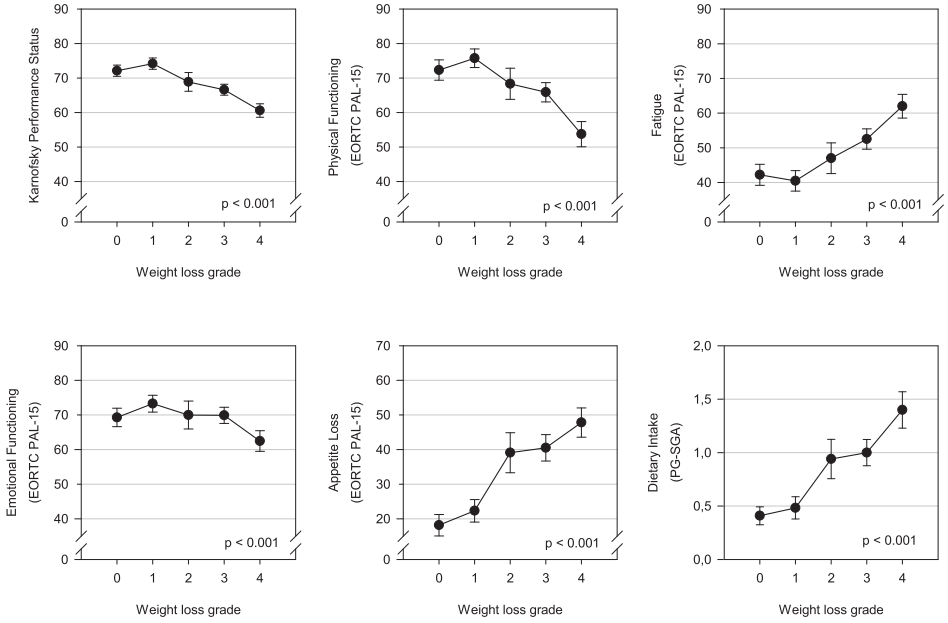
Figure 4 is based on the imputed dataset and presents the likelihood of surviving patients progressing or improving according to the WLGS dependent on their baseline weight loss grade. There was a slightly higher tendency of progression of cachexia in grade 1 compared with grade 0, while the risk was considerably higher in grade 2. The tendency towards improvement declined over the last three grades.

Table 4. Median survival, unadjusted and adjusted HRs, and *P*-values by weight loss grade

Weight loss grade	*n*[a]	Number of deaths	Median survival [days] (95% CI)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[b]	*P*
0	312	156	407 (312–502)	1.0		1.0	
1	313	164	301 (244–358)	1.2 (1.0–1.5)	0.11	1.2 (0.9–1.4)	0.20
2	128	78	247 (154–340)	1.5 (1.1–1.9)	0.004	1.3 (1.0–1.7)	0.08
3	328	233	161 (137–185)	2.0 (1.6–2.5)	<0.001	1.9 (1.5–2.3)	<0.001
4	246	186	119 (93–145)	2.6 (2.1–3.2)	<0.001	2.2 (1.8–2.8)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Five patients were excluded from the adjusted analysis because of missing values of independent variables.
[b]Adjusted for age, sex, and cancer type and stage.

Figure 3 Relationship between the different cachexia domains and weight loss grade (error bars: 95% confidence intervals). Analysis of variance and test for linear trend were significant for all cachexia domains ($P < 0.001$); this was confirmed by non-parametric analouges (Kruskal–Wallis test and Jonckheere–Terpstra test) in physical functioning, fatigue, emotional functioning, appetite loss, and dietary intake due to the non-normal distributions of these variables.



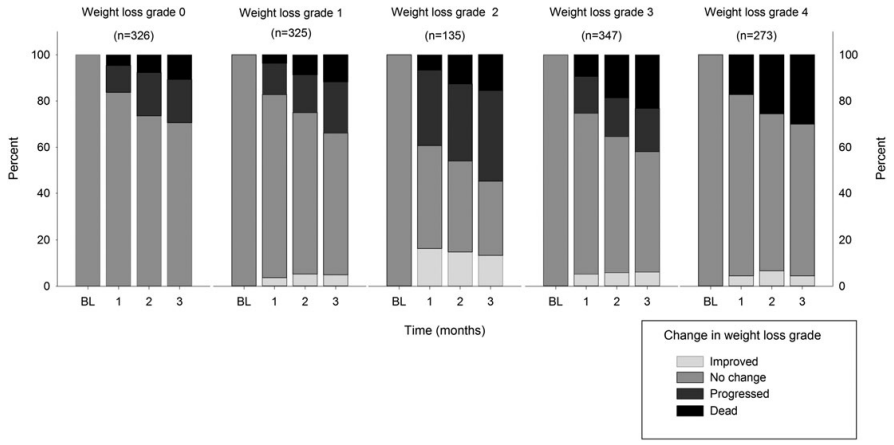
After 3 months, the proportions of patients with weight loss grades 0 to 3 progressing to a more advanced weight loss grade were 19%, 22%, 39%, and 19%, respectively. Conversely, those with weight loss grade 1 to 4 improving to a lower weight loss grade were 5%, 13%, 6%, and 4%, respectively.

Discussion

The present study has confirmed the prognostic validity of the WLGS in an independent, prospective cohort of patients with incurable cancer. Moreover, the WLGS also has concurrent validity in relation to established cachexia domains and predicts cachexia progression. It has also been demonstrated that the addition of cachexia domains to the WLGS serves to improve its prognostic accuracy.

