Malnutrition – the search for consensus

An evaluation of the suggested ESPEN malnutrition criteria in light of the criteria for malnutrition as presented in the Norwegian National guidelines

Master thesis by Cathrine Bus Holth

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Cathrine Bus Holth

Abstract

Background: The European society of clinical nutrition and metabolism (ESPEN) recently published a consensus for malnutrition criteria. After initial identification of nutritional risk, ESPEN suggests three alternative criteria for the malnutrition diagnosis: 1) Low body mass index (BMI) (<18.5 kg/m^2), 2a) a combination of weight loss (WL) and low BMI or 2b) a combination of WL and low fat free mass index (FFMI).

Objective: Our aim was to evaluate the newly suggested ESPEN malnutrition criteria (EMC) in light of the currently used Norwegian national criteria for malnutrition (ICD-10 NO) in cancer patients. Furthermore, we aimed to examine the overlap of the three ESPEN criteria, and whether dual energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) as method for determining FFMI was decisive for the outcome of criterion 2b.

Methods: We recruited 69 outpatient cancer patients. The patients were assessed for nutritional risk using Patient-Generated Subjective Global Assessment (PG-SGA) and Nutrition risk screening 2002 (NRS-2002), and considered for malnutrition using the EMC and the ICD-10 NO. FFMI was measured using DXA (Lunar iDXA, GE Healthcare) and BIA (Seca BCA 515). Agreement was assessed by description of percentages and overlap, analyses of sensitivity, specificity, positive and negative predicative value and kappa measure of agreement.

Results: Initial assessment by PG-SGA and NRS-2002 showed that 41 (59.4 %) and 31 (44.9 %) patients were at nutritional risk respectively. EMC and ICD-10 NO identified 16 (23.2 %) and 29 (42.0 %) patients as malnourished respectively. Compared to ICD-10 NO, the EMC showed a sensitivity of 52 %, specificity of 92 %, and kappa value of 0.33. A majority of the patients categorized as malnourished by ICD-10 NO only, met the WL criteria of alternative 2 in the EMC, but due to the lack of concurrent low BMI or low FFMI they did not meet the malnutrition diagnosis by the EMC. When using the EMC, the criterion including low FFMI identified a majority of the patients as malnourished as compared to the criteria including BMI. Assessment of FFMI showed similar results using BIA and DXA.

Conclusion: The newly suggested malnutrition criteria by ESPEN showed limited agreement to the Norwegian malnutrition criteria. The disagreement was primarily caused by EMC not considering WL alone a criterion for malnutrition. Further, the ESPEN malnutrition criterion including low FFMI identified more patients than the criteria including BMI. BIA (Seca BCA 515) and DXA (Lunar iDXA GE Healthcare) both identified low FFMI similarly.

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Abbreviations

Academy The Academy of Nutrition and Dietetics

ASM Appendicular Skeletal Muscle mass

ASMI Appendicular Skeletal Muscle mass Index

ASPEN American Society for Parenteral and Enteral Nutrition

BIA Bioelectrical Impedance Analysis

BMI Body Mass Index

BCA Body Composition Analyzer

COPD Chronic Obstructive Pulmonary Disease

CRP C-reactive protein

CRC-NORDIET study Norwegian Dietary Guidelines and Colorectal Cancer Survival study

CT Computed Tomography

DXA Dual Energy X-ray Absorptiometry

EMC ESPEN Malnutrition Criteria

ESPEN The European Society of Clinical Nutrition and Metabolism

FM Fat Mass

FFM Fat Free Mass

FMI Fat Mass Index

FFMI Fat Free Mass Index

GI Gastro Intestinal Tract

HGS Hand Grip Strength

HN Head and Neck cancer

ICD-10 NO International classification of diseases version 10 Norwegian malnutrition criteria

BCA Body Composition Analyzer

MNA Mini Nutrition Assessment

MRI Magnetic Resonance Imaging

MUST Malnutrition Universal Screening Tool

MST Malnutrition Screening Tool

n number of members in a sample (in tables and figures)

NICE National Institute for Health and Care Excellence

NRS-2002 Nutrition Risk Screening 2002

PG-SGA Patient-Generated Subjective Global Assessment

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

SD Standard Deviation

SMM Skeletal Muscle Mass

TBW Total Body Water

WHO World Health Organization

WL Weight Loss

1 Introduction

1.1 Malnutrition – the search for a definition.

Directly translated the word malnutrition means bad nutrition (1). In principle, the word malnutrition could be used in all situations where a person's nutritional need is not met. This could be due to a deficit, imbalance or excess of macro- or micro nutrients. Malnutrition is most widely used in the meaning of energy- or protein deficit and subsequent failure of meeting one's nutritional need (2, 3). For the purpose of the present thesis, malnutrition will further be referred to in the latter meaning, synonymous to undernutrition.

Over the years, there have been many attempts of defining the term malnutrition and reaching consensus on the diagnostic criteria for this condition (4-6). National Institute for Health and Care Excellence (NICE) guidelines in 2006 defined malnutrition as a "*a state in which a deficiency of nutrients such as energy, protein, vitamins and minerals causes measurable adverse effects on body composition, function or clinical outcome"(*(7), p. 5). These guidelines also presented criteria for malnutrition and risk of malnutrition (7). In 2009 the Norwegian Directorate of Health published the "*National guidelines on preventing and treatment of malnutrition*" ((8) p.72). These Norwegian guidelines (8) presented diagnostic criteria for nutritional risk, moderate and severe malnutrition based on the NICE guidelines (7) and European guidelines for nutritional screening by The European Society of Clinical Nutrition and Metabolism (ESPEN) (9). In 2010 the International consensus guideline committee proposed etiology-based diagnoses of adult malnutrition, and differentiated between *starvation-related malnutrition, chronic disease-related malnutrition* and *acute disease- or injury-related malnutrition* (10, 11). The consensus of these definitions was reached through cooperation with both the American Society for Parenteral and Enteral Nutrition (ASPEN) and ESPEN. In 2012 The Academy of Nutrition and Dietetics (Academy) and ASPEN published a list of six characteristics they suggested should be included in the identification and documentation of malnutrition (12). The six characteristics were as follows: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that could sometimes mask weight loss and diminished functional status as measured by hand grip strength (12). The identification of two or more of these characteristics was recommended for diagnosis, but the specific cut-off for

each characteristic was not settled (12). The latest contribution to this list was by ESPEN in 2015 where a consensus statement for diagnostic criteria for malnutrition was published (3). These consensus criteria will be further presented in **section 1.9**. ESPEN used the following definition for malnutrition *"a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"*((3) p. 335 and (2) p.3). This list is only examples of the ongoing controversy and debate concerning the term and diagnostic criteria for malnutrition. In the ESPEN guidelines for definitions and terminology of clinical nutrition published in 2016, the global nutrition community was urged to reach agreement on the diagnostic criteria for malnutrition (2). A global leadership conversation on malnutrition recently found place, where the latest opinions on the subject was discussed (13).

International classification of diseases version 10 (ICD-10) is an international classification system for systematic recording and processing of information on mortality and morbidity across country boarders developed by the World Health Organization (WHO) (14, 15). Malnutrition is mainly covered by code E40-E46. Code E.40 to E.42 and E45 covers marasmus, kwashiorkor and stunting and are not frequently present in the western world. The most commonly used codes regarding malnutrition are E43, E44 and E46. A general description for the codes is presented by WHO, but no specific criteria are listed for the use of these codes.

The controversies regarding the reach of a universal and general definition for malnutrition evolve around what factors to include as well as the specific criteria and cut-off levels of these. The mechanisms and pathophysiology of malnutrition is far from settled, and lately inflammation is a hot topic for discussion (5, 10, 11). The cause of malnutrition is also complicated by underlying diseases, which have led to definitions of disease specific malnutrition syndromes as cachexia (complex metabolic syndrome associated with underlying disease leading to loss of weight and muscle mass) (16), cancer cachexia (cancer related multifactorial malnutrition syndrome) (17), and sarcopenia (syndrome characterized by loss of muscle mass, primary or secondary to cause or disease) (18). In the ESPEN guidelines for definitions and terminology of clinical nutrition published in 2016 (2) a diagnoses tree of malnutrition was presented. The classification went from nutritional risk to a general

malnutrition diagnosis to etiology-based diagnoses. The organization of the etiology based diagnoses corresponds well with the International consensus guideline committee's proposal of etiology-based diagnoses as mentioned earlier (10, 11), and it seems like there is an emerging agreement on separating the starvation related undernutrition and disease related malnutrition with and without inflammation.

1.2 Nutritional risk screening

Due to the lack of internationally accepted malnutrition diagnosis and diagnostic criteria, nutritional risk screening tools are often used to identify malnutrition. The purpose of nutritional risk screening tools is to identify patients who have poor nutritional status (19) and where nutritional inadequacy cause clinical risk (9). The risk screening tool identifies those at nutritional risk who should receive nutritional treatment in order to avoid becoming malnourished or to prevent further deterioration of nutritional status and is thus an important preventive measure against malnutrition. The term nutritional risk is not specific as nutritional risk screening tools are developed with different purposes like prediction of outcome of surgery and other treatment, effect of nutritional treatment or reduced overall survival (2, 20). Some tools are developed based on a specific patient population, while others again claim a more general use (20). In addition, the assessments often include identification of both causes and outcome of malnutrition (5). Over the years, numerous risk screening tools have been developed, and patient population, age and purpose of the tool should be taken into consideration when choosing which instrument to use in the specific patient population (19, 20).

1.3 Prevalence

The lack of an internationally accepted consensus on the term and definition of malnutrition is reflected in the often inconclusive and inconsistent results of research on the subject and the widespread confusion (13). In addition the study population and the underlying diagnosis also affect prevalence (21). Due to the lack of consensus, studies presenting prevalence use various definitions on malnutrition. The definitions range from defining own criteria for malnutrition, to using risk screening tools or national criteria for malnutrition. The following paragraph represents the variety and wide ranges of prevalence that exists in the literature.

Prevalence ranges from 10-60 % in hospitals (21), others report 20-50 % depending on method, criteria and patient population (22). In Swiss hospitals, the prevalence of nutritional risk using Nutrition risk screening 2002 (NRS-2002) was reported to be 18.2%, with higher prevalence in elderly patients (23). A Norwegian survey from 1999 identified malnutrition in surgical patients by assessment of weight loss and BMI beyond certain cut-offs and found that 39 % of the patients were malnourished (24). A Norwegian survey using NRS-2002 showed an overall prevalence of nutritional risk of 29% (25), and the prevalence was higher in patients with infections, cancer and pulmonary diseases (26). Another Norwegian survey of non-demented hospitalized elderly (mean age 79.6 years) showed a nutritional risk prevalence of 45.4 % ranging from 20-60% depending on the hospital ward, this survey also used NRS-2002 as risk screening tool (27). A European survey identified 32.6 % of hospitalized patients as at nutritional risk by NRS-2002 (28). Another European survey showed similar results using NRS-2002 to assess nutritional risk, showing an over-all prevalence of 27 % (29). A review presenting prevalence of malnutrition in English hospitals and care homes showed a prevalence ranging from 11-45 % (30), depending on nutritional risk tool, hospital ward and age. An Australian publication reported malnutrition prevalence of around 40 % in Australia (31).

1.4 Causes of malnutrition

Even though there is progress within the field of malnutrition, the complete pathophysiology of malnutrition is still not fully understood (6, 22).

Malnutrition caused by starvation alone can be due to processes preventing the ingestion of food. Examples of such factors are access to food (famine and starvation), age, mental condition (e.g. presence of depression or psychological disease), anorexia nervosa, drug abuse, socioeconomic status and poverty (22, 31, 32). Mechanical or functional alterations of the digestive tract can also lead to malnutrition due to affected ingestion and absorption, or increased losses of the nutrients (10, 11, 21, 31, 32).

The most common cause of malnutrition in hospitalized patients is disease (21, 22). Insufficient food intake combined with inflammation is key mechanisms for the

understanding of the condition (10, 11). Reduced appetite often follows the inflammatory response to disease (10, 11), the psychological burden of disease or it can be a side effect of the treatment (22) and leads to reduced food intake. Mechanical or functional alterations of the digestive tract due to disease or treatment of disease (e.g. surgery) can affect ingestion and absorption of micro- and macro nutrients or lead to increased losses of these (4, 22, 32). In addition, many diseases increase or alter both the metabolism and requirements of specific nutrients in the body, and can also lead to increased resting energy expenditure (32, 33).

For hospitalized patients, both the psychological impact of being hospitalized as well as the change of meal routines and type of food can affect the appetite. Many medical procedures also require fasting, and thereby also interfere with food intake (34). In addition, medical treatment often has side effects affecting appetite and nutritional status (22)

1.5 Effects and Outcome

One of the first systematic trials on starvation was done in Minnesota during the Second World War by Ancel Keys. His research was the first in the field of understanding the mechanisms and effects of starvation on the body, and he also showed that nutrition affects the mind in addition to the physiological effects on the body (35) .

During starvation, the body induces a range of metabolic changes in order to handle the reduced intake of nutrients. The physiological response to fasting goes through several phases – from early fasting to long-term starvation, and through these phases different body stores are drained (36). While excess energy is stored as fat in the body, there exists no such storage for excess proteins, and all proteins in the body have a function (37). In the initial phase of starvation functional proteins are utilized, until depletion of the fat stores takes over. The use of fat spares the functional proteins who are essential for cellular function (37). The human body has dealt with starvation and periods with limited access to food throughout evolution, and has developed mechanisms to spare body protein (33, 37). When loss of weight is due to starvation alone, for examples as a consequence of reduced food intake, these ancient and effective mechanisms will commence. In this case, equal loss of organ mass in the body is seen, and protein loss is spared (6).

In disease-related malnutrition the rate of protein loss is increased as compared to the protein loss seen during starvation (38). The inflammatory response is strongly associated to the loss of lean body mass and muscle function as opposed to patients without inflammatory disease (38). In the case of weight loss due to disease, the loss of proteins in the body is not evenly distributed between the organs, depending on which organs is affected by the disease, in addition proteins are utilized as part of the immune defense and the net effect is loss of protein (6). Both starvation and disease related malnutrition will lead to weight loss. However, weight loss due to starvation will be reversed if food supply is reintroduced, while adequate food supply will not always be sufficient to reverse disease related malnutrition because the underlying cause of the weight loss is complex and not alone driven by the lack of food (17, 33, 38)

Because disease often is the cause of malnutrition in hospitalized patients, the analysis of the prognostic effect of malnutrition poses a great challenge as it is nearly impossible to distinguish between outcome of the malnutrition and outcome of the disease (22). Results of research done on malnutrition assessing prevalence, clinical outcome and effect of treatment are also completely dependent on the specific definition of malnutrition that is used (21). Nevertheless, the main adverse effects of weight loss and reduced nutritional status is impaired immune function, delayed wound healing, increased length of recovery from disease, loss of muscle mass, reduced physical function and subsequent increased economic costs (10, 11, 22, 31, 39). Loss of lean body mass and functional proteins leads to a reduced capacity of the body to handle additional stressors, and thus leads to increased morbidity, in addition to reduced quality of life (6).

Loss of muscle mass is emerging as an important factor in the understanding of malnutrition and its effects. It is increasingly seen as an important explanation for the malfunction that often follows malnutrition, e.g. reduced respiratory function (6). Fat free mass in muscle and organs represents the metabolic active tissue in the body, and therefore also plays a role in the tolerance to medical treatment and the presence of side effects (40). This is especially prominent in cancer patients receiving chemotherapy, where it is seen increasing toxicity with decreasing muscle mass and fat free mass (41, 42). Loss of fat free mass is associated to increased morbidity and mortality in patients with a range of chronic and acute diseases (40, 43). The loss of fat free mass or muscle mass increase morbidity and mortality both because

the reduced function in itself leads to physical weakness limiting everyday tasks, sense of independency and quality of life, but it is also clinically presented as increased vulnerability to infections and complications, reduced tolerance to treatment and poorer disease specific prognosis (40).

Loss of muscle mass is also increasingly important to identify in a world where obesity is an increasing problem (44), as extensive overweight can camouflage weight loss and loss of muscle mass. Overweigh and obese patients can suffer from malnutrition, low muscle mass and subsequent increased mortality and morbidity. This is described by Gioulbasanis, Martin (45) where more than 60 % of the overweight or obese patients with metastatic cancer were found to be at nutritional risk (using mini nutrition assessment (MNA) as nutritional risk screening tool) or malnourished. In several studies it is shown that many malnourished patients have a normal BMI, for example a Norwegian survey showed that 12 % and 11 % of overweight and obese patients respectively, were at nutritional risk according to NRS-2002 (26). The term sarcopenic obesity is used on patients with high BMI and low muscle mass, and has been shown to be detrimental in line with undernutrition (46). In cancer patients, loss of muscle mass in obese patients is associated with reduced survival and poorer prognosis (47).These patients are often overlooked by health care personnel because they seem to have extensive energy depots (45). Many of these patients are happy to lose weight after a lifetime on various diets, and therefore lack motivation for meeting their nutritional needs (48).

1.6 Body composition assessment

Body composition and loss of muscle mass can be assessed by numerous methods ranging from physical assessment (38) and assessment of hand grip strength (49) to more advanced methods as bioelectrical impedance analysis (BIA), dual energy x-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) (50-54).The most commonly available method in clinical practice is probably bioelectrical impedance analysis, while DXA is currently more available for research purposes (KILDE).

Bioelectrical impedance analysis (BIA) is an easy, non-invasive, relatively inexpensive and quick method for assessing body composition (50, 51, 55). BIA describes body composition at a two compartment level, and gives data on fat mass (FM) and fat free mass (FFM) (53). When performing the analysis, the body is regarded an electrical conductor, and the method is based on the principle that electrical resistance is different in different body compartments. An electrical current will always choose the line of least resistance. Because skeletal muscle mass in the body represents a large volume and have low resistance due to its high content of electrolytes, the skeletal muscle will be the main conductor of the electrical current. Opposite, fat and bone represent poor electrical conductors (50, 55-57).

When performing BIA, the body offers two types of resistance namely reactance Xc (arising in the cell membranes) and resistance R (extra- and intracellular fluid), both designated by the unit Ohm Ω (50). Based on the information on reactance and resistance from the BIA measurement, numerous equations are developed to estimate skeletal muscle mass (50, 51, 55). In addition, the newest BIA apparatus automatically converts the information from the raw data (resistance and reactance) to estimates of skeletal muscle mass and give this information directly on the outprints. Often the manufacturers will not release their equations. This will make the provided information specific for each manufacturer and apparatus and according to the software and equations used. If the equation included in the software is not validated for the population using it, an equation validated for the current population in regard to pathology or disease, age and ethnicity should be chosen (51).

DXA is an increasingly common, established and reliable method for assessing body composition and is considered quick, non-invasive and safe (58, 59). The method for assessing body composition using DXA is based on physics. A small dose of low-radiation x-ray is sent through the body and the attenuation of the radiation is different in the three body compartments bone, fat and lean body mass. DXA was originally developed to assess bone mineral content, but it was soon discovered to be a useful method for assessing body composition. The radiation dose is considered small and safe for repeated measures, and is comparable to less than one day's background radiation (58-61). DXA can analyze the body in regions of interest or the body as a whole. DXA can also provide information on fat mass and fat free mass.

In regards to the assessment of muscle mass and sarcopenia, appendicular skeletal muscle mass (ASM) assessed by DXA was recognized as a good indicator for skeletal muscle mass already early in the 1990s (62, 63). Appendicular skeletal muscle mass is the lean mass of both arms and legs reflecting the muscle mass of the extremities (62) ASM was later standardized for height squared (ASM/height $(m)^2$) giving the appendicular skeletal muscle mass index (ASMI) that is still used today (64). This index based on DXA measurements are commonly used for assessing sarcopenia (18, 65-67).

1.7 Risk groups

Hospitalized patients with acute illnesses like severe sepsis, burns and trauma, or chronic diseases like cancer, liver failure, chronic obstructive pulmonary disease (COPD), rheumatic disease are among the patient groups at high risk of developing malnutrition (3, 22). Cachexia is an eminent problem in chronic diseases, and the prevalence is estimated to be 35 % in COPD patients, 30 % in cancer (all types), 10 % of patients with rheumatoid arthritis and 50 of patients with chronic kidney disease (68). In a Norwegian hospital, the highest prevalence of nutritional risk as diagnosed by NRS-2002 was seen in patients with infection, cancer and pulmonary disease (26). Other risk groups are the elderly, children, patients with physical disabilities, drug addicted, people living under poor conditions and people affected of nature disasters, war or famine (10, 11, 22, 31).

In hospitals, malnutrition is frequently seen in cancer patients (69). Cancer patients are especially at risk of malnutrition due to the nature of the disease and its effect on the metabolism, in addition to side effects of treatment and psychological stress related to the disease (70). Deterioration of nutritional status and the weight loss seen in cancer patients are due to a complex metabolic syndrome and rarely owing to reduced food intake alone (70, 71). The location of the disease and the type of treatment also affects the malnutrition (72, 73), and malnutrition is often seen in patients with cancer in the gastro-intestinal (GI) tract, head and neck cancer and lung cancer (70, 74). A majority of patients have suffered great weight loss during their disease (75), and weight loss is an important indicator of malnutrition in cancer patients (76). In patient with esophageal, stomach or pancreatic cancer, 75 % was at high nutritional risk when using MUST as screening tool (76). A nutritional screening of 1000

outpatient cancer patients showed that 40 % of the patients had lost >10 % of their weight, and 34 % were at nutritional risk using NRS-2002 (72). A Spanish survey using NRS-2002 to assess nutritional risk in cancer patients, found an overall prevalence of 34 % at hospital admission (77). When assessing the subgroups, 50 % of patients with upper GI tumors, 45 % of pancreatic cancer and 40 % of the patients with cancer in the lower GI tract were at nutritional risk (77). Rizzi, Mazzuoli (78) showed a nutritional risk prevalence in patients with neoplastic disease at 57.1 % and a prevalence of undernutrition of 17.6 % when undernutrition was defined as involuntary WL > 10 % over the last 3-6 months. A survey of nutritional risk in cancer outpatients showed that 32 % was at nutritional risk using NRS-2002 (79).

Weight loss in cancer patients was recognized as a prognostic factor for morbidity and mortality in cancer patients already back in 1980 (73). Weight loss and reduced nutritional status in cancer patients are strongly associated with increased mortality and morbidity (80-82), and is also associated with increased length of hospital stay and increased economic costs (77). Recently a grading system for the association between weight loss and mean survival in cancer patients was developed (83). The grading system was shown to be robust independently of cancer type, stage and other more traditional prognostic factors (83).

Also in cancer patients, the loss of muscle mass is cause of many of the negative outcomes of malnutrition like a reduced physical function and increased mortality and morbidity (42, 69, 75). In a study off 55 metastatic breast cancer patients, low muscle mass was associated to increased toxicity and reduced time of tumor progression (84). Another study of 1473 cancer patients showed the loss of muscle mass, independently of BMI, was associated to a poorer prognosis (46).

1.8 Prevention and treatment

"When a sick person commits himself to the total, unquestioning care of his doctor, his nutritional health at least should be assured"((85) p. 4)

In his article from 1974 Charles E. Butterworth expressed his concerns regarding the presence of malnutrition in modern hospitals and the lack of proper attention on the problem (85). In spite of an enormous development and progress within the field of medical science over the last decades, the problem of malnutrition in hospitals is unfortunately still as relevant today as 40 years ago (39, 86).

