Master's thesis in clinical nutrition

Malnutrition in cancer patients receiving palliative care

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I hope the insights from my thesis contribute meaningfully to the existing literature on malnutrition in cancer patients and motivate others to continue developing the field of research.

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Abstract

Background and aims: Palliative cancer patients are at high risk of developing malnutrition because of both the disease and its treatment. These patients often experience challenges that affect their food intake and thus nutritional deficiencies. Malnutrition is associated with reduced survival, reduced response to treatment and impaired quality of life.

Objectives: The overall aim of this longitudinal observational study was to explore nutritional status and nutritional intake longitudinally in a cohort of patients with cancer commencing on palliative radiotherapy.

To our knowledge this is the only study investigating nutritional status in a palliative cancer population with including detailed information on food intake

Methods: This thesis is based on data collected a multicentre, international longitudinal observational study, the Palliative Radiotherapy and Inflammation Study (PRAIS). A sample of 180 patients recruited at Oslo University Hospital was included in the analysis. Data from consultations before start of radiotherapy treatment, three and eight weeks after were collected using CRFs. Nutritional status was assessed with the abridged Patient-Generated Subjective Global Assessment (aPG-SGA), complemented with measures of inflammatory status defined by C-reactive protein (CRP) levels. Food intake was assessed using the 24-recall interview method.

Results: 180 patients were analysed in this study (mean age 66 years, 58.9% men), of these 47 (26%) were lost to follow-up at week eight. Of the study patients, 72.7% were categorized as malnourished, of these 24.4% had severe and 48.3% had moderate malnutrition. Severely patients had higher median CRP, lower median survival and lower mean energy intake than patients with no malnutrition. 53.1% of patients had malnutrition and inflammation, while 19.6% had malnutrition without inflammation. Malnourished patients with inflammation had a significantly lower median (Q1-Q3) survival of 19 (9-38) weeks, compared to 41 (18-97) and 55 (30-91) weeks among patients with malnutrition without inflammation and patients with no malnutrition, respectively. Patients with malnutrition with inflammation had a mean (SD) energy intake at baseline of 23 (10) kcal/kg at baseline, while patients with malnutrition

without inflammation and patients with no malnutrition had a mean energy intake of 29 (15) and 28 (9) kcal/kg, respectively. All patient groups had a mean weight loss from baseline to week eight, with the highest weight loss seen among patients with malnutrition with inflammation (-2.5 (4.3) kg).

Conclusion: The prevalence of malnutrition among the study patients were high. malnutrition was associated with short survival, low energy and protein intake, independently of malnutrition degree. All malnutrition groups investigated had a mean weight loss over the follow-up period, even if energy expenditure was stable and reached estimated energy expenditure, thus supporting that there is more to weight loss in cancer patients than reduced energy intake.

This study demonstrates poor prognosis among patients the palliative cancer patients. The results of this thesis imply that including a factor for inflammatory status through measures of for example CRP can be a useful additional tool in understanding the palliative cancer patients' situation and prognosis. Our findings also support the concept of individual nutritional support based on patients' presentation and marker of inflammation, considering the heterogeneity among these patient groups as demonstrated in this study. Thus, including evaluation of CRP can be a great additional tool in understanding the patients' situation and prognosis

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List of abbreviations

aPG-SGA Abridged Patient Generated Subjective Global Assessment

ASPEN the American Society for Parenteral and Enteral Nutrition

BMI Body Mass Index

CRF Case Report Forms

CRP C-Reactive Protein

DRM Disease-Related Malnutrition

ESPEN European Society for Clinical Nutrition and Metabolism

GLIM Global Leadership Initiative in Malnutrition

NCP Nutrition Care Process

NIS Nutrition Impact Symptoms

PAL Physical Activity Level

PG-SGA Patient Generated Subjective Global Assessment

PRAIS the Palliative Radiotherapy and Inflammation Study

PROM Patient Reported Outcome Measure

REE Resting Energy Expenditure

SGA Subjective Global Assessment

TEE Total Energy Expenditure

WHO World Health Organizati

1. Introduction

1.1 Cancer

Cancer is a leading cause of mortality and morbidity in the world (1). The term cancer covers a large group of diseases recognized by abnormal and rapid cell growth (2). Cancer can spread to other sites and organs of the body, this is called metastasizing and is the leading cause of deaths related to cancer (2). In Norway, 35 515 new cancer cases were reported in 2020, and 10 981 cancer related deaths. The most frequent cancer types are prostate cancer, breast cancer, colorectum cancer and lung cancer (3, 4).

Generally, survival rates have improved in the past decades due to a combination of diagnosing at earlier stages of the disease, prevention, more individualized adapted treatment (5). According to the Norwegian cancer registry three in four survive their cancer (6). The remaining is uncurable and will receive life prolonging treatment and palliative care. Due to advancement in cancer treatment patients in a palliative setting are expected to live longer with their disease and, thus the palliative population is growing (7).

1.1.1 Palliative care

When the disease cannot be cured the focus of the treatment shifts from curing the disease to relief of symptoms, maintaining quality of life, and prolonging life which is the basis of palliative care (8, 9). The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients (adults and children) and their families who are facing the problems associated with life-threatening illness," (8). In 2020 WHO estimated that 40 million people are in need of palliative care, where 34 % of these have cancer (10).

In cancer treatment the focus is on the tumor, while in palliative care the main focus is on the patient. Patient inclusion is an important aspect to palliative care, including focus on both tumor treatment and the patient and their next of kin (7). It is recommended that palliative care start early in the oncology care and that patients are encouraged to voice their individual information about what is important to them and to express problems as they wish (11, 12).. Such a patient centred approach aims to better understand the patient and the patients' needs

(11, 12), Thus, the treatment in palliative care follows the symptom burden and not only the disease. Several studies have shown that interventions from an interdisciplinary care team aiming to improve or maintain function can improve survival and quality of life and reduce symptom intensity (13, 14). The patients' reaction to disease, physically, mentally socially, and spiritually should be taken into account (15), as well as satisfaction of the patient's family and their needs (7).

1.2 Nutritional challenges in palliative cancer patients

The Norwegian directory of health reports that up to 85% of palliative patients experience weight loss (16). Reasons for this include symptoms related to disease and treatment, and reduced food intake. In in addition, the patient might develop cancer related cachexia, which is common in patients with advanced cancer (16, 17).

1.2.1 Symptom burden and reduced food intake

Dependent on cancer type and stage patients receive different anti-cancer treatment, with different side-effects. For example, common side-effects to chemotherapy are anorexia, nausea and vomiting (18). Such symptoms can be considered nutrition impact symptoms (NIS) as they can negatively affect nutritional intake (17, 19). These also include pain, dysphagia, mouth soreness, diarrhoea, and constipation (9). The symptom burden is generally increased in advanced cancer.

NISs are related to reduced dietary intake and weight loss, and thus it is suggested that these symptoms are strong predictors of reduced food intake, and malnutrition (20). In addition to physical symptoms that comes with the disease, the patients often experience physiological distress, with symptoms such as anxiety and stress (7).

If these challenges are not addressed the patient will be especially prone to developing malnutrition (16). Therefore, regular nutritional assessment, also referred to as nutritional screening is recommended (17)

1.2.3 Malnutrition in cancer

Malnutrition associated with increased morbidity and mortality (21). Malnutrition is defined as nutritional imbalance (21) or, as defined by WHO, "deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients" (22). According to ESPEN guidelines 10-20% of cancer related deaths are estimated to be attributed to the secondary effects of malnutrition (23). In addition to reduced survival malnutrition can contribute to decreased physical

function, response to treatment and quality of life, increased length of hospital stay and health care costs (21, 24).

Cancer patients are especially prone to malnutrition as both the disease and treatment of the disease can affect nutritional status. ESPEN points to tree major negative effects that treatment and the tumor can bring along; reduced energy intake, inflammation, and fatigue with low physical activity (23). Weight loss in these patients can be a consequence of metabolic changes, altered and/or inadequate food intake, reduced uptake and/or utilization of nutrients (23).

In the ESPEN guidelines three forms of malnutrition are described (figure 1): disease-related malnutrition with inflammation (DRM), disease-related malnutrition without inflammation and malnutrition without disease (25). Malnutrition without disease can be related to socioeconomic or physiological factors such as social inequities or self-neglect or it can hunger-related. “DRM with inflammation is a catabolic condition characterized by an inflammatory response, including anorexia and tissue breakdown, elicited by an underlying disease” (25). With increasing degree of inflammation the basal metabolic rate may increase and cause more muscle- and weight loss than other forms of malnutrition (26). Causes of malnutrition in DRM without inflammation might be dysphagia, neurologic or psychological disorders (25). DRM with inflammation can be acute, for example related to trauma, or it can be chronic, also known as cachexia (25).

Prevalence of malnutrition reported varies between studies as there is no international standard for diagnosing malnutrition in specific populations (27). However, global diagnose criteria are currently being implemented (28). Results from a non-systematic search of existing literature regarding malnutrition prevalence in patients with cancer are presented in table 1. This search resulted in a malnutrition prevalence that varied from 31%-76% and reflects a heterogeneity in existing studies.