The present study has several implications for the management of cancer cachexia. Firstly, the findings support the observation made previously by Martin *et al.*[12] that survival significantly worsens with increasing weight loss grade and are consistent with several other publications showing that patients with involuntary weight loss have a poor prognosis.[4,18,19] Looking at weight loss grades 1 and 2 individually, survival did worsen compared with that at weight loss grade 0. However, the difference did not reach

Figure 4 Bar charts for each baseline weight loss grade (0–4) showing the likelihood of improvement to preceding or progress to subsequent grades or death at 1, 2, and 3 months of follow-up.



statistical significance, although weight loss grade 2 showed a tendency towards significance. Failure to reach significance may be due to the smaller sample in the present study compared with the study by Martin *et al.*[12]

Secondly, the WLGS not only predicts survival but the present findings suggest that it may also be useful in cachexia classification as it has concurrent validity in relation to established cachexia domains. Of these, dietary intake and appetite loss were the factors most strongly related to increasing grade, which is not surprising given that these factors are central in the pathophysiology of cancer cachexia.[20] From grades 0 to 4, dietary intake changed from a mean value of 0.4, representing a near normal intake of nutrients (normal intake is score 0), to 1.4, which represents a reduced intake of normal food (or feeding by nasogastric tube or vein) (score 1) or intake of little solid food (score 2).[14] KPS changed from a mean value close to 70 to close to 60, the difference being the ability to fully care for oneself vs. requiring occasional assistance.[17] Appetite loss and fatigue changed by a score of 20, which is considered to be a definite clinical significant change. Physical functioning changed by a score of 18, which is considered to be a moderate change, and emotional functioning changed by a score of 6, which is considered to be a small change.[16]

Performance status, appetite loss, and physical and emotional functioning improve prognostication of survival independently of the WLGS. This suggests that they can be used in combination with the WLGS to further improve the prognostic ability of the system. Future research should examine their full potential to classify cancer cachexia.

The third and, arguably, the finding with the greatest potential clinical relevance was that weight loss grade was predictive of the likelihood of cachexia progression. The risk of progression was considerably higher in weight loss grade 2 compared with that in weight loss grade 0 or 1. This suggests that more patients have started on the cachexia trajectory in weight loss grade 2 than in weight loss grade 0 or 1. Notably, the percentage of patients receiving chemotherapy was similar in patients with weight loss grades 0–2 (47%, 55%, and 50%, respectively), so less anti-cancer treatment does not seem to explain the increased risk of cachexia progression in weight loss grade 2. Regarding the two most severe grades of the WLGS (grades 3 and 4), the probability of improvement decreased, reflecting that irreversibility increases as cachexia becomes more advanced. This is consistent with the findings of Prado *et al*. who found that weight gain is unlikely to occur in the last 90 days of advanced cancer patients' lives.[21] Overall, the risk of progression to more severe grades superseded the rate of improvement at any grade (with the obvious exception of grade 4), confirming the progressive nature of cachexia.

So how might these findings influence practice? One such way is the early identification of patients where cachexia interventions should be implemented. As less than a quarter of patients with grades 0 and 1 have cachexia progression, it would seem sensible to start cachexia intervention for patients with grade 2 where the likelihood of progression is greater. That way, one might avoid over-treating many patients. This strategy is supported by the finding that patients with grade 2 have a higher symptom load (appetite loss and fatigue), lower dietary intake, and poorer function than patients with lower weight loss grade. Thus, grade 2 seems to fit the description of pre-cachexia in the consensus definition.[11] At the other end of the scale, patients with grade 4 had a median survival of a little over 3 months and a mean KPS close to 60. This is in accordance with the

description of refractory cachexia in the consensus definition, and aggressive treatment attempts against cachexia, as well as chemotherapy, should be avoided in this group of patients.[11] Instead, the attention should be given to palliation and immediate symptom relief.

The main limitation of this study was the expected, but considerable, attrition that may have affected the longitudinal analyses. Presumably, the high dropout rate was caused by patients deteriorating and becoming too weak to continue participation. This was addressed by performing imputations of missing values aiming to reduce the risk of bias. Another limitation was the lack of information on important cachexia domains such as systemic inflammation and objective measures of muscle and fat mass. Systemic inflammation is interesting because it is considered a driver of cancer cachexia,[6] and markers of inflammation could potentially be important in diagnosing cachexia. Measures of muscle and fat mass could have explained whether observed weight gain was due to improvement of cachexia or due to accumulation of fluids or shifts in body composition. Nevertheless, concurrent validity could be evaluated with regard to important cachexia domains such as appetite, food intake, and physical function. Furthermore, because cachexia development is likely to be affected by the response to chemotherapy, nutrition, and other treatments of cachexia, one cannot claim that this study describes the natural development of cachexia in an untreated population. Nevertheless, it describes the development of cachexia in a population without *systematic* intervention against cachexia. The strengths of this study are the longitudinal design and the large number of patients included from several countries, both rare in palliative research.

Conclusion

Our findings support that the WLGS predicts survival and is in keeping with the cancer cachexia phenotype. Furthermore, the addition of key cachexia domains improves prognostic accuracy of the WLGS. Prospective clinical trials should examine the WLGS's ability to stratify cachexia treatments. This could have significant implications for clinical practice and challenge the widely accepted paradigm that cancer cachexia is an inevitable consequence of advanced disease.

Acknowledgements

The European Palliative Care Cancer Symptom study is a collaborative effort between the European Palliative Care Research Centre (PRC) and the European Association for Palliative Care Research Network (EAPC-RN). The study was approved by all appropriate ethical committees and was conducted in keeping with the Helsinki declaration. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle.[22]

This study was funded by the Joint Research Council at Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital-Trondheim University Hospital (6070); Norwegian Cancer Society; Helsinn.

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Conflicts of interest

F.S. has had punctual advisorships for Acacia, ACRAF, Amgen, Baxter, Celgene, Danone, Fresenius, GlaxoSmithKline, Grünenthal, Helsinn, ISIS Global, Millennium/Takeda, Mundipharma, Novartis, Novelpharm, Nycomed, Obexia, Otsuka, Ono, Pharm-Olam, Pfizer, Psioxus, PrIME, Santhera, Sunstone, Teva, and Vifor. He has received unrestricted industry grants for clinical research from Celgene, Fresenius, and Helsinn. He has participated in a clinical cachexia trial lead by Novartis.

O.M.V., D.B., A.W., P.F., V.E.B., M.J.H., S.K., B.L., and T.S.S. declare that they have no conflicts of interest.