In a Norwegian survey on hospitalized patients, only 53% of the patients identified as being at nutritional risk by NRS-2002, received active nutritional treatment and only 5 % was seen by a dietician (87). The survey was a point prevalence study repeated over a time frame of two years, and the proportion of patients receiving nutritional treatment did not increase during this time (87). A study among Scandinavian physicians and nurses showed that there was little agreement between the attitudes regarding nutritional assessment and treatment, and the concrete actions carried out (88). There was agreement across the countries that simple screening methods, nutrition support team, nutritional education, nutritional resources and use of guidelines would improve the clinical performance (88). Another study investigated the attitudes among oncologists toward nutritional treatment of cancer patients. This study revealed that even though the physicians recognized that nutritional status played a role in the outcome for the patients, they had problems identifying patients at risk, evaluating what constitutes a severe weight loss and in general reported lack of knowledge and difficulties in finding time for the nutritional assessment (89). In addition, nutritional guidelines were requested (89). A British study revealed that the proportion of patients with gastrointestinal cancer and weight loss that was referred to a dietician was unsatisfying; this was most prominent in the outpatients (90). Martin, de van der Schueren (74) wanted to investigate and find what prevents implementation of nutrition care in patients with head-, neck and esophageal cancer. The lack of evidence based guidelines founded on high quality research showing consistent results was sorely missed, the lack of knowledge on how to perform nutritional assessment and intervention, the role and attitude of health care personnel in regards to nutrition, a continuous presence of the dietician (or lack of so) and the patient characteristics were the main factors identified to affect the nutritional intervention. A focus group of health care personnel concluded that two main areas for improvement emerged, where the one was to further increase the quality and consistency of the evidence of nutritional intervention, and the second was to standardize implementation of nutritional care (74)

Unfortunately, there is a lack of strong evidence on the effect of nutritional intervention in the treatment of malnutrition. Repetitive comprehensive reviews on malnutrition show a large degree of heterogeneity in the research done and inconsistency in the results of nutritional intervention (91-94). A systematic literature review of dietary treatment of weight loss in cancer patients also showed disappointing results (95) . Nevertheless, new evidence is emerging continuously showing promising results of close and individually tailored dietary counseling in various patient groups (96-98). In colorectal cancer patients, there are shown improvements of nutritional outcomes, quality of life on a short term basis and improved long term prognosis in the patients receiving early and individually tailored nutritional intervention (96, 98).

When the cause of malnutrition is starvation, reintroduction of sufficient food intake will reverse the malnutrition. During reintroduction of food in these patients, one of the greatest concern is the risk of developing refeeding syndrome (99).

In the case of disease-associated malnutrition where inflammation is present, food intake will not treat the malnutrition completely (33, 38, 75). Even though reintroduction of adequate food intake alone is not sufficient to reverse malnutrition completely, insufficient food intake will lead to further deterioration of nutritional status (10, 11). In the lack of effective treatment of disease related malnutrition, the most important strategy, independently of the underlying disease, is early recognition of nutritional risk and prevention of malnutrition (33, 70). In malnutrition wasting syndromes, a multimodal treatment strategy aiming at effective treatment of the underlying disease and inflammation parallel with nutritional and anabolic treatment is currently the most promising option (100-102). Muscaritoli, Molfino (103) introduced the idea of a “parallel pathway” in cancer patients. The parallel pathway is a close nutritional follow up parallel with medical treatment from the early onset of disease, and with close cooperation between health care personnel. This principle can also be adapted to other chronic diseases as well. The purpose of the close follow up is early identification and correction of declining nutritional status. In this way the onset of nutritional deterioration and malnutrition can be prevented or delayed (103). This principle corresponds well to the method used in previously mentioned studies by Ravasco’s showing successful results (69, 96, 98)

To sum up, given the inconsistent and inconclusive evidence currently accessible, the most important actions regarding nutritional therapy is early identification and nutritional assessment followed by close, tailored and disease specific nutritional treatment aiming at meeting the nutritional need parallel with disease specific medical treatment (21, 104). In addition, dieticians should promote the use of currently existing evidence based guidelines by ESPEN, ASPEN and national guidelines in order to make sure that all patients receive the same treatment.

1.9 The need for agreement

Through the previous sections various aspects on malnutrition have been discussed and the current status of the condition is briefly presented. There are many gaps to fill when it comes to malnutrition. The most apparent and fundamentally important need to meet is the need for a unified definition of malnutrition and the diagnostic criteria. This is needed in order to be able to correctly identify malnutrition, to be able to predict severity of the condition and prognosis and to be able to give the right and best nutritional treatment. Documentation and registration is important for statistical purpose like prevalence and for economic refund as this is often based on diagnosis code, but also in the purpose of the communication between health care personnel about the nutritional treatment of the patient. An internationally accepted definition of the condition is fundamental also in order do good research that is necessary for moving the field of nutrition forward (3, 13, 105).

1.10 Diagnostic criteria for malnutrition - An ESPEN consensus statement

As mentioned in **section 1.1**, the latest contribution for reaching consensus on the malnutrition criteria is the suggested diagnostic criteria for malnutrition by ESPEN(3). The new criteria were reached through a modified Delphi process. The group consisted of participants representing various fields within health care, namely medicine, surgery, intensive care, oncology and geriatrics (3).

These new criteria as presented by ESPEN are shown in **figure 1.** The consensus presents three criteria, where the first consists of low body mass index (BMI), and the second and the

third include a combination of weight loss (WL) and either low BMI or low fat free mass index (FFMI).

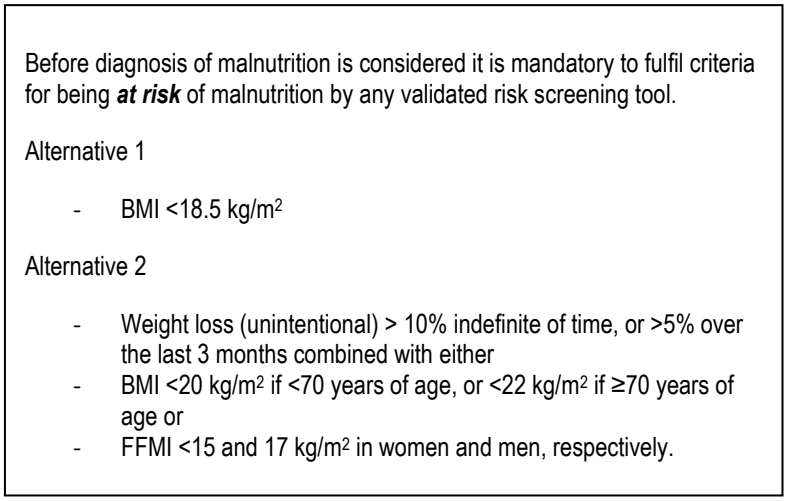


Figure 1 ESPEN malnutrition criteria, adapted from Cederholm et. al (3)

Fat free mass (FFM) represents the fat free compartment of the body and is also an indicator of the muscle mass of the body. Fat free mass index (FFMI) is the FFM normalized for height squared (m^2). By including FFMI in the new diagnostic criteria, the increasing recognition of muscle mass as an important prognostic factor for malnutrition-associated morbidity and mortality (see **section 1.5**) is acknowledged. As stated earlier (**section 1.5**), there exists a range of methods for the assessment of body composition. The most commonly available method in clinical practice is probably bioelectrical impedance analysis, while DXA is currently more available for research purposes.

So far only a few publications on the utility of the new ESPEN malnutrition criteria (EMC) have been published. Sanz-Paris, Gomez-Candela (106) assessed prevalence and clinical outcome, and showed increased length of hospital stay and increased mortality in malnourished patients as diagnosed by the EMC. Guerra, Fonseca (107) assessed the concurrent and predictive validity of the EMC in hospitalized patients. Concurrent validity was determined as compared to Patient-Generated Subjective Global Assessment (PG-SGA), where sensitivity of 17.1 % and specificity of 98.3% was shown. Malnutrition as diagnosed

by the EMC was also associated with lower risk of being discharged from the hospital (107). Sanchez-Rodriguez, Marco (108) and Rojer, Kruizenga (109) both reported prevalence of malnutrition in different populations as diagnosed by the EMC, and Sanchez-Rodriguez, Marco (108) also assessed the clinical relationship between malnutrition as diagnosed by the EMC and sarcopenia. The prevalence of malnutrition reported in these publications is presented in **table 1**. EMC have to our best knowledge not yet been compared to other diagnostic tools for malnutrition other than PG-SGA. PG-SGA is a nutrition assessment tool and not a diagnostic tool as such (110). Some of the mentioned publications assessed which of the three ESPEN malnutrition criteria were met, although this was not part of the main aim of the studies

Table 1 Publications using the ESPEN malnutrition criteria

Study	Study population		Method FFM	Nutrtional risk screening		Total Malnutrition	Espen criteria [a]		
		n		Tool	%[b]	%[b]	1 (%[b])	2a (%[b])	2b (%[b])
Sanchez-Rodriguez, Marco (108)	Post –acute care geriatric unit	88	BIA	MNA-SF	100	19.3	4.5	7.9	17.0
Rojer, Kruizenga (109)	Healthy young individuals	179	BIA	SNAQ[c]	0	0	0	0	0
	Healthy old individuals	306	BIA	SNAQ[c]	0.5	0.5	1	0	0
	Geriatric outpatients	135	BIA	SNAQ[c]	10	7	1	7	6
	Acutely ill middle aged patients	105	BIA	SNAQ[c]	30	14	6	9	13
Guerra, Fonseca (107)	Hospitalized patients	632	BIA	NRS-2002[d]	57.1	12.1	-	-	-
Sanz-Paris, Gomez-Candela (106)	Hospitalized geriatric diabetic patients	1014	NA	MNA-SF	37.4	6.7	4.9	9.2	-
Poulia, Klek (111)	Outpatients	784	NA	NRS-2002	13.5	6.4	-	-	-
	Hospitalized	362	NA	NRS-2002	27.9	11.3	-	-	-

FFM Fat Free Mass, BIA Bioelectrical impedance analysis, SNAQ short nutritional assessment questionnaire, MNA-SF Mini-Nutritional Assessment-Short Form, NA not assessed,

a) **1)** BMI <18,5 kg/m^2 **2a)** weight loss >10 % indefinite of time, or > 5% over the last month combined with BMI <20 kg/m^2 if < 70 years of age, or <22kg/m^2 if ≥ 70 years of age **2b)** weight loss >10 % indefinite of time, or > 5% over the last month combined with FFMI <15 and <17 kg/m^2 in women and men respectively (3).
b) % of total patient population
c) Rojer, Kruizenga (109) show prevalence of malnutrition independently of snaq tool result. Because after the study was performed, snaq was shown to be less valid in outpatients.
d) initial screening

The newly suggested ESPEN criteria clearly state that all patients need to be screened for nutritional risk prior to the malnutrition assessment. They also strongly request that nutritional risk should have its own ICD-10 code, to ensure early treatment of these patients and for economic purposes (3). The purpose of a nutritional screening tool and a malnutrition diagnostic tool is different and it is as ESPEN states, important to clearly distinguish between these. The first needs to be sensitive and has a preventive purpose, the patients are identified early so that prompt intervention can be implemented and malnutrition avoided or delayed, the second seeks to identify established malnutrition and needs to be more specific (3). Established malnutrition will need more intense treatment and will also likely have a worse prognostic outcome (3). If research does not differentiate between nutritional risk and malnutrition, the results will be inconsistent and inconclusive, as is evident from the research on the field as described in the previous sections. There is therefore a need for clear definition of malnutrition and nutritional risk in order to identify and distinguish between the two conditions, both in terms of research, prevalence and nutritional therapy. ESPEN has now suggested diagnostic criteria for malnutrition, these criteria has to the best of our knowledge not yet been evaluated against any other *diagnostic* tool for malnutrition or in cancer patients.

2 Objectives

The European society of clinical nutrition and metabolism (ESPEN) recently published a consensus statement for malnutrition criteria (3). After initially being identified as at nutritional risk, ESPEN suggests three alternative criteria for meeting the malnutrition diagnosis: low body mass index (BMI) (<18,5 kg/m^2) ***or*** a combination of unintentional weight loss (> 10% indefinite of time, or >5% over the last 3 months) and low BMI (<20 kg/m^2 if <70 years of age, or <22 kg/m^2 if ≥70 years of age) ***or*** a combination of weight loss and low fat free mass index (FFMI <15 and 17 kg/m2 in women and men, respectively).

Our aim was to **evaluate the newly suggested ESPEN malnutrition criteria** in light of the currently used criteria for malnutrition as presented in the National guidelines on prevention and treatment of malnutrition published by the Norwegian Directorate of Health (8) in an outpatient cancer population. Furthermore, we aimed to examine **which of the ESPEN criteria were met** by the patients diagnosed as malnourished according to these criteria and the potential overlap. Finally, we wished to examine **whether DXA or BIA as method for determining fat free mass index was critical for categorizing low FFMI.**

3 Subjects and methods

3.1 Study population

Potential participants were all patients over 18 years of age who were undergoing cancer treatment at the Division of cancer Medicine, Oslo University Hospital, and who were referred to The Nutrition Outpatient Clinic for nutrition counselling. According to The European Society of Clinical Nutrition and Metabolism (ESPEN) ((69)p.7) a cancer patient is a patient with a cancer diagnosis anywhere in the course of the cancer treatment; from diagnosis to treatment (curative or symptomatic) to follow up or palliative care. All participants were cancer patients by this definition.

Cancer was subdivided according to location into the categories head and neck (HN), Pancreas, gastro-intestinal tract (GI) or Others. Cancer in the GI tract included intestinal- and ventricular cancer, cancer in the esophagus, liver and bile tracts, and nevro-endocrine cancer originating in the intestines. HN-cancer included cancer in the nose, pharynx, tonsils, salivary glands, gingiva and tongue. The remaining patients who did not fall under any of the categories mentioned above, were categorized as Others, this included genital, breast, thymus and lung cancer, cancer in the central nervous system (CNS), lymphoma and malignant melanoma.

Criteria for exclusion were expected survival less than three months. Contraindications for using BIA and DXA were also considered exclusion criteria. Carrying electronic implants, e.g. cardiac pacemakers or active prostheses, and pregnancy are the contraindications for using BIA and DXA respectively.

3.2 Ethics

The Norwegian Regional Committees for Medical and Health Research Ethics (REC), region South East, considered the present project to be health service research, and therefore it did not fall under the committees' field of application **(appendix 1).** When research does not fall under the field of application of the REC, careful consideration must be done regarding

confidentiality. In this case the project has to be registered and approved by the commission for privacy protection, Oslo University Hospital. This registration was processed and approved (case number 2016/1087) **(appendix 2)**.

All patients participating in the project signed a written consent form (**appendix 3)**. Only staff and researchers bound by professional confidentiality had access to patient information. All personal information and sensitive data on forms and papers were deidentified. The key connecting identification number with the personal identification was kept locked separately from the data collection. All data were registered and processed using identification number only. The data collection consisted of forms and papers from each participant, and were organized in folders and kept locked when not used. Information about diagnosis, treatment and CRP were retrieved from the patient journal.

3.3 Recruitment and data collection

The outpatient nutrition care clinic offers nutritional counselling to patients at Oslo University Hospital after referral from their attending physician. Routinely before their consultation with the dietician, all patients coming to the clinic are first met by a nurse. The nurse performs a nutritional assessment using Patient-generated Subjective Global Assessment (PG-SGA) and assesses height, weight and performs bioelectrical impedance analysis (BIA).

Patients were recruited to the present study at the outpatient nutrition care clinic on the day of their scheduled appointment with the dietician. The dieticians working at the clinic were familiar with our study and the exclusion criteria, and assessed eligibility of their patients prior to the consultation. If the patients were considered eligible, one of the two master students carried out the initial assessment in the place of the nurse. Both students had undergone thorough training by the nurse. During the time set for the initial nutrition assessment, patients were assessed following normal routines in the clinic as described in the previous paragraph, in addition they were invited to participate in the study and were given oral and written information about the project. Independently of their participation in the project, the initial nutritional assessment and consultation with the dietitian was carried through as scheduled.

After the consultation with the dietician, patients who wished to participate in the study met directly with the master student again, signed the written consent form and the rest of the assessment was completed. The patients answered questions about background, social status, appetite, food intake and weight history, this assessment was performed as an interview. Body composition was assessed using DXA, and muscle function was assessed by hand grip strength and blood samples were taken. All information needed for both the malnutrition diagnostic tools and NRS-2002 screening was assessed during the interview and from the PG-SGA form. Diagnosis of malnutrition by the Norwegian malnutrition criteria and the ESPEN malnutrition criteria and nutritional risk by NRS-2002 was considered after the assessment of each patient. The methods will be described in further details in the following sections.

All the data needed from each patient were assessed on the same occasion, and no further encounters between the patient and researcher were necessary. The time used for the assessment after the consultation with the dietician ranged from 20 minutes to an hour, depending on the patient's condition and interest.

The data collection was performed by two master students who both used the same data material, but we had different objectives for our thesis.

3.4 Nutritional risk assessment

The ESPEN malnutrition criteria clearly state that patients need to be assessed for nutritional risk before assessment for malnutrition (3). The Norwegian National guidelines also emphasize the importance of nutritional risk screening (8). Therefore the purpose of the initial nutritional risk assessment in this project was to identify patients at nutritional risk who should be further assessed for malnutrition using the two sets of diagnostic criteria. PG-SGA is recommended for nutritional assessment in cancer patients, while NRS-2002 was chosen to represent a general screening tool recommended for hospitalized patients. The terms nutritional assessment and nutritional risk assessment tool is further used in the meaning of the initial assessment and screening of nutritional risk performed by PG-SGA and NRS-2002 respectively.

3.4.1 Patient-generated Subjective Global Assessment (PG-SGA)

PG-SGA was developed from the original Subjective Global Assessment (SGA) of nutritional status developed by Detsky in 1987, SGA was developed to assess nutritional status in an easy, non-invasive and standardized way (112). The main purpose of SGA and PG-SGA was to identify patients at risk of complications when hospitalized and who would benefit of nutritional intervention (110, 112). Outcome of subjective global assessment (SGA) and PG-SGA has been correlated to measures of morbidity (increased length of stay in hospital and increased risk of complications), quality of life and anthropometric measures as loss of body weight (110, 112-115). PG-SGA is an established and validated nutrition assessment tool (110, 114), recommended for nutritional assessment in various patient groups (8, 116) and in particular for the oncology patients (69, 110, 112-115, 117, 118) and in outpatient cancer patients (118).

The PG-SGA form used was a Norwegian translation (**appendix 4a and 4b**) and developed from Ottery (110) and Bauer, Capra (114). The Norwegian translation was carried out by Clinical Nutritionist and research fellow (PhD candidate) Hanna Ræder to be used in the Norwegian Dietary Guidelines and Colorectal Cancer Survival study (CRC-NORDIET study). The Norwegian translation is currently being validated.

PG-SGA contains two sections. Part 1 (**appendix 4a**) generates subjective information on weight, weight history, food intake, symptoms and activity level (ranging from normal to bedbound). In part 2 of the assessment, the patient is given a score for medical condition, metabolic stress (fever etc.) and for the physical examination. The physical examination observes loss of subcutaneous fat stores, muscle wasting and presence of edemas. Each of these traits is assessed and global fat-, muscle and fluid status are scored (110, 112, 119).

The PG-SGA was done according to the existing procedure at the clinic (**appendix 5**) and as described in the visual training manual downloaded from http://pt-global.org/ (120) . Patients filled out part 1 in the waiting room before the consultation. The clinical assessment of part 2 (**appendix 4b**) was carried out and scored by the clinician. The patients were classified as A (well nourished), B (moderately malnourished) or C (severely malnourished). Even though the scored PG-SGA was used, only the three categories and not the score were considered in

this project. The purpose of the PG-SGA in this current project was to categorize the patients for nutritional risk for further assessment of the malnutrition diagnosis. Category A was considered no nutritional risk, while category B and C were considered nutritional risk. To facilitate result analysis and to make comparisons, the three PG-SGA categories were converted into the two categories at nutritional risk and no nutritional risk.

3.4.2 Nutrition risk screening 2002 (NRS-2002) and NRS-2002 associated questionnaire

NRS-2002 was developed by Kondrup, Rasmussen (121) in cooperation with an ad hoc ESPEN working group (121). The main aim of this tool was to identify patients with severe illness, severe malnutrition or a combination of both, who would benefit from nutritional treatment (121) . NRS-2002 is now widely established and recommended by various guidelines and the Norwegian guidelines for use in hospitalized patients (8, 9, 19). Its predictive validity has been assessed both retrospectively and prospectively and reliability has been assessed and found applicable (122), and it is shown to be able to predict morbidity (19, 28). The four initial questions alone are also shown to predict morbidity and mortality (25). It has also recently been amongst the recommended nutritional risk screening tools in cancer patients (69). It is used for nutritional risk in cancer patients (79, 123) but it is to our knowledge not validated in a cancer population.

The nutrition risk screening tool NRS-2002 contains two parts, one initial and one main screening. If the answer is yes to any of the initial questions, the screening precedes to the main part. The initial questions concern BMI, weight loss, reduced food intake and serious illness. The second part of the risk screening gives a score based on the degree of weight loss, the extent of the reduction in food intake, the BMI, the severity of the disease and age. If the score is three or more, the patient is considered to be at nutritional risk. A risk score <3 is considered no risk (121). We used the NRS-2002 form as it is presented in the National guidelines on preventing and treatment of malnutrition ((8) p. 40-41), see **appendix 6**.

The NRS-2002 associated questionnaire (**appendix 7**) is a questionnaire developed by dieticians at Rikshospitalet, Oslo University hospital, as part of the training of nutrition students in how to do nutritional screening using NRS-2002. The questionnaire is used as an

aid to gather the information needed for the NRS-2002 main screening and includes questions regarding weight history (usual weight and involuntary weight loss), presence of edema, nutritional treatment and food intake. The questionnaire assesses usual pre-diagnostic body weight and the time frame for the total WL in months. In addition, the patients are also asked to answer yes or no on having experienced weight loss (WL) the previous 1, 3 and 6 months. Food intake is assessed by asking the patients to grade their food intake over the last week to "same amount eaten as normal (100%)", "more than half of normal (50-75 %)", "less than half (25-50 %)" and "less than a quarter of normal intake (0-25 %)". In the present study the NRS-2002 associated questionnaire was conducted as an interview by the researchers.

Because we consider cancer a severe illness, and because inflammation often is present early in the course of this disease (17, 69, 124), the answer of the fourth initial question of the NRS-2002 "is the patient severely ill?", was yes in all patients. The main screening was completed in all patients. Information on height, weight and BMI were obtained on the day of assessment. Information on WL was based on the information from the NRS-2002 associated questionnaire and percent WL was calculated as described in **section 3.6.3**. Regarding the food intake criteria, the information from the NRS-2002 associated questionnaire was used. Severity of the disease was considered based on the diagnosis and the patients general health condition, and presence of recent invasive treatment like surgery, chemotherapy etc.

3.5 Malnutrition diagnosis

Both malnutrition diagnostic criteria include the variables weight loss (WL) of various time frames and body mass index (BMI). In addition, the ESPEN malnutrition criteria include assessment of fat free mass (FFM) and the Norwegian criteria include food intake. In the following sections the two diagnostic tools will be presented, and the methods used for the assessment of the various variables will also be described in further detail.

