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ST. OLAVS HOSPITAL
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God ernæringspraksis for kreftpasienter.

Ernæringsutredning; diagnostiske kriterier og sammenheng med overlevelse og helserelatert livskvalitet hos pasienter med avansert tykk- og endetarmskreft.

Avhandlingen bygger på fire studier.

Artikkel 1. Denne studien undersøker meninger til 2759 sykepleiere, 1753 sykehusleger og 359 kliniske ernæringsfysiologer (kef) fra Skandinaviske sykehus om bruk av kef'enes fagkompetanse i sykehus. Sykepleiere og leger som ser kef to eller flere ganger per uke i motsetning til de som ser kef sjeldnere enn to ganger per uke prioriterte klinisk ernæring høyere i avdeling, hadde oftere internundervisning om ernæring, fant det enklere å identifisere underernærte pasienter og pasienter som trengte ernæringsstøtte. Studien viser at sykepleiere og leger som ser kef oftere enn to ganger per uke har større fokus på ernæring.

Artikkel 2. I denne studien ble ernæringsstatus til 46 kreftpasienter som ble innlagt i en palliativ enhet undersøkt med hjelp av objektive kriterier og skjemaet "Subjective Global Assessment" (SGA). I følge de objektive kriteriene; vekttap, BMI, hudfoldtykkelse, armmuskelomkrets, S-Albumin og S-Pre-albumin var 28 pasienter underernært. Med SGA var 30 pasienter vurdert som underernært. SGA hadde en sensitivitet på 96% for å påvise underernæring. Underernærte pasienter hadde flere spiserelaterte symptomer og spiste mindre matporsjoner. Vi fant at to tredjedeler av pasientene var underernært og at SGA var valid som metode for å undersøke ernæringsstatus blant kreftpasienter med avansert sykdom.

Artikkel 3. Her er ulike metoder for å måle nedgang i ernæringsstatus hos 77 pasienter med avansert tykk- og endetarmskreft undersøkt. Videre ble metodenes evne til å predikere pasientenes overlevelse studert. 28 pasienter hadde sarkopeni, 32 hadde ernæringsrisiko, 26 var underernært og 16 hadde kakeksi (CCSG) mens 41 hadde kakeksi (EPCRC). De ulike metodene overlappet hverandre ufullstendig. Studien viste at en stor andel av pasientene hadde dårlig ernæringsstatus. Det å ha kakeksi (CCSG) eller å være underernært predikerte kortere overlevelse.

Artikkel 4. I denne studien ble ernæringsstatus og livskvalitet undersøkt hos 50 nyhenviste pasienter til Kreftavdelingen for vurdering av kjemoterapi for avansert tykk- og endetarmskreft. Pasientene hadde lavere livskvalitet sammenliknet med normalbefolkningen. De som var underernærte eller hadde kakeksi (EPCRC-SGA) hadde både statistisk og klinisk signifikant dårligere livskvalitet enn de øvrige pasientene. Etter 3 måneder økte 13 pasienter vekt og de forbedret flere livskvalitetsparametre. Syv pasienter tapte vekt og de forverret livskvaliteten signifikant, mens de pasientene som var vektstabile hadde uendret livskvalitet.

Tolking. Den høye andelen av underernæring blant pasientene indikerer at mer bør gjøres for å forebygge underernæring tidligere i pasientforløpet. Underernæring og kakeksi kunne ikke holdes i fra hverandre med de metodene som ble undersøkt. Vekttap som kriterium er for uspesifikt til å diagnostisere kakeksi. Det er behov for å utvikle metoder for å påvise nedbrytning av muskulatur som kjennetegner kakeksi. En undersøkelse av ernæringsstatus gjennom et pasientforløp vil kunne avdekke tidspunkter for når intervensjoner bør settes inn mot underernæring.