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APPENDIX 5:

Paper III

Vagnildhaug et al. BMC Palliative Care (2019) 18:46
https://doi.org/10.1186/s12904-019-0429-2

BMC Palliative Care

RESEARCH ARTICLE Open Access

A prospective study examining cachexia predictors in patients with incurable cancer

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Abstract

Background: Early intervention against cachexia necessitates a predictive model. The aims of this study were to identify predictors of cachexia development and to create and evaluate accuracy of a predictive model based on these predictors.

Methods: A secondary analysis of a prospective, observational, multicentre study was conducted. Patients, who attended a palliative care programme, had incurable cancer and did not have cachexia at baseline, were amenable to the analysis. Cachexia was defined as weight loss (WL) > 5% (6 months) or WL > 2% and body mass index< 20 kg/m^2. Clinical and demographic markers were evaluated as possible predictors with Cox analysis. A classification and regression tree analysis was used to create a model based on optimal combinations and cut-offs of significant predictors for cachexia development, and accuracy was evaluated with a calibration plot, Harrell's c-statistic and receiver operating characteristic curve analysis.

Results: Six-hundred-twenty-eight patients were included in the analysis. Median age was 65 years (IQR 17), 359(57%) were female and median Karnofsky performance status was 70(IQR 10). Median follow-up was 109 days (IQR 108), and 159 (25%) patients developed cachexia. Initial WL, cancer type, appetite and chronic obstructive pulmonary disease were significant predictors ($p \leq 0.04$). A five-level model was created with each level carrying an increasing risk of cachexia development. For Risk-level 1-patients (WL < 3%, breast or hematologic cancer and no or little appetite loss), median time to cachexia development was not reached, while Risk-level 5-patients (WL 3–5%) had a median time to cachexia development of 51 days. Accuracy of cachexia predictions at 3 months was 76%.

Conclusion: Important predictors of cachexia have been identified and used to construct a predictive model of cancer cachexia.

Trial registration: ClinicalTrials.gov Identifier: NCT01362816.

Keywords: Cachexia, Pre-cachexia, Weight loss, Cancer, Palliative care

Background

Cachexia is present in up to half of patients with cancer [1]. It adversely affects the well-being of many patients with cancer by inducing progressive weight loss as well as impairing appetite, physical function and quality of life [2]. Moreover, cachexia increases mortality and impedes delivery of anti-cancer treatment [3].

To date, there is no licensed treatment and no standard of care for patients with cancer cachexia. Corticosteroids have been shown to improve fatigue [4] and progestins have improved weight loss, however lack of positive effects on lean body mass, physical function or nutritional intake means that these agents have limited clinical benefits [5]. Further, the side effects of these drugs often outweigh potential benefits. Recently, selective androgen receptor modulators and ghrelin agonists have been examined in this area, however lack of demonstrable effects on lean body mass and/or function mean that these have not been granted regulatory approval for the treatment of cachexia [6, 7].

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One of the reasons that the aforementioned and other agents may have proven inefficacious is that they may not have been used at the optimal time point and/or in patients truly at risk of developing cachexia. It has been argued that to optimise efficacy of cachexia medications, treatment should be initiated as early as possible [8]; even before cachexia is established, termed pre-cachexia. Pre-cachexia is the first part of a cachexia staging system based on a trajectory format with the latter two being cachexia and refractory cachexia [9]. In this staging system, cachexia was defined as more than 5% weight loss in 6 months, or more than 2% weight loss if low body mass index (< 20 kg/m^2) or sarcopenia were present. Refractory cachexia ensues when the cancer becomes procatabolic and unresponsive to anti-cancer treatment.

Pre-cachexia was proposed as a stage where early clinical and metabolic signs such as anorexia and inflammation were present, but substantial weight loss was not [9]. The intention was to separate patients likely to develop cachexia from those who are not. However, diagnostic criteria were not suggested, and the challenge remains to optimally stratify patients into high and low risk groups. Several attempts at defining criteria for pre-cachexia have been made. These attempts have mostly been based on cross-sectional data or analyses of overall survival, study designs that are inadequate in showing if the criteria in question imply a greater risk of developing cachexia over time [10–12].

Therefore, the primary aim of this study was to identify which factors most strongly predict development of cachexia in a prospective cohort of patients with incurable cancer. Secondary aims were to construct a model to predict cachexia based on the optimal combinations and cut-offs of the identified predictors, and to evaluate the model's accuracy.

Methods

Patients and study design

Between April 2011 and October 2013, 1739 patients from 30 centres across Europe (27), Canada (2) and Australia (1) were included in the European Palliative Care Cancer Symptom study (EPCCS). The participating centres are presented in the main publication originating from this study [13]. EPCCS was a prospective observational study conducted by the European Palliative Care Research Centre (PRC) (https://oslo-universitetssykehus.no/avdelinger/kreftklinikken/avdeling-for-kreftbehandling/prc) and the European Association for Palliative Care (EAPC) Research Network (https://www.eapcnet.eu/research/research-network). The overall aim of the EPCCS study was to improve the understanding of symptom development, and how these symptoms may best be assessed and classified in order to improve symptom management. Eligible patients met the following key inclusion criteria: ≥18 years of age; with incurable cancer and attending a palliative care program. Data pertaining to cancer cachexia were retrieved from this dataset and assessed as part of the present study.

Data collection and assessments

Patients were assessed at baseline and then approximately every 4 weeks for at least three follow-up visits or until death. The following information was collected: Demographical data (age, gender, geographical region and treatment setting [inpatient, outpatient, home care]), disease specific data (cancer type and stage [localized vs. metastatic]), height, current body weight and patient reported weight loss in the 6 months prior to inclusion. Weight loss at subsequent visits was calculated by adding measured weight change to baseline reported weight loss. Cachexia was diagnosed at first occurrence of either a) weight loss > 5% since 6 months prior to inclusion or b) weight loss > 2% since 6 months prior to inclusion if current body mass index (BMI) < 20 kg/m^2. All patients were assessed for cachexia at baseline. If anyone had insufficient data to be assessed for cachexia at baseline, data from the first follow up visit was used as baseline registrations if available. Only patients without cachexia at baseline were included in the analysis.