When considering whether patients met the diagnostic criteria for malnutrition, measured values were not rounded up or down to meet the criteria or cut-offs. Total net WL in the given time frame of the criteria was considered independently of current weight trend or stabilization of WL.

The term diagnostic tool is further used about the Norwegian National criteria for malnutrition and the ESPEN criteria for malnutrition, and the diagnosis of malnutrition is used when patients meet these criteria.

3.5.1 National guidelines on prevention and treatment of malnutrition

The Norwegian Directorate of Health has published national guidelines on malnutrition with suggested criteria for the diagnosis with corresponding ICD-10 codes (8). These criteria are pesented in **figure 2** and will further be referred to as Norwegian ICD-10 criteria (ICD-10 NO). Of special interest is the interpretation of E46 as a nutritional risk group, while the original title according to WHO is unspecified protein- and energy malnutrition. The patients were assessed for malnutrition using the criteria as shown in **figure 2**. If they met any of the criteria listed, they were given the appropriate diagnosis.

Nutritional risk (corresponds to ICD-10 code E46)
One of the following categories:
- NRS 2002 score ≥3
- PG-SGA category B or C
- MUST score >1
- MNA score <11

Moderate undernutrition (corresponds to ICD-10 code E44)
At least *one* of the following criteria must be met:
- Involuntary weight loss >10% previous 3-6 months *or* >5 % previous 2 months
- BMI <18,5 kg/m^2 (> 70 years: BMI <22)
- BMI <20 (>70 years: BMI <22) and simultaneously involuntary weight loss >5% previous 6 months
- Food intake <50 % of estimated energy need

Severe undernutrition (corresponds to ICD-10 code E43)
At least *one* of the following criteria must be met:
- ≥ 15 % involuntary weight loss previous 3-6 months or >5 % involuntary weight loss previous month
- BMI < 16 (>70 years: BMI < 18,5)
- BMI < 18,5 (> 70 years: BMI < 20) and simultaneously involuntary weight loss >5 % previous 3 months
- Food intake < 25 % of estimated energy need

Figure 2 Norwegian malnutrition criteria with corresponding ICD-10 NO codes.

This diagnostic tool gives four alternative diagnoses: no malnutrition, nutritional risk (E.46), moderate undernutrition (E.44) and severe undernutrition (E.43). To facilitate analysis and comparison to the ESPEN criteria for malnutrition, being moderately- or severely malnourished were considered malnourished.

3.5.2 The European Society of Clinical Nutrition and Metabolism (ESPEN)

The patients were assessed for malnutrition using the diagnostic criteria for malnutrition suggested by The European Society of Clinical Nutrition and Metabolism (ESPEN) consensus statement (3).

As presented in **figure 1** there are three options for meeting these ESPEN consensus malnutrition criteria:
1) BMI <18,5 kg/m^2
2a) a combination of weight loss (WL) and low body mass index (BMI) or
2b) a combination of WL and low fat free mass index (FFMI).

Cut-offs for WL, BMI and FFMI are shown in **figure 1**. The ESPEN malnutrition criteria (EMC) will further be referred to as EMC, and the criteria will be referred to as criterion 1, 2a and 2b as described above.

The cut-off presented for FFMI is given in kg/m^2. The consensus statement lists various methods for measuring body composition, without specifying any preferred method. We used both BIA and DXA to estimate fat free mass (FFM), and FFMI was calculated as presented in **figure 3**. Both DXA and BIA give fat mass as a direct variable on the printout. When presenting results, unless otherwise specified, FFMI was assessed using DXA.

FFMI was calculated as follows with both BIA and DXA:

Fat Free Mass (kg) = Total Mass (kg) – Fat mass (kg)

Fat Free Mass Index = Fat Free Mass (kg)/height $(m)^2$

Figure 3 Calculation of fat free mass index (FFMI).

3.6 Anthropometry

3.6.1 Height and weight

Height was measured in a standing upright position using SECA 264 wireless stadiometer. Patients were asked to stand with feet close together and heels touching the back plate while standing up straight, with the back of the head touching the pillar of the apparatus and watching straight forward. Height was registered to the closest one decimal, 0,1 cm.

The scale used for bioelectrical impedance analysis (BIA), weighs the patient in addition to performing the body composition analysis. This was done using the Seca Body Composition Analyzer (BCA) 515 (Seca Birmingham, United Kingdom). The patients were weighed in light clothing and barefoot, and were asked to empty their pockets before the measurements. Body weight was registered to the nearest one decimal, 0,1 kg.

3.6.2 Body mass index

Body Mass Index (BMI) was calculated as body weight (kg)/height(m)^2. The Seca BCA 515 calculates BMI and this number was registered to the nearest one decimal.

BMI was divided into classes according to WHO classification underweight <18.5, normal weight 18.5-24.9, pre-obesity 25.0-29.9 and obesity >30 kg/m2 (125).

BMI <20 kg/m^2 (<70 years) and < 22 (>70 years) kg/m^2 were considered low (3, 8). These cut-offs were used in tables for descriptive purposes

3.6.3 Weight history

All patients were weighed on the day of the examination. Information about previous weight was obtained from part 1 of the PG-SGA form and from the NRS-2002 associated questionnaire. Both these forms have been described in detail in the previously (**section 3.4.1 and 3.4.2**). From these two forms it was possible to calculate percent WL over the last 1 and 6 months, in addition to total percent WL and the time frame for the total WL. Time span of the WL within 6 months was obtained from the question where they were asked to answer yes

or no to having experienced WL last over the last 1,3 and 6 months. If obvious inconsistency was seen in the self-reported weight, previous weight was found in medical journal. This was only done in one patient.

Percent weight loss (% WL) was calculated based on self-reported previous weight compared to the present measured weight on the day of assessment rounded to nearest whole kg. See **figure 4** for calculation.

%WL = ((self-reported previous weight (kg) – todays measured weight, rounded to nearest kg) x 100) / self-reported previous weight (kg)

Example: Patient used to weight 62 kg 1 month ago, measured weight 59,3 kg today.
((62 – 59) x 100) / 62 = 4,8 % WL during last month

WL Weight Loss,

Figure 4 Calculating % WL.

Ongoing WL was defined as all WL >0% over the last 1 month.

In the case of recent voluntary weight loss, the intentional weight loss was not considered when performing nutritional assessment. Both diagnostic criteria and PG-SGA clearly states *involuntary WL* in their criteria.

3.7 Body composition

3.7.1 Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (BIA) was performed using the Seca Body Composition Analyzer (mBCA) 515 (Seca Hamburg Germany). Software was Seca analytics 115. Version 1.4.505.5554. The Seca BCA 515 performs a 8-point analysis based on multiple frequencies and uses a measurement current of 100 µA .The measurement frequencies are: 1; 1.5; 2; 3; 5; 7.5; 10; 15; 20; 30; 50; 75; 100; 150; 200; 300; 500; 750; 1,000 kHz. The printout gives estimates on various factors, including fat mass (FM), fat free mass (FFM), fat mass index (FMI), fat free mass index (FFMI) and skeletal muscle mass (SMM) in arms, legs and torso.

The Seca BCA needs information on a range of factors before doing the analysis, information on height and weight was measured by the Seca BCA in the same sequence as the body composition analysis. Information on sex, age and ethnicity was added into the machine manually prior to the measurement. The Equation used by the software is not revealed by the manufacturer but it was developed using a four compartment model and dilution techniques as reference in 124 healthy Caucasian men and women aged 18-65 years, with a BMI of 18.5-35 kg/m^2 (126). The equation has also been validated in a multi-ethnic population of 130 men and women aged 18-65 years with a BMI of 19.8-33.7 kg/m^2 (126). Normal ranges for the measures of body composition were developed based on 1050 healthy adults aged 18-65 years (127). To be certain that the same equation was used on all patients the ethnicity was standardized to Caucasians on all participants.

The procedure for BIA measurement used at the Nutrition Outpatient Clinic was followed (**appendix 8).** The Seca BCA consists of a base platform with attached handrail. Patients were measured in a standing upright position. Electrodes for the feet are on the base platform, while hand electrodes are on the handrail. On the handrail there are three alternative spaces to place the hands in order to optimize the hand- and arm position. All patients were barefoot and in light clothing. They were asked to empty their pockets before the measurement. Feet without socks were placed with the forefoot on the front foot electrode, and the heel on the rear foot electrodes on the indicated areas on the base platform. Patients were asked to grasp the handrail, with the finger spacer between the middle finger and the ring finger. The middle set of hand electrodes were chosen in all patients. The electrodes were cleaned with alcohol swabs after use between each patient.

According to the user manual (128), the bioimpedance measurements should not be performed on persons with electronical implants (e.g. cardiac pacemakers) or active prostheses, neither on people connected to electronic life support systems or portable electronic medical devices. A safety setting ensuring that the subjects are not in any of the categories above appears on the screen of the Seca BCA 515 before starting the analysis. These questions were red out loud to the subjects by the person performing the measurement.

3.7.2 Dual energy x-ray absorptiometry (DXA)

Lunar iDXA encore version 16 (© GE Healthcare, Buckinghamshire, United Kingdom) was used for assessing body composition. Lunar iDXA (GE Healthcare) uses fan-beam technology with a 64-channel detector. The printout gives information on a range of factors including lean body mass (LBM) which is body mass without bone and fat, fat free mass (FFM), fat mass (FM), bone mineral content and ASMI (appendicular (muscle mass of arms and legs) skeletal muscle index).

Whole body scans were performed on all patients for assessing body composition, and the scanning of each subject was done according to the procedure routinely used at The Nutrition Outpatient Clinic (**appendix 9**). Patients were asked to remove all metal objects like watch, jewelry etc. before the scanning found place. They were also told to take of their shoes, and were given trousers without metallic zipper or buttons to change into. The subjects were placed lying down on their back and positioned within the lines indicated on the table, see **figure 5**. After the patient was placed on the bench, the clinician inspected from the top of the bench that the patient's body was straight, centered according to the center line and with equal proportions of the body on each side of the center line.

Subjects who were longer than the indicated area were placed with the head above the upper line, so that the feet were within the scanning area. Subjects wider than indicated by the lines were placed with the right side of the body within the indicated lines as shown in the right part of **figure 5**. In this case the half of the body within the scanning area was mirrored so that an estimate of the whole body was calculated by the machine. Four participants exceeded the indicated area of the scan table in length, and one patient in width.

Daily calibration of the scanner was performed with the manufacturer's spine and soft tissue phantom.

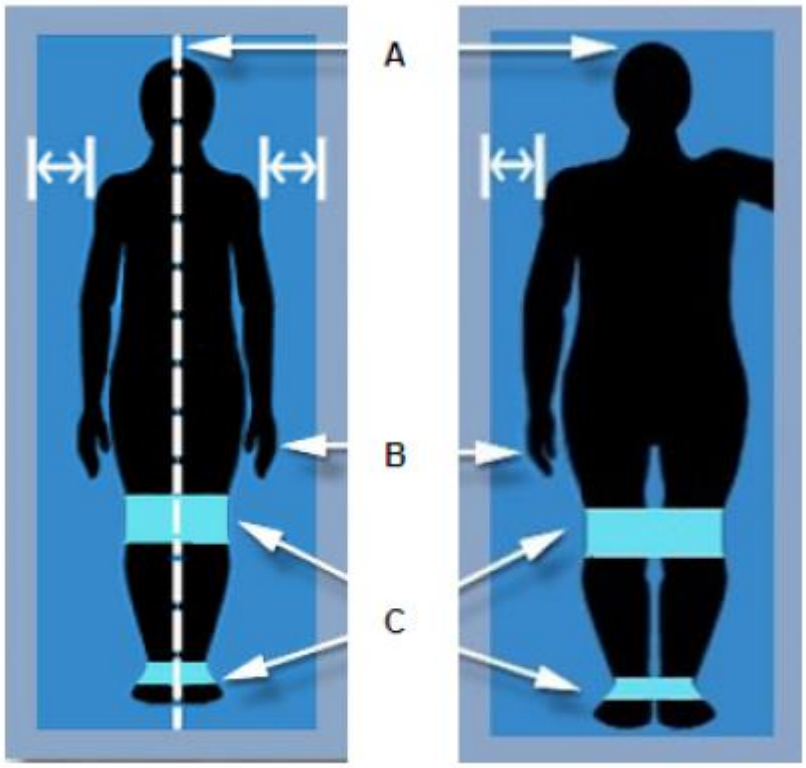


Figure 5 Body position during DXA scan

The figure is derived from manufacturer's user manual

A: Head should be placed about 3 cm below the upper line

B: Hands should be placed alongside the body, with a small gap between the body and the arms. Palm of the hand facing the thigh and thumbs pointing up.

C: Straps were attached around knees and feet to increase stability.

3.8 Other variables

In addition to the assessment of variables directly connected to the nutritional risk and malnutrition diagnostic criteria, other variables associated with malnutrition were also assessed in all patients. These variables were used for descriptive purposes in the results.

3.8.1 Hand grip strength

Hand grip strength (HGS) was assessed using Kern Map 80 K1 Hand grip dynamometer, a strain gage instrument. We used the standardized procedure for HGS measurement retrieved from The CRC-NORDIET study, see **appendix 10**. This procedure was followed in all patients. All values were noted, and the highest value in kg was registered with one decimal.

Hand grip strength <20 kg and <30 kg for women and men respectively, was considered low (18). All results of HGS presents max value, independently of left or right.

3.8.2 Blood sample

C-Reactive Protein (CRP)

The Ambulatory nutrition care clinic routinely takes blood samples of their patients, and blood sample for the project was performed according to the routines at the clinic and analyzed at the clinical laboratory at Oslo University hospital. The lowest detectable value of CRP is 0.6 mg/L, values below this was reported as <0.6mg/L.

Cut-off for sign of systemic inflammation was CRP >10 mg/L (69, 129, 130).

3.9 Statistics

All statistical analyses were performed using IBM SPSS Statistics version 22.
Significance level was set at p-value <0.05.

The term prevalence is used as defined by Fletcher, Fletcher (131).
Prevalence is "*the proportion of persons in a defined population at a given point in time having the condition in question."* ((131) p. 118).

3.9.1 Categorical variables

Categorical data was presented as number (n) and percent (%). Categorical variables was compared using contingency tables, and assessment of sensitivity, specificity and positive and negative predicative value were performed as shown in **figure 6** (132).

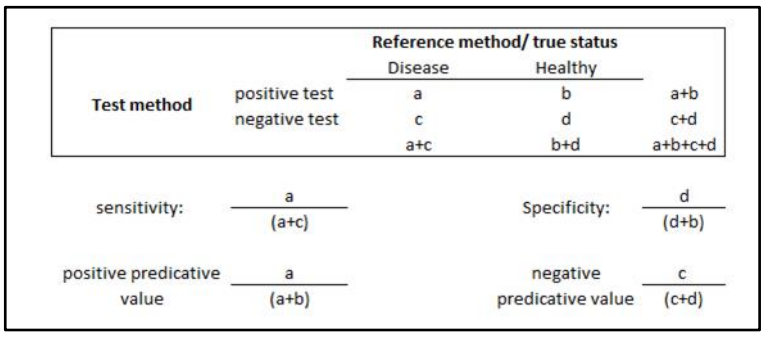


Figure 6 Calculation of sensitivity, specificity and positive and negative predicative value

There is a lack of consensus for the cut-off of acceptable sensitivity and specificity, therefore we used the cut-offs presented by van Bokhorst-de van der Schueren, Guaitoli (20) when evaluating the agreement. A sensitivity and specificity >80 % was considered *good*, sensitivity or specificity <80% but both > 50 % was considered *fair*, while sensitivity or specificity < 50 % was considered *poor* (20). Kappa values were also used to assess level of agreement between the classifications. Again, the cut-off values presented by van Bokhorst-de van der Schueren, Guaitoli (20) were used. Value 1 is considered *perfect agreement*, >0.6 were considered *good agreement*, 0.4-0.6 was considered *moderate agreement* and <0.4 *poor agreement*. These cut-offs also agree with those presented by others (20, 133, 134)

When analyzing agreement between the two diagnostic tools, the population consisted of those who initially had been identified as at nutritional risk.

Chi square test was used to compare proportions of two categorical variables in independent groups. This test assumes an expected frequency of >5 in 80 % of the cells. Where this assumption was not met, Fishers exact test was used (133, 135)

3.9.2 Continuous variables

Normality was assessed by considering the histogram, presence of non-significant Shapiro-Wilk test of normality (p-value >0,05) and normal Q-Q Plot. In cases where Shapiro-Wilk was borderline significant, visual inspection of the histogram was used for the final decision(133). Continuous variables showing normal distribution were described using mean and standard deviation. Continuous variables not showing normal distribution were presented using median and 25- and 75 percentiles (133).

When comparing normally distributed groups, t-tests were used. Independent samples t-test was used to compare mean values of continuous variables in two independent groups. Levene's test was used to assess equality of variances, significance level > 0.05 was assumed equal variance (133). Paired samples t-test was used to compare mean difference when different methods were used on the same patient population.

When comparing groups where normality was not seen, non-parametric methods were used. Mann-Whitney was used to compare two independent groups showing a non-normal distribution (133). For non-parametric comparison of more than two groups, Kruskal-Wallis was done, using Mann-Whitney U test post hoc to identify in which groups the significant difference was seen. The post hoc test was combined with Bonferroni adjustment of the p-value, dividing the significance level (p-value <0.05) by number of test intended to use (133).

4 Results

4.1 Study population

4.1.1 Subject characteristic and anthropometric measures

In total, 69 cancer patients participated in the current study. Of these, 27 (39.1%) were women and 42 (60.9%) were men. The patients had a mean age of 63 years, age ranging from 31-87 years. Subject characteristics are presented in **table 2.**

Mean hand grip strength (HGS) was 23.3 kg and 36.7 kg in women and men respectively, and 17 patients had low HGS. When it came to self-reported food intake, 30 (43.5 %) patients reported to eat less than normal, 7 of these patients reported to eat less than half as compared to normal intake.

Cancer in the GI tract was the most prevalent cancer form, seen in 26 (37.7 %) patients. Cancer pancreas and head and neck (HN) cancer were the second most common sites, with 15 (21.7%) and 13(18.8 %) patients in each of the groups, respectively.

Anthropometric measures are presented in **table 3**. FFMI was assessed both by BIA and DXA, and on a group level there were no significant differences in the mean values depending on the method. In women, however, paired samples t-test showed a statistically significant mean difference of 0.35 kg/m^2 between FFMI measured using BIA and by DXA, (p-value =0.009).

Table 2 Subject characteristics in all participating cancer patients (n= 69)

		value
Age, years	mean (SD)	62.6 (12.7)
	min-max	31.0-87.0
sex		
female	n (%)	27 (39.1)
male	n (%)	42 (60.9)
social status		
living alone	n (%)	23 (33.3)
living together	n (%)	46 (66.7)
smoker	n (%)	10 (14.5)
Snus [a)]	n (%)	2 (2.9)
Education [b)]		
Low	n (%)	29 (42.0)
Medium	n (%)	19 (27.5)
High	n (%)	21 (30.4)
Diagnosis		
HN	n (%)	13 (18.8)
Pancreas	n (%)	15 (21.7)
GI	n (%)	26 (37.7)
Others	n (%)	15 (21.7)
Treatment		
Surgery	n (%)	46 (66.7)
Chemotherapy	n (%)	38 (55.1)
Radiotherapy	n (%)	30 (43.5)
Self-reported food intake, as compared to normal intake [c)]		
100 %	n (%)	39 (56.5)
50-75 %	n (%)	15 (21.7)
50 %	n (%)	8 (11.6)
< 25 - 50 %	n (%)	7 (10.1)
HGS		
women	mean (SD)	23.3 (5.3)
men	mean (SD)	36.7 (7.2)
Low HGS [d)]	n (%)	17 (24.6)
CRP [e)]	median (25-75p)	1.6 (0.7-6.3)
Inflammation [f)]	n (%)	10 (14.5)

CRP C-reactive protein, GI cancer in the gastro intestinal tract, HGS Hand grip strength max value, HN cancer in the head and neck region, p percentile, SD Standard Deviation,
a) n=68
b) Low = elementary school, medium = high school to college. High = university degree or higher
c) Assessed by NRS-2002 associated questionnaire
d) HGS < 30 kg (men) and <20 kg (women) (18)
e) n=59
f) CRP >= 10 mg/L (129, 130)

Table 3 Anthropometric measures in the total population of cancer patients (n=69)

		All (n=69)			Female (n=27)			Male (n=42)		
		mean (SD)	**median (25-75p)**	**min - max**	**mean (SD)**	**median (25-75 p)**	**min - max**	**mean (SD)**	**median (25-75p)**	**min - max**
Height	cm	172.8 (7.8)	173.0 (167.0-179.0)	155.0-189.0	167.5 (6.1)	166.0 (164.0-171.5)	155.0-181.0	176.2 (6.9)	177.0 (171.0-181.0)	159.0-189.0
Weight [a)]	kg	70.5 (15.4)	68.3 (61.3-77.7)	42.8-135.7	63.6 (11.9)	62.8 (57.1-67.4)	42.8-95.8	75.0 (15.9)	70.6 (66.1-78.5)	49.6-135.7
BMI [a)]	kg/m^2	23.6 (4.1)	22.8 (20.8-25.1)	15.2-39.6	22.7 (4.2)	21.2 (20.5-24.8)	15.2-33.1	24.1 (4.0)	23.3 (21.6-25.9)	17.9-39.6
FFMI (DXA)	kg/m^2	16.6 (2.2)	16.7 (14.8-18.0)	12.9-24.2	14.9* (1.3)	14.6 (14.0-15.6)	12.9-17.5	17.7 (2.0)	17.6 (16.6-18.8)	13.3-24.2
FFMI (BIA)	kg/m^2	16.6 (2.5)	16.6 (14.5-18.0)	11.9-25.2	14.5*(1.5)	14.2 (13.5-15.2)	11.9-18.0	17.9 (2.1)	17.6 (16.7-19.1)	12.6-25.2

All variables are normally distributed unless stated otherwise. BIA Bioelectrical impedance analysis, BMI Body Mass Index, DXA Dual energy x-ray absorptiometry, FFMI Fat Free Mass Index, p percentile, SD Standard deviation

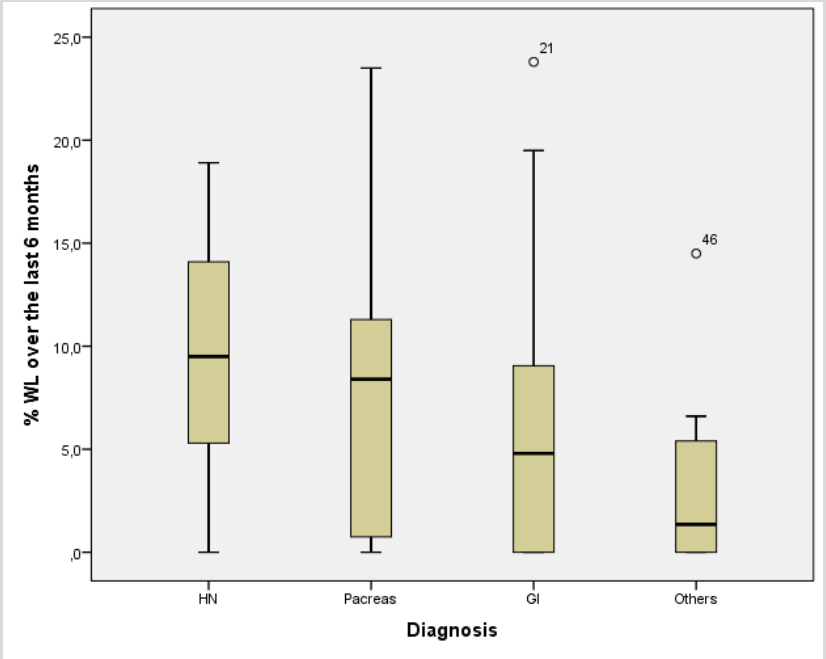
*p=0.009. Paired samples t-test showed significant difference in FFMI depending on assessment method. Mean difference (DXA-BIA): 0.35 kg/m^2

[a)] Not normal distribution in males due to presence of outlier

4.1.2 Weight loss history

Voluntary weight loss was reported in 4 of the 69 patients. When analyzing the remaining 65 patients, 53 (81.5 %) had lost weight during the disease and 25 (38.5%) patients had ongoing WL. The median (25-75p) percent WL over the last 1 month was 0.0 % (0,0-3,0), over the last six months was 5.3 % (0.0-10.0) and total WL was 6.3 % (1.5-12.2), minimum – maximum values in the three groups ranged from 0.0-14.9%, 0.0-23.8 % and 0.0-41.9 % respectively. The time frame for total WL showed a median of 5 months (4-12 months).