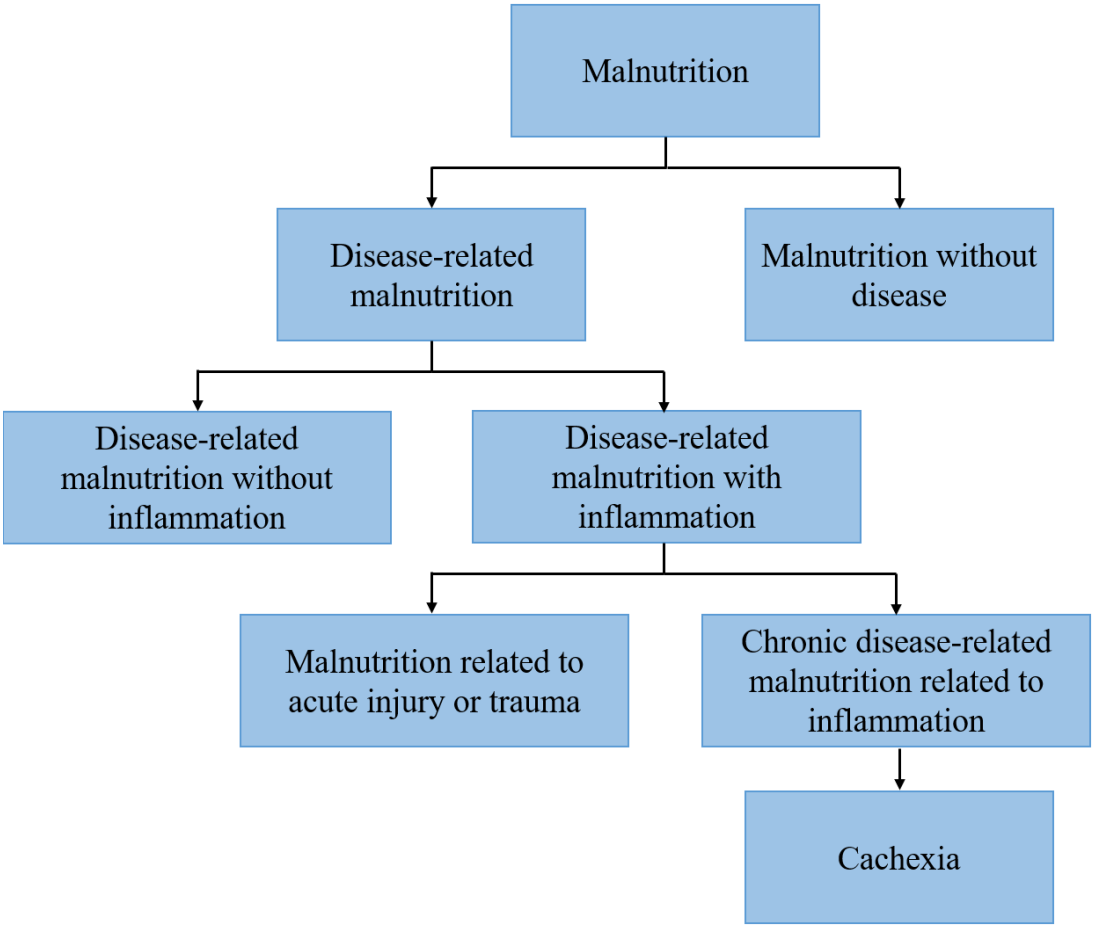

***Figure 1**: Basic division of malnutrition. Based on a figure from Cederholm et al. (25)*

***Table 1**:Prevalence of malnutrition in studies including cancer patients and different screening tools*

Study	Sample size	Cancer diagnose[a]	Screening tool	Malnutrition prevalence[b]
Bauer J. et al. (29), (2002)	n = 71	Lymphoma (49%), breast (13%)	SGA	76%
Carriço M. et al.(30), (2021)	n = 355	Breast (26%), colorectal (16%), lung (15%)	aPG-SGA	69.3%
Groot D. (31), (2020)	n = 246	Breast (45%), gynaecology (13%)	aPG-SGA	31%
Gabrielson DK. Et al. (32) (2013)	n = 90	Breast (46%), colorectal (24%)	aPG-SGA	36%
Seguera A. et al. (33) (2005)	n = 781	Lung (22.9%), colo-rectal (13.2%), breast (13%)	aPG-SGA	52%
Silva FR. et al. (34), (2015)	n = 277	Multiple types	PG-SGA	71.1%

[a]The most frequent cancer diagnoses reported, [b]Total prevalence of malnutrition reported in the study, including moderate and severe malnutrition. SGA: Subjective Global Assessment, aPG-SGA: abridged Patient-Generated Subjective Global Assessment, PG-SGA: Patient-Generated Subjective Global Assessment

1.3 Cancer cachexia

About 50-80% of cancer patients are affected by cancer cachexia (35), and patients with advanced cancer are especially at risk. Cancer cachexia is characterised by loss of muscle mass with or without fat loss as an effect of reduced food intake and/or altered metabolism caused by disease and/or treatment of the disease (25, 35, 36). Other features of the syndrome are anorexia, inflammation, and insulin resistance. Cachexia is often recognized by weight loss, but both cancer patients with and without obesity are at risk of developing cachexia (23). Patients with cachexia might experience reduced function, loss of appetite, early satiety, and fatigue (37). Consequences of cachexia include reduced quality of life and tolerance to anticancer treatment (37).

Much is still unknown about cancer cachexia, and there is still no established effective treatment. In 2011 Fearon et al. published a formal consensus paper that described a framework for cancer cachexia (36). In this paper cancer cachexia was defied as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment." (36). Diagnosis of cancer cachexia is based on weight loss (>5% over the past 6 months), low BMI (<20 kg/m^2) combined with weight loss (>2%) or presence of sarcopenia combined with any degree of weight loss (36).

Further the paper describes the trajectory of cachexia, as it is described as a syndrome of three stages. This shows that cachexia develops progressively, from precachexia to cachexia to refractory cachexia and death, though not all patients go through all three stages (36). Pre-cachexia is recognized by involuntary weight loss (≤5%), anorexia and metabolic changes. Certain factors, such as cancer diagnose, stage whether inflammation is present, food intake and response to treatment, determine the risk of progression to cachexia (36). When the patient is no longer responding to antitreatment, the cachexia has developed to refractory cachexia. This stage is characterized by active catabolism, low performance status and short expected survival (<3 months) (36, 37). Treatment at the different stages of cachexia might differ. In precachexia, the aim of treatment is to halter weight loss or increase weight and increase physical function, while in refractory cachexia the treatment focus is symptom relief and to maintain quality of life (37).

1.3.1 Altered metabolism in cancer

One of the key factors of cancer cachexia is altered metabolism and some patients have increased resting energy expenditure (REE). However, some cancer patients might also be hypometabolic (38). As there are individual differences between cancer patients in relation to cancer type and stage, body composition and treatment, among other, one cannot assume that energy expenditure is equally increased or decreased for all patients (38). Recent nutritional guidelines conclude that while REE is often increased in cancer patients, total energy expenditure (TEE) has been shown to not be increased or even to be lower when comparing these patients to healthy individuals (39). This might be explained by a reduction physical activity. Thus, guidelines recommend that energy expenditure for cancer patients is estimated the same way as for healthy individuals, generally between 25-30 kcal/kg/day (23, 40, 41). The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends a protein intake of minimum 1 g/kg/day up to 1.5 g/kg/day if possible (39).

1.3.2 Inflammation in cancer cachexia

Inflammation is thought to be one of the most important factors leading to the wasting in, and detrimental consequences of, cachexia. The tumor releases inflammatory factors that can cause systemic inflammation (23). These affect the brain, muscle, liver, and adipose tissue function. In the brain the cytokines can lead to signalling that cause anorexia by altering appetite signals from the central nervous system (23, 42). Through an anabolic and catabolic imbalance, cytokines can cause muscle wasting, thus leading to impaired physical function and activity (23, 35). In liver, cytokines can impair drug clearance and thus increase risk of cancer treatment toxicity. As well, cytokines can lead to depletion of fat stores as they stimulate increase of lipolysis and cause a defective lipogenesis (23). Production of acute phase-proteins in the liver, such as C-reactive protein (CRP), and reduced albumin levels, is part of the systemic inflammation seen in cachectic patients. Circulating concentrations of CRP and albumin can be used separately or in combination as a prognostic factor and to grade severity of the inflammation (23, 43). CRP is suggested as a diagnostic criterion for cachexia (40, 44), it was introduced as a phenotypic criterion for diagnosing malnutrition by the Global Leadership Initiative in Malnutrition (GLIM) in 2019 (45).

1.4 Nutrition care process

Appropriate competence in clinical nutrition is an important component of a multidisciplinary palliative team. Prevention, early identification of patients' risk, accurate diagnosis,

personalized intervention, and follow-up are cornerstones of nutritional care also in palliative care (11). The nutrition care process (NCP) is a systematic approach used by dietitians and nutrition professionals to provide optimal nutrition care (41, 46). The NCP consists of four interconnected steps: nutrition assessment, nutrition diagnosis, nutrition intervention and nutrition monitoring (46). Nutrition assessment consists of screening of patients with a validated tool to identify patients at nutritional risk, this is further described below. The assessment is this then is followed by nutrition diagnosis where data from assessment is used by nutrition and dietetic professionals to identify the problem, determines the cause, and reveal symptoms. In nutrition intervention an intervention determined and planned to target the nutritional problem identified before implementing these actions. This is followed monitoring and evaluation (46).

1.4.1 Nutrition assessment

Nutritional assessment is a way to systematically collect and classify data to describe an individuals' nutritional status (46). Data collection includes screening of malnutrition risk, anthropometric measurements, biomedical data and data and food intake (46).

Nutritional guidelines recommend that nutritional risk is evaluated at early stages of cancer using a two-step approach (25, 40). First, a screening should be done, to detect those at risk of malnutrition. According to ESPEN nutritional intake, weight change and body mass index (BMI) should be monitored at the point of diagnosis to detect early signs of nutritional challenges (23). The use of validated nutritional screening tools, developed to detect nutritional risk, is recommended. One example is the abridged patient generated-subjective global assessment (aPG-SGA) (47).

In the 1990s The Patient Generated-Subjective Global Assessment (PG-SGA) was introduced to assess nutritional status, developed by Ottery et al (47). PG-SGA is a validated screening tool and often referred to as a "gold-standard" in nutritional assessment (27, 48). The PG-SGA is as a modified version of the Subjective Global Assessment (SGA), developed specifically for use in an oncology setting, and is a validated method for this population (32, 47-50). The tool classifies patients as well-nourished, moderately malnourished/at malnutrition risk or severely malnourished (47).

The abridged version of this screening tool, aPG-SGA, also commonly referred to as PG-SGA short form, consist of the first four boxes of the PG-SGA. The four parts of aPG-SGA is based on patient-reported weight, food intake, nutritional impact symptoms (NIS), and performance

status (48). If malnutrition or malnutrition risk is present patients should be further assessed and nutritional interventions is indicated (40). A patient's energy intake in relation to energy needs and biochemical data are examples of data that should be collected for nutrition assessment.

Several methods to assess food and energy intake are developed and available for clinical use and for research. The 24-hour dietary recall interview is a retrospective method that can be used at several levels (51). The respondent is interviewed and asked to report everything they consumed over the last 24 hours (52).

To estimate REE indirect calorimetry is thought to be the gold standard (27, 39). However, when measuring REE in large populations this can be time consuming and expensive, in addition it is often not available. Thus, equations based on weight, height and age are developed (53). Most of these equations are based on healthy individuals. It is often assumed that energy expenditure is increased in cancer patients and that they are hypermetabolic, however they might as well be hypometabolic (54), cachexia affect the patients to different degrees.

1.4.2 Nutrition diagnosis

Nutrition Diagnosis can be defined as, a nutrition practitioner's identification and labelling of an existing nutrition problem that the practitioner is responsible for treating (46). In 2018 GLIM criteria were proposed as an evidence-based framework for diagnosing of malnutrition across different clinical settings and populations (45). This resulted in a consensus on malnutrition diagnosis consisting of a two-step approach to diagnosing malnutrition. In the first step a validated screening tool (e.g., PG-SGA) is used to identify patients at risk of malnutrition. In step two GLIM introduces a division of malnourished patients by inflammatory condition, defined by serum CRP values (27, 45).

1.5 Significance of this thesis

Previous studies show that reduced food intake, weight loss and poor nutritional status are related to reduced quality of life and tolerance of cancer treatment (55, 56). The present study provides data on nutritional status and energy and protein intake in a palliative population. Unique in this study is that complete data on food intake are available for each patient at several timepoints. Few other studies have assessed patients using aPG-SGA in this specific patient group.

It is well known that malnutrition is common among patients with advanced cancer, reduced food intake and cachexia are likely to contribute to this (55). However, not much is known about the actual energy and protein intake in palliative cancer patients and there is a lack of studies investigating actual food intake in relation to nutritional status in this patient group.

Furthermore, few previous studies have included a factor for inflammation in nutritional assessment in palliative cancer patients using the aPG-SGA, as suggested by new GLIM criteria.

To our knowledge this is the only study investigating nutritional status in a palliative cancer population with including detailed information on food intake.

2. Objectives

The overall aim of this master thesis is to explore nutritional status and nutritional intake longitudinally in a cohort of patients with cancer commencing on palliative radiotherapy.