Performance status was assessed according to Karnofsky Performance Status (KPS) (0–100). Comorbidities in terms of heart disease, renal disease, chronic obstructive pulmonary disease (COPD) or arthritis were registered.

The dataset was not sufficiently large to assess the risk of cachexia development of each individual cancer type. Thus, cancer type was grouped a priori into one of three categories: Low risk - Breast cancer and haematological cancers (lymphoma, leukemia and myelomatosis); High risk – pancreatic and gastric cancer; Neutral risk - all other cancers. This was based on previous literature on cancer type and association with cachexia [14, 15].

The following patient reported outcome measurements (PROMs) were registered: Food intake was assessed as "less than usual", "more than usual" or "unchanged" according to the abridged Patient-Generated Subjective Global Assessment (aPG-SGA) [16]. Physical and emotional functioning (0 [worst] - 100 [best]), anorexia and fatigue (0[best] – 100 [worst]) were assessed according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) C15 PAL [17]. Both instruments are widely used, and well validated in the target population.

Statistical considerations

Patients who developed cachexia during follow up were identified and the remaining patients were censored at the time of their last body weight registration. Time to cachexia development or censoring was calculated. Univariable Cox Proportional Hazards method was used to estimate hazard rate ratios (HR) for cachexia development with the

following predictors assessed at baseline: Age, gender, cancer type (low risk, neutral risk or high risk), cancer stage, comorbidity, weight loss, BMI, performance status, physical functioning, emotional functioning, fatigue, food intake and appetite. All predictors with p-value < 0.20 were included in a multivariable Cox model. Multicollinearity among the candidate predictors was checked by estimating Spearman's correlation coefficients. The least significant predictors were dropped from the multivariable model one by one in a manual backwards selection, until only significant predictors remained. All possible interactions among the remaining predictors were examined and added to the model if significant. Due to known association between COPD and lung cancer [18], a sensitivity analysis specifically adjusting for lung cancer alongside the a priori cancer type categorization (low risk, neutral risk, high risk) was performed.

In order to construct a model that uses optimal combinations and cut--offs of the identified risk factors to predict cachexia development, a classification and regression tree (CART) analysis for failure time data was used. CART is a non-parametric data-mining procedure which examines all possible cut-offs of every variable to create separate subgroups of significantly different risks. It repeatedly splits the population based on the variable and cut-off that most optimally stratifies risk of cachexia development in the current group. It stops when significant divisions no longer can be performed. The final subgroups were compared, and adjacent subgroups with similar risk of cachexia development were merged to create levels of increasing risk of cachexia development. Kaplan-Meier curves were plotted for each risk-level, and both log-rank test for differences in cachexia development probabilities among risk levels, and test for trend in cachexia development probabilities (i.e. cachexia development probability of Risk-level 1 ≤ Risk-level 2 ≤ … ≤ Risk-level 5) were performed. To assess accuracy of this model, a calibration plot was created by plotting predicted vs. observed risk at 3 months, and Harrell's c-statistic was estimated to assess discriminatory capacity. In addition, receiver operating characteristic (ROC) curve analysis at 3 months in patients alive and still on study was performed. For the different possible cut-offs of a diagnostic test (all possible cut-offs for the "prediction function" from the model in this case), the ROC curve is a plot of the true positive rate (sensitivity, i.e. the proportion of patients correctly classified by the model among those actually developing cachexia) against the false positive rate (1- specificity, i.e. the proportion of patients wrongly classified as "developing cachexia" by the model, among those actually not developing cachexia). This was done to evaluate if a cut-off with both high sensitivity and high specificity for the prediction of cachexia development could be identified. A two-sided p-value of < 0.05 was considered significant in all analyses, unless stated otherwise. Stata version 13.1 (College Station, Texas, USA) was used for statistical analyses, and the Stata-module Cart [19] was used for the CART-analysis.

Results

A flow chart of patient selection is shown in Fig. 1. Of the 1739 patients included in the EPCCS-study, 425 patients (24%) were excluded because of missing data necessary to classify patients as cachexic or not cachexic. Six-hundred-and-eighty-six patients (39%) already had cachexia at baseline and therefore were inadmissible to further analysis, leaving 628 (36%) patients to the final analysis.

Patient characteristics are shown in Table 1. The median age was 65 years (IQR 17), 359 (57%) were female and median KPS was 70 (IQR 10). One-hundred-and-fifty-nine patients (25%) developed cachexia during follow-up. For affected individuals, cachexia occurred in a median time of 63 days (IQR 79). Overall, minimum follow-up was 16 days and median follow-up was 109 days (IQR 108).

Table 2 shows a univariable analysis of potential predictors of cachexia development. Gender, weight loss, performance status, food intake, appetite loss, cancer type and COPD were all significant predictors ($p \leq 0.02$). In addition, physical functioning and cancer stage were included in the multivariable analysis due to p-values < 0.20. Physical functioning and KPS (0.53, $p < 0.001$) and appetite and food intake (0.54, $p < 0.001$) had correlation coefficients > 0.5.