Figure 7 shows the % WL over the last six months when the groups were divided according to cancer diagnosis. The difference in median % WL among the groups was non-significant (p=0.11).



HN head- and neck cancer, GI cancer in the GI tract, WL weight loss

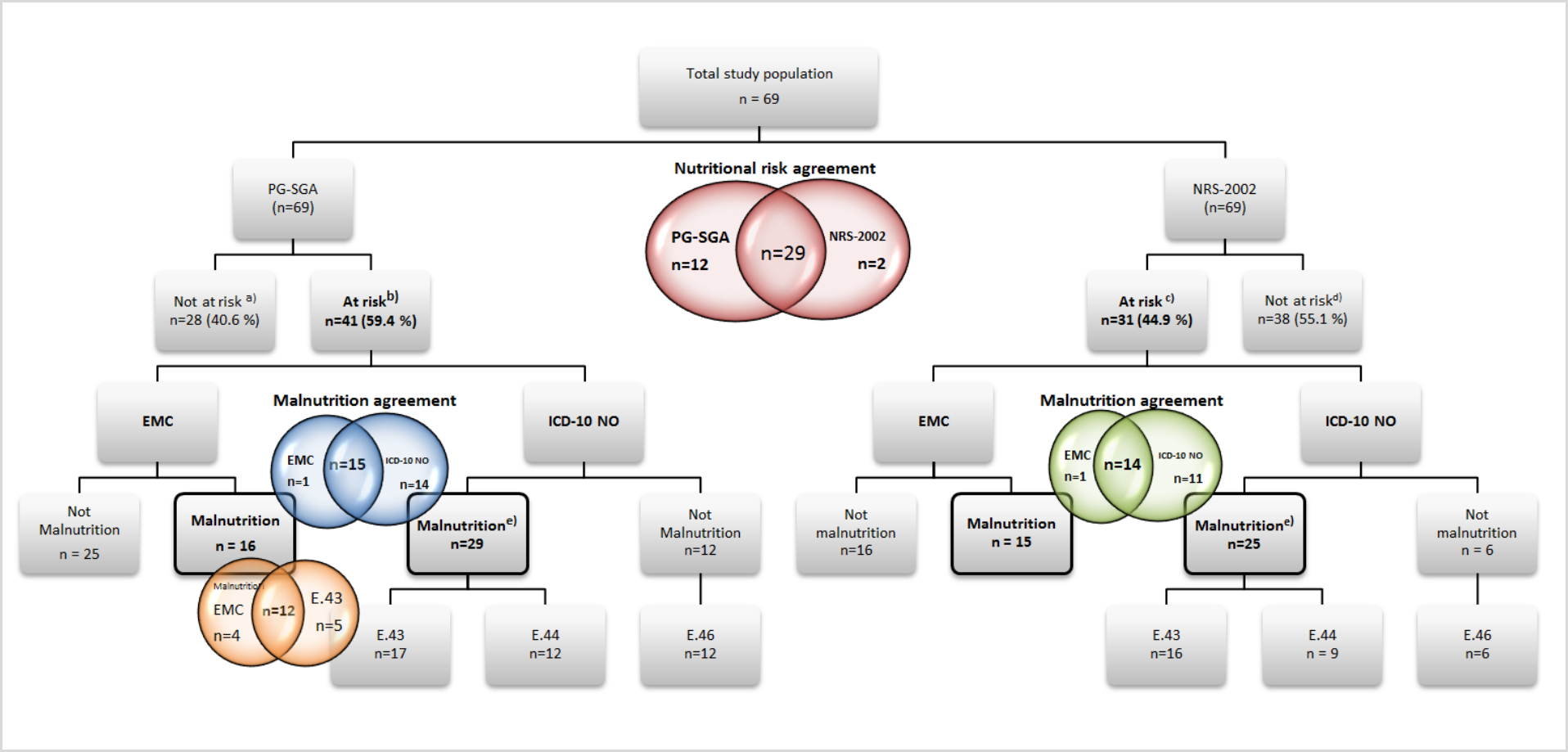
Figure 7 Percent weight loss over the last 6 months according to diagnosis

4.2 Results of nutritional risk assessment and assessment for malnutrition

The patients were assessed for nutritional risk using PG-SGA and NRS-2002, and diagnosed for malnutrition as defined by the ESPEN malnutrition criteria (EMC) and the ICD-10 NO criteria. **Figure 8** shows the results of the nutritional risk assessment and malnutrition assessment using two different assessment tools for nutritional risk and the two sets of diagnostic criteria for malnutrition.

When using PG-SGA as a nutritional risk assessment tool, 41 (59.4 %) of the patients were identified as being at nutritional risk, while 31 (44.9 %) were at nutritional risk using NRS-2002 for screening. When subdividing PG-SGA into its three categories, 28 (40.6 %) patients were in category A well-nourished, 33 (47.8 %) patients were in category B moderately malnourished and 8 (11.6%) patients were in category C severe malnourished.

Because PG-SGA is a validated assessment tool in cancer patients, this was used as initial assessment tool in all results further presented. When using ICD-10 NO as diagnostic tool, 29 patients (42.0 %) were malnourished, of these 12 (17.4%) were moderately malnourished, and 17 (24.6%) severely malnourished. When diagnosed according to the ESPEN malnutrition criteria (EMC), 16 patients (23.2%) were diagnosed as malnourished.



E.46 Nutritional risk category (ICD-10 NO), E.44 moderate malnutrition (ICD-10 NO), E.43 severe malnutrition (ICD-10 NO), EMC ESPEN Malnutrition Criteria, ICD-10 NO International classification of diseases version 10 Norwegian malnutrition criteria, NRS-2002 Nutrition risk screening 2002, PG-SGA Patient-generated Subjective Global Assessment,

a) PG-SGA category A
b) PG-SGA category B and C merged as at risk
c) NRS-2002 score ≥3
d) NRS-2002 score <3
e) ICD-10 categories moderate and severe malnutrition merged to malnutrition category

Figure 8 Flowchart of results showing nutritional risk assessment and subsequent malnutrition assessment. Overlap figure shows agreement between the methods. Area of the overlap figures is not proportional to numbers

4.3 Evaluation of the ESPEN malnutrition criteria in light of ICD-10 NO

4.3.1 Agreement between the methods

The blue overlap figure on the left branch of **figure 8** shows that 15 of the 16 patients categorized as malnourished as diagnosed by the ESPEN malnutrition criteria (EMC), were also identified as malnourished by ICD-10 NO. However, 14 patients were categorized as malnourished as diagnosed by ICD-10 NO, but not by the EMC.

The results of the sensitivity and specificity analysis between the two diagnostic tools and between the two nutritional risk assessment tools are shown in **table 4**. The EMC showed *fair* agreement as compared to ICD-10 NO. Only about half of the patients (15/29) diagnosed as malnourished according to ICD-10 NO were malnourished according to the EMC criteria, giving a sensitivity of 52%. On the other hand, 11 of the 12 patients categorized as not malnourished as diagnosed by ICD-10 NO were also categorized as not malnourished by the EMC, for a specificity of 92%. Of the total 16 patients diagnosed as malnourished by the EMC, 15 were also malnourished as diagnosed by the ICD-10 NO, giving a positive predictive value of 94%. Of the 25 patients categorized as not malnourished by ESPEN, 11 were not malnourished as diagnosed by ICD-10 NO, giving a negative predictive value of

Table 4 Agreement between the nutritional risk assessment tools in the total population (n=69) and between diagnostic tools after the patients were identified as at nutritional risk (n=41).

Reference method	Compared method	Kappa r (p-value)	Sensitivity %	Specificity %	PPV %	NPV %
PG-SGA[a)]	NRS-2002	0.60 (<0.001)	71	93	94	68
ICD-10 NO[b)]	EMC	0.33 (<0.001)	52	92	94	44
ICD-10 NO E.43[c)]	EMC	0.54 (<0.001)	71	83	75	80

E.43 severe malnutrition (ICD-10 NO), EMC Espen Malnutrition Criteria, ICD-10 NO International classification of diseases version 10 Norwegian malnutrition criteria , NPV Negative predictive value, NRS-2002 Nutrition risk screening 2002, PG-SGA Patient-generated Subjective Global Assessment, PPV positive predicative value, r kappa agreement value

a) PG-SGA category A equalize NRS-2002 no risk category, PG-SGA categories B and C merged and equalize a NRS-2002 score ≥3, at nutritional risk
b) Categories are merged to be comparable to the EMC. The ICD-10 NO categories E.44 moderate malnutrition and E.43 severe malnutrition was merged to equalize the EMC malnutrition category.
c) Only ICD-10 NO category E.43 (severely malnourished) was considered malnourished.

44% (131). The Kappa measure of agreement compares the two diagnostic tools for overall agreement, without assuming a reference or gold standard method. Kappa showed *poor* agreement.

At the lowest left branch of **Figure 8**, the number of patients categorized as malnourished by the EMC (n=16) corresponds well to the number of severely malnourished (E.43) according to the ICD-10 NO (n=17). **Table 4** shows that the sensitivity increased when only E.43 was considered malnourished in the analysis. Because both sensitivity and specificity were <80 %, the agreement was still considered *fair*. The kappa value increased from *poor* to *fair*. The orange overlap figure below the left branch shows that the agreement is not consistent, and 5 patients categorized as severely malnourished by ICD-10 NO were not so by EMC. Three patients that were not in the ICD-10 NO E.43 category were in the E.44 category and one was in the E.46 category.

When it comes to the two nutritional assessment tools, analysis of these were performed with PG-SGA regarded the reference method. Of the 41 patients recognized as at nutritional risk by PG-SGA, 29 were also categorized as at risk by NRS-2002, giving a sensitivity of 71%.

4.3.2 Disagreement between EMC and ICD-10 NO

In the blue overlap figure on the left branch of the flow chart (**figure 8**) it is shown that 14 patients are given the malnutrition diagnosis by ICD-10 NO only. One patient was recognized as malnourished only by the EMC.

The one patient categorized as malnourished by EMC and not by ICD-10 NO had a considerable WL exceeding the WL cut-off, combined with BMI below cut-off. This WL found place more than 1 year ago. ICD-10 has a maximum time frame of WL of 6 months.

Of the 14 patients only diagnosed as malnourished by ICD-10 NO, 9 (64.3%) were in the ICD-10 subcategory E.44, and 5 (35.7%) were in the severely malnourished ICD-10 subcategory E.43. Of these 14 patients, 12 (85.7%) had a weight loss of >5 % over the last 3 months or >10 % indefinite of time, and thus met the weight loss criteria of the second

alternative in the ESPEN malnutrition consensus statement. However, the lack of concurrent low BMI or low FFMI prevented these patients from meeting the ESPEN malnutrition criteria and being categorized as malnourished. Out of the 12 patients who met the ESPEN WL criteria, 6 (50.0 %) had a FFMI or BMI within one unit from cut-off. See **appendix 11** for further details on what criteria these 14 patients met when they were assessed by the two diagnostic tools. Test for sensitivity, specificity and kappa measure of agreement between ICD-10 NO and the EMC was done again when these six borderline patients were categorized as malnourished by the EMC. The sensitivity and specificity increased to 72% and 98% respectively which are still considered *fair* agreement, while kappa measure of agreement increased to 0.72 which is *good* agreement.

In **table 5** some factors often included in malnutrition assessment, like WL, BMI, food intake, muscle function and muscle mass (12) are compared between the 16 patients categorized as malnourished by ESPEN and the 14 only categorized as malnourished by ICD-10 NO. There was a great overlap between the patients identified as malnourished by ICD-10 NO and those identified as malnourished by the EMC. The 16 patients identified by the ESPEN malnutrition criteria also represent all the 15 patients where there was agreement between the methods.

When comparing the 14 patients only recognized as malnourished as diagnosed by ICD-10 NO with the 16 patients categorized as malnourished by the EMC, there were significant difference in WL over the last month, muscle mass (as indicated by FFMI) and BMI. All these three are factors included in the ESPEN malnutrition criteria. There were overall little difference in the rest of the describing factors, see **table 5.**

The patients categorized as malnourished by EMC had a significantly higher WL over the last 1 month than the patients only diagnosed as malnourished by ICD-10 NO. When investigating this further, looking again at 14 patients only diagnosed by ICD-10 NO, most of the patients had their WL over the last 2-6 months, only 3 had WL over the last month. There were more patients having ongoing WL in the malnourished patients as diagnosed by EMC, but the difference was not significant. **Table 5** also shows that all the 14 patients only recognized as malnourished by the ICD-10 NO criteria were in the normal and overweight BMI categories.

Table 5 Characteristics of the patients diagnosed as malnourished by ICD-10 NO (n=14) and the patients diagnosed as malnourished according to ESPEN consensus criteria (n=16). The 15 patients where there was agreement between the two diagnostic tools are also included in these 16 patients. Percent is presented by columns.

		Malnutrition only ICD-10 NO, not EMC (n=14)	EMC (and ICD-10 NO)[a] (n=16)	p-value[b]
Sex				
women	n (%)	4 (28.6)	6 (37.5)	0.71
men	n (%)	10 (71.4)	10 (62.5)	
Diagnosis				
ENT	n (%)	4 (28.6)	4 (25.0)	
Pancreas	n (%)	5 (35.7)	3 (18.8)	0.36
GI	n (%)	2 (14.3)	7 (43.8)	
Others	n (%)	3 (21.4)	2 (12.5)	
Treatment				
Surgery	n (%)	8 (57.1)	10 (62.5)	0.77
Chemotherapy	n (%)	8 (57.1)	10 (62.5)	0.77
Radiotherapy	n (%)	7 (50.0)	7 (43.8)	0.73
BMI				
<18.5	n (%)	0 (0.0)	3 (18.8)	0.23
18.5-24.9	n (%)	10 (71.4)	12 (75.0)	1.00
25-29.9	n (%)	4 (29)	1 (6.3)	0.16
BMI* **	mean (SD)	24.0 (2.1)	20.5 (2.7)	0.001
Low BMI [c]	n (%)	1 (7.1)	4 (25.0)	0.34
HGS				
women	mean (SD)	21.3 (1.4)	23.3 (8.2)	0.65
men	mean (SD)	36.0 (8.5)	32.2 (5.0)	0.24
Low HGS [d]	n (%)	4 (28.6)	6 (37.5)	0.71
Ongoing WL	n (%)	8 (57.1)	11 (68.8)	0.51
% WL over the last 1 month[e]*	median (25-75p)	1.5 (0.0-3.0)	6.2 (0.0-7.4)	0.03
> 5 %**	n (%)	3 (21.4)	11 (68.8)	0.01
% WL over the last 6 months[e]	median (25-75p)	11.0 (6.6-14.1)	10.0 (7.8-17.5)	0.67
> 15 %	n (%)	2 (14.3)	5 (31.3)	0.40
> 10 %	n (%)	7 (50.0)	8 (50.0)	1.00
FFMI DXA				
women	mean (SD)	15.6 (1.4)	13.7 (0.8)	0.19
Men***	mean (SD)	18.4 (0.8)	15.7 (1.2)	<0.001
Low FFMI [f]**	n (%)	1 (7.1)	15 (93.8)	<0.001
CRP [g]	median (25-75p)	2.1 (0.8-6.0)	2.4 (1.2-21.1)	0.50
Inflammation[g]	n (%)	3 (21.4)	4 (25.0)	1.0

BMI body max index, CRP c-reactive protein, DXA Dual Energy X-ray Absorptiometry, EMC Espen Malnutrtion Criteria, FMI Fat free mass index, HGS hand grip strengt max value, WL weight loss

* significant Mann Whitney U test, ** significant Chi square,*** significant independent samples t-test

a) FFMI assessed by DXA

b) independent samples t-test for normally distributed continuous variables, mann whitney u-test for non-normal contribution in continuous variables, chi-square in categorical variables, Fishers exact test when the assumption for chi square (of >5 patients in each cell) was not met in categorical variables

c) BMI <20 kg/m2 (if age <70 years) or BMI <22kg/m2 (if age >70 years) Cederholm, Bosaeus (3) Guttormsen and Helsedirektoratet Avdeling (8)

d) HGS < 30 kg (men) and <20 kg (women) Cruz-Jentoft, Baeyens (18)

e) Involuntary WL only

f) FFMI <17kg/m2 (men) and < 15 kg/m2 (women) Cederholm, Bosaeus (3)

g) n=28

h) CRP ≥ 10 mg/L Fearon, Voss (129) and Laird, Kaasa (130)

4.4 ESPEN diagnostic criteria for malnutrition

4.4.1 Criteria and overlap

After initial nutritional risk assessment with PG-SGA, 16 patients met one or more of the ESPEN malnutrition criteria and were diagnosed as malnourished. **Figure 9** shows proportions of the patients meeting each criterion. The figure shows that a majority of the patients met the criterion 2b, WL combined with low FFMI.

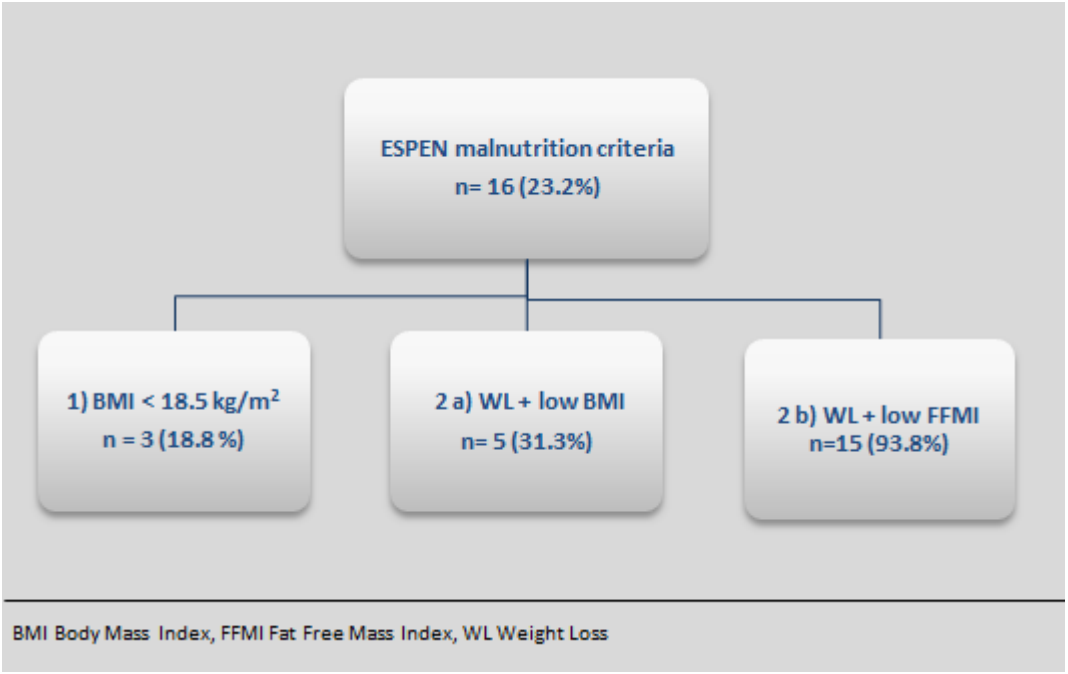


Figure 9 Proportion of patients meeting each of the ESPEN malnutrition criteria.

Further, several patients met more than one criterion simultaneously; this is presented in an overlap figure, **figure 10**. If method for assessment of FFMI had not been available, only 5 of the 16 (31.3%) patients would have been recognized as malnourished.

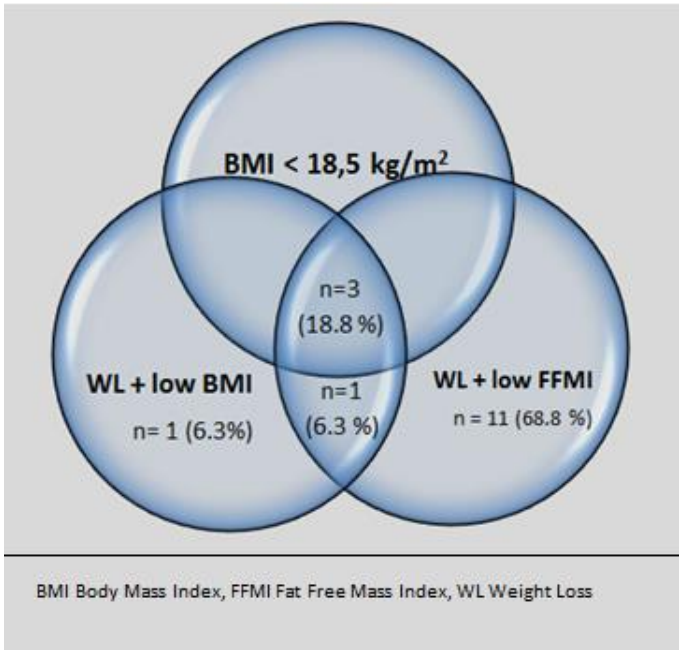


Figure 10 Overlap figure, ESPEN malnutrition criteria. The figure shows the proportion of patients meeting each of the ESPEN malnutrition criteria. Area of the overlap figures is not proportional to numbers.

4.4.2 FFMI assessment method

Of the 16 patients diagnosed with malnutrition according to the ESPEN criteria, 15 were recognized by criteria 2b) and assessment of FFMI. The assessment of FFMI was done by DXA (Lunar iDXA GE Healthcare) in all results presented. If BIA (Seca BCA 515) had been used to assess FFMI, 16 patients would have had a FFMI below cut off in combination with WL and thus met the ESPEN malnutrition criteria. **Figure 11** shows the agreement in patients meeting criteria 2b when BIA and DXA were used to assess FFMI. There was agreement between the methods in 14 patients.