More specifically, the thesis aims to:

- Investigate prevalence and degree of malnutrition
- Compare patient characteristics, survival and energy and protein intake according to degree of malnutrition and inflammation status
- Compare energy and protein intake in relation to estimated energy and protein requirements
- Describe development of nutritional status and energy and protein intake over time over time
- Explore associations between energy intake, estimated energy and protein requirements and weight loss

3. Methods

3.1 Study design

This master thesis has used data collected in a multicentre, international longitudinal observational study, the Palliative Radiotherapy and Inflammation Study (PRAIS) (57). The master thesis is based on data from Oslo University Hospital.

3.2 Study population

In the PRAIS study a total of 574 patients from seven centres in Europe were enrolled (57). A sample of 180 patient was included at Oslo University Hospital between January 2015 and December 2017. All patients received treatment for painful cancer related bone metastases. However, out of the seven centres included in the study, complete dietary data was only obtained from the participants at the Oslo University Hospital. Consequently, this sample was selected for this study.

Eligibility criteria in the PRAIS study included established cancer diagnosis, bone metastases, referral to palliative radiotherapy for verified (CT/MRI) painful bone metastasis, age equal to or above 18 years, and ability to comply with trial procedures (57). Exclusion criteria were on-going radiotherapy, radiotherapy administered within the previous four weeks or pathological fractures in bones (57).

3.3 Data collection

Patients referred to palliative radiotherapy were approached by the study team. The first study consultation was done one hour before their first radiotherapy fraction. In the PRAIS study data was collected at the first consultation before start of radiotherapy (baseline) and then three, eight, 16, 24 and 52 weeks after completed radiotherapy (57). On these consultations information was obtained to fill out case report forms (CRFs). For this thesis, PRAIS-data collected at baseline and week three and eight after completion of radiotherapy were used. Information on serum CRP was retrieved from medical records, while demographic data and patient reported outcomes were reported by the patients in the CRFs.

Demographic data

The following demographic and clinical variables were selected from the CRFs in this thesis: age, gender, weight, height, living situation, length of education, primary diagnosis, and date of diagnosis and death.

3.4 Nutritional assessment

Abridged Patient-Generated Global Assessment (aPG-SGA)

Nutritional assessment to evaluate degree of malnutrition as well as energy and protein intake, measured body weight, food intake by 24-hour recall and aPG-SGA was collected. In the aPG-SGA patients were asked to report information on weight history, food intake, NIS and physical function. Additionally, information on energy and protein intake was collected from 24-hour recall interviews. Body weight was measured at every consultation. Weight measured at baseline and week eight was used to determine if the patient had stable weight or had lost or gained weight. Stable weight was defined as a weight change within ±2% from baseline to week eight. Weight change was described in kilos change from baseline to week eight.

To calculate total number of symptoms for self-reported NIS from box 3 in the aPG-SGA was collected (appendix 1). Self-reported information on physical activity from box 4 was used to estimate physical activity level (PAL) (table 3).

A total score was summed from the four boxes of aPG-SGA for each patient. This score was used to determine degree of malnutrition, from no malnutrition (≤1) to moderate malnutrition also commonly referred to as "at malnutrition risk" in other studies (2-8), to severe malnutrition (≥9) (47) (figure 2, appendix 1).

Assessment of food intake

24-hour dietary recall

Standardized 24-hour recalls were completed to collect data on food intake (58, 59). Patients were interviewed face-to-face by trained professionals and asked to recall food intake from the previous day, midnight to midnight. Household measures from a photographic booklet were used to estimate portion sizes, these were translated to weight. The data were calculated using the software package Aivo 2000 (SVIO AB, Stockholm, Sweden). The Norwegian food composition tables (60) were used as the nutrient database supplemented with own recipes and brand information. Registration of food intake at the three time points was done by two trained study personnel and the master student. Data on energy and protein intake were subtracted from these interviews by registration.

Estimating total energy expenditure

There is no consensus on what equation should be used to estimate REE in patients with cancer or palliative patients. However, studies have shown that the Mifflin-ST is among the equations with the narrowest limits of agreement when compared to indirect colorimetry in

patients with cancer. (61, 62). Based on available literature the Mifflin-ST Jeor equation was considered to be appropriate to use to estimate REE at group level in this population (61, 63, 64). Weight, height, and age from the CRFs were used in these estimations.

Table 2: *The Mifflin-ST Jeor equation*

Male:	9,99*W + 6,25*H – 4,92*A + 5
Female:	9,99*W + 5,25*H - 4,92*A – 161

Mifflin et al. 1990 (62). W: weight (kg), H: height (cm), A: age (years)

To estimate the total energy expenditure a factor for physical activity was added based on conversion of self-reported physical activity from aPG-SGA (box 4) to PAL values adapted from Nordic Nutrition Recommendations 2012 (65). Physical activity ranged from normal activity with no limitations, to spending most of the day in bed. This gave the patients a PAL ranging from 1,6 for those with normal activity to 1,2 for those with the lowest activity level (table 2).

Table 3*: aPG-SGA box 4 alternatives and corresponding PAL*

«I will describe my activity the last month as»:	**PAL**
Normal, no limitations	1,6
Not normal, but have been up and had some activity	1,5
Not been feeling well, but have been up for more than half of the day	1,4
Some activity, spent most of the day in bed or chair	1,3
Spent most of the day in bed	1,2

Physical activity level based on Nordic Nutrition Recommendations 2012 (65) conversed from aPG-SGA box 4 (47). aPG-SGA: abridged Patient-Generated Subjective Global Assessment, PAL: physical activity level

Malnutrition with or without inflammation

Patients categorized with malnutrition, either moderate or severe, were further categorized for malnutrition according to inflammatory status. Serum CRP was used to define inflammatory status, where a CRP above 5 mg/l indicated systemic inflammation. Thus, two new groups were formed, malnutrition with inflammation and malnutrition without inflammation (figure 2).

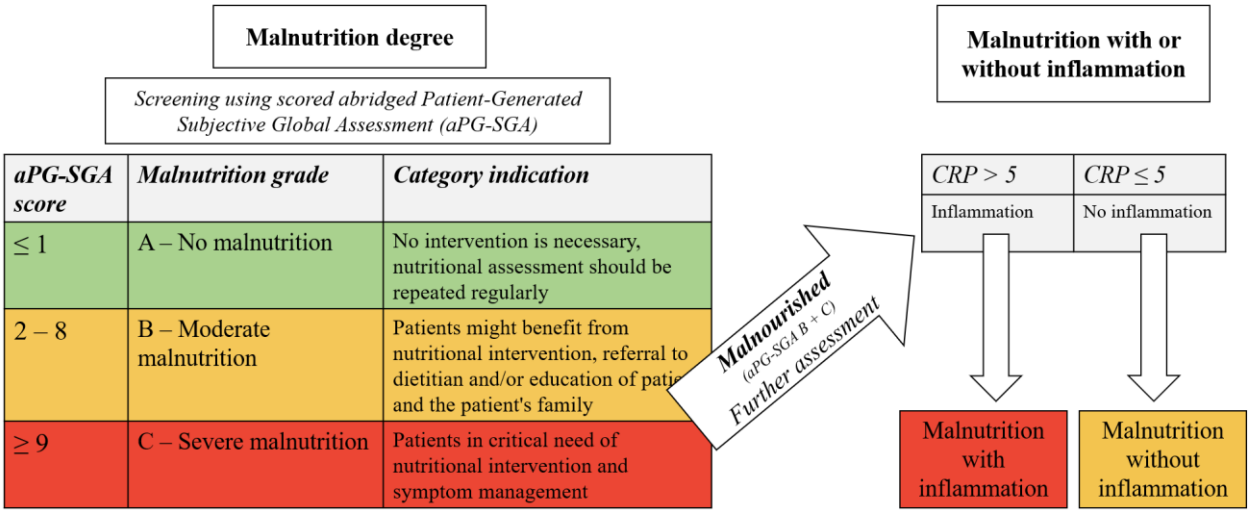

***Figure 2**: The process of categorizing patients into malnutrition groups. Grading of malnutrition was done using the scored abridged Patient-Generated Subjective Global Assessment. Patients categorized as malnourished (score>1) were further assessed using data on serum C-reactive protein (CRP) to divide patients into malnutrition with or malnutrition without inflammation. CRP was measured in mg/l.*

3.6 Statistics

Characteristics of study participants are presented using frequencies, means with standard deviations (SD) or medians with interquartile range (Q1-Q3), depending on normality. QQ-plots were used to establish normality. Pearson's Chi-square test was used to compare categorical data. One-way ANOVA for parametric test was used to compare categorical and continuous variables. Overall changes in mean (energy and protein intake, energy expenditure, weight) from baseline to week eight were compared using paired samples t-test. Significance level was set at 5%. Survival was calculated from date of study inclusion. All statistical analyses were performed using SPSS Statistics 26 for Windows. Graphs were created using Microsoft Excel (version 2203).

3.7 Ethics

The PRAIS study was approved by the Regional Committee for Medical and Health Research Ethics (REC Protocol Approval 2013/1126) (57) (Appendix 2, 3 and 4). All patients provided written informed consent before inclusion. The study was carried out in accordance with ICH GCP and the World Medical Association Declaration of Helsinki (1964). All data were handled anonymously, patients were only identified by a study number (57).

4. Results

4.1 Enrolment

A total number of 180 patients were included (figure 3). At week eight of 47 (26 %) patients were lost to follow up. Of these were 29 (16%) deceased and 18 (10%) were lost due to various reasons. Typical reasons given were not being able to complete the questionnaires, bad general condition, and progression of the disease.

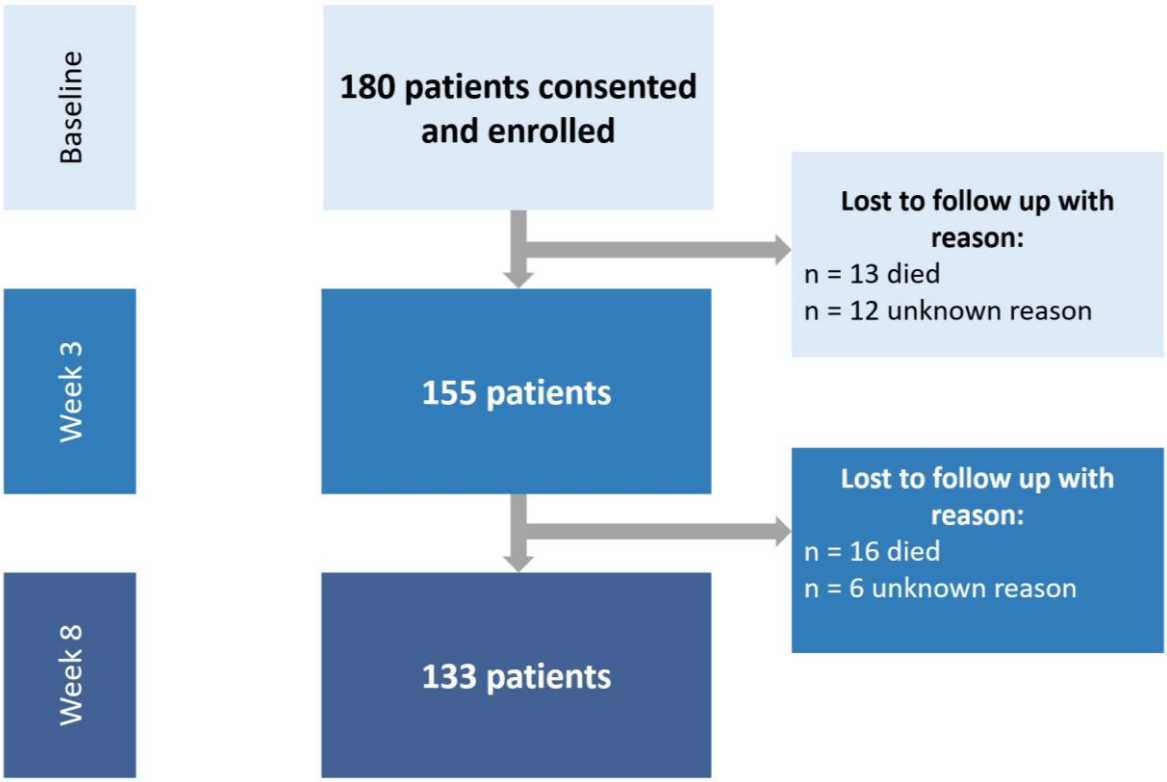

***Figure 3**: Flowchart of patients included in the analysis*

4.2 Baseline characteristics

Baseline characteristics are summarized in table 4. Of the patients included 106 (58.9%) were men and 74 (41.9%) were women. The mean (SD) age was 66 (9.8) years, 66 (9.5) for men and 62.5 (9.9) for women (p=0.016). Men had a significant higher BMI than women, with a mean (SD) BMI of 25.5 (4.4) kg/m^2 versus 24 (4.7) kg/m^2 (p=0.025). Median (Q1-Q3) survival was 31 (12-62) weeks, 29.5 (12-62) in men and 31 (12-63) in women (p=0.943)