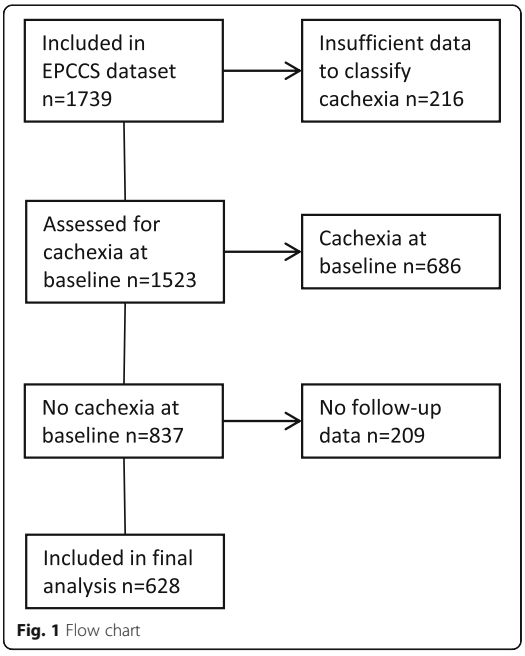

Fig. 1 Flow chart

Table 1 Baseline patient characteristics

Patient characteristics ($n = 628$)		
Median Age at inclusion (IQR)	65	(17)
Gender f (%)		
Female	359	(57)
Male	269	(43)
Geographical region f (%)		
Europe	578	(92)
Canada	43	(7)
Australia	7	(1)
Cancer type f (%)		
Low risk cancer	184	(29)
Breast	171	(27)
Haematological	13	(2)
Neutral risk cancer	410	(65)
Lung	125	(20)
Colorectal	70	(11)
Prostate	48	(8)
Female genitalia	36	(6)
Head and neck	24	(5)
Urinary	20	(3)
Hepatobiliary	17	(3)
Sarcoma, connective and soft tissue	17	(3)
Small intestine	11	(2)
Oesophageal	8	(1)
Other	34	(5)
High risk cancer	33	(5)
Pancreatic	24	(4)
Gastric	9	(1)
Cancer stage f (%)		
Local	83	(13)
Metastatic/disseminated	543	(87)
Treatment setting		
Inpatients	56	(9)
Outpatients	483	(78)
Home care	77	(13)
Anti-cancer treatment		
Chemotherapy	337	(54)
Hormonal therapy	81	(13)
Radiotherapy	35	(6)
Other	47	(7)
No treatment	173	(28)
Median Karnofsky PS (IQR)	70	(10)
Weight loss (6 months) f (%)		
< 1%	535	(85)
1–5%	93	(15)
Mean BMI (SD)	25.5	(4.5)
Comorbidities f (%)		
Heart disease	165	(26)
COPD	62	(10)
Arthritis	51	(8)
Renal disease	17	(3)

Abbreviations: *IQR* interquartile range, *PS* performance status, *SD* standard deviation, *COPD* chronic obstructive pulmonary disease

Table 2 Univariable analysis

Univariable analysis			
	HR	95% CI	*p*
Age at inclusion	1.01	1.00–1.03	0.06
Gender			
Male	1.5	1.1–2.0	0.01
Female	1		
Weight loss (6 months)	1.6	1.4–1.7	< 0.001
BMI	0.99	0.95–1.03	0.53
Karnofsky PS (0–100)	0.98	0.97–1.00	< 0.01
Fatigue (0–100)	1.00	1.00–1.01	0.26
Physical functioning (0–100)	0.99	0.99–1.00	0.09
Emotional functioning (0–100)	1.00	0.99–1.01	0.67
Food intake			
Less than usual	1.7	1.2–2.4	< 0.01
More than usual	1.0	0.6–1.7	0.93
Unchanged	1		
Appetite loss (0–100)	1.01	1.01–1.02	< 0.001
Cancer stage			
Metastatic/disseminated	1.7	1.0–2.9	0.07
Local	1		
Cancer type[a]			
High risk cancer	4.4	2.4–8.1	< 0.001
Neutral risk cancer	2.1	1.4–3.1	< 0.001
Low risk cancer	1		
Heart disease	0.9	0.6–1.3	0.55
Renal disease	1.4	0.6–3.1	0.45
Arthritis	1.4	0.8–2.3	0.22
COPD	1.7	1.1–2.7	0.02

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *PS* performance status, *COPD* chronic obstructive pulmonary disease
[a]Low risk - Breast cancer, lymphoma, leukaemia; High risk – pancreatic and gastric cancer; Neutral risk - all other cancers

After manual backward selection, where insignificant predictors were removed one by one, weight loss, cancer type, appetite and COPD all remained significant ($p \leq 0.04$) and were kept in the model (Table 3). A significant interaction ($p < 0.01$) was demonstrated between weight loss and cancer type, signifying that the effect of cancer type on risk of developing cachexia became less important if weight loss already was high. Thirty percent of patients with lung cancer had COPD in contrast to the overall COPD prevalence of 10%. Thus, a sensitivity analysis was performed adjusting for lung cancer alongside the a priori cancer type classification. This analysis showed that patients with lung cancer had a slightly higher risk of cachexia development compared to patients classified as having neutral risk cancer (HR [95%CI] 2.7 [1.4–5.2] vs 2.5 [1.4–4.3], respectively) and risk attributable to COPD fell slightly and COPD no longer significantly predicted cachexia development (HR 1.5 [0.9–2.6]).

Figure 2 shows the CART-analysis. Weight loss, cancer type and appetite loss could be used to identify six groups of patients, each with a homogenous risk of cachexia development within the group. Two groups from adjacent branches of the classification and regression tree were combined due to similar hazard ratios, resulting in a model of five levels of increasing risk of cachexia development:

1. < 3% weight loss, low risk cancer type and no/little appetite loss
2. < 3% weight loss and either low risk cancer type and quite a bit/very much appetite loss OR neutral risk cancer type and no/little appetite loss
3. < 3% weight loss, neutral risk cancer type and quite a bit/very much appetite loss
4. High risk cancer type
5. 3–5% weight loss

Table 3 Multivariable analysis

Multivariable analysis			
	HR	95% CI	p
Weight loss	1.9	1.5–2.2	< 0.001
Cancer type[a]			
Low risk	1		
Neutral risk	2.5	1.5–4.3	< 0.01
High risk	6.3	2.9–13.8	< 0.001
Appetite loss (0–100)	1.005	1.000–1.011	0.04
COPD	1.6	1.0–2.6	0.04
Interactions with weight loss			
Medium risk cancer	0.8	0.7–1.0	0.06
High risk cancer	0.6	0.4–0.9	< 0.01

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease
[a]Low risk - Breast cancer, lymphoma, leukaemia; High risk – pancreatic and gastric cancer; Neutral risk - all other cancers

Figure 3 shows the Kaplan-Meier curves for time to cachexia development in these five risk-levels. Median time to cachexia development was not reached in Risk-level 1, 249 days for Risk-level 2, 175 days for Risk-level 3, 145 days for Risk-level 4 and 51 days for Risk-level 5. Log-rank test for differences in cachexia development probabilities and test for trend in cachexia development probabilities were both significant ($p < 0.0001$), confirming that probability of cachexia development not only differed between levels, but was increasing with increasing risk-level.