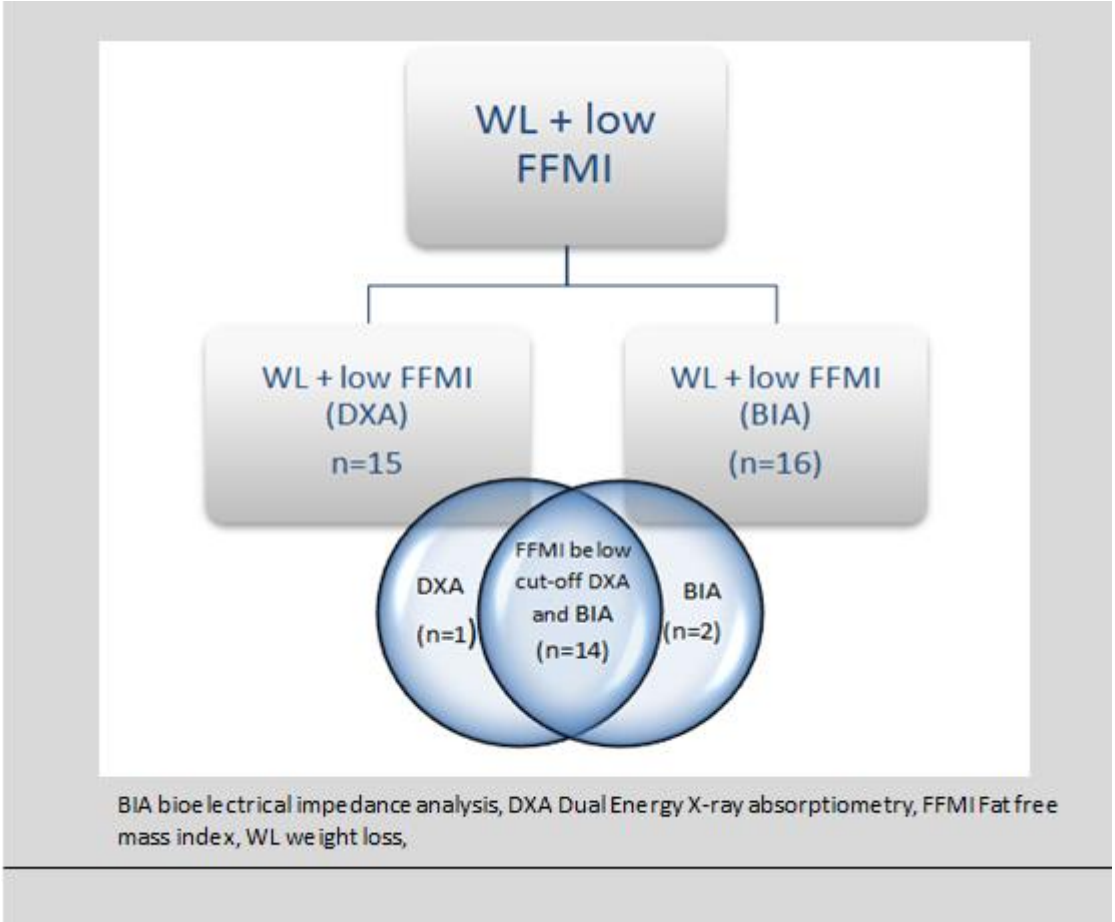


Figure 11 Overlap figure ESPEN malnutrition criterion 2b. The figure shows number of patients meeting the ESPEN malnutrition criteria 2b (unintentional weight loss >10 % indefinite of time or >5 % over the last 3 months combined with FFMI <15 and 17 kg/m2 in women and men respectively) when two different methods (BIA (Seca BCA 515) and DXA (Lunar iDXA GE Healthcare) are used to assess FFMI.

Table 6 shows that in the three cases where there were no agreement between the categorization of FFMI by BIA and DXA, the difference was marginal and the inconsistency was within one unit from the cut-off. This shows that in the patients diagnosed by the EMC, the method for assessing FFMI was not decisive for the outcome. This result only applies for the patients who met the EMC criteria.

Table 6 FFMI values, disagreement between the body composition assessment methods. The table shows absolute values of fat free mass index in the 3 patients where there was disagreement between the methods. BIA (Seca BCA 515)and DXA (Lunar iDXA GE Healthcare)

sex	cut-off FFMI[a)] kg/m^2	FFMI (DXA) kg/m^2	FFMI (BIA) kg/m^2
male	<17	16,9	17,6
male	<17	17,0	16,7
female	<15	15,7	14,5

Grey area indicates that FFMI cut-off (ECM)) were met.
FFMI Fat free mass index BIA bioelectrical impedance analysis,
DXA Dual Energy X-ray absorptiometry,

a) EMC FFMI cut-off

5 Discussion – Subjects and methods

5.1 Study population

A wide term was used to define cancer patients (69), leading to the inclusion of patients with a variety of different types of cancer and in all stages of the cancer disease from newly diagnosed to those receiving palliative care. This meant that their nutritional condition varied and that the cause of the malnutrition would differ from simple starvation to nutritional deterioration caused by the underlying disease and treatment. In cancer patients it is not always possible to distinguish between these causes and conditions, and therefore our group of patients represents the clinical reality of patient care. The heterogeneity of the group could be viewed as a weakness of this study due to the reasons just described, nevertheless, one of the purposes of the ESPEN malnutrition criteria is to be used independently of underlying disease.

Because prevalence of weight loss and malnutrition is high in cancer patients (136), this is an ideal group for studying malnutrition. On the other hand, the complexity of this diagnosis can complicate the malnutrition assessment. This could lead to an overestimation of malnutrition, because most likely other factors than nutritional intake affects the deterioration of nutritional status. A majority of the patients had experienced WL during the course of the disease or had ongoing WL. This corresponds well to other studies in cancer patients, where WL were reported in 40-90% of the patients investigated (73, 137, 138). The prevalence reported varied depending on the cancer type and stage, but was typically higher in patients with cancer in ENT, GI or pancreas (73, 137, 138). This corresponds well to the results presented in the present study, also showing a tendency of greater WL in these cancer groups. Almost half (43.5%) of the patients in our study reported reduced appetite as compared to normal intake. Anorexia and reduced food intake is often seen in cancer patients (136) and in malnutrition (32).

A total of 32 592 new cancer cases were reported in Norway in 2015 (139), with men having a slight majority of the cases (54 %). The lifetime cancer prevalence in Norway, meaning the number of people having had a cancer diagnosis during their life, at the end of 2014 was 252 997 people (139). Cancer caused 10 971 deaths in 2014, with cancer in lung, colon, prostate,

pancreas and breast causing the highest number of deaths (140, 141). The mean age of our patient group is 62.6 years, which corresponds well to Norwegian cancer statistics showing that a majority of patients with cancer are diagnosed after 50 years of age (140).The three most common types of cancer in Norway in men are prostate, lung and colon, and in women over 50 years are breast, colon and lung (139). Our patient group does not represent the most common causes of cancer in Norway, but represents types of cancer that are strongly associated to weight loss and nutritional challenges (70, 76, 77). The patients who are referred to the outpatient clinic are those who are expected to encounter or who already experience difficulties in meeting their nutritional need, and therefore consequently often are the patients with the types of cancer that affect nutritional status more.

When it comes to other factors reflecting nutritional status, hand grip strength (HGS) is an often used indicator for physical function (49). A comprehensive international study presenting reference values for HGS based on healthy adults in 21 countries showed a median HGS of 27 kg and 46 kg in women and men respectively, in the age group 51-60 years. In the age group 61-70 years, median HGS was 25kg and 42 kg respectively (49). Our patients had a mean hand grip strength (HGS) of 23.3 kg and 36.7 kg in women and men respectively, indicating a lower physical function compared to a healthy population.

5.2 Study design and statistics

5.2.1 Study design

The present project is of cross-sectional survey nature and all data on the study subjects was assessed at the same occasion. Cross-sectional surveys are sensitive for selection bias (142). Participation in the study, survival and length of survival can affect the outcome. Patients in the current study were recruited from an outpatient clinic and were all living at home at the time of the assessment. The reasons given for not wanting to participate in this survey was time restraints (n=7), lack of interest (n=2) and a majority did not have the energy and was tired due to the disease and the treatment (n=8). In addition the assessment of eligibility was based on subjective considerations made on the day of the assessment and on knowledge of the patients from earlier consultations. This indicates that the patients who participated were in better shape than the ones who declined the invitation.

The study was minimally invasive and the patients did not have to come back for follow-up or go through any intervention. The methods represent clinical reality which can be considered both a strength and a limitation, because it is less standardized but it is more related to reality.

The aim of this thesis was to evaluate the outcome when using two diagnostic tools for the assessment of malnutrition, even though the cancer complicates the reasons for the malnutrition, the diagnostic tools were used in the same patient group and thus this uncertainty affects both the diagnostic tools equally. In this way the results are not affected by differences between the study populations (20).

Because two master students did the assessment, there could be potential problem with interrater agreement. To avoid this, classification into nutritional risk category and malnutrition category by the various methods was standardized, criteria were red literally and all cases were discussed before giving the final nutritional diagnosis.

5.2.2 Statistics and data analysis

As discussed in the introduction, there exists no agreement on how to identify the true malnourished patients. A range of strategies and diagnostic criteria are suggested, but there are no consensus on what criteria to include and what cut-offs are the right ones. Even when using objective body composition assessment methods, there are no clear cut-offs. It all depends on the specific patient, their initial nutritional status and physical state, age, ethnicity, sex, the disease, stage and severity of the disease, treatment and so on. This affects our results, especially when comparing the two diagnostic tools. The Norwegian criteria for malnutrition (ICD-10 NO) has to our best knowledge not been validated as a whole, neither do we know anything about its prognostic value. Therefore these criteria are not superior to the ESPEN malnutrition criteria (EMC), even though they are more established clinically. Nevertheless, in the lack of a true gold standard, when analyzing sensitivity, specificity, PPV and NPV, ICD-10 NO was chosen as the reference method. One must also remember that a test method can never perform better than the reference method it is compared to, even if it in reality is a better test (131). Therefore, all these results must be interpreted with caution. ICD-10 NO is far from being a gold standard, and the analysis of sensitivity and specificity was done to identify the level of agreement and to identify the cause of disagreement. In addition,

kappa measure of agreement was also presented. This method assesses the level of agreement without stating superiority of the one method over the other.

The number of patients was also a limitation, of the 69 patients only 16 and 29 patients were recognized as malnourished by EMC and ICD-10 NO respectively, which limits the possibility to reach statistical significance even if a difference is present. Many of the factors like FFMI and HGS need to be divided according to sex, and the groups became small when they were compared. Therefore the main outcome of this thesis was to describe the outcome when using the EMC, and to understand and describe the agreement and causes for disagreement between the two diagnostic tools.

Because comparisons are made, it is challenging to stay neutral and not present the results as if ICD-10 NO is superior. It is not the purpose of this thesis to *compare* as such, but to present the differences that occur when using the two methods.

5.3 Methods

5.3.1 Anthropometry and weight history

Height and weight were measured using the same scale and according to a standardized procedure in all patients. The scales are calibrated annually by the manufacturer. The lack of standardization of time since last meal, void of urinary bladder could affect weight. Time of the day for measurement could affect both height and weight, and posture can affect height measurement.

When calculating percent WL based on self-reported previous weight, this includes a considerable degree of uncertainty. Self –reported previous weight is measured on the patient's own home scales, while today's weight was measured on our scale. There can often be substantial difference in measured weight depending on whether the same scale is used or not. Self-reported weight also includes uncertainty and is discussed in the literature (143, 144). Yet, it is still considered a valid and reliable method for assessment (145, 146). The accuracy of self-reported weight is also shown to depend on current BMI, weight changes, and cognitive status (147). Some of this uncertainty was accounted for when rounding to the

nearest whole kg when calculating the percent WL, but still these numbers are far from certain. The aim of assessing weight history was to be able to evaluate the trend of the weight development, and this purpose was as we saw it robust enough to handle some degree of inaccuracy. On the other hand, we had to be strict and read cut-offs of the diagnostic criteria literally, and a patient who had a WL of 9.5 % was not considered to have met the criteria that states >10 % WL. In this way the uncertainty around the method for assessing percent weight loss together with the strict understanding of the criteria, could have led to misclassification.

All patients having a WL > 0% during the last 1 month was considered to have ongoing WL. The number of patients with ongoing WL could be overestimated due to the low cut-off value for assessment of ongoing weight loss. Because there is no certain way to know whether a small WL is real or due to measurement uncertainty, and because it is important to detect WL early in cancer patients, this cut-off was chosen. The purpose of assessing ongoing WL was descriptive and did not affect the outcome of the diagnostic tools.

5.3.2 Hand grip strength

The instrument used for assessing hand grip strength could not be adjusted according to hand size. This could be beneficial for subjects with large hands who will get a better grip, compared to people with smaller hands. In addition, measuring hand grip strength in people suffering from arthrosis in their hand joints or other injuries, will affect the measurement. In this way, factors that are not related to muscle strength can affect the result of the measurement. Still hand grip strength is considered an indicator of general status, and being able to predict morbidity and mortality in general (49, 148), and also in cancer patients (149).

5.3.3 CRP

CRP is an unspecific indicator of systemic inflammation. An elevated CRP-value is not necessarily a sign of a cancer specific immune response. CRP values should therefore always be interpreted in light of the patient situation and general condition. A raised CRP together with WL in absence of clinical infection could be a sign of cachexia and cancer related WL (150). In the current study, the purpose of CRP was descriptive, and did not affect the outcome of the malnutrition assessment.

5.4 Body composition

5.4.1 Bioelectrical impedance analysis (BIA)

When performing BIA, the calculation of fat free mass and skeletal muscle mass is based on a tissue's ability to conduct an electric current, therefore abnormal hydration- and electrolyte status will affect the estimation (50, 51). In patients with diseases that affect this, BIA should be used with caution and after careful considerations.

In a review of the use of BIA in cancer patients, BIA showed large variability and a weak validity, and it was questioned whether this assessment method should be used in individual cancer patients (56). The lack of an established and generally accepted equation to use in cancer patients was one of the reasons for choosing to use the information from the Seca mBCA 515 output. Also, using the information on the printout is more representative for clinical reality. The mean age of our patient group is 62.6 years, and was in the upper range of the validation studies performed for the used equation. In addition the equation has not been validated in cancer patients.

In addition to stable hydration- and electrolyte balance and using an equation validated for the given population according to disease, sex, age and ethnicity, there is a range of factors known to influence the BIA measurement and should be standardized as far as possible. Ideally patients should be fasting, have an empty bladder and should not have exercised on the same day (51). When doing repeated BIA measurements to follow up a patient over time, conditions such as time of the day, body - and limb position and position of electrodes should be standardized in each measurement as far as possible (51). In our study we recruited patients continuously and BIA measurement was standardized as far as it was practically feasible as described in **section 3.7.1**.

In light of the lack of a validated equation for cancer patients, the lack of ideal standardization of the measurement and the possibility that cancer patients could have disturbed hydration status, the presented results of the BIA measurement must be interpreted with careful consideration, especially at an individual level.

5.4.2 Dual energy x-ray absorptiometry (DXA)

Even though DXA is considered a reliable method for assessment of body composition, its status as a gold standard for body composition has been questioned (151), and CT and MRI are the gold standards for measuring body composition (58, 59, 65). Nevertheless, DXA is considered the chosen method for clinical assessment of body composition (53, 59, 66) and is DXA also considered a reference method when validating BIA (50, 53).

Limitations of DXA lie in the assumptions on which the technique is based. For example, hydration status can affect the DXA accuracy because DXA makes assumptions regarding the hydration of FFM (152). Nevertheless the hydration can range from 68.2% to 78.2% without significantly altering the estimated fat mass therefore DXA is still considered robust in respect of hydration of lean body mass (153). However, presence of severe ascites, edema or other states of significant over-hydration can cause errors in the body composition estimates, this requires such a severe alteration in hydration that it in most clinical cases will not be a relevant (152).

Further, the accuracy of the measurement is based on factors like body size and thickness, body position on the table, calibration of the apparatus, the software and the manufacturer-dependent definition of region of interest (154, 155). Therefore manufacturer, choice of models within the same manufacturer, software updates and other factors will affect the reliability and comparability of results (58).

For the purpose of this study, DXA was seen as a robust method for assessment of body composition, and is the reference method for which BIA is compared against. Only one of our patients had visible low-grade ankle edema, the rest did not have noticeable edemas or ascites. Alterations in the hydration of the tissues caused by the disease and treatment could occur in cancer patients without being visibly noticeable. This could affect the accuracy of the DXA assessment. In regards of standardization of position on the table and calibration procedures based on manufacturer's instruction manual were strictly followed as described in **section 3.7.2**.

5.5 Nutritional risk assessment

5.5.1 Nutritional risk screening 2002 (NRS-2002)

As stated in the method (**section 3.4.2**), the purpose when making this screening tool was to identify patients who would benefit of nutritional intervention due to disease or established undernutrition in hospitalized patients (16). This implies that the decline in the nutritional state has commenced, and thus NRS-2002 may not be an ideal screening tool for cancer patients where a deterioration of nutritional status needs to be identified as early as possible. This is also the reason why PG-SGA is used in all main results presented. NRS-2002 was included to represent an often used screening tool in hospitalized patients.

In this study of cancer patients, we found the fourth of the initial questions "is the patient severely ill?" challenging. We chose, as explained in the method part, to say yes in all patients and proceed to the main screening. The intention of this question is to identify increased metabolic stress (9, 121). This issue is highly relevant in cancer patients, as the cancer often affects the metabolism of the patients and that inflammation often presents early (33, 70, 156), and could therefore not be ruled out during a screening process. This choice could lead to an overestimation of patients proceeding to the main screening.

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

In the present project, PG-SGA was used in the purpose of identifying nutritional risk. This is debatable as PG-SGA is a nutritional assessment tool (110, 114), it is a fairly extensive and time-consuming as compared to screening tools (20) and the staff performing the assessment needs to be trained (110, 157). Strictly, it categorizes patients into malnutrition categories, but it is called a assessment tool and not a diagnostic tool (110). The PG-SGA short form (PG-SGA SF) was developed because it was acknowledged that a full PG-SGA assessment can be too time- and resource (in form of health care personnel) consuming in large hospitals (118).

The reason for using PG-SGA as a nutritional risk assessment tool in this present study is because it is a widely recommended assessment tool in cancer patients (69, 110, 113-115, 117), and there is a lack of screening tools validated specifically for cancer patients (118), even though malnutrition screening tool (MST) has also been validated in cancer patients (158). The scored PG-SGA has been shown to be a quick and reliable assessment tool in cancer patients (114, 115), and has been correlated with worsened outcome like increased length of hospital stay, increased risk of complications, reduced quality of life etc. (110, 113-115). In addition PG-SGA has been regarded a screening tool by others despite its methodological drawbacks (159), and has been shown to be used for nutrition screening, assessment and outcome measures (158). Another argument of more practical nature is that at the Nutrition Outpatient Clinic where the data collection was performed, all patients are routinely assessed using PG-SGA before consultation with the dietician.

Among other the critics of PG-SGA are that its accuracy depends on the observers' experience. The researchers performing PG-SGA in the current project had no prior experience in using this tool. To meet this weakness, the researchers were therefore trained by an experienced nurse who also could be consulted through the whole study period. In a study on medical students learning to use PG-SGA, the experienced clinician and the newly trained students agreed upon what patients were not malnourished and what patients where malnourished, but the students showed difficulties in distinguishing between the moderately and severely malnourished compared to the clinician (160).

When only performing PG-SGA once, it is very hard to correctly score the physical assessment due to the lack of a basis of comparison. The patient could have been lean all its life, but categorized as being deficient by a clinician without having lost any muscle mass. On the other hand an athletic patient with an excessive muscle mass could be considered without deficiency despite a great loss because of the initial high muscle mass. Therefore communication and regular assessment is important. PG-SGA includes more factors than the physical examination in the total score, and therefore this weakness is not decisive for the final categorization of nutritional status.

Another weakness of the PG-SGA is the self-reported weight, when scoring percent WL. Methodological considerations on self-recorded weight are discussed previously (**section 5.3.1**).

5.6 Malnutrition diagnosis

Common for both of the diagnostic tools was that they did not specify how one should consider the current weight development. There were no descriptions on how to consider those cases where there had been a great net WL, but recent weight gain indicated an improved nutritional state. If patient A had lost 15 % body weight over a period of 6 months, but recently regained 4 %, patient A had a net WL of 11%. Nevertheless, the nutrition status of Patient A was improving. Patient B had lost 11 % body weight over the last 6 months and was still having an ongoing WL. Of these two patients, patient A was in a better nutritional state than patient B (112), but they both had the same net WL of 11%. Patient B would need urgent nutritional treatment to prevent further decline in his nutritional status. Patient A had suffered a considerable WL and would most likely still be fragile and at nutritional risk. He would still need follow-up. By definition they both met the criteria of > 10% WL over the last 6 months, but their nutritional status still differs.

Because one clinician's judgement will differ from another's, we chose to read the all criteria literal. This could affect the malnutrition diagnosis. Recent weight stabilization or weight gain, as exemplified with patient A in the previous section, was not considered as long as the net weight loss exceeded the cut-off. This meant that patients that clinically no longer were considered malnourished due to recent stabilization were categorized as malnourished because they met the cut-off. This could lead to an over estimation of patients meeting the WL criteria. This would affect ICD-10 NO most as WL alone meets the criteria. On the other hand, the strict interpretation of the criteria could also lead to an underestimation of patients meeting the FFMI cut-off, because patient with FFMI of 17.0 or 17.3 was not considered to have met the FFMI cut-off saying <17kg/m^2. Clinically these patients would probably have been considered to have met the criteria. This issue will be discussed further in relation to specific results.

The Norwegian National guidelines on prevention and treatment of malnutrition (8) were completed in 2009 and presented criteria for meeting the ICD-10 codes E.46, E.43 and E.44 (**figure 2**). These criteria are well established in the clinical practice of Norwegian dieticians and are also presented as part of the Clinical nutrition education program at University of Oslo. A weakness of the criteria is that, to our best knowledge, the ICD-10 NO criteria as a whole have not been validated and predictive validity has not been assessed. Another weakness is that the criteria are not international which can limit the generalizability of our results.

6 Discussion - Results

6.1 Nutritional status

PG-SGA identified 59.4 % of the patients at nutritional risk, and 44.9 % were identified as at nutritional risk using NRS-2002. Depending on the diagnostic criteria, 23.2 % and 42.0 % of all the patients were categorized as malnourished using the EMC and the ICD-10 NO criteria respectively. This shows us that in a heterogenic group of cancer patients, the nutrition risk prevalence and malnutrition prevalence are high, and the prevalence depends on what nutritional assessment tool and malnutrition criteria are used. The proportions of patients being malnourished and at nutritional risk in this project correspond well with the prevalence ranges that exist in the literature as mentioned in the introduction under **section 1.3** and **1.7**. Most studies are done in hospitalized patients, but a study on 1453 outpatient cancer patients used NRS-2002 to assess nutritional risk and showed a nutritional risk prevalence of 32% (79). These patients had various cancer diagnoses, with a majority having cancer in the stomach, colon and lung (79). In our study malnutrition and nutritional risk are assessed in the same population and still the inconsistency is prominent, this underscores the problem of doing research on malnutrition and the need of universal agreement on the diagnosis and diagnostic criteria for malnutrition.