The most frequent diagnose were gastro/intestinal cancer (26.7%, n=48), followed by prostate (22.2%, n=40) and breast cancer (20%, n=36). Among male patients, prostate cancer was the

most frequent cancer diagnosis (37.7%, n=40), while breast cancer comprised almost half of the female cancer cases (47.3%, n=35).

Most patients were living with spouse/partner (55%, n=99), although more women than men were living alone (29.7%, n=22, versus 16%, n=17, p=0.005). The most frequent level of education was ten to twelve years education (38.9%, n=70).

***Table 4**: Characteristics of study participants at baseline, and differences between men and women*

Characteristics	**Total**	**Male**	**Female**	**p-value** [a]
Total, n (%)	180 (100)	106 (58.9)	74 (41.1)	
Age, mean (SD) years	66 (9.8)	66 (9.5)	62 (9.9)	0.016[b]
Weight, mean (SD) kg	76.4 (17.4)	82.4 (14.9)	67.9 (17.2)	<0.001[b]
Height, mean (SD) cm	174.3 (9.4)	179.6 (7.2)	166.6 (6.4)	<0.001[b]
BMI, mean (SD) kg/m^2	24.9 (4.6)	25.5 (4.4)	24 (4.7)	0.025[b]
Survival, median weeks (Q1-Q3)	31 (12-62)	30 (12-62)	31 (12-63)	0.943[c]
Cancer diagnosis, n (%)				<0.001[d]
Breast cancer	36 (20)	1 (0.9)	35 (47.3)	
Prostate cancer	40 (22.2)	40 (37.7)	0	
Lung cancer	26 (14.4)	11 (10.4)	15 (20.3)	
Gastro/intestinal cancer	48 (26.7)	33 (31.1)	15 (20.3)	
Urological cancer	15 (8.3)	13 (12.3)	2 (2.7)	
Other	15 (8.3)	8 (7.5)	7 (9.5)	
Living situation, n (%)				0.005[d]
Alone	39 (21.7)	17 (16)	22 (29.7)	
With spouse/partner	99 (55)	67 (63.2)	32 (43.2)	
With spouse/partner and child(ren)	32 (18.7)	20 (18.9)	12 (16.4)	
With child(ren)	8 (4.4)	1 (0.9)	7 (9.5)	
With other adults	1 (0.6)	1 (0.9)	0	
Education, n (%)				0.557[d]
9 years	23 (12.8)	15 (14.2)	8 (10.8)	
10 – 12 years	70 (38.9)	37 (34.9)	33 (44.6)	
College or university = 4 years	53 (29.4)	31 (32.1)	19 (25.7)	
College or university > 4 years	33 (18.3)	20 (18.9)	13 (17.6)	

[a] Significance level p<0.05, [b] independent samples t-test, [c] Independent-Samples Median Test, [d] Chi-square test between men and women, BMI: Body Mass Index

4.3 Prevalence of malnutrition

Baseline characteristics of patients according to malnutrition degree at baseline are presented in table 5. Almost three out of four patients (72.7%, n=131) were classified as malnourished at baseline according to aPG-SGA (score>1). Of the malnourished patients 24.4% (n=44) were categorized as severely malnourished (aPG-SGA score ≥ 9) and 48.3% (n=87) were categorized as moderately malnourished (aPG-SGA score 2-8).

Overall, there is no statistically significant differences in diagnosis between the groups with and without malnutrition (p=0.055). Among patients with both severe and moderate malnutrition gastro/intestinal cancer was the most frequent diagnose (29.5%, n=13, 26.4%, n=23, respectively), while prostate cancer was the most frequent diagnose among patients with no malnutrition (34.7%, n=17).

Median CRP (Q1-Q3) among severely malnourished patients at baseline was significantly higher among severely malnourished compared to moderately malnourished patients, 26 (6-90) mg/l, versus 15 (0-35) mg/l (p=0.001) and 0 (0-14) mg/l patients with no malnutrition (p=0.001). Median (Q1-Q3) CRP levels for patients with no malnutrition were 0 (0-14) mg/l and was significantly lower than for malnourished patients (p=0.001).

Percentage of patients who were deceased at week eight differed significantly between patients with severe, moderate and no malnutrition (p<0.001). The highest percentage of deceased patients at week eight was seen among patients with severe malnutrition at baseline (31.8%, n=14). 13.8% (n=12) of patients with moderate malnutrition were deceased, while 6.1% (n=3) of the patients with no malnutrition were deceased at week eight.

NIS is part of the aPG-SGA scoring and thus patients classified with severe malnutrition had the highest median (Q1-Q3) prevalence of NIS compared to moderate and no malnutrition, as expected (7.3 (36) versus 4.7 (1.8), versus 0, p<0.05) The most frequent symptoms reported in the population were no appetite (35%, n=63), early satiety (27.8%, n=50), nausea (23.3%, n=42) and altered taste (21.1%, n=38).

***Table 5**: Patient characteristics according to degree of malnutrition*

	Severe malnutrition n (%) = 44 (24.4)	**Moderate malnutrition** n (%) = 87 (48.3)	**No malnutrition** n (%) = 49 (27.2)	**p-value**[a]
Gender, n (%)				0.021[b]
Male	23 (52.3)	46 (52.9)	37 (75.5)	
Female	21 (47.7)	41 (47.1)	12 (24.5)	
Cancer diagnosis, n (%)				0.055[b]
Breast cancer	10 (22.7)	18 (20.7)	8 (16.3)	
Prostate cancer	4 (9.1)	19 (21.8)	17 (34.7)	
Lung cancer	6 (13.6)	16 (18.4)	4 (8.2)	
Gastro/intestinal cancer	13 (29.5)	23 (26.4)	12 (24.5)	
Urological cancer	3 (6.8)	6 (6.9)	6 (12.2)	
Other	8 (18.2)	5 (5.7)	2 (4.1)	
CRP, median (Q1-Q3)	26 (6-90)	15 (0-35)	0 (0-14)	0.001[c]
Survival, median weeks (Q1-Q3)	13 (7-35)	30 (16-62)	55 (30-91)	<0.001[c]
Deceased at week 8, n (%)	14 (31.8)	12 (13.8)	3 (6.1)	<0.001[b]

[a] Significance level <0.05,[b] Chi-Square test for more than one categorical variable, [c] Independent-Samples Median Test
aPG-SGA: Abridged Patient-Generated Subjective Global Assessment, CRP: C-Reactive Protein
Severe malnutrition: aPG-SGA score ≥ 9, moderate malnutrition: aPG-SGA score 2-8, no malnutrition: aPG-SGA score ≤ 1

4.3.2 Malnutrition with or without inflammation

To further explore the malnourished patients according to inflammation patients with any degree of malnutrition were grouped according to CRP above or under or equal to a 5 mg/l level. Characteristics of malnourished patients with inflammation or without inflammation (are presented in table 6. Median (Q1-Q3) CRP among patients with malnutrition with inflammation was 26 (14-71) mg/l.

More women than men had malnutrition without inflammation (62.9%, n=22 versus 37.1%, n=13, respectively, p=0.002). Among patients with malnutrition with inflammation gastro/intestinal cancer was the most frequent diagnose (28.4%, n=2), while breast cancer was the most frequent among patients with malnutrition without inflammation (34,3%, n=12, p=0.117).

Median (Q1-Q3) survival for patients with malnutrition with inflammation were 19 (9-38) weeks, 41 (18-97) weeks for patients with malnutrition without inflammation and 55 (30-91) weeks for patients with no malnutrition (p<0.001). At week eight 24.2% (n=23) of patients with malnutrition with inflammation were deceased, while 5.5% (n=2) of patients with malnutrition without inflammation were deceased (p=0.002).

Patients with malnutrition with inflammation reported a mean (SD) score of 3.6 (3.5) NIS, while patients with malnutrition without inflammation reported a mean (SD) number of 4.2 (3.7) NIS. Among patients with malnutrition with inflammation the most frequent NIS were no appetite and early satiety while among the malnourished without inflammation no appetite and nausea were the most frequent NIS.

***Table 6**: Patient characteristics of malnutrition groups divided by malnutrition and inflammation*

	Malnutrition with inflammation n (%) = 95 (53.1)	**Malnutrition without inflammation** n (%) = 35 (19.6)	**No malnutrition** n (%) = 49 (27.4)	**p-value**[a]
Gender, n (%)				0.002[b]
Male	55 (57.9)	13 (37.1)	37 (75.5)	
Female	40 (42.1)	22 (62.9)	12 (24.5)	
Cancer diagnosis, *n (%)*				0.117[b]
Brest cancer	16 (16.8)	12 (34.3)	8 (16.3)	
Prostate cancer	17 (17.9)	6 (17.1)	17 (34.7)	
Lung cancer	18 (18.9)	4 (11.4)	4 (8.2)	
Gastro/intestinal cancer	27 (28.4)	9 (25.7)	12 (24.5)	
Urological cancer	8 (8.4)	1 (2.9)	6 (12.2)	
Other	9 (9.5)	3 (8.6)	2 (4.1)	
CRP, median (Q1-Q3)	26 (14-71)	0	0 (0-14)	<0.001[c]
Survival¸ median weeks (Q1-Q3)	19 (9-38)	41 (18-97)	55 (30-91)	<0.001[c]
Deceased at week 8, n (%)	23 (24.2)	2 (5.7)	3 (6.1)	0.002[b]

[a] Significance level <0.05. [b] Chi-Square test for more than one categorical variable,
[c] Independent-Samples Median Test,
aPG-SGA: Abridged Patient-Generated Subjective Global Assessment, CRP: C-Reactive Protein
Malnutrition with inflammation: aPG-SGA score>1 and CRP>5, Malnutrition without inflammation: aPG-SGA score > 1 and CRP ≤ 5, no malnutrition: aPG-SGA score ≤ 1

4.4 Energy and protein intake

4.4.1 Energy intake in relation to expenditure

Mean baseline energy intake and estimated expenditures are presented in table 7, for groups divided by malnutrition degree according to aPG-SGA. Statistically significant differences in relation to energy intake and expenditure were seen between these groups at baseline. Patients with severe malnutrition had lower mean (SD) energy intake and expenditure than patients with moderate and no malnutrition. This was reflected by the ratio between energy intake and energy expenditure, showing that mean (SD) ratio for patients with severe malnutrition was 0.87 (0.45), compared to 0.98 (0.43) and 0.97 (0.31) among patients with moderate and severe malnutrition.