The calibration plot shown in Fig. 4 demonstrates that the risk-level model accurately predicts the observed risk of cachexia development at 3 months, however a Harrell's C-statistic of 0.71 indicates only modest ability to discriminate between patients who will and will not develop cachexia. Figure 5 presents sensitivity and specificity of cachexia predictions at 3 months for all possible cut-offs between risk-levels in the subsample of patients still alive and remaining in the study after 3 months ($n = 372$). A risk-level ≥ 2 yielded a sensitivity of 95% and a specificity of 35% of predicting cachexia development, while a risk-level ≥ 3 yielded a sensitivity of 47% and a specificity of 88%. Hence, there was no single cut-off with both a high sensitivity and high specificity of predicting cachexia. Area under the curve was 0.76, signifying an accuracy in ability to discriminate between patients with and without cachexia of 76% at 3 months, and is comparable to the corresponding Harrell's c-statistic.

Discussion

This study shows that initial weight loss, cancer type, appetite loss and COPD are significant and independent predictors of cachexia in patients with incurable cancer. Based on this, we identify five levels of risk of cachexia development.

The cachexia definition is based mainly on weight loss, and thus, initial minor weight loss below the assigned criteria [9] have been considered indicative of pre-cachexia in several studies [10–12]. The present study confirms that there is an increased risk of further weight loss and eventual development of cachexia when minor weight loss is present. However, the present study also identifies several other risk factors that predict cachexia, independently of weight loss. Among these is cancer type, which has been associated with, and assumed to predict cachexia [14]. The findings of the present study confirm this and demonstrate that a classification of cancer type into low risk cancer (breast cancer and hematologic cancers), high risk cancer (pancreatic and gastric tumours) and neutral risk cancer (all other cancers) significantly predicts cachexia development. However, findings from the CART analysis show that when weight loss is 3% or more, cancer type does not add further to the risk of cachexia development. Contrary to cancer *type*, cancer *stage* (localized vs. metastatic) was not shown to predict cachexia significantly, although a trend was noted in the univariable analysis. The

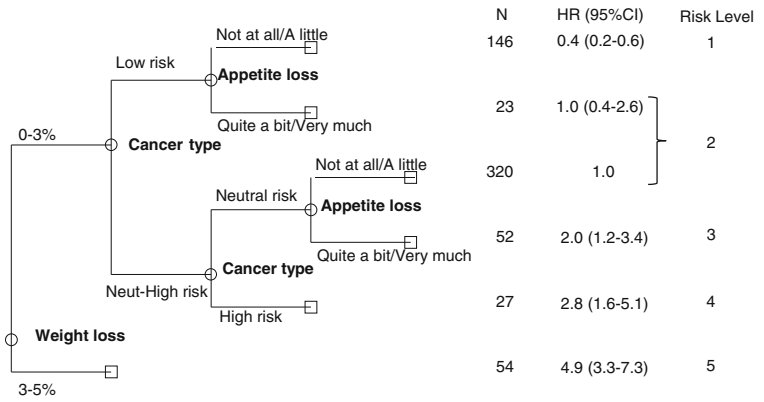

Fig. 2 Classification and regression tree (CART) analysis. The study population is divided repeatedly according to optimal cut-offs of the variables weight loss (rounded to the nearest integer), cancer type and appetite loss into subdivisions of significantly different hazard rates. Adjacent subdivisions from different branches with similar hazard rates are combined resulting in five risk-levels. Hazard ratios (HR) are reported relative to the branch with neutral risk cancer type and no or little appetite loss

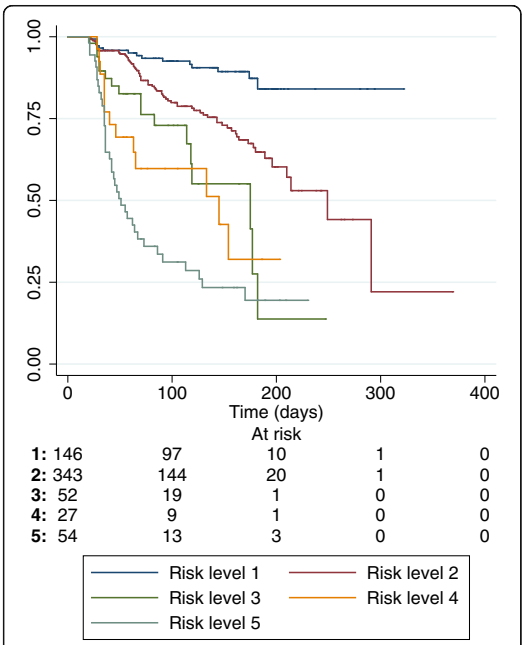

Fig. 3 Kaplan-Meier plot of time to cachexia development depending on risk-level. Median time to cachexia development was not reached in level 1, 249 days for level 2, 175 days for level 3, 145 days for level 4 and 51 days for level 5. Log-rank test and test for trend in failure time-analysis were both significant ($p < 0.0001$)

study is not suitable to draw conclusions about cancer stage, however, since the majority of the study population (87%) had metastatic cancer.