It is outside the scope of this study to do a thorough discussion of the results of the nutritional risk assessment. Still, the inconsistency seen between the nutritional risk assessment tools is worth to mention. Because PG-SGA is a validated nutrition assessment tool in cancer patients (69, 110, 114), this was used in all results presented. In cancer patients it is important that the assessment tool is sensitive so that any signs of deterioration of nutrition status are identified early and nutritional intervention is started as soon as possible (150, 161, 162). In **section 5.5.2,** the use of PG-SGA for the initial nutritional risk assessment was discussed. Among the arguments discussed is that PG-SGA is more extensive than a screening tool and it has also been suggested that both SGA and PG-SGA are not sensitive enough to be used as screening tools (157, 159, 163). It is therefore interesting to note that PG-SGA identified more patients than NRS-2002 in this current study. The sensitivity and specificity analysis showed *fair* agreement of NRS-2002 as compared to PG-SGA. The kappa value of agreement showed *fair* to *good* agreement between the methods. NRS-2002 was developed to identify hospitalized

patients with severe illness, who are malnourished or have a degree of both illness and undernutrition and who would benefit from nutritional support (121). When using the ICD-10 NO criteria, 81 % of the patients identified by NRS-2002 were identified as malnourished (**figure 8**). This could indicate that in cancer patients, NRS-2002 is better at diagnosing more established malnutrition. This is in agreement of the purpose of this diagnostic tool and suggests that NRS-2002 might not be sufficiently sensitive in cancer patients. In line with our results, another study in patients with cancer in the head and neck region showed similar sensitivity of NRS-2002 as compared to PG-SGA (123). This study concluded that in cancer patients, a NRS-cut off of ≥3 was better at recognizing patients with established malnutrition, and suggested a cut off ≥2 was more appropriate and more sensitive in cancer patients (123). Another study comparing NRS-2002 and SGA in hospitalized patients also showed inconsistency between the two methods, with 28 % of the patients at nutritional risk according to NRS-2002, while 39 % were at risk (SGA B or C) when using SGA (164). Both nutritional tools predicted mortality, but NRS-2002 was a stronger predictor than SGA (164), again this agrees with this tool being less sensitive and better at identifying established malnutrition. Another study in patients with advanced colorectal cancer presented opposite results, with NRS-2002 identifying more patients that PG-SGA (165).

To conclude, our results clearly illustrates that the prevalence of malnutrition and nutritional risk is dependent on the assessment tools and criteria used. This underlines the importance of using nutritional assessment and screening tools validated for the specific patient population, and that the purpose of the tool and what variables it assesses, should also be considered when choosing a nutritional risk screening- or assessment tool. The inconsistency in the results also highlights the need for an international agreement upon diagnostic criteria for malnutrition.

6.2 Evaluation of the ESPEN criteria for malnutrition in the light of ICD-10 NO

When it comes to malnutrition, one of the main challenges is that there exists no gold standard for the assessment (2, 3, 12, 20, 166). When interpreting the results on sensitivity, specificity, PPV and NPV presented here it is important to keep in mind that when doing these analyses, the test method can never be better than the reference standard it is compared

agains, even if it in reality is a better method (131). We do not know whether the reference method (ICD-10 NO) identifies the true malnourished patients. The use of ICD-10 NO as a reference method in our analyses has been discussed previously (**section 5.2.2 and 5.6**). The *fair* sensitivity of the ECM as compared to ICD-10 NO means that fewer patients were identified as malnourished by the EMC than by ICD-10 NO. We cannot for sure say whether ICD-10 NO identifies too many patients as malnourished or whether ESPEN identifies too few. On the other hand, the high specificity means that we can be fairly certain that the patients identified as malnourished by the EMC, are malnourished as diagnosed by the ICD-10 NO. A high specificity goes at the expense of sensitivity, meaning that some cases will be missed (131). The clinical consequences of a misdiagnosis must be taken into consideration when assessing this. Because ESPEN clearly states that all patients must be screened for nutritional risk before considering diagnosis, patients that are misclassified will still be identified as at nutritional risk and hopefully receive nutritional treatment. It is more crucial for a nutritional risk screening tool to be sensitive than a diagnostic tool, because the patients who are missed by a screening tool will not receive the required treatment.

The kappa value tells us about the agreement without assuming that the one method is superior to the other. The kappa value of agreement between the ICD-10 NO and the EMC in our study was low and shows us that the overall agreement was poor.

The sensitivity of the ECM as compared to ICD-10 NO increased to 71 %, but the specificity decreased to 83 % when comparing only the severely malnourished patients (E.43) as diagnosed by ICD-10 to the malnourished as diagnosed by EMC. Kappa value of agreement also increased to 0.54, which is moderate. This could indicate that there is a small tendency for the EMC to identify the more severely malnourished patients according to ICD-10 NO, but this tendency is inconsistent as showed by the low sensitivity and also seen in the orange overlap figure.

Of the 16 patients categorized as malnourished by the ESPEN malnutrition criteria, 15 were also identified as malnourished by ICD-10 NO. In that sense it was a great overlap between the two diagnostic criteria. ICD-10 NO identified 14 additional patients as malnourished.

There was statistical significant difference in WL over the last 1 month, FFMI and BMI between the 14 patients only recognized as malnourished by the ICD-10 NO and the 16 patients malnourished as diagnosed with EMC (also representing the 15 patients where there was agreement). All these factors are included in, and thus reflect, the diagnostic criteria of the ESPEN malnutrition diagnosis. To be categorized as malnourished by the EMC, BMI or FFMI have to be low, concurrent with weight loss (WL). Therefore it is to be expected that in the group that did not meet the EMC, BMI and FFMI is above the cut-off. The difference in the time aspect of WL is interesting, but the finding is inconclusive on whether it is because the EMC identified early WL better, or because of the methodological concerns that will be mentioned in the next section. Other factors that are associated with malnutrition like appetite, HGS and inflammation showed no difference between the groups. Note that the numbers are small, especially in the groups divided according to sex.

It is rather apparent from reading the ESPEN criteria that WL alone is not sufficient for meeting the diagnosis, as the combination of WL together with either low FFMI or low BMI is needed to be diagnosed as malnourished (3). However, this does not necessarily have to mean that fewer patients would be identified as malnourished; this depends on the FFMI and BMI cut-off. It could be possible that a severe WL in most patients would result in BMI or FFMI under cut-off, and therefore most patients with severe WL would be identified as malnourished. However, our results show that quite a few patients with a considerable WL were not diagnosed as malnourished by the EMC. Of the 14 patients only recognized as malnourished by ICD-10 NO, 12 met the WL criteria of the second alternative of the EMC, but did not have concurrent low BMI or FFMI. Two methodological factors need to be taken into consideration when looking at these numbers. First, 6 of the 12 patients who met the ESPEN WL criterion had a BMI or FFMI 0.1-1.0 units away from cut-off. If we had been less strict on reading the cut-off literally, these patients would have been diagnosed as malnourished according to the EMC based on the WL criterion being met, and FFMI/BMI being so close to the cut-off. When this was tested and the 6 patients were categorized as malnourished by EMC, sensitivity, specificity and kappa value increased substantially. This could indicate that our method of reading the criteria strictly led to an underestimation of patients being diagnosed as malnourished by the EMC as compared to how they would have been diagnosed in clinical reality, and thus increased the disagreement between ICD-10 NO and EMC. Nevertheless, six patients with considerable WL were still not categorized as

malnourished according to the EMC because of lack of concurrent low BMI or FFMI. Secondly, when considering if the WL criteria were met, only total net WL within the given timeframe was considered. Among the 14 patients only recognized by ICD-10 NO, the main timeframe for WL was 2-6 months. This could indicate that some of these patients had recent weight stabilization over the last weeks or month, but due to total net WL they still met the malnutrition criteria. In a clinical reality, the recent weight stabilization would most likely have been taken into consideration and the patient would maybe not have been considered malnourished anymore. This could lead to an overestimation of patients being categorized as malnourished by the ICD-10 NO. These two methodological concerns could lead to an overestimation of the disagreement between the methods.

Weight loss (WL) has long been recognized as an indicator of loss of energy- and protein depots (110, 112, 167), increased surgical risk (168) and a key indicator of malnutrition (3, 8, 12, 33, 169). The ICD-10 NO WL criteria (**figure 2**) agrees with other WL cut-offs for severe malnutrition, e.g. both Academy/ASPEN consensus (12) and PG-SGA(114) categorize a WL >5 % in 1 month and > 10 % WL in 6 months as severe WL.WL exceeding these cutoffs are also shown to be associated with increased surgical risk (168), general morbidity and mortality (170, 171) and malnutrition in cancer patients (169). The question is whether a considerable WL alone is sufficient to be an indicator of malnutrition or not, which is currently, to our best knowledge, without consensus.

Severe weight loss alone is not considered sufficient to meet the ESPEN malnutrition criteria in absence of low BMI or low FFMI. In a letter to editor correspondence this issue was addressed (172, 173), exemplified with a patient with an 8 % WL over the last month. This patient was not categorized as malnourished despite the WL, due to the lack of concurrent low FFMI or low BMI. Cederholm (172) argues that this patient was still early in his disease trajectory and that a FFMI and BMI above cut-off suggest that he still has energy- and muscle depots. It was stated that this patients is clearly at nutritional risk and needs nutritional intervention, but he is not yet malnourished. Another reader of the ESPEN consensus on malnutrition also questioned this matter in a letter to the editor by Lacrosse et.al (174). In a group of 24 patients with a NRS-2002 score of ≥3 and an average WL of 15 %, none of the patients where categorized as malnourished by the ESPEN criteria. This was due to an average BMI of 25,9 kg/m^2 and no option for body composition assessment (174). Cederholm

(175) argues that the BMI over cut-off reflects good energy stores, but again he underscores that the patient is at obvious nutritional risk and should receive nutritional treatment . The type of treatment for the patients at risk and the malnourished patients was not specified. In both these replies a great confidence that values over the chosen cut-offs indicates good energy- and protein stores, even in the presence of great WL, is expressed (172, 175). In the publication of the ESPEN malnutrition criteria, the chose cut-off for BMI in combination with WL was reached through consensus in the groups, while the cut-off for FFMI was based on one Swiss publication presenting reference values for FFMI and FMI in a study of 5635 women and men (3). It was emphasized that reference values should be relevant for ethnic variations (3). Strong clinical evidence that values above these cut-offs indicate good energy- and protein stores are missed. Our results showed that the two alternative criteria of alternative 2 in the EMC was shown to not identify equal proportions of patients as malnourished, indicating that the chosen cut-offs for BMI and FFMI are questionable. In the following sections the chosen FFMI cut-off is also discussed.

The aim of the ESPEN malnutrition criteria is to offer a general malnutrition definition that can be used independently of etiology (3). In the consensus statement ESPEN seeks to be able to identify:

> *..simple, clear and generally applicable diagnostic criteria of malnutrition in the sense of energy and protein store depletion. The intention was to provide criteria that are independent from etiologic mechanisms, and that can be used for all patients and in all clinical settings.((3) p. 336)*

WL is a sign of malnutrition independently of etiology, but the underlying cause will differ. Therefore to include severe weight loss as its own criterion for the malnutrition diagnosis could correspond well to their aim of a general applicability.

To conclude, there was inconsistent agreement between the patients diagnosed as malnourished by ICD-10 NO and by the EMC. Methodological factors could have influenced and overestimated the disagreement. The categorization of patients 0.1-1.0 units above the cut-offs for FFMI and BMI as malnourished by the EMC, lead to an increased agreement between the two diagnostic tools. Also considering only the severely malnourished patients as

diagnosed by the ICD-10 NO when comparing the two diagnostic tools increased sensitivity, but at the expense of specificity. Our evidence suggests that a number of patients did not fall below the cut-off of BMI and FFMI in spite of a considerable weight loss and therefore were not identified as malnourished by the EMC. A review of the existing evidence and a consensus is needed to decide whether WL alone should be sufficient to get a diagnosis of malnutrition, and also to settle the cut-off for such WL. Of clinical importance is also the treatment of nutritional risk and malnutrition and whether this will differ between the two conditions.

6.3 ESPEN consensus criteria for malnutrition

6.3.1 Meeting the criteria and overlap

The work group presenting the EMC (3) recognized that it was not realistic to assume that all clinics have access to equipment for measuring body composition, therefore measurement of FFMI was not mandatory, and WL in combination with BMI was presented as alternative for meeting the malnutrition diagnosis. In the absence of body composition assessment, the malnutrition diagnosis is based only on BMI, either alone or in combination with WL. If the two criteria in alternative 2 of the EMC were true equals, this would not be a problem, as the same patients ideally should have been identified. What our results show, in agreement with others (108, 109), are that the majority of patients is recognized as malnourished based on the criterion of WL combined with low FFMI. Therefore, when FFMI cannot be assessed, two things happen: First, the remaining factor for the malnutrition diagnosis is BMI (either alone or in combination with WL) and secondly fewer patients are recognized as malnourished.

The ESPEN malnutrition criteria have just recently been published, and only a few studies assessing these criteria have been issued, see **table 1**. Only two of these studies presented what criteria were met, but in line with our results they showed that most of the patients were recognized by the criteria including WL and low FFMI. Two of the studies presented overlap figures, and there was a great overlap in criteria 2a and 2b, but criteria 2b identified an additional portion (108, 109). The only population where the number of patients recognized with criteria 2a and 2b were more similar was in the geriatric outpatients group and also here

showing a great overlap (109). This could indicate that the average BMI in the population plays a role, and that criteria 2a and 2b shows greater agreement in populations with a low average BMI, like in an elderly geriatric outpatient population. The remaining studies said nothing about the overlap in meeting the criteria.

BMI is a controversial indicator of nutritional status and various BMI cut-offs are suggested to identify malnutrition (83, 176). BMI says nothing about body composition, and body composition is increasingly recognized for its role in predicting morbidity and mortality and also plays an increasingly important role in the assessment of malnutrition (60, 177). Even in patients with stable weight and BMI, loss or deficiency of muscle mass can still occur (178, 179). Obese patients can have low muscle mass and thereby increased morbidity and mortality despite their high BMI (46, 47). On the other hand, it has also been shown that high BMI predicts increased survival and an advantage in chronic diseases, the so-called obesity paradox (180, 181), but it seems like body composition is key for understanding this phenomenon (182, 183). Therefore, even though a higher BMI indicates energy stores, both hospitalized patients and cancer patients with a normal or high BMI can still be at nutritional risk or have worsened prognosis (12, 26, 45, 184). A study on the use of BMI for assessment of nutritional status in heart failure patients concluded that BMI was not an appropriate variable in this patient group mainly because BMI lacks sensitivity for the fluid retention and loss of muscle mass often seen in this patient group (185). In addition, overweight and obesity is an increasing problem in the world (44, 186), which further complicate the utility of BMI as a cut-off for malnutrition.

In a before mentioned letter to the editor by Lacrosse et.al (174) (**section 6.2)** the concern of using the EMC when body composition cannot be assessed was addressed. Cederholm (175) acknowledges that loss of protein stores can also have found place in patients with BMI within the normal ranges. It is recognized that in the absence of body composition assessment the malnutrition diagnosis as described by the EMC will be hard to apply and will be limited to BMI and fewer patients will be diagnosed (175). It is recommended that simpler measures of protein stores like hand grip strength or arm muscle circumference could be considered in the absence of body composition assessment (175).

Another consideration regarding BMI as a criterion for the malnutrition diagnosis, is that BMI is included in a majority of screening tools. The logic of having a malnutrition diagnostic tool that in practice is only based on BMI, and therefore assess the same factor as the screening tool, is questioned (5).

To conclude, in absence of body composition assessment, the EMC is only based on BMI, either alone or in combination with WL. This itself could be unfortunate as BMI is a controversial indicator of nutritional status. Our results showed, in agreement with other recent publications, that the criterion including low FFMI identifies more patients than the criteria including BMI. In clinical practice assessment of body composition is far from routine practice.

6.3.2 Assessment of Fat Free Mass Index

In the present study, assessment of FFMI by BIA (Seca mBCA 515) and DXA (Luar iDXA GE Healthcare) for deciding which patients fell below the FFMI cut-off in the EMC gave similar results. In the whole population, assessment of FFMI by BIA and DXA also showed agreement. When separating the group according to sex, among women there was a significant difference in FFMI depending on the method for assessment, with BIA slightly underestimating FFMI as compared to DXA. Bearing in mind that FFMI is an index, the difference is bigger than it seems. Still the difference was not of clinical importance for the intended use in the current study. An underestimation of FFMI by BIA as compared to DXA would lead to more patients being below the FFMI cut-off, and thus we would most likely not miss any patients by using this method. Bioelectric impedance spectroscopy (BIS) is shown to underestimate FFM as compared to DXA in cancer patient (187), while others studies have showed that BIA estimation of skeletal muscle mass correlates well with DXA in hospitalized elderly patients, although it depends on the equation used (188). Others again show that BIA overestimated FFM as compared with DXA in healthy adults (189), and in healthy young adults (190). In these results presented, bioelectrical impedance analysis is done on various scales from diverse manufacturers. Nevertheless, this wide variation of results shows that when using BIA in hospitalized patients, there is need for knowledge concerning the various equations, witch population the equation is validated for, technical qualities of the specific manufacturer and the built-in equation. In addition there is need for knowledge on what

factors can affect the measurement, and witch of these factors are present in the specific patient population (50, 51).

The FFMI cut-off given in the EMC has been discussed (106, 108, 109) because the cut off in women corresponds to the 25 percentile and the cut-off in men corresponds to the 10 percentile in the Swiss reference population it is referred to (191). On the other hand, this publication (191) also presented FFMI for various BMI classes, and a BMI of 18.5 corresponds to a FFMI of 16.7 and 14.6 in men and women respectively. These latter FFMI values correspond better to the FFMI cut-offs presented in the EMC. This shows that in theory, the FFMI cut-off of criterion 2b corresponds with the BMI cut-off of criteria 2a. As shown in our results, unfortunately criteria 2a and 2b do not seem to equalize each other in practice. That the cut-off for women corresponds to the 25 percentile could lead to more women than men being identified as malnourished. In our study more men than women were diagnosed as malnourished, 65.5 % and 62.5 % of the malnourished patients were men as diagnosed by ICD-10 NO and the EMC respectively. This could also reflect the study population where 60.9 % was men.

While the EMC only presents a cut of for fat free mass, DXA measurement provides more details. In regards to the assessment of muscle mass and sarcopenia, appendicular skeletal muscle mass (ASM) assessed by DXA was recognized as a good indicator skeletal muscle mass already early in the 1990s (62, 63). Appendicular skeletal muscle mass is the lean mass of both arms and legs reflecting the muscle mass of the extremities (62). Baumgartner et.al (64) standardized ASM for height squared, and developed the appendicular skeletal muscle mass index (ASMI) that is still used today (ASMI = ASM/height $(m)^2$). This index based on DXA measurements are commonly used for assessing sarcopenia (18, 65-67).
An often used cut-off for low muscle mass when assessing skeletal muscle mass using DXA in cancer patients (17, 69) and general for sarcopenia (18) is ASMI <7.26 kg/m^2 for men and <5.45 kg/m^2 for women first presented by Baumgartner (64) in 1998. This cut-off is later cited repeatedly; by Cruz-Jentoft et.al (18) in Age and Ageing in 2010, by Fearon et.al (17) in The Lancet in 2011 and latest by Arends et.al (69) in 2016 in Clinical Nutrition. The study by Baumgartner et.al (64) is an epidemiologic study of sarcopenia among elderly in New Mexico. The cut-off for sarcopenia used by Baumgartner et.al (64) in this publication was again based on another study, the *Rosetta Study* by Gallagher et.al (192) published in 1997.

Subjects in this study were 148 women and 136 men of Caucasian and African-American ethnicity. Both the two publications discuss the representativeness of the population on which the cut-off is based, because it small, not randomly selected and rather arbitrarily chosen (64, 192). This indicates that even if a cut-off is often cited in the literature, it could still need an update. Finding, considering and presenting method-specific cut-offs is a great task, but on the other hand it would be greatly valued by clinicians. Often one cut-off is not representative for all patients, and ideally the cut-off should be specific for sex, age, ethnicity, method, specific producer (and version) etc. (13). Bosy-Westphal and Muller (179) present interesting insights when choosing a definition for loss of skeletal muscle mass, while Coin et.al (193) in their study showed the various outcomes when using different cut-offs and definitions for low muscle mass. This points out the existing confusion regarding the cut-off for low muscle mass, and why it is challenging for clinicians to figure out on their own. Therefore, reviews of the existing evidence, further research and agreement are needed, and will be much valued by clinicians who can finally use this information in practice.

All methods have different advantages, and method-specific cut-offs would provide a higher accuracy according to the specific method. Method specific cut-offs would also be beneficial because body composition assessment varies according to the clinical situation, in cancer patients for example, CT scans are routinely done to establish the stage of the cancer (5, 46). Therefore a cut-off based on this method could increase the utility of the EMC.

To conclude, assessment of FFMI by BIA (Seca mBCA 515) and DXA (Lunar iDXA GE Healthcare) gave similar results. Nevertheless there is room for further refinement of the suggested FFMI cut-off. In addition, method-specific cut-offs would be valued. This would contribute to a more accurate variable according to the specific method.

6.3.3 ESPEN malnutrition criteria in cancer patients

It is stated in the publication of the ESPEN malnutrition criteria that the suggested malnutrition diagnosis is aimed to be general and could be used independently of the underlying diagnosis (3). Because the suggested malnutrition diagnosis is general, there is need for further assessment of underlying disease in order to facilitate the best specific treatment (3). In our group of cancer patients, the etiology specific malnutrition subcategory

is cancer cachexia. An international consensus definition of cancer cachexia was published in 2011 by Fearon et.al (17). This group defined cachexia as follows:

> *A multifactorial syndrome defined 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. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. ((17)p.490)*

For cancer patients it is of great importance that nutritional status is assessed as soon as possible and that nutritional intervention is initiated early (69, 150, 162). As the definition says, nutritional therapy cannot fully reverse already established cancer cachexia. It also seems that the more severe the WL and cachexia are, the more resistant to nutritional treatment (17, 83). The cachexia criteria (not shown) have a much lower WL cut-off than EMC both because it is important to recognize the condition as soon as possible, but also because other factors as anorexia, inflammation, type of cancer and treatment plays a role when setting this diagnosis. This means that the EMC will identify patients late in the cachexia trajectory, and therefore also in a more refractory state of the condition. EMC does not claim to be disease specific or able to identify cancer cachexia, but the publication discusses the possibility that the malnutrition subcategories are related and at least partly over arched by the general malnutrition term (3). The ESPEN publication presents a conceptual tree of nutritional disorders where malnutrition is at the top (3). A diagnosis cannot be both general, embracing more specific subcategories, and at the same time specific and identify the most severe cases.

6.4 Malnutrition – the patient

Malnutrition and change in physical appearance, loss of function and increasing helpfulness can also affect psychological well-being, social situations and family relations (194). Loss of appetite will affect meals and the social context around this. Many patients and the families of the patients experience great challenges concerning food intake (195), these challenges are

met by various strategies, and pressure on the patient to eat can find place and can be cause for conflict between family and patient, and between the family and health care personnel (194). Severe weight loss where the patient experience that one's clothes become too big and bones start to protrude through the skin can be experienced frightful both by the patient itself and his or hers loved ones (194). A qualitative study identified three main areas with room for improvement (196). These three areas were health care personnel seeing and acknowledging the patient's weight loss, the need for information given to both patient and the family and finally the need for intervention by health care personnel (196).