Further, as presented in Figure 4, patients with malnutrition with inflammation had a mean (SD) energy intake and estimated energy expenditure was of 23 (10) kcal/kg and 26 (4) kcal/kg at baseline, respectively. Both patients with malnutrition without inflammation and patients with no malnutrition had an energy intake that was higher their estimated energy expenditure, however not significantly.

At baseline the mean (SD) ratio between energy intake and energy expenditure was 0.88 (0.38) reflecting insufficient intake in relation to energy needs. Patients with malnutrition without inflammation had a mean (SD) ratio between energy intake and expenditure of 1.13 (0.54) (p=0.004).

***Table 7**: Energy and protein intake in relation to expenditure and differences between malnutrition groups*

	Severe malnutrition	**Moderate malnutrition**	**No malnutrition**	**p-value**[a]
Energy expenditure, mean kcal/kg (SD)	25 (4)	27 (4)	29 (3)	0.001[b]
Energy intake, Mean kcal/kg (SD)	22 (12)	26 (12)	28 (9)	0.021[b]
Ration energy intake/expenditure, mean (SD)	0.87 (0.45)	0.98 (0.43)	0.97 (0.31)	0.361
Protein intake, mean g/day (SD)	0.8 (0.5)	1 (0.5)	1.2 (0.6)	0.001[b]

[a]Significance level <0.05, [b] One-way ANOVA for parametric test for mean difference between groups divided by malnutrition degree at basleine

***Table 8**: Energy and protein intake in relation to expenditure and differences between malnutrition groups*

	Malnutrition with inflammation n (%) = 95 (53.1)	**Malnutrition without inflammation** n (%) = 35 (19.6)	**No malnutrition** n (%) = 49 (27.4)	**p-value**[a]
Energy expenditure, mean kcal/kg (SD)	26 (4)	26 (4)	29 (3)	<0.001[c]
Energy intake, mean kcal/kg (SD)	23 (10)	29 (15)	28 (9)	0.01[c]
Ration energy intake/expenditure, mean (SD)	0.88 (0.38)	1.13 (0.54)	0.97 (0.31)	0.009[c]
Protein intake, mean g/kg (SD)	0.86 (0.44)	1.13 (0.63)	1.2 (0.58)	0.001[c]

[a]Significance level <0.05, [b] One-way ANOVA for parametric test for mean difference between malnutrition groups at baseline

4.4.2 Protein intake

Patients with malnutrition with inflammation at baseline reported a mean (SD) protein intake of 0.86 (0.44) g/kg at baseline (figure 5). The mean (SD) protein intake at baseline of patients with malnutrition without inflammation surpassed the lower limit of recommended protein intake at 1 g/kg (1.13 (0.63) g/kg). Differences in protein intake was statistically significant different between the malnutrition groups (p=0.001).

4.5 Changes in energy and protein intake over time

4.5.1 Energy intake

Data on estimated energy expenditure, energy intake, protein intake and weight for patients with available data at week eight are presented in table 8. Comparison of energy intake and estimated energy expenditure is illustrated in figure 2.

Mean energy intake increased from baseline to week eight for the total population. The mean (SD) total increase was highest for patients with malnutrition with inflammation (21 (8) kcal/kg to 27 kcal/kg (11), p=0.003). Patients with malnutrition without inflammation increased their mean (SD) energy intake from 29 (15) to 31 (11) kcal/kg (p=0.866).

4.5.2 Protein intake

An increase in mean (SD) protein intake was seen for patients with malnutrition with inflammation and patients with no malnutrition. For patients with malnutrition with inflammation mean (SD) protein intake increased from 0.83 (0.41) g/kg to 1.01 (0.41) g/kg (p=0.008). A decrease in protein intake was seen among patients with malnutrition without inflammation, from a mean (SD) protein intake of 1.23 (0.64) g/kg at baseline to 1.09 (0.35) g/kg at week eight (p=0.292).

4.6 Weight development

A significant negative weight development from baseline to week eight was seen for the total population decreasing from mean (SD) 76.3 (16.3) kg to 74.6 (15.5) kg (p<0.001). The mean weight reduction was highest among malnourished patients with inflammation where mean (SD) weight change was -2.5 (4.3) kg compared to -1 (2.2) kg among patients with malnutrition without inflammation and -0.9 (3.8) kg for patients with no malnutrition (p=0.086). Totally 60% (n=33) of the malnourished patients with inflammation lost weight during follow up (weight loss>2%) compared to 32.1% (n=9) of malnourished without inflammation and 27.5% (n=11) among those without malnutrition (p=0.019) (figure 6).

***Table 9**: Development of energy expenditure and intake, protein intake and weight and comparison between malnutrition groups*

	Malnutrition with inflammation n = 50	**Malnutrition without inflammation** n = 25	**No malnutrition** n = 35
Energy expenditure			
Baseline	26 (4)	26 (4)	29 (3)
Week 8	27 (4)	26 (4)	29 (3)
P-value	0.006	0.766	0.672
Energy intake, mean kcal/kg (SD)			
Baseline	21 (8)	31 (13)	28 (10)
Week 8	27 (11)	31 (11)	28 (9)
P-value	0.003	0.866	0.666
Protein, g/kg (SD)			
Baseline	0.83 (0.41)	1.23 (0.64)	1.22 (0.64)
Week 8	1.01 (0.42)	1.09 (0.35)	1.1 (0.36)
P-value	0.008	0.292	0.353
Weight, mean (SD) kg			
Baseline	77.9 (16.7)	68.4 (12.4)	80.2 (16.8)
Week 8	75.4 (15.4)	67.4 (12.5)	79.3 (16.3)
P-value	<0.001	0.035	0.159
***Overall weight change [a]**, mean (SD) kg*	-2.5 (4.3)	-1 (2.2)	-0.9 (3.8)

p-value calculated using paired samples t-test to compare change in mean from baseline to week eight, significance level <0.005, [a] weight change from baseline to week eight

Total weight loss was lower with higher ratio between energy intake and energy expenditure. A significant positive correlation was found between ratio between energy intake and energy expenditure at baseline and total weight change over the eight-week period. The same was seen between energy intake per kg body weight at baseline and weight change (r= 0.235, p=0.01).

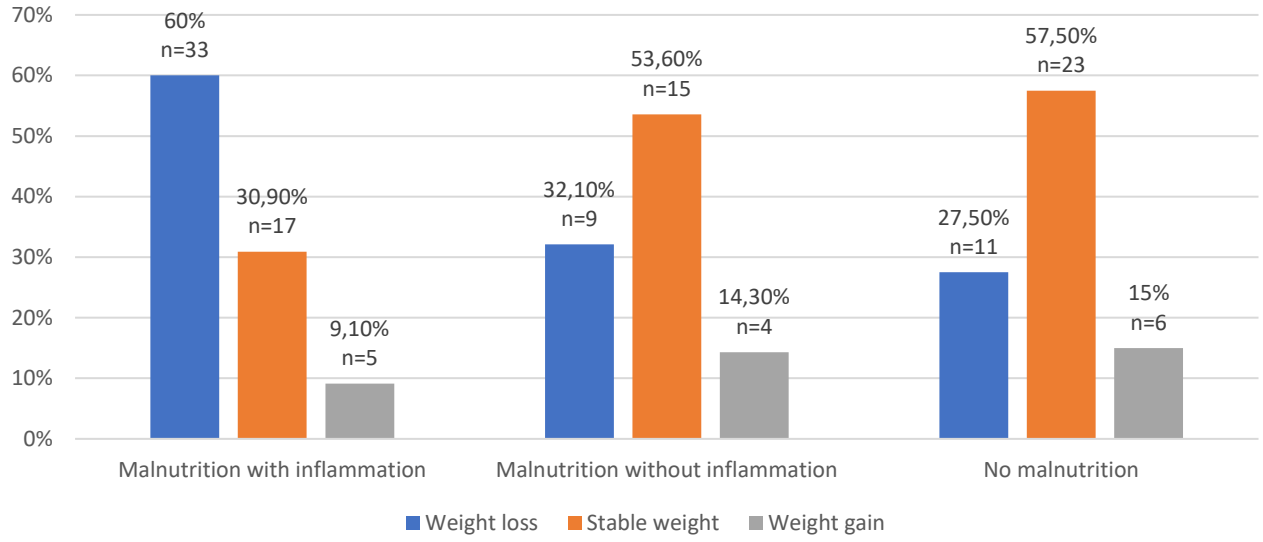

***Figure 5**: Percentage of patients with weight loss, stable weight and weight gain in groups defined by aPG-SGA and inflammatory status at baseline. Weight loss: ≥2% weight loss from baseline to week eight, stable weight: <2% weight loss or weight gain from baseline to week eight, weight gain: ≥2% weight gain from baseline to week 8, aPG-SGA: Abridged Patient-Generated Subjective Global Assessment*

5. Discussion

5.1 Main findings

In a group of 180 palliative cancer patients almost 75% were malnourished according to the validated screening tool aPG-SGA. Of these 24.4% had severe malnutrition and 48.3% had moderate malnutrition. The patients with malnutrition showed low energy and protein intake, high CRP and shorter survival, compared to those without malnutrition. Patients with severe malnutrition had poorer outcomes than patients with moderate malnutrition

Having malnutrition with inflammation compared to having malnutrition without inflammation seem to impact outcomes more than degree of malnutrition, and was associated with shorter survival, higher symptom burden, lower energy and protein intakes well as more weight loss during follow-up.

Thus, our findings support the concept of malnutrition diagnosis and nutritional support implementing cancer patients' presentation and markers of inflammation.

5.1. Discussion of methods

5.1.1 Study design

The prospective nature of the PRAIS study allows to examine a sequence of events and give comprehensive information on change in energy and protein intake, and weight over time, in addition to associations of malnutrition and inflammation. (66). The design makes it possible to investigate several outcomes and to calculate rate of certain outcomes and related factors (67). This makes us able to, for instance, investigate the association between malnutrition degree and factors such as weight and energy and protein intake development. Following a population over time gives us a real-time picture (67) of the patients after receiving radiotherapy and while they undergo palliative care.

5.1.2 Study population

This population consist of palliative cancer patients that are commencing on radiotherapy for cancer induced bone pain (57). Patient recruitment in populations at this stage of life may be challenging. Generally drop-out rates tend to be high in palliative populations (68).

In total 26% were lost to follow-up over the eight-week follow-up period. Studies with similar populations show similar attrition rates. In fact, a review by Hui D. et al show the exact same attrition rate (26%, (95% CI: 23-28%)) at the primary end-point of the study, and refers to

studies with rates between 20-46% (69). A high loss to follow-up is expected in this population. The palliative oncology population consist of frail patients with high disease burden (69). Expected survival is short and they are affected by symptoms related to disease and treatment. Inpatient deterioration, increasing symptom burden, and death are often the main drop-out reason (69).