Appetite loss is central in the cachexia pathophysiology. It is believed that mediators of cachexia affect the hypothalamus in such a way that the central drive to eat weakens [20]. In turn, this might contribute to an

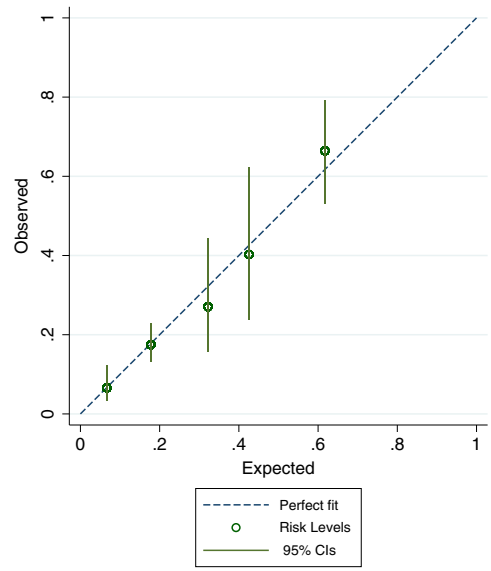

Fig. 4 Calibration plot showing the risk of cachexia development after 3 months, as predicted by the risk-level model, plotted against the observed risk

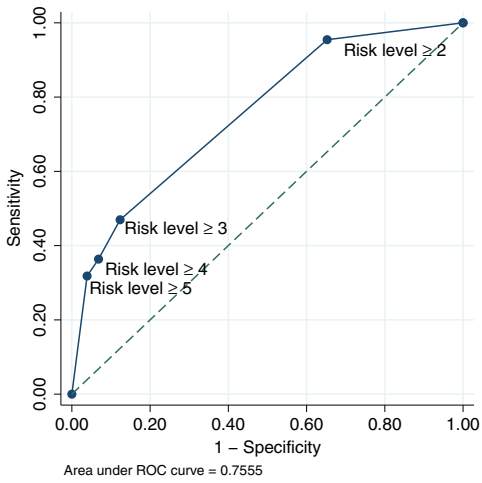

Fig. 5 Sensitivity and specificity of cachexia prediction at 3 months when using different cut-offs of risk-level to divide patients into a high or low risk group of cachexia development. Risk-level ≥ 2 yields a high sensitivity (95%), while risk-level ≥ 3 yields a high specificity (88%). No single cut-off yields both a high sensitivity and high specificity

accelerated weight loss through lowered dietary intake. However, conscious control of eating may sometimes prevail over appetite loss [21], and the present study therefore examines both appetite loss and food intake as possible predictors of cachexia. Appetite loss is shown to predict cachexia development independently and appears to be especially important in predicting cachexia in patients with little weight loss (< 3%) and low or neutral risk cancer. Food intake did not independently predict cachexia development, however, and reasons for this might be collinearity (correlation coefficient 0.53) with appetite loss and/or inadequate estimation of food intake.

Patients with COPD had an increased risk of developing cachexia. And although a sensitivity analysis showed that this was partly due to collinearity with lung cancer (which was not explicitly adjusted for in the main analysis), there was still a clear trend towards increased risk of cachexia development. This might be because COPD, as many other chronic diseases, sometimes leads to cachexia. A conservative estimate of the prevalence of cachexia in COPD is 5% [22]. COPD might therefore impose an extra risk of cachexia development on patients with cancer. However, in the subsequent CART-analysis, COPD did not significantly discriminate between groups of patients in terms of cachexia risk, indicating that its role as a risk factor is inferior to the other three significant factors. Notably, heart disease, renal disease and arthritis did not predict cachexia development, although also these conditions are associated with cachexia [22].

Measurements of physical performance applied in the present study (the Karnofsky scale and the physical function scale of the EORTC QLQ C15 PAL) did not predict cachexia development, independently. Analysis of collinearity showed a moderate correlation between Karnofsky and physical function (correlation coefficient 0.54), and collinearity can sometimes explain why two variables that otherwise would be significant, both end up non-significant when present together in a multivariable model. However, this did most likely not explain the lack of significant contribution to the model in the present study as the backward selection in the multivariable analysis ensured that the least significant of the two predictors were rejected from the model before the other. Impaired physical performance is partly caused by the progressive loss of muscle mass that accompanies cachexia [23], and is considered a late symptom [9]. This might be a more likely explanation of why markers of physical performance did not predict cachexia.

Implications for clinical practice and future research

The present study demonstrates that information on cancer type, appetite loss and COPD improves accuracy of cachexia prediction when added to the established cachexia classifier, weight loss. This is especially true in patients with no or minimal weight loss (< 3%), whereas in patients with weight loss between 3 and 5%, development of cachexia is imminent, regardless of other factors. Based on these predictors, patients can be stratified into five different risk-levels of cachexia development. Cachexia development is not likely if in Risk-level 1, and conversely, for patients in Risk-level 3 or greater the risk of cachexia development is high. As such, the risk-levels enable the clinician to select which patients must be followed more closely with respect to cachexia development and ensure early adequate therapeutic intervention. To the researcher, this could improve patient selection in intervention trials aiming at preventing cachexia, by including only patients at risk of developing cachexia.

No *single* cut-off in this five-level risk ladder has both high sensitivity and high specificity of predicting cachexia. Thus, no single criterion was identified that accurately diagnosed pre-cachexia. Future research should attempt to improve prediction of cachexia development, and thereby improve the diagnosis of pre-cachexia. A likely path towards this aim is to examine the role of inflammatory markers in predicting cancer cachexia. Inflammation is a central part of cachexia pathophysiology and considered a driver of cachexia development [2], and it is likely that markers of systemic inflammation would improve accuracy of cancer cachexia prediction. Thus, the addition of inflammatory markers to the

predictors identified in the present study is a necessary next step towards diagnosing pre-cachexia.