Through the work with this project most of the aspects discussed are of practical nature, but the patient must never be forgotten. When a condition is recognized and diagnosed, there will be an expectation that efficient treatment can be offered (150). To give a hospitalized patient a malnutrition diagnosis on top of everything else can be a hard message to receive, particularly if there is little efficient treatment to offer. Therefore, we need to remember that behind every malnutrition diagnosis is a vulnerable person who is fighting a battle, and that there is a reason why this person became malnourished. Independently of the diagnostic criteria for malnutrition, the person suffering from this condition should always be acknowledged and seen.

7 Conclusion

Our evaluation of the newly suggested ESPEN malnutrition criteria led us to following conclusions:

- There was low level of agreement between the national Norwegian malnutrition criteria and the EMC. The disagreement was primarily caused by EMC not considering WL alone a criterion for malnutrition.

- In line with other recent studies, our results suggest that the ESPEN malnutrition criterion including low FFMI identifies more patients than the criteria including only BMI (alone or combined with weight loss). This indicates that fewer patients will be identified as malnourished in the absence of body composition assessment, and the malnutrition diagnosis will be based only on BMI (alone or in combination with weight loss).

- BIA (Seca mBCA 515) and DXA (Lunar iDXA, GE Healthcare) as method for assessing FFMI gave similar results. Method-specific cut-offs for FFMI are not presented in the ESPEN consensus statement on diagnostic criteria for malnutrition.

In addition, our assessment of this patient population using various nutritional risk assessment tools and malnutrition diagnostic criteria showed that prevalence of nutritional risk and malnutrition varies according to the tools and criteria used. This highlights the importance of using assessment tools validated for the given patient population and that there is an urgent need for an international agreement on the diagnostic criteria for malnutrition.

8 Future perspectives

When it comes to the newly suggested ESPEN malnutrition criteria, they are a valuable attempt to meet the need for consensus on malnutrition. Nevertheless, further investigation and refinement of the criteria could be done in the following regards:

- Body composition assessment is far from being routine in clinical practice. As body composition assessment is not mandatory when giving the malnutrition diagnosis according to the ESPEN malnutrition criteria, the remaining criteria should be able to identify approximately the same patients. Alternative methods for assessment of body protein stores when body composition cannot be assessed should be presented to make sure to not miss any patients in absence of body composition measures.

- As overweight is an increasingly common condition, the outcome of using the new ESPEN malnutrition criteria in an overweight population of hospitalized patients should be investigated both when body composition is assessed and not.

- Refinement of the chosen cut-off for BMI, FFMI and WL. There exists extensive research on WL, FFMI and BMI in the literature. The need for further research for identifying cut-offs and their predictive value should be clarified after a review of the current evidence.

- Consider whether weight loss alone could be a diagnostic criterion for malnutrition. Identify the ideal cut-off in regards to predictive value

- As the malnutrition diagnosis is specific, it increases the importance of sensitive risk screening tools and clear guidelines for nutritional intervention provided for the at risk population. It is extremely important to make sure that patients who do not meet the criteria for malnutrition but are at nutritional risk, are not forgotten and receives appropriate treatment. The suggestion of an ICD-10 code for nutritional risk is strongly supported to increase focus on the patients at nutritional risk.

- Compare the ESPEN malnutrition criteria with other *diagnostic* tools to investigate the agreement and disagreement.

- Further research to obtain strong evidence-based recommendations for the treatment of nutritional risk and malnutrition is needed.

Through the use of various nutrition assessment tools and diagnostic criteria when working with this thesis, it is clear that the clinical reality does not always fit into specific criteria and there will always be grey areas. Exemplified with patients having a total great WL, but over the last month have stabilized and increased their weight. Should the recent weight stabilization or the total weight loss be weighed more when considering the nutritional status of this patient? This is relevant in all criteria presenting a cut-off for weight loss. Could this patient fit into a nutritional risk category? The rate of the weight loss and the time frame is also an important clinical indicator, as an ongoing progressive weight loss is more severe than a slower weight loss, even though both can be detrimental. When Detsky in 1987 published SGA, he also described in detail the interpretation and use of the criteria and exemplified with case examples (112). This was helpful when using PG-SGA, and similar description was missed when using the other nutrition assessment methods. It would be helpful if the new diagnostic criteria could contain case examples showing how to use the criteria in clinical reality. This would increase the utility of the criteria and show that the authors know the clinical reality and can use of their clinical experience to guide others in the process of considering the clinical situation.

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Appendices

Appendix 1 The Norwegian Regional Committees for Medical and Health Research Ethics (REC), region South East, reply to application.

Appendix 2 Recommendation from the Department for Privacy Protection

Appendix 3 Written consent form

Appendix 4a) PG-SGA part 1

Appendix 4b) PG-SGA part 2

Appendix 5 PG-SGA procedure

Appendix 6 Nutrition risk screening 2002 (NRS-2002)

Appendix 7 Nutrition risk screening 2002 (NRS-2002) associated questionnaire

Appendix 8 Procedure for performing bioelectrical impedance analysis (BIA)

Appendix 9 Procedure for performing dual energy x-ray absorptiometry (DXA) analysis

Appendix 10 Procedure for measuring hand grip strength

Appendix 11 Table 1 Appendix. Disagreement between EMC and ICD-10 in the 14 patients who were diagnosed with malnutrition by ICD-10 only

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Knut W. Ruyter	22845518	05.10.2015	2015/1525/REK sør-øst A
			Deres dato:	Deres referanse:
			18.08.2015	

Vår referanse må oppgis ved alle henvendelser

Hilde Brekke
Universitetet i Oslo

2015/1525 Ernæringsstatus og ernæringsbehandling ved risiko for underernæring

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 17.09.2015. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikkloven § 4.

Forskningsansvarlig: Universitetet i Oslo
Prosjektleder: Hilde Brekke

Prosjektbeskrivelse (revidert av REK)

Formålet med dette prosjektet er å undersøke og sammenligne bruk av ulike verktøy for å identifisere underernæring blant pasienter som er henvist til Ernæringspoliklinikken ved Senter for klinisk ernæring og Oslo Universitetssykehus.

Pasienter som gjennomgår kirurgi i mage/tarm (for eksempel ved kreft) og pasienter med tarmsykdommer (ulcerøs kolitt, Crohns syksom, Irritabel tarm) er i risiko for underernæring og tap av fettfri masse. Underernæring og tap av fettfri masse er vist å korrelere med dårligere livskvalitet og dårligere toleranse for behandling. Nasjonale retningslinjer tilsier at alle pasienter skal kartlegges og behandles for underernæring, men dette skjer i utilstrekkelig grad i dag. Det er derfor ønskelig med nøyaktige og brukervennlige metoder for å identifisere underernæring. Nåværende kriterier for underernæring bruker ICD10 som diagnosekodeverk. Nye diagnosekriterier foreslått i en ESPEN-basert konsensus inkluderer enten vekttap og KMI eller fettfri masse-indeks. Fettfri masse kan måles ved hjelp bioelektrisk impedanse eller DXA.

Ett annet formål er å følge opp pasienter som får ernæringsbehandling for underernæring ved Ernæringspoliklinikken med hensyn til ernæringsstatus og livskvalitet. Reinnleggelse, liggetid og overlevelse hos pasienter som får behandling kommer til å sammenliknes med tilsvarende pasienter ved Oslo universitetssykehus i 2014, før henvisning til ernæringspoliklinikken startet.

Det er angitt at omlag 60 pasienter skal inngå i studien, rekruttert blant pasienter som henvises til Ernæringspoliklinikken. I første omgang er dette pasienter med kreft (gastro) og andre pasienter med mage-tarmsykdommer som ulcerøs kolitt, Crohns sykdom, irritabel tarm og cøliaki. Behandlingen som tilbys i prosjektet er ernæringsbehandling av klinisk ernæringsfysiolog etter retningslinjer for behandling ved underernæring, det skal ikke gis behandling utover det som normalt tilbys som rutinebehandling.

Det skal i prosjektet inngå opplysninger om utdannelse, yrke, ernæringsstatus (vekt, høyde, appetitt, kvalme, livskvalitet, fettfri masse og muskelmasse (DXA, Bioelektrisk impedanse), energiomsetning i hvile (indirekte kalorimetri), gripestyrke. Det er videre planlagt innhentet opplysninger fra journal, inkludert

sykehistorie, klinisk kjemiske analyser, patologisvar og bildediagnostikk.

I tillegg er det planlagt kobling til variable fra følgende registre:

- Dødsårsaksregisteret: Dødsårsak med underliggende årsaker og dato for død
- Kreftregisteret: Diagnose, alvorlighetsgrad, stadieinndeling
- Norsk pasientregister (NPR): ICD10 diagnoser og prosedyrekoder
- Reseptbasert legemiddelregister (Reseptregisteret): Medikament type, dose og dato for utlevering
- Nasjonalt register over hjerte- og karlidelser (Hjerte- og karregisteret): ICD10 diagnose og prosedyrekoder

Det planlegges å ta blodprøver og eventuelt vevsprøver til prosjektet.

Komiteens vurdering

Komiteen forstår prosjektet som todelt. Del en er en sammenligning av to metoder for å måle underernæring. Formålet dreier seg om å undersøke selve metodene og hvilken av disse som er best til å diagnostisere underernæring. Etter REKs vurdering er denne delen av prosjektet å anse som helsetjenesteforskning.

Helsetjenesteforskning er et flerfaglig vitenskapelig felt hvor man studerer hvordan sosiale faktorer, finansieringssystemer, organisatoriske strukturer og prosesser, helseteknologi og personellatferd påvirker tilgang til helse - og omsorgstjenester, kvaliteten og kostnadene ved helse og omsorgstjenester, og endelig helse og velvære. Helsetjenesteforskning er også forskning på forbedring av helsetjenesten og effektiv bruk av ressurser for samfunnet. I helsetjenesteforskningen studerer man blant annet hvordan helsetjenester leveres, hvordan de er utformet, og hvordan helsetjenesten fungerer som system.

Prosjektets del to innebærer oppfølging av pasienter hvor man sammenligner effekten av ernæringsbehandling, ved å sammenligne re-innleggelse, liggetid og overlevelse hos pasienter som har fått oppfølging på poliklinikken med pasienter ved Oslo universitetssykehus som ikke fikk slik oppfølging. Etter komiteens syn er denne delen av prosjektet å forstå som kvalitetssikring.

Kvalitetssikring kan defineres som prosjekter, undersøkelser, evalueringer o.l. som har som formål å kontrollere at diagnostikk og behandling gir de intenderte resultater, eller har som formål å etterprøve behandlingsvirksomhet i alle deler og ledd, herunder å studere om beste behandlingsmetode følges.

Hverken helsetjenesteforskning eller kvalitetssikring er omfattet av helseforskningslovens virkeområde, som omfatter prosjekter med det formål å skaffe ny kunnskap om helse og sykdom, jf. helseforskningsloven § 2 og § 4 a, og slike prosjekter er dermed ikke fremleggingspliktig for REK.

I prosjektet er det oppgitt at det skal benyttes en rekke helseopplysninger fra nevnte registre. Det er imidlertid ikke gitt noen begrunnelse for hvorfor opplysningene skal innhentes, hva de skal brukes til eller hvordan de skal sammenstilles med prosjektopplysningene.

Slik komiteen forstår prosjektet er det ikke nødvendig med helseopplysninger fra registre for å nå prosjektets formål. Prosjektleder må avklare bruk av helseopplysninger fra helseregistre med personvernombudet for forskning og med registereiere. Hvis prosjektet skulle ha behov for dispensasjon fra taushetsplikt fra REK må en redegjørelse for hvordan variable fra nevnte registre skal knyttes opp mot studiens endepunkt foreligge.

Appendix 1

Vedtak

Prosjektet faller utenfor helseforskningslovens virkeområde, jf. § 2, og kan derfor gjennomføres uten godkjenning av REK. Det er institusjonens ansvar å sørge for at prosjektet gjennomføres på en forsvarlig måte med hensyn til for eksempel regler for taushetsplikt og personvern.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK Sørøst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Knut W. Ruyter
Avdelingsdirektør

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PERSONVERNOMBUDETS TILRÅDING

Til:	Hilde Kristine Brekke
Kopi:	
Fra:	Personvernombudet ved Oslo universitetssykehus
Saksbehandler:	Henrik Lindgren Jensen
Dato:	29.01.16
Offentlighet:	Ikke unntatt offentlighet
Sak:	Personvernombudets tilråding til innsamling og databehandling av personopplysninger
Saksnummer/ ePhortenummer:	2016/1087

Personvernombudets tilråding til innsamling og behandling av personopplysninger for prosjektet:

"Metoder for kartlegging av ernæringsstatus"

Vi viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er personvernombudets tilråding av prosjektet.

Med hjemmel i personopplysningsforskriften § 7-12, jf. helseregisterloven § 5, har Datatilsynet ved oppnevning av personvernombud ved Oslo Universitetssykehus (OUS), fritatt sykehuset fra meldeplikten til Datatilsynet. Behandling og utlevering av person-/helseopplysninger meldes derfor til sykehusets personvernombud.

Databehandlingen tilfredsstiller forutsetningene for melding gitt i personopplysningsforskriften § 7-27 og er derfor unntatt konsesjon.

Personvernombudet tilrår at prosjektet gjennomføres under forutsetning av følgende:

1. Databehandlingsansvarlig er Oslo universitetssykehus HF ved adm. dir.
2. Avdelingsleder eller klinikkleder ved OUS har godkjent studien.
3. Behandling av personopplysningene / helseopplysninger i prosjektet skjer i samsvar med og innenfor det formål som er oppgitt i meldingen.
4. Data lagres som oppgitt i meldingen. Annen lagringsform forutsetter gjennomføring av en risikovurdering som må godkjennes av Personvernombudet.
5. Studien er frivillig og samtykkebasert. Innmeldte samtykke benyttes.
6. Eventuelle fremtidige endringer som berører formålet, utvalget inkluderte eller databehandlingen må forevises personvernombudet før de tas i bruk.
7. Kontaktperson for prosjektet skal hvert tredje år sende personvernombudet ny melding som bekrefter at databehandlingen skjer i overensstemmelse med opprinnelig formål og helseregisterlovens regler.

8. Data slettes eller anonymiseres ved prosjektslutt 26.01.208 ved at krysslisten slettes og eventuelle andre identifikasjonsmuligheter i databasen fjernes. Når formålet med registeret er oppfylt sendes melding om bekreftet sletting til personvernombudet.

Prosjektet er registrert i sykehusets offentlig tilgjengelig database over forsknings- og kvalitetsstudier.

Med hilsen

Henrik Lindgren Jensen
Personvernrådgiver

Oslo universitetssykehus HF
Stab pasientsikkerhet og kvalitet
Seksjon for personvern og informasjonssikkerhet

Epost: personvern@oslo-universitetssykehus.no
Web: www.oslo-universitetssykehus.no/personvern

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET METODER FOR KARTLEGGING AV ERNÆRINGSSTATUS

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke og sammenligne metoder for å kartlegge ernæringsstatus. Du forespørres om å delta i studien ettersom du har blitt henvist til Ernæringspoliklinikken ved Universitetssykehuset i Oslo. Universitetet i Oslo, Avdeling for ernæringsvitenskap, Seksjon for klinisk ernæring er ansvarlig for forskningsprosjektet. Universitetssykehuset i Oslo er ansvarlig behandlingen du får og denne er den samme uansett om du ønsker å delta i forskningsprosjektet eller ikke.

HVA INNEBÆRER PROSJEKTET?

Ernæringsstatus har vist å ha en sammenheng med hvordan pasienter tolererer ulike former for medisinsk behandling. Underernæring forekommer hyppig ved en rekke sykdomstilstander. Det finnes ulike metoder for å diagnostisere underernæring, samt ulike definisjoner på underernæring. Diagnostisering kan skje ved kartlegging av vekttap, appetitt, måling av vekt og høyde, måling av gripestyrke (i hånd) og eventuelt måling av kroppssammensetning. Nasjonale retningslinjer sier at alle pasienter ved norske sykehus skal kartlegges for underernæring og behandles hvis de er i risiko for dette, eller ved etablert underernæring. Studien vil bidra til å øke kunnskapen om hvilke metoder for kartlegging av underernæring som både er praktisk gjennomførbare i klinisk praksis og som også gir den mest korrekte diagnosen.

Det vil stilles spørsmål om din vekt og vektutvikling, samt appetitt og andre ernæringsrelaterte faktorer. Høyde og vekt måles med ett instrument som også måler mengden muskler og fett i kroppen (SECA, bioelektrisk impedanse). Blodprøver tas. Samtlige av disse målingene inngår i rutinemessig behandling ved Ernæringspoliklinikken. Som deltager i studien kan du dessuten bli spurt om du vil svare på noen flere spørsmål om deg selv og din helse (utdannelse, yrke, sivil status etc), måle muskelmasse med ett apparat som også viser bentetthet i skjelettet (DXA). Håndens gripestyrke vil også måles med et enkelt verktøy. En del av undersøkelsene gjøres rutinemessig på ernæringspoliklinikken og vil uansett bli gjort i løpet av tiden som er satt av til din konsultasjon. Ytterlige undersøkelser og målinger vil ta ca. 15-30 minutter ut over konsultasjonen. Alle målingene gjøres på samme dag som konsultasjonen du kom hit for, og det vil ikke bli nødvendig å følge opp disse målingene.

Dersom du velger å ikke delta i studien, eller trekker deg underveis, vil du fortsatt få den samme behandlingen som hvis du deltar i studien. Du kan trekke deg når som helst, uten å oppgi grunn. Du vil sannsynligvis gjennomgå noen færre prosedyrer dersom du velger å ikke delta. Uansett deltakelse vil de prosedyrer som anses som nødvendige for korrekt behandling bli gjennomført. Grad av oppfølging vil avhenge av hva som anses som nyttig og nødvendig for deg, uavhengig av deltakelse i studien.

Appendix 3

Metoder for kartlegging av ernæringsstatus

I prosjektet vil vi innhente og registrere opplysninger om deg. Det kan bli aktuelt å innhente informasjon fra din journal. Opplysninger som registreres om deg er relevante opplysninger for studien, dette innebærer følgende undersøkelser:

Undersøkelser du vil gjennomgå uavhengig om du ønsker å delta i studien eller ikke:

- Spørreskjemaer som omhandler din vekt, appetitt, matinntak, symptomer fra mage/tarm, fysisk aktivitet, funksjonsnivå i hverdagen og liknende.

- Det vil bli målt vekt og høyde
- Måling av kroppssammensetning, det vil si hvor mye muskler og fett kroppen består av. Dette gjøres med en metode som heter bioelektrisk bioimpedanse (med en maskin som heter SECA), og målingen foregår mens du står barføtt på en vekt i 2-3 minutter.

Undersøkelser du vil gjennomgå i tillegg dersom du deltar i studien Hvis du ikke deltar i studien kan det likevel vurderes som aktuelt å gjøre de samme undersøkelsene:

- Blodprøvetakning (CRP)
- Måling av kroppssammensetning med et annet apparat, som også kan måle bentetthet i skjelettet. Denne målingen er en slags røntgenundersøkelse; DXA (dual energy x-ray absorptiometry). Undersøkelsen er risiko- og smertefri, og stråledosen som benyttes er minimal. Du vil ligge stille på ryggen i 10-15 minutter på en åpen røntgenbenk, mens en scannearm vil bevege seg over kroppen din (uten fysisk kontakt).
- Måling av håndens gripestyrke med et enkelt verktøy, som er en klype du skal klemme sammen så hardt du klarer.

Undersøkelser du vil gjennomgå kun hvis du deltar i studien

- Spørreskjemaer som omhandler sivil status, yrke, utdanning og liknende

MULIGE FORDELER OG ULEMPER

En mulig fordel med å delta i studien er at du får vite flere detaljer om din ernæringsstatus, som for eksempel muskelmasse. I tillegg kan benskjørhet kan oppdages tidlig ved bruk av DXA-måling. Du blir i så fall henvist til spesialister. DXA-måling krever at man kan ligge stille i 10-15 minutter. Blodprøvetaking kan forbindes med visst ubehag ved stikk i armen. En ulempe kan også være at undersøkelsene på Ernæringspoliklinikken vil ta noe mer tid enn det ellers ville gjort.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Hilde Brekke, Tlf 22851261.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Det er kun personell med taushetsplikt som har adgang til navnelisten og som kan finne tilbake til deg.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg samt prøvene som tas vil bli anonymisert og slettet senest 2026-01-01

FORSIKRING

Ved deltagelse gjelder pasientskadeloven (Lov om erstatning ved pasientskader (pasientskadeloven)).

OPPFØLGINGSPROSJEKT

Dersom det på et senere tidspunkt vil bli aktuelt med et oppfølgingsprosjekt av denne undersøkelsen, vil du bli kontaktet igjen.

ØKONOMI

Studien og er finansiert gjennom eksisterende resurser ved Universitetet i Oslo og Oslo Universitetssykehus.

GODKJENNING

Prosjektet klassifiseres som helsetjenesteforskning og er godkjent av Personvernombudet ved Oslo Universitetssykehus (2016/1087).

Samtykke til deltakelse i PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

Rolle i prosjektet

Pasient-generert Subjektiv Global Måling

Pasient-ID: | **Visitt:**

1. Vekt

Nåværende og tidligere vekt:

Jeg veier nå _____ kg
Jeg er _____ cm høy

For 1 måned siden veide jeg _____ kg
For 6 måneder siden veide jeg _____ kg

I løpet av de 2 siste ukene har min vekt:

- ☐ Gått ned (1)
- ☐ Ikke endret seg (0)
- ☐ Økt (0)

Boks 1: ☐

2. Matinntak

Sammenlignet med mitt vanlige inntak, vil jeg vurdere mitt matinntak de siste månedene som:

- ☐ Uforandret (0)
- ☐ Mer enn vanlig (0)
- ☐ Mindre enn vanlig (1)

Jeg spiser nå (besvares kun ved redusert matinntak):

- ☐ Normal mat, mindre mengde (1)
- ☐ Lite fast føde (2)
- ☐ Bare flytende føde (3)
- ☐ Bare næringstilskudd (3)
- ☐ Veldig lite/ingenting (4)
- ☐ Kun sondeernæring/ intravenøs ernæring (0)

Boks 2: ☐

3. Symptomer

Jeg opplever følgende problem som har hindret meg fra å spise nok mat de to siste ukene: (kryss av på alle passende alternativer)

- ☐ Ingen problemer (0)
- ☐ Oppkast (3)
- ☐ Sår i munnen (2)
- ☐ Følte ikke for å spise (3)
- ☐ Diare (3)
- ☐ Endret smak (1)
- ☐ Kvalme (1)
- ☐ Munntørrhet (1)
- ☐ Blir fort mett (1)
- ☐ Forstoppelse (1)
- ☐ Luktsensitivitet (1)
- ☐ Svelgeproblemer (2)
- ☐ Smerter (3). Hvor?_____
- ☐ Utmattethet
- ☐ Annet (1) (f.eks: depresjon, vanskeligheter med innkjøp, tannproblemer)

Boks 3: ☐

4. Aktivitet og funksjon

I løpet av den siste måneden vil jeg karakterisere mitt aktivitetsnivå som:

- ☐ Normalt med ingen begrensinger (0)
- ☐ Ikke som normalt, men kan være oppe og gjøre noen normale aktiviteter (1)
- ☐ Føler ikke for å gjøre noe, ligger i senga/sitter i stolen under halvparten av dagen (2)
- ☐ Har liten evne til å utføre aktiviteter, tilbringer mesteparten av dagen i senga/stolen (3)
- ☐ Sengeliggende, står sjeldent opp (4)

Boks 4: ☐

FYLLES UT AV FORSKER:

Total poengsum Boks 1-4: ☐ **A**

Total PG-SGA-score (A-D): ☐

SGA-kategori:

1. Scoring av vekttap

Bruk data fra 1 mnd tilbake om tilgjengelig. Legg til et ekstra poeng om pasienten har gått ned i vekt de siste 2 uker. Poengsummen overføres fra Boks 1.