Data on cancer patients in palliative in Norway are scarce. It is not expected that this cancer population is representative for the Norwegian cancer population, as these patients are at late stages of their cancer. However, distribution between gender and cancer diagnose seem to be fairly similar, as 58.9% were men and 41% were women in the current study, compared to 54% and 46% among those with newly diagnosed cancer in 2020 (4). Among the most prevalent cancer types were prostate, breast and lung cancer reflecting the distribution of diagnoses within the general Norwegian cancer population (4).

Selection bias

The high drop-out rate is an important consideration in clinical oncology studies. This can possibly lead to selection bias (69), which is often a methodological challenge in observational studies (70). An example of selection bias in palliative care research is when the healthiest individuals are those that are able to participate clinical studies (70), leading to reduced external validity of the results (71), implying that results can then not be applied to other samples or studies (71). If this is the case, we can expect that the actual prevalence of and degree of malnutrition with or without inflammation can be even higher than shown in the current study, as it is seen that higher disease burden might be related to increased prevalence of malnutrition (23).

5.1.4 Evaluation of nutritional assessment

aPG-SGA

All nutritional assessment in this study were performed using baseline data. There is no gold standard for nutritional assessment in cancer patients (72). Nevertheless, aPG-SGA is a well validated nutritional screening tool in the oncology setting (73). In this study aPG-SGA was used to identify patients with malnutrition (47). The aPG-SGA consists of the first four boxes of the PG-SGA. The total score of these boxes result in 80-90% of the total scoring result of the PG-SGA (48). It has been shown that both aPG-SGA and PG-SGA cover all three domains of the consensus-based definitions of malnutrition by both ESPEN (74) and the American Society for Parenteral and Enteral Nutrition (ASPEN) (21, 48). These domains

include: 1: nutrient balance; 2: body shape, body size and body composition; and 3: physical function (72). Thus, it is considered appropriate to use aPG-SGA in assessment of the patients in this study.

By only including the first four boxes of the PG-SGA the aPG-SGA method omits the part of the PG-SGA that require physical examination This makes it possible for the patient to independently fill out the questionnaire, that normally require health professionals, making the method simple, non-invasive and less time consuming. Some limitations to the method should also be noted. These include the requirement of retrospective data, which opens for recall bias, and may affect the accuracy of the results. The two first boxes of the questionnaire are based on the patients' ability to recall previous weight and food intake. Challenges can be related to patients not knowing their previous weight or not having the equipment to measure weight correctly at home. Over- and underreporting of weight is common, women tend to overreport and men tend to underreport their weight (75). On the other hand a study by Tamakoshi et al. show that body weight over a long follow-up shows good accuracy (76). In a qualitative study describing cancer patient experience with self-completing the aPG-SGA, challenges in relation to reading too fast and skipping words were noted (77). Some patients also found some of the alternatives difficult to interpret and too imprecise. However, the majority of patients found the aPG-SGA to be easy to use and to understand (77). A Study by Groot et al. reported that 97% of the included cancer patients found the aPG-SGA questionnaire easy to complete (31).

In this study information on NIS are based on the patients' subjective experience of symptoms that affect their nutritional intake as reported in box three in the aPG-SGA questionnaire. The aPG-SGA has been recognized as a patient reported outcome measure (PROM) (78). It is demonstrated that use of PROMs is the best way to collect information on symptoms in patients, as health care workers have a tendency to underestimate both the frequency and burden of patients' symptoms (78, 79)

Assessment of food intake

All information on food intake was collected from retrospective methods, from the aPG-SGA and 24-hour recall interviews. These methods have high respondent rate and low respondent burden (78). Food intake reported retrospectively by the PG-SGA has shown to be associated with the respondents' actual food intake (78).

24-hour recall

In the current study 24-hour recalls were completed at all three time points to collect detailed data on food intake. In this frail patient group, a reason for drop-out is that the patient is not able to fill out questionnaires or complete the interview. Thus, methods chosen should be easy to complete and not time-consuming. An advantage of the 24-hour recall is the short time required s to complete the interview (about 20 minutes) (78). Using prospective methods, such as 3-7 days food diaries, would have covered a longer time-period and given a more detailed picture of actual food intake at individual level as it would be able to capture day-to-day variations (78). At individual level one single interview is not sufficient to say something about the habitual diet. However, the aim in this study was not to investigate energy and protein intake at individual level. Multiple single interviews from different individuals will provide reliable dietary assessment on group or populational level (51). Means in the population and between groups were used to say something about the energy and protein intake at group level.

24-hour recall method has its limitations, one cannot know what the patient actually eats and have to trust their recollection and descriptions. Recalling all food intake and quantities may be challenging for the patient. As well it may be challenging for the interviewer to correctly interpret the patient, emphasizing the importance of trained personnel. Registration of food intake into the database was done by trained study personnel and the master's student, which opens errors in relation to different interpretations of the interviews. Day-to-day variations occur and treatment, especially radiotherapy, might affect food intake negatively.

Estimating total energy expenditure

It is stated that weight loss seen in cancer patients is caused by increased metabolism (hypermetabolism), which in turn increases REE, rather than reduced food intake (54). A Barecellos et al. commonly used equations for estimating energy expenditure, including the Mifflin-ST Jeor equation, were compared to REE measured by indirect calorimetry in a group of cancer patients (61). The indirect calorimetry revealed that REE was higher in the patients than what was estimated using the equations, thus supporting the understanding that metabolism is increased in patients with advanced cancer and cachexia. When calculating TEE in individuals with disease a stress factor is often added, to adjust for the increased REE. However, this factor is not included in estimation of TEE in this thesis. Studies have shown that although REE often is increased in cancer patients, especially patients with advanced cancer, it might just as well be decreased (38). In addition patients with advanced cancer often experience fatigue and reduced physical activity (23), which can adjusts for the increased

REE. Therefore, several clinical guidelines recommend that energy expenditure in cancer patients is calculated as for healthy individuals (39, 40). In addition, energy expenditure, as energy intake, was calculated at group level in this study. Considering the heterogeneity in the population, reduced physical activity and recommendations it was concluded that REE combined with a PAL was sufficient to estimate TEE. It should however be noted that not including a stress factor may be a source of error. If a stress factor had been added in these estimations, estimated energy expenditure would be more or less increased in all patients. Thus, results found in this thesis, showing a low energy intake compared to expenditure for most patients, would possibly be reinforced.

There is no specific recommended equation to estimate REE in cancer patients or patients with advanced disease as such. Equations developed for estimating energy expenditure are .. on healthy individual. Thus, using predictive equations on individual level is not recommended in cancer patients (61). However, studies comparing the estimations calculated by the Mifflin-ST Jeor equation to indirect calorimetry in cancer patients have found it to be a suitable method to estimate energy expenditure (63, 64). If the choice of prediction equation in fact has been a source of error and effected the results it is hard to say whether actual REE would be higher or lower than found in this study. Considering the two contradictions earlier discussed, regarding if and how REE is changed in patients with cancer. In general prediction equations tend to overestimate REE, however it is commonly believed that cancer patients have an increased REE.

Protein recommendations

Insufficient protein intake is common in cancer, and it is suggested that protein intake should be increased in cancer patients compared to in healthy individuals due to muscle wasting (80). Generally, there are small differences in recommendations in protein intake in cancer patients. Guidelines commonly recommend that protein intake should be at least 1.2 g/day in cancer patients (40, 80). It is also suggested that even higher intakes might be necessary to maintain muscle mass (80). However, expecting protein intakes this high was considered unrealistic in this population. It was chosen to follow ESPEN recommendations when estimating a protein requirement. The guideline recommend that protein intake is above 1g/kg, and preferably higher, up to 1.5 g/kg (39).

Anthropometric measures

Patients' measured body weight at each consultation were used in estimations of energy expenditure and protein requirements. There are limitations to using body weight isolated. Body weight does not take body composition or body composition changes into account and can be affected by water retention. However, comparing weight at group level can give valuable information. In addition, weight has prognostic significance (81).

5.2 Discussion of results

Baseline characteristics of this population show a short median (Q1-Q3) survival, 31 (16-62) weeks, this is not surprising as this is a population with advanced cancer. Cancer patients in general are prone to malnutrition. In addition, among the most prevalent cancer diagnoses in the population are prostate, gastric and lung cancer, which are cancer diagnoses known to be especially associated with high prevalence of malnutrition (82). To identify patients at nutritional risk or with malnutrition and be able to provide optimal nutrition care, the first step of the nutrition care process is screening (46).

5.2.1 Malnutrition prevalence and degree

This study resulted in a total malnutrition prevalence of 72.8% including both those with severe and moderate malnutrition. This is within the high end of the range of what is found in previous studies, ranging from 30.9% - 76%, as illustrated by Table 1. Prevalence of malnutrition in cancer patients vary greatly between studies. There might be several explanations for this, one being the fact that the cancer type and stage might differ, in addition to whether patients receive tumor directed treatment or not. Patients in this study have advanced cancer and short expected survival and are more prone to malnutrition than patients with newly diagnosed cancer. Nonetheless, differences in age, population size and assessment methods may also explain why prevalence differs between studies.

The malnutrition prevalence of 72.8% found in this study was high, but comparable to the findings of a multitude of previous studies. For example, Seguera et al. reported a malnutrition prevalence of 52% in a group of patients with advanced cancer, where the most frequent diagnoses were lung, colon, and breast cancer (33). Additionally, Bauer et al. found a total prevalence of malnutrition of 76% cancer patients when using the SGA (29). Bauer et al.'s study, however, only considered hospitalized patients. Further, Carriço et al. found a prevalence of 69% in a group of cancer patients undergoing chemotherapy, with the majority of cancer diagnoses being breast and lung cancer (30).

One of the limitations in comparing studies using aPG-SGA in cancer patients is the differences in cut-off for the definition of malnutrition, degree, and risk. Cut-off in this study was set to aPG-SGA score ≥ 1, as is a commonly used cut-off (30). A study by Groot et al. demonstrates how different cut-offs can contribute to different results between studies (31). This study included patients in an ambulatory setting. aPG-SGA was used for nutritional assessment and a cut-off at ≥ 5 was set to indicate risk of malnutrition. This resulted in 31% of patients at risk of malnutrition. If a cut-off at score ≥ 1 had been used in this study, the malnutrition prevalence would have been 79.4%, and results would have been closer to what is found in the current study (31).

In the current study a cut-off that some studies consider to be low was used. However, the classification of malnutrition degree show significant differences between patient group defined by aPG-SGA score < 1, 2 - 8, and ≥ 9, in regards to CRP, survival, energy and protein intake and weight development. Thus, it can be argued that a low cut-off is necessary to capture all patients with some degree of malnutrition or nutritional challenges.

Dividing patients by degree of malnutrition revealed significant differences in energy and protein intake, CRP, survival and frequency of NISs between the groups. Noticeably median (Q1-Q3) CRP was almost doubled for patients with severe malnutrition compared to patients with moderate malnutrition (26 (6-90) mg/l versus 15 (0-35) mg/l) while median (Q1-Q3) weeks survival was more than twice as high for patients with moderate malnutrition compared to patients with severe malnutrition (30 (16-62) versus 13 (7-35) weeks). This made it interesting to further investigate the malnourished population considering CRP level as a measure of inflammation.