Appraisal of study design

The strength of this study is that it examines factors related to cachexia development in a large longitudinal cohort of patients, and thus enables the identification of factors that predict cachexia development and their relative importance. As is common in many studies in palliative care, the number of missing follow-up observations was relatively high. It is likely that a worsening in physical condition is among the reasons for patients dropping out, and this would decrease statistical power and may introduce a bias. To mitigate this effect, Cox proportional hazards method was used to let each patient contribute with his or her time on the study. Furthermore, to increase power of statistical analysis, patients with insufficient data at baseline, but with sufficient data at first follow-up visit were included with the latest visit as baseline. This was considered appropriate due to the open study design, which allowed inclusion of patients at any time point in their disease trajectory. The CART method is a data mining procedure that is simple to understand and gives an intuitive result. As the calibration plot (Fig. 4) shows, the resulting risk-level model fit the observed risk very well. This is expected when evaluating the model on data from which the model was developed, and the CART methodology may be criticised for creating models that are overfitted to the data, and thus reduce the external validity. By only including significant factors from the Cox model, the risk of overfitting is reduced, and, in addition, the resulting CART model seems clinically plausible. No objective measurements of body composition were available when assessing cachexia. Effect on weight change by accumulation of third space fluids or shifts between fat and muscle mass could therefore not be assessed. However, the adapted definition used in this study has previously been validated [10], and it could be argued that this definition is of greater clinical practical value as objective measures of body composition not always are available in the clinical setting. As mentioned above, no markers of systemic inflammation were assessed as possible predictors of cachexia development. Although the EPCCS study allowed for registration of incidental C-reactive protein measurements performed within 3 days before inclusion, too few observations were available to enable statistical inferences.

Conclusion

The present study identifies important risk factors for development of cachexia and suggests how these should be combined to optimally stratify patients in terms of cachexia risk. Future research should validate these results and evaluate if addition of markers of systemic inflammation can improve accuracy.

Abbreviations

aPG-SGA: abridged Patient-Generated Subjective Global Assessment; BMI: Body Mass Index; CART: Classification and regression tree analysis; COPD: Chronic obstructive pulmonary disease; EAPC: European association for Palliative Care; EORTC-QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EPCCS: European Palliative Care Cancer Symptom study; HR: Hazard ratio; IQR: Interquartile range; KPS: Karnofsky performance status; PRC: European Palliative Care Research Centre; PROMs: Patient reported outcome measurements; ROC: Receiver operating characteristic

Acknowledgements

An abstract of this paper was presented as a poster at the annual conference of the European Society for Medical Oncology (ESMO) in 2018. The European Palliative Care Cancer Symptom study (EPCCS) is a collaborative effort between the European Palliative Care Research Centre (PRC), and the European Association for Palliative Care – Research Network (EAPC-RN):

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Authors' contributions

MJH and SK were primary investigators of the EPCCS study. MJH, SK, FS, BL, CB and VEB were all members of the project management or project steering committee, and were responsible for planning the study, writing the protocol and conducting the study. MJH, SK, FS, BL, CB, VEB, AW and MN were all responsible for patient recruitment at their respective sites. OMV carried the major responsibility for data analysis and writing the manuscript, while TSS, BL and CB (statistician) made major contributions to this work. All authors reviewed and commented on the manuscript during writing, and also read and approved the final manuscript.

Funding

The European Palliative Care Cancer Symptom study (EPCCS) was partially funded by grant no. 6070 from the Joint Research Council at Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital-Trondheim University Hospital. Additionally, PRC has received unrestricted

grants from The Norwegian Cancer Society and Helsinn on basis of this and other projects.

Availability of data and materials
The dataset generated and analyzed in the current study is not publicly available. This is because there were no financial compensations offered to the research collaborators other than free access to the dataset. As analyses on parts of the dataset are still ongoing, it has not been made publicly available, but may be available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was conducted in keeping with the Helsinki declaration and its amendments. All patients had to provide written informed consent. The protocol was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (reference number 2010/2945) corresponding to the location of the Project Management Office. In addition, the ethics committees/institutional review boards of following centers gave ethical approval for the study: Southern Adelaide Palliative Services, Adelaide, South Australia (AU), University Hospital, Ghent (BE), Comprehensive Cancer Centre, Vratsa (BG), Cross Cancer Institute, Northern Alberta (CA), The Edmonton Zone Palliative Care Program, Alberta (CA), Cantonal Hospital, St. Gallen (CH), Kantonsspital Graubünden, Chur (CH), Rigshospitalet, Copenhagen (DK), Bispebjerg Hospital, Copenhagen (DK), Hospital Universitario Arnau de Vilanova, Lleida (ES), Clínica Universidad de Navarra, Pamplona (ES), Hospital Centro de Cuidados Laguna, Madrid (ES), Institut Catala D'Oncologia, Barcelona (ES), Cancer Prevention Centre (CPC) Tblisi (GE), Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (IT), Hospital of Piacenza, Piacenza (IT), Hospice Villa Speranza, Rome (IT), Istituti Clinici di Perfezionamento Hospital, Milan (IT), U.O. Complessa Cure Palliative e Terapia del Dolore Istituti Clinici di Perfezionamento, Milan (IT), University of L'Aquila, L'Aquila (IT), Arcispedale Santa Maria Nuova Reggio Emilia (IT), St. Olavs University Hospital, Trondheim (NO), Oslo University Hospital, Oslo (NO), Haraldsplass Deaconess Hospital, Bergen (NO), Øya Community Hospital, Trondheim (NO), Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon (PT), St Gemmas Hospice, Leeds (UK), West Lothian Community Specialist Palliative Care Team, Edinburgh (UK), Nottingham University Hospitals, Nottingham (UK), Marie Curie Cancer Care Glasgow Hospice, Glasgow (UK).

Consent for publication
Not applicable.

Competing interests
BL has received honoraria from Helsinn.
FS has had punctual advisorships (boards, expert meetings) for Danone, Grünenthal, Helsinn, ISIS Global, Mundipharma, Novartis, Novelpharm, Obexia, Ono Pharmaceutical, Psioxus Therapeutics, PrIME Oncology, Sunstone Captial, Vifor. On behalf of his institution, he has received unrestricted industry grants for clinical research from Celgene, Fresenius and Helsinn. He has participated in a clinical cachexia trial lead by Novartis.
OMV, CB, MJH, VEB, AW, MN, SK and TSS declare that they have no competing interest.

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Received: 31 August 2018 Accepted: 20 May 2019
Published online: 04 June 2019

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