Vekttap (1 mnd)	Poeng	Vekttap (6 mnd)
>10 %	4	>20 %
5-9,9 %	3	10-19,9 %
3-4,9 %	2	6-9,9 %
2-2,9 %	1	2-5,9 %
0-1,9 %	0	0-1,9 %

Poeng 1: ☐

2. Scoring av medisinsk tilstand

Alle relevante diagnoser_____
Eventuelt sykdomsstadium (I-IV) _____

Kategori:	Poeng
Kreft	1
AIDS	1
KOLS	1
Kronisk hjertesvikt	1
Tilstedeværelse av liggesår, åpne sår eller fistler	1
Tilstedeværelse av traume	1
Alder > 65 år	1
Kronisk nyresvikt	1

Poeng 2: ☐ **B**

3. Scoring av metabolsk stress

Økt metabolsk stress fører til økt behov for protein og energi. Legg sammen poengene fra hver av stressfaktorene.

Stress	**Ingen (0)**	**Lav (1)**	**Moderat (2)**	**Høy (3)**
Feber	Ingen feber	37,2-38,3 °C	38,3-38,9 °C	>38,9 °C
Varighet av feber	Ingen feber	<72 timer	72 timer	>72 timer
Kortikosteroider	Ingen steroider	lav dose (<10 mg/dag)	moderat dose (10-30 mg/dag)	høy dose (>30 mg/dag)

Poeng 3: ☐ **C**

4. Fysisk undersøkelse

Dette er en subjektiv evaluering av kroppssammensetning basert på fett-, muskel- og væskestatus. Scorene skal ikke legges sammen, men brukes i en helhetsvurdering av mangler/væskeopphopning. Muskelsvinn påvirker totalvurdering mer enn lite fettmasse.

Fett-lager:				
Orbitalt fett lager	0	1+	2+	3+
Triceps skinfold	0	1+	2+	3+
Nedre ribben	0	1+	2+	3+
Global fettstatus	**0**	**1+**	**2+**	**3+**

Væske-status:				
Ankelødem	0	1+	2+	3+
Sakralt ødem	0	1+	2+	3+
Ascites	0	1+	2+	3+
Global væskestatus	0	1+	2+	3+

Muskel-status:				
Temporalis (tinningen)	0	1+	2+	3+
Pectoralis (kragebein)	0	1+	2+	3+
Deltoids (skulder)	0	1+	2+	3+
Interosseous muskel	0	1+	2+	3+
Scapula (skulderben)	0	1+	2+	3+
Quadriceps (lår)	0	1+	2+	3+
Gastrocnemius (legg)	0	1+	2+	3+
Global muskelstatus	**0**	**1+**	**2+**	**3+**

Poengsystem:

Ingen mangel	= 0 poeng
Mild mangel	= 1 poeng
Moderat mangel	= 2 poeng
Alvorlig mangel	= 3 poeng

Poeng 4: ☐ **D**

5. PG-SGA Global Assessment kategorier

Kategori	**A: Velernært**	**B: Moderat underernært**	**C: Alvorlig underernært**
Vekt	Ingen vekttap	≤ 5% vekttap på 1 mnd, eller 10 % vekttap på 6 mnd	> 5% vekttap på 1 mnd, > 10 % vekttap på 6 mnd
Næringsinntak	Ingen mangel	Redusert inntak	Dramatisk reduksjon i inntak
Symptomer	Ingen	Symptomer (Boks 3)	Symptomer (Boks 3)
Funksjon	Ingen reduksjon	Moderat reduksjon	Alvorlig reduksjon
Fysisk undesøkelse	Ingen mangel	Mild til moderat tap	Alvorlige tap

Appendix 4b

ECOG: GASTROINTESTINALE SYMPTOMER

Symptom	**0**	**1**	**2**	**3**	**4**
Kvalme	Ingen	Kan innta tilfredsstillende mengde mat	Matinntaket er betydelig redusert, men er fortsatt mulig	Ubetydelig matinntak	
Oppkast	Ingen	1 episode siste 24 timer	2-5 episoder siste 24 timer	6-10 episoder siste 24 timer	>10 episoder siste 24 timer eller i behov for parenteral støtte
Diaré	Ingen	2-3 x fler avføringsepisoder/dag enn vanlig	4-6 x fler avføringsepisoder/dag enn vanlig eller nattlig avføring eller moderate kramper	7-9 fler avføringsepisoder/dag enn vanlig eller inkontinens eller alvorlige kramper	>10 fler avføringsepisoder/ dag enn vanlig eller slimet/blodig diaré eller i behov for parenteral støtte
Sår i munnen	Ingen	Smertefrie sår, rødhet/betennelse eller mild sårhet	Smertefull rødhet/betennelse, ødem eller sår, men kan innta mat	Smertefull rødhet/betennelse, ødem eller sår og kan ikke innta mat	Behov for parenteral eller enteral støtte

Prosedyre for utfylling av PG-SGA-skjemaet

Ved oppmøte:
Pasienten får utdelt del 1 av PG-SGA-skjemaet markert med sitt ID-nummer. Skjemaet skal fylles ut på egenhånd før samtale med klinisk ernæringsfysiolog (KEF).

Utfylling del 1:
Del 1 baserer seg på selvrapporterte data.

Spørsmål 1: Vekt

- Vekt skal fortrinnsvis være selvrapportert.
- Spør pasienten om nåværende vekt er basert på måling her eller på selvrapportering. *Skriv en kommentar dersom det er målt vekt som er fylt inn.*
- Dersom pasienten er usikker eller ikke vet vekt for hhv 1 og 6 måneder siden kan man enten
    - Be de fylle inn vekten de «vanligvis» veier i 6-månedersrubrikken eller
    - La feltene stå åpen slik at man kan fylle inn målt vekt i ettertid
- Dersom pasienten ikke har fylt ut feltene overfor, og du har tilgjengelig vekt fra inklusjon, V2 eller V3, kan disse brukes ved henholdsvis V2, V3 og V4 (for å registrere vekt for 6 mnd siden).
  Skriv en kommentar dersom du har fylt inn målt vekt.

- Vekten som måles samme dag brukes som nåværende vekt. Dersom pasienten er usikker på vekt for hhv 1 og 6 måneder siden brukes vekten de "vanligvis" veier og noteres i 6 måneders rubrikken. Dersom pasienten ikke har oversikt over hva de vanligvis veier brukes vekt funnet ved inklusjon og noteres i 6 måneders rubrikken.

Spørsmål 2: Matinntak

- Første spørsmål besvares av alle. Andre spørsmål besvares av de som har rapportert at de har et redusert matinntak sammenliknet med sitt vanlige inntak. Begge spørsmål skal fylles ut.

Spørsmål 3: Symptomer

- Pasienten krysser av for alle aktuelle symptomer som har hindret matinntak de siste 2 ukene. *Symptomer som ikke har påvirket matinntaket skal ikke være med her.*

Spørsmål 4: Aktivitet og funksjon

- Pasienten krysser av for ett passende alternativ.

KEF ser over skjemaet for å forsikre om at alle punkter er korrekt utfylt før del 2 gjennomføres.

Utfylling del 2:
Del 2 av PG-SGA-skjemaet fylles ut av KEF i samtale med pasienten.
Før gjennomgang av skjemaet informerer KEF om at det først vil bli stilt noen spørsmål angående pasientens helsetilstand, for at det deretter vil gjøres en fysisk undersøkelse som går ut på å vurdere muskel og fettstatus.

Spørsmål 1: Scoring av vekttap

- KEF regner ut vekttap siste måned etter avsluttet samtale med pasienten, og denne delen tas ikke med i samtale med pasienten. Dersom ikke vekt for 1 måned siden er tilgjengelig brukes vekt for 6 måneder siden, eller vekt "vanligvis". Dette finner man under spørsmål 1, del 1.

Spørsmål 2: Medisinsk tilstand

- Det skal krysses av dersom pasienten har én/flere av de aktuelle tilstander som er listet opp. Traume vil ikke være et aktuelt punkt da dette ville omfattet sykehusinnleggelse. Alle pasienter ved visitt 2, 3 og 4 defineres som kreftpasienter.

Spørsmål 3: Metabolsk stress

- Feber og varighet av feber er selvrapportert. Dersom pasienten ikke vet om han/hun har feber noteres det som ingen feber.
- Kortikosteroider: bruk av dette er selvrapportert.

Spørsmål 4: Fysisk undersøkelse

- Pasienten informeres om at det nå skal gjøres en fysisk undersøkelse som innebærer at KEF vil kjenne på tinning, området rundt øynene, overkropp, lår, legger og ankler. Be pasienten kle av seg på overkroppen. Trøye/t-skjorte skal av på menn. Kvinner kan beholde BHen på. Informer hele tiden om hva du har tenkt til å gjøre FØR du gjør det.
- Se/kjenn på tinninger og poser under øyne.
- Se/kjenn på skuldre, langs kragebeinet og skulderbladene.
- Klyp i subkutant fett over triceps på baksiden av armen, midt mellom toppen av skulderen og albuespissen. Klyp i subkutant fett over biceps, på høyde med der man kløp over triceps.
- Be pasienten strekke ut armene ned mot gulvet og kjenn etter konturer av muskler (biceps/triceps).
- Be pasienten ta på seg klærne igjen og notér det du har funnet så langt.
- Be pasienten å sette seg og be han/hun presse pekefinger og tommel på begge hender sammen. Se/kjenn etter når pasienten hhv presser fingrene sammen/slapper av.
- Informer pasienten om at du skal kjenne på lår/legger mens han/hun blir sittende. Klyp tak i quadriceps på oversiden av låret og på sidene ca 15 cm fra kneet. Ta deretter tak i leggmuskelen fra knehasen og kjenn nedover til midt på leggen.
- Kjenn/se tilslutt på anklene. Spør om pasienten har vært/er plaget av ødemer/væskeopphopning/har hatt acsites.
- Noter hva du har funnet. Be eventuelt om å få kjenne igjen om du er usikker på egen observasjon.
- *Spør pasienten om egen oppfatning av fysisk form, fysisk aktivitet og grunn til eventuell vektnedgang for å kunne gi et helhetsinntrykk av pasienten. Skriv notater etter at pasienten er fulgt ut.*

Screening av ernæringsmessig risiko (NRS 2002)[4)]

Innledende screening

		JA	NEI
1	Er BMI < 20,5?		
2	Har pasienten tapt vekt i løpet av de siste ukene?		
3	Har pasienten hatt redusert næringsinntak de siste ukene?		
4	Er pasienten alvorlig syk?		

Ja Dersom svaret er JA på noen av disse spørsmålene, gjennomføres hovedscreeningen på neste side.

Nei Dersom svaret er NEI på alle svarene, gjennomføres innledende screening ukentlig. Dersom pasienten skal gjennomgå planlagt større kirurgi, skal en forebyggende ernæringsplan vurderes for å unngå assosiert ernæringsrisiko.

Gjennomføres hos pasienter som fyller minst ett av kriteriene i innledende kartlegging

Hovedscreening - vurdering av risikograd

Score	Ernæringstilstand	Score	Sykdommens alvorlighetsgrad
0	Normal ernæringstilstand	0	Ikke syk
1	Vekttap 5-10% siste 3 mnd. og/eller Matinntak 50-75% av behov i mer enn en uke	1	**En pasient med kronisk sykdom eller en pasient som har gjennomgått et mindre kirurgisk inngrep.** Leverchirrose, nyresvikt, kronisk lungesykdom, kreftpasienter, pasienter med collum femoris fraktur, etter cholecystectomi og laparaskopiske operasjoner.
2	Vekttap > 5% siste 2 mnd. eller BMI= 18.5-20.5 + redusert allmenntilstand eller matinntak 25–60% av behov siste uke	2	**En pasient med tydelig redusert allmenntilstand pga sin sykdom.** Alvorlig pneumoni, inflammatorisk tarmsykdom med feber, akutt nyresvikt, større kirurgiske inngrep som kolektomi og gastrektomi, ileus, anastomoselekkasje og gjentatte operasjoner.
3	Vekttap > 5% siste måned eller BMI < 18.5 + redusert allmenntilstand eller Matinntak 0-25% av behov siste uke.	3	**En pasient som er alvorlig syk.** Store apopleksier, alvorlig sepsis, intensivpasienter (APACHE>10), benmargstransplantasjoner, store hodeskader, brannskader>40% og alvorlig akutt pancreatitt.

Ernæringsscreening (NRS-2002)

Oslo universitetssykehus

Dato:_____

Avdeling: _____ Rom:_____

Pasient: □ Kvinne □ Mann Fødselsår:_____

Innleggelsesdato (OUS, Rikshospitalet): _____

Innleggelsesårsak/sykdom: _____

Antropometri

Høyde: _____ Vekt: _____ Når ble vekten målt? _____

Hva pleier du å veie? _____ Når sist veide du dette? _____

Vektutvikling:

Har du hatt ufrivillig vekttap?

I siste 1 måned? □ Ja □ Nei Hvis ja, hvor mye?_____

I siste 3 måneder? □ Ja □ Nei Hvis ja, hvor mye?_____

I siste 6 måneder? □ Ja □ Nei Hvis ja, hvor mye?_____

Kommentar: _____

Har du hevelser i kroppen (ødemer)? □ Ja □ Nei □ Vet ikke

Kommentar: _____

Ernæring

Hvor mye har du spist den siste uken?

□ Samme mengde som jeg pleier (100 %)

□ Mer enn halvparten av normalt (50-75 %)

□ Mindre enn halvparten av normalt (25-50 %)

□ Mindre enn fjerdedel av normalt (0-25 %)

Kommentar: _____

Tar du næringsdrikker? □ Ja □ Nei Hvis ja, hvor mange per dag?_____

Kommentar: _____

Får du sondeernæring? □ Ja □ Nei □ Vet ikke

Kommentar: _____

Får du intravenøs ernæring? □ Ja □ Nei □ Vet ikke

Kommentar: _____

NRS score:_____

Instruksjon for bruk av bioimpedansemåler ved Ferdighetssenteret.

1. Start Seca vekt (on/off i hjørnet av skjermen) om den ikke allerede er på (grønt eller hvitt lys rundt knappen)
2. Start PC. Om den står på, switch user og log inn.
3. Gå til startmenyen, søk opp og start programmet Seca Analytics 115. (Hvis problem med å starte er det mulig at noen allerede er innlogget i Seca-programmet med annen bruker. Kan du finne personen? Hvis ikke må du tvinge en omstart av PC med å holde start-knappen inne.)
4. Logg inn med brukernavn: student og Passord:student
5. Ta av sko og strømper samt ringer (hvis de går av). Har du tørre hender, gni inn litt fuktighetskrem (står på skrivebordet).
6. Mål midjemål midt mellom hoftekammen og nederste ribbein. Målebånd i øverste skuff til venstre for vekten. Skriv opp tallet og ha det tilgjengelig når du senere står på vekten.
7. Skru på høydemåler, on-knapp høyre side. Hold inne svart klemme bak på høyre side og dra høydemåleren opp/ned for å aktivere den.
8. Stå under høydemåleren med helene helt inn til kanten. Stå rett. Trykk «send» (nederste knapp høyre side på høydemåleren)
9. Stå opp på vekten med helene kant-i-kant med markert område for helen.
10. Hold i svart håndtak/gelender, midterste av de tre høydenivåene. To fingre på hver side av svart markør.
11. Trykk Bia på skjermen, deretter Continue. Du får spørsmål om bruk av pacemaker. Svar nei hvis nei. Hold hendene på håndtaket. Målingen tar ca 20 sek.

12. Trykk continue. Legg inn PAL-verdi hvis du vet tallet, alternativt gå til information og klikk på det som beskriver deg best.
13. Legg inn midjemål (obs i meter for eks 0,83 m) og trykk enter
14. Trykk så confirm
15. La ID stå tom og fyll i fødselsdato (obs rekkefølge :mmddåååå)
16. La surname stå tom og skriv for eksempel initialer med dato (f eks hkb211015) og trykk enter.
17. Trykk Create. Velg det som passer din profil. Etnisitet vil oftest være Caucasian. Trykk continue/confirm.
18. Trykk confirm igjen.
19. Save. Du får nå oppgi PIN koden for Student. Den er 33800. Enter
20. Målingen dukker nå opp på PC skjermen i Seca-ruten.
21. For å skrive ut en pdf som oppsummerer resultatet:
22. Start/vekk opp skriveren som står på skrivebordet.
23. Dobbelklikk på målingen du akkurat har gjort.
24. Gå til examination results
25. Trykk Print på grå meny i overkant
26. Kryss i ruten «with patient text»
27. Trykk på symbolet for skriver eller tryk Ctrl P
28. Velg Laser Jet 400 ett stykke ned på listen (etter fax).
29. Steng åpent dokument.
30. Save? Ikke nødvendig – målingen ligger i mappen.
31. Steng Adobe
32. Close pasient.
33. Logg ut eller gjør ny måling.

34. Det står desinfeksjonssprit og papir på skrivebordet. Tørk av håndtak og vektens stå-flate med sprit.

Appendix 9

Instruksjon for bruk av DXA

- **Kalibreres hver dag før bruk.**
- **Bruk pute, pledd/laken ved behov.**
- **Ta av all metall som pasienten/deltageren har på seg (BH er ok)**
- **Ta av skoene**

Oppstart:

1. Start PC, om den står på, switch user og log inn.
2. Start iDXA programvare.
3. Ved oppstart daglig, gjennomfør kvalitetssikring (kalibrering).

- Trykk kvalitetssikring
- Trykk Start
- Plasser KS-blokken i riktig posisjon som anvist på PC-skjermen. Plasser blokken slik at laser er i midtpunktet.
- Trykk OK.
- Rapport skrives ut, rapporten arkiveres
- Trykk Lukk

Legg til pasient:

1. Velg database som pasienten skal lagres inn under, ved behov lag ny database.
2. Trykk Opprett ny pasient.
3. Legg inn navn, fødselsdato, høyde, vekt, kjønn og etnisitet (vil oftest være Caucasian).

- Trykk OK

Start måling:

1. Trykk på ikon Mål
- Velg scanneområde (for eksempel hele kroppen)
- Trykk Posisjon
- Plasser pasienten/deltageren i riktig posisjon som anvist på PC-skjermen.
- Trykk Start
- Ved måleslutt kan pasienten/deltageren komme ned fra benken og ta på seg sko andre eiendeler.

Etter målingen:

1. Gå gjennom ScanCheck, kryss av.
2. Trykk ROI`s

- Juster linjene på venstre bilde (for eksempel hele kroppen)
- juster linjen rett under haken
- juster linjen rett over hoftene

3. Ved utskrift, trykk Rapporter
4. Trykk Lagre
5. Trykk Lukk
6. Trykk Avslutt
7. Trykk Slå av
8. Trykk OK

- **Det står desinfeksjonssprit og papir tilgjengelig, tørk av benken.**

Prosedyre for måling av gripestyrke

Måling av gripestyrke – bruk av MAP Hand grip dynamometer

- Forberedelse: Gjør klar dynamometeret. Som hovedregel bør grønne fjærsett brukes for kvinner (40 kg) og blå fjærsett brukes for menn (80 kg) (se **bilde 1**). Trykk på *"zero"* for å skru på apparatet. Om apparatet ikke viser 0,0 ved oppstart, trykk *«zero»* på nytt. Forsikre deg om at apparatet er stilt inn på "kg" og "max".

Bilde 1.

- Instruksjon: La deltakeren sitte på en stol uten armlene, med laveste ribbein i høyde med bordplaten. Be deltakeren holde testarm i 90^0 vinkel, mens motsatt arm hviler.
- Posisjonering kraftgrep: Håndflaten og fingrene skal lukkes tett rundt gripeinnretningen (se **bilde 2**). La deltakeren få prøve å klemme rundt gripeinnretningen før testen igangsettes.

Bilde 2.

- Ved oppstart: Deltaker klemmer så hardt som mulig rundt gripeinnretningen. Det vil pipe fra dynamometeret når testen er ferdig.
- Les av maksimalt oppnådde gripestyrke.
- Øvelsen skal gjennomføres på høyre og venstre arm, tre ganger annenhver gang. Alle verdier noteres på rapportskjema, og den høyeste verdien per arm brukes i analyser.

Appendix 11

Table 1 Appendix. Disagreement between EMC and ICD-10 in the 14 patients who were diagnosed with malnutrition by ICD-10 only. Each line represents one patient (1-14).

	ESPEN Malnutrition criteria[a)]		ICD-10 NO	
Nr	**Criteria met**	**Weight loss**		**Criteria met[b)]**
1	WL only, ***borderline*** [c)] ***BMI and FFMI***	> 5 % over the last 3 months	E.43	> 5 % WL last month
2	WL only, ***borderline*** [c)] ***FFMI***	> 5 % over the last 3 months	E.43	> 5 % WL last month
3	WL only	> 5 % over the last 3 months	E.43	> 5 % WL last month
4	WL only	> 10 % indefinite of time	E.43	>15 % WL last 6 months
5	WL only	> 10 % indefinite of time	E.43	> 15 % WL last 6 months
6	WL only	> 10 % indefinite of time	E.44	> 10 % WL last 3-6 months
7	WL only	> 5 % over the last 3 months	E.44	> 5 % WL last 2 months
8	WL only	> 10 % indefinite of time	E.44	> 10 % WL last 3-6 months
9	low BMI and low FFMI only	No WL	E.44	BMI < 20 if > 70 y
10	WL only, ***borderline*** [c)] ***BMI and FFMI***	> 5 % over the last 3 months	E.44	>5 % over the last 2 months
11	WL only, ***borderline*** [c)] ***FFMI***	>10 % indefinite of time	E.44	> 10 % WL last 3-6 months
12	WL only, ***borderline*** [c)] ***FFMI***	> 10 % indefinite of time	E.44	>10 % WL last 3-6 months
13	WL only, ***borderline*** [c)] ***FFMI***	> 5 % over the last 3 months	E.44	> 5 % over the last 2 months
14	no criteria met	No WL	E.44	low food intake

BMI body mass index, EMC ESPEN malnutrition criteria, E.44 Moderate malnutrition, E.43 severe malnutrition, FFMI Fat Free Mass Index, ICD-10 NO International classification of diseases version 10 Norwegian malnutrition criteria, Nr Number, WL weight loss,

a) ESPEN malnutrition criteria alternative 1: BMI <18.5 kg/m^2 or alternative 2: ***a combination of*** unintentional WL (>10% indefinite of time, or >5 % over the last 3 months) ***and*** **1) low BMI (**<20 kg/m2 if < 70 years or <22 kg/m2 if >=70 years) **OR 2) low FFMI** (<15 and 17 kg/m2 in woman and men, respectively).

b) se **figure 2** in methods describing the ICD-10 NO criteria

c) borderline 0,1-1,0 unit from cut-off