Malnutrition with and without inflammation

All patients with malnutrition (aPG-SGA score≥1) were grouped by whether inflammation was present or not. New GLIM criteria have suggested that inflammation should be a factor included in nutritional assessment, after patients at risk of malnutrition are identified (28). In addition, ASPEN includes a fourth domain to the definition of malnutrition which includes inflammatory factors (21, 72). Cachexia is common in patients with advanced cancer, and it is expected that the main part of this population is affected by cachexia to some degree. Thus, inflammation was considered when assessing the patients.

Grouping by presence of inflammation or not affected several outcomes. Patients with malnutrition without inflammation were more similar to patients with no malnutrition than

patients with malnutrition and inflammation considering energy and protein intake, survival and weight loss.

Naturally, patients with malnutrition without inflammation had a CRP of zero as this is part of the definition of this group. A median of zero was also found for patients without malnutrition, however, the interquartile range was 0-14 indicating that some patients without malnutrition have increased CRP levels, this might insinuate a risk of later developing malnutrition with inflammation. Thus, underlining the importance of measures to prevent this development.

Malnourished patients experienced a mean frequency of about 4 different NIS at baseline. Symptom management is an important part of palliative care and success in nutritional treatment is depending in sufficient symptom control. It is shown that symptoms negatively affect energy intake, poor quality of life (55).

Though interesting differences are observed when dividing patients by inflammation these results must be interpreted with caution. It is not established whether the advanced degree of the disease cause inflammation or if the inflammation itself evokes symptoms (57).

5.2.2 Energy and protein

Neither patients with severe nor moderate malnutrition reached their mean estimated energy expenditure at baseline. Interestingly, when the malnourished patients were divided into groups with and without inflammation only those with inflammation had a mean (SD) energy intake lower than mean (SD) estimated energy expenditure, with an energy intake of 23 (4) kcal/kg versus estimated energy expenditure of 26 (10) kcal/kg (table 8). This aligns the findings of Bye et al. in a study including patients with advanced pancreatic cancer (55). The study showed a tendency towards a lower energy intake among patients with shorter survival. As previously described in the current study, patients with malnutrition with inflammation were the patients with the shortest median survival.

Interestingly, patients with malnutrition without inflammation had a higher mean energy intake at baseline than patients with no malnutrition. In accordance with existing literature, inflammation seems to be related to a lower food intake, explanations for this may be related to the associations between systemic inflammation, anorexia and cachexia (23, 55).

Increased REE due to hypermetabolism as well as a multitude of NIS related to the disease and its treatment will likely lead to changes in energy intake that in turn causes weight loss.

However, some patients show weight loss without reduction in energy intake, indicating that there is more to weight loss than reduced energy intake among advanced cancer patients. However, it should be noted that estimated energy expenditure in this study was fairly low compared to a general recommendation for patients with cancer cachexia of 29 kcal/kg (83). Interestingly this is the exact mean estimated energy expenditure for patients with no malnutrition at baseline (29 (3) kcal/kg) at both baseline and week eight. There is a possibility that estimations on energy expenditure is too low for patients with cachexia in this study due to increased REE. However, we did not measure REE in this study and estimated group level expenditures which might be both an over and underestimation of actual energy needs. Therefore, a low energy intake might contribute to weight loss to a larger extent in some patients as the true energy intake and expenditure might differ more than we can estimate

Mean estimated energy expenditure for patients with malnutrition with and without inflammation was similar (26 (4) kcal/kg). The low energy intake among patients with malnutrition with inflammation cannot be explained by patients being smaller, as the Mifflin-ST Jeor equation takes weight and height into account (62). Thus, inflammation seems to affect energy intake subsequently causing weight loss – the key feature of the cancer cachexia definition (36).

5.2.3 Nutritional status and energy and protein intake over time

In this study data at baseline, week three and week eight was available. When looking at changes over time, it was decided to compare data at week eight with data at baseline. The population we were interested in investigating longitudinally was the population that survived until at least week eight. From week three to week eight 16 patients died and 6 were lost to follow-up due to unknown reasons. In addition, we did not expect there to any significant changes in the short time period between baseline and week three.

Not surprisingly, all three patient groups had a mean reduction of weight over the eight week follow-up period. Weight loss is common among patients with advanced cancer, and is often seen in palliative care (84). A worsening of weight loss is as the patient approaches end of life is common (17).

Among patients with malnutrition with inflammation both energy intake and protein intake increased significantly ($p<0.005$). Interestingly, while this was the only patient group with an increase in mean energy and protein intake, they still had the highest mean weight loss over the eight week period with a mean (SD) weight reduction of 2.5 (4.3) kg ($p<0.001$). This

supports the theory that these patients are affected by cachexia, and not being simply malnourished. Emphasizing that there is more to weight loss than changes in food intake in patients with advanced cancer. Despite no changes in energy expenditure or intake over the follow-up period, patients with malnutrition without inflammation experienced a small but significant mean weight reduction (-1 (2.2) kg, p=0.035). Patients without inflammation had no significant changes in mean (SD) energy expenditure or energy or protein intake. They still experienced some weight loss, though not significant (p=0.159).

Though weight was statistically decreased from baseline to week eight among patients with malnutrition this does not equal clinical significance. Little literature exist on what a clinically significant weight loss is in this patient group. But it is of importance as it is shown that weight loss in patients with advanced cancer is associated with reduced quality of life and survival (55). Martin et al. reports that a percentage of weight loss that is considered of clinical importance by oncologists vary between 5-20% (81). Due to the short follow-up period in this study patients were considered as having weight loss if they lost more than 2% of their body weight from baseline to week eight (36). This was done to capture all patients with a negative trend in weight development. By this definition 60% of patients with malnutrition with inflammation had weight loss compared to 32.1% of patients with malnutrition without inflammation (figure 5). Again, demonstrating the poor nutritional status among patients with malnutrition and inflammation.

5.2.4 Clinical consequences

When any degree of malnutrition is detected, screening should be followed by nutritional assessment to then decide what course of nutrition intervention is necessary, following the NCP (80). In this thesis nutritional assessment and nutrition diagnosis were used in line with this approach. The following nutrition diagnosis, intervention and monitoring is beyond the scope of this thesis.

Although palliative cancer patients in general are heterogenous with respect to survival, the majority in our cohort had a short expected survival, median (Q1-Q3) of 31 (12-62) weeks (17). There are several aspects to consider when assessing the palliative cancer patient and considering nutritional interventions. Firstly, a clinical evaluation of whether the patient will benefit from nutritional intervention has to be asked is needed. WHOs definition of palliative care is 2-fold (8), including improvement or maintenance of quality of life and symptom control and alleviation (22). It has been shown that impaired nutritional status and cancer

cachexia are associated with poor quality of life in patients with incurable cancer (Oliveira). However, there is lack of evidence that nutritional interventions will improve quality of life in patients with advanced cancer (85) and the effects of dietary interventions in cachexia have been questioned (86). The treatment effects should outweigh the burden and futile treatment should be avoided. At the last stages of life aiming to improve nutritional status can be an additional burden and source of frustration to both the patient and the next of kin (86).

On the other hand, optimal symptom treatment also implies addressing NIS and nutritional interventions can also alleviate symptoms such as e.g., diarrhoea and constipation in itself. As shown in this study, palliative cancer patients are commonly affected by burdensome NIS, and some are treatable and thus might improve patients' food intake and nutritional status.

Dividing patients with malnutrition by inflammatory status demonstrated significant differences in survival. Thus, including evaluation of CRP can be a great additional tool in understanding the patients' situation and prognosis. By PG-SGA definition, patients with score ≥ 9, defined as severely malnourished in the current study, are patients in critical need of nutritional intervention (figure 2) (47). However, this study demonstrates that patients with moderate malnutrition can have equally poor prognosis as patients with severe malnutrition if inflammation is present.

Patients with or without malnutrition that have not yet developed malnutrition have longer survival than patients with inflammation. It is plausible to believe that these patients with or without malnutrition, showing longer expected survival, may benefit from nutritional intervention. Thus, these patients should not be overlooked in favour of the severely malnourished patients in the clinic as they are at great risk of developing malnutrition and cachexia. Taken together, personalized evaluation and nutritional treatment is needed in cancer patients in a palliative setting.

6. Conclusion

This thesis explored nutritional status and nutritional intake in 180 patients with cancer commencing on palliative radiotherapy.

Three out of four patients had malnutrition to some degree, and one out of four were severely malnourished, when assessed using the aPG-SGA. Presence of malnutrition was associated with increased CRP, reduced survival, and low energy and protein intake compared to requirements.

Further categorization of malnourished patients revealed that patients with inflammation significantly differed from patients without inflammation in that they had a significantly shorter survival, lower energy and protein intake and a higher weight loss than patients without inflammation or without malnutrition. This implies an association between inflammation and adverse outcomes in palliative cancer patients. Outcomes among patients with malnutrition without inflammation were similar to outcomes among patients with no malnutrition.

As commonly seen when investigating advanced cancer populations, few patients reached their estimated energy expenditure or recommended protein intake. In addition all groups experienced a mean weight loss. However, there is more to weight loss than reduced energy intake in patients with advanced cancer. The patients that most clearly differed from their recommendations were patients where both malnutrition and inflammation were present, highlights the role of inflammation in relation to weight loss in patients with advanced cancer. This is supported by the observation that patients with inflammation seemed to lose weight independent of reaching energy needs or not.

The results of this thesis imply that including a factor for inflammatory status through measures of for example CRP can be a useful additional tool in understanding the palliative cancer patients' situation and prognosis. Our findings support the concept of individual nutritional support based on patients' presentation and marker of inflammation. However, we cannot by the results of this thesis state that inflammation is the cause of the observed negative outcomes, as it is not established whether inflammation itself is the cause for the outcomes or if the inflammation and symptoms can be caused by the severity of the disease. Consequently, further research on this topic is needed to provide additional colour on the topic.

7. References

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8. Appendices

Appendix 1. The Abridged Patient-Generated Subjective Global Assessment

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

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____kg
I am about _____ cm tall

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

During the past two weeks my weight has:

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

Box 1 ☐

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

☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking

☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0) **Box 2** ☐

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

☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3) _____
☐ other (1)** _____
**Examples: depression, money, or dental problems

☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
☐ fatigue (1)

Box 3 ☐

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

☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

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

Additive Score of Boxes 1-4 ☐ **A**

email: faithotterymdphd@gmail.com or info@pt-global.org

Appendix 2. REC approval number 1

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Øystein Lundestad	73597507	10.07.2013	2013/1126/REK midt
			Deres dato:	Deres referanse:
			28.05.2013	

Vår referanse må oppgis ved alle henvendelser

Pål Klepstad
Intensivavdelingen

2013/1126 Palliativ strålebehandling mot kreftsmerter

Forskningsansvarlig: St Olavs Hospital
Prosjektleder: Pål Klepstad

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 21.06.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Bakgrunn: Strålebehandling er en vanlig måte å behandle smertefulle skjelettmetastaser på, og for 6 av 10 fungerer behandlingen. En kan i dag ikke forutsi for hvilke pasienter behandlingen vil virke. Det samme gjelder for ufrivillig vekttap blant kreftpasienter, såkalt kakeksi. Det finnes ingen metoder for å forutsi hvem som kommer til å utvikle dette. Gjennom en internasjonal, longitudinell studie (PRAIS) av pasienter som får strålebehandling for smertefulle skjelettmetastaser ønsker en å samle kliniske data om denne sammenhengen. Den norske delen av studien vil inkludere 600 pasienter (+400 i valideringsgruppe) for å utvikle et klassifiseringssystem som kan forutsi respons på strålebehandling. En ønsker å opprette en spesifikk biobank og se nærmere på demografiske, kliniske og biologiske/genetiske markører, samt egenrapportering av smerte. Hovedmålet med studien er å finne ut hva som kan forutsi hvem som vil oppleve en smertelindring av behandlingen, men studien vil også innebære å finne ut om en kan identifisere hvem som vil utvikle kakeksi og hvordan betennelsesreaksjoner henger sammen med smerteintensitet og ufrivillig vekttap.

Vurdering
Komiteen har vurdert søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Studien er omfattende og har et aktverdig formål. Prosjektet framstår som forsvarlig, og hensynet til deltakernes velferd og integritet er ivaretatt. Også opprettelsen av den spesifikke forskningsbiobanken "PRAIS biobank" framstår som forsvarlig. Pål Klepstad er ansvarshavende person for biobanken.

Vilkår for godkjenning (prosjekt)

1. Det er et visst spenningsforhold mellom følgende to påstander i forespørselen: "Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien" og "[h]vis du samtykker til å delta i studien, gir du også samtykke til at vi kan lagre alle blodprøver og all informasjon som vi har samlet inn om deg gjennom studien i en såkalt forskningsbiobank ...". Det bes om at den første påstanden korrigeres i henhold til planlagt senere forskning, evt. at det informeres bedre om dette tidligere i skrivet (f.eks. andre avsnitt). Det må være klart for deltakerne at de gir et bredt samtykke til senere forskning.

Besøksadresse:
Det medisinske fakultet
Medisinsk teknisk forskningssenter 7489
Trondheim

E-post: rek-midt@medisin.ntnu.no
Web: http://helseforskning.etikkom.no/

2. Ettersom det skal gis et bredt samtykke i denne studien, har også deltakerne krav på jevnlig informasjon om prosjektet (generelle positive og negative funn, kommersiell utnytting, mm.). Dette framgår av § 14 i helseforskningsloven (hfl.). Det bes om at dette etterleves. Utsending av "nyhetsbrev" eller jevnlig oppdaterte nettsider vil normalt sett være tilstrekkelig for å imøtekomme kravet.
3. Deltakere skal sikres mulighet for sletting av prøver og data, såfremt disse ikke allerede er inngått i en analyse eller vitenskapelig publikasjon. Det må informeres om dette i forespørselen.
4. Det bør i forespørselen også informeres om hvor lang tid deltakerne må sette av til senere oppfølging. I den nåværende versjonen informeres det kun om estimert tidsbruk for utfylling av første spørreskjema.
5. Komiteen ber om å få ettersendt informasjon om hvilke utenlandske institusjoner materiale skal overføres til (så snart dette er klarlagt).
6. På grunn av omfanget av studien ber komiteen om at det sendes inn en løpende rapport hvert 3. år, ved utgangen av året. Første rapport bes forelagt innen 31.12.2016. Rapportene skal inneholde informasjon om a) funn i studien, b) hvilken informasjon som er gjort tilgjengelig for deltakerne, c) hvilke institusjoner og tilhørende prosjekt som til enhver tid er tilknyttet studien, og d) eventuelt annen viktig informasjon om prosjektet.
7. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen og vilkår for godkjenning, og etter de bestemmelser som følger av helseforskningsloven med forskrifter.
8. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Prosjektdata skal oppbevares i minimum 5 år etter prosjektslutt.

Vilkår for godkjenning (biobank)

1. Komiteen forutsetter at forskningsansvarlig institusjon har de nødvendige godkjenninger for å kunne foreta genetiske prediktive undersøkelser av denne art, jf. bioteknologiloven § 5-3.
2. Materiale i forskningsbiobanker skal oppbevares og behandles forsvarlig. Oppbevaring og behandling skal skje med respekt for giveren av materialet, jf. hfl. § 27. Dersom biobanken opphører, nedlegges eller overtas av andre, skal det søkes REK om tillatelse, jf. hfl. § 30.
3. Komiteen ber om at det sendes inn en løpende rapport hvert 3. år, ved utgangen av året. Første rapport bes forelagt innen 31.12.2016. Rapportene skal inneholde informasjon om a) hvilke prosjekter som til enhver tid er tilknyttet PRAIS biobank, b) eventuelle endringer i styringsform og/eller eierforhold, og c) eventuelt annen informasjon om biobanken som kan ha betydning for REK.
4. Godkjenningen er gitt under forutsetning av at biobanken driftes i henhold til dens beskrivelse i søknaden og protokollen, og i henhold til de bestemmelser som følger av helseforskningsloven med forskrifter.

Vedtak
Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner prosjektet og opprettelsen av spesifikk forskningbiobank med de vilkår som er gitt. Pål Klepstad er ansvarshavende person for "PRAIS biobank".

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 27.11.2023, jf. hfl.
12. Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Siri Forsmo
Professor, dr.med. MPH
Nestleder, REK midt

Øystein Lundestad
Rådgiver

Kopi til: jo-asmund.lund@stolav.no
siv.morkved@stolav.no
biobankregisteret@fhi.no

Appendix 3. REC approval number 2

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Linda Tømmerdal Roten	73597507	31.01.2014	2013/1126/REK midt
			Deres dato: 17.01.2014	**Deres referanse:**

Vår referanse må oppgis ved alle henvendelser

Pål Klepstad
St. Olavs Hospital

2013/1126 Palliativ strålebehandling mot kreftsmerter

Forskningsansvarlig: St Olavs Hospital
Prosjektleder: Pål Klepstad

Vi viser til søknad om prosjektendring datert 17.01.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK midt på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

Det søkes her om godkjenning av følgende prosjektendringer:

1. Ragnhild Habberstad som ny prosjektmedarbeider.
2. Inklusjon av et spørreskjema (PHQ-9) med spørsmål om depresjon/psykisk helse.
3. Spesifisering av tidligere nevnt eksklusjonskriterium «pathological fractures» til «pathological fractures in long bones (e.g. femoral or humoral shaft fractures)».

REK midt har vurdert søknad om prosjektendring, og har ingen forskningsetiske innvendinger mot endringene av prosjektet. Under forutsetning av at vilkårene oppfylles er hensynet til deltakernes velferd og integritet er fremdeles godt ivaretatt.

Vilkår for godkjenning

1. Komiteen ber om at det i forespørselen informeres om at deltakere også vil bli spurt om forhold vedrørende depresjon/psykisk helse i forbindelse med den behandlingen de gjennomgår.
2. Revidert informasjonsskriv skal sendes komiteen til orientering. Vennligst benytt e-postadressen post@helseforskning.etikkom.no og "REK midt 2013/1126" i emnefeltet.
3. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen og prosjektendringene datert 17.01.2014. Prosjektet må også gjennomføres i henhold til tidligere vedtak i saken og de bestemmelser som følger av helseforskningsloven med forskrifter.
4. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Av kontrollhensyn skal prosjektdata oppbevares i 5 år etter prosjektslutt, for deretter å slettes eller anonymiseres, jf. helseforskningsloven § 38.

Besøksadresse:
Det medisinske fakultet
Medisinsk teknisk forskningssenter 7489
Trondheim

E-post: rek-midt@medisin.ntnu.no
Web: http://helseforskning.etikkom.no/

Vedtak

Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner søknad om prosjektendring med de vilkår som er gitt.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Sven Erik Gisvold
Dr.med.
Leder, REK midt

Linda Tømmerdal Roten
Rådgiver

Kopi til: *jo-asmund.lund@stolav.no; rek-midt@medisin.ntnu.no*

Appendix 3. REC approval number 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Karoline Bjørstad Berget	73597509	17.12.2014	2013/1126/REK midt
			Deres dato: 29.11.2014	**Deres referanse:**

Vår referanse må oppgis ved alle henvendelser

Pål Klepstad
St. Olavs Hospital

2013/1126 Palliativ strålebehandling mot kreftsmerter

Forskningsansvarlig: St Olavs Hospital
Prosjektleder: Pål Klepstad

Vi viser til søknad om prosjektendring datert 29.11.2014,e-post med delstudiens protokoll mottatt 09.12.2014 og e-post med tillegg til informasjonsskrivet mottatt 17.12.2014. Henvendelsene ble behandlet av leder for REK midt på fullmakt, med hjemmel i helseforskningsloven § 11 og forskrift om behandling av etikk og redelighet i forskning § 10.

Prosjektleder ønsker følgende endring:

- Nina Aas, Hanne Stensheim, Aasta Bye, Marianne Jensen Hjermstad, Jon Håvard Loge, Trude Cammilla Frøseth, Ellem Bjerkeset, Torunn Elin Wester, Erik Schistad Staff og Heeg Elvebakken som nye prosjektmedarbeidere
- Legge til fire nye spørsmål for å forbedre analysen med hensyn til depresjon, smerte og ernæring. To spørsmål handler om depresjon, og to spørsmål om røyking og alkoholvaner.
- Følge malen for Charlson comorbity index ved baseline for å bedre rapportering av komorbiditet. Charlson comorbidity index vil gi et standardisert mål som kan regnes til en validert totalindeks som en vet er relatert til pasientenes prognose.
- Senteret i Oslo vil gjennomføre en delstudie med moduler for og i mer detalj å undersøke ernæring og matinntak
- Senteret i Oslo vil fullføre hele Leeds Asssessment of Neuropathic pain, det vil si to undersøkelser (sensitivtet for berøring og prikk med spiss)
- Tillegg til informasjonsskrivet (gjelder delstudien)

Vurdering
REK midt har vurdert søknad om prosjektendring. Komiteen har ingen forskningsetiske innvendinger mot endringen av prosjektet. Under forutsetning av at vilkårene nedenfor tas til følge, er hensynet til deltakernes velferd og integritet fremdeles godt ivaretatt.

Vilkår for godkjenning

1. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen og prosjektendringen datert 17.01.2014 og 29.11.2014. Prosjektet må også gjennomføres i henhold til tidligere vedtak i saken og de bestemmelser som følger av helseforskningsloven med forskrifter.
2. Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.
3. Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 27.11.2023 (6 måneder etter prosjektslutt), jf. hfl. § 12.

Besøksadresse:
Det medisinske fakultet
Medisinsk teknisk forskningssenter 7489
Trondheim

Telefon: 73597511
E-post: rek-midt@medisin.ntnu.no
Web: http://helseforskning.etikkom.no/

4. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Av kontrollhensyn skal prosjektdata oppbevares i 5 år etter sluttmelding er sendt REK. Data skal derfor oppbevares til denne datoen, for deretter å slettes eller anonymiseres, jf. hfl. § 38.

Vedtak
Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner søknad om prosjektendring med de vilkår som er gitt.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Sven Erik Gisvold
Dr.med.
Leder, REK midt

Karoline Bjørstad Berget
Seniorkonsulent

Kopi til: *jo-asmund.lund@stolav.no; siv.morkved@stolav.no; personvernombudet@stolav.no*