Navn kandidat: ***Lene Thoresen***
Institutt: ***Institutt for Kreftforskning og Molekylær Medisin***
Veiledere: ***Ursula G. Falkmer og Gunilla J. Frykholm***
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Trondheim, December 2011 ***Lene Thoresen***

List of Papers

Paper I

Thoresen L, Rothenberg E, Beck AM, Irtun Ø.

Doctors and nurses on wards with greater access to clinical dietitians have better focus on clinical nutrition. *J Hum Nutr Diet* 2008; 21:239-247

Paper II

Thoresen L, Fjeldstad I, Krogstad K, Kaasa S, FalkmerUG.

Nutritional status of patients with advanced cancer: the value of using the subjective global assessment of nutritional status as a screening tool. *Palliative Medicine* 2002; 16:33-42

Paper III

Thoresen L, Frykholm G, Lydersen S, Ulveland, Baracos V, Prado C, Birdsell L, Falkmer U.

Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *2011, Submitted to Clinical Nutrition.* This paper has been revised and resubmittet to "Clinical Nutrition" after delivery of this thesis

Paper IV

Thoresen L, Frykholm G, Lydersen S, Ulveland, Baracos V, Birdsell L, Falkmer U.

The association of different criteria for nutritional assessment with health-related quality of life in patients with advanced colorectal carcinoma. Accepted 26. December 2011. *Eur J Cancer Care*, 2012; DOI:10.1111/j.1365-2354.2012.01327.x

Abbreviations

5-FU	5-Fluorouracil
ADA	American Dietetic Association
ALP	Alkaline phosphatase
ASPEN	American Society of Parenteral and Enteral Nutrition
BAPEN	British Association for Parenteral and Enteral Nutrition
BMI	Body mass index
CCSG	Cancer Cachexia Study Group
CRC	Colorectal cancer
CRP	C - reactive protein
CT	Computed tomography
DXA	Dual-energy X-ray Absorptiometry
EFAD	European Federation of the Associations of Dietetitians
EORTC	European Organization for Research and Treatment of Cancer
EPCRC	European Palliative Care Research Collaborative
ESPEN	European Society for Clinical Nutrition and Metabolism
FLIRI	5-Fluorouracil (F), Folinate (L), Irinotecan (IRI)
FLOX	5-Fluorouracil (F), Folinate (L), Oxaliplatin(OX)
FLv	5-Fluorouracil (F), Leucovorin (Lv)
FOLFOX	Folinic Acid (FOL), Fluorouracil (F), Oxaliplatin (OX)
HR	Hazard ratio
HR-QoL	Health-Related Quality of Life
HU	Hounsfield unit
ICDA	International Confederation of Dietetic Associations
IDNT	International Dietetics & Nutrition Terminology
IL	Interleukin
KRAS gene	v-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog
LDH	Lactate dehydrogenase
mCRC	Metastatic colorectal cancer
MAMC	Mid-upper arm muscle circumference
MRI	Magnetic resonance imaging
NCP	Nutrition care process
NICE	National Institute of Clinical Excellence
NRS-2002	Nutritional risk screening-2002
PG-SGA	Patient-generated subjective global assessment
RCT	Randomized controlled trials
SCRINIO	Screening Nutritional Risk in Oncology
SGA	Subjective global assessment
TGF-β	Transforming growth factor-β
TNF-α	Tumour necrosis factor-α
TSF	Triceps skin fold
QoL	Quality of Life
VEGF	Vascular endothelial growth factor
WBC	White blood cell count
WHO	World Health Organization
XELOX	Capecitabin (XEL), Oxaliplatin (OX)

Introduction

Incidence and survival of cancer

Each year, approximately 27,500 persons get cancer and 11,000 die of cancer in Norway.[1] Cancer is the second leading cause of death after coronary disease and accounts for 26 per cent of deaths. While the death rate of coronary heart disease has decreased during the last two decades, the death rate of cancer has increased over the same period. In 2010, the ratio of death from coronary heart disease to cancer death was 1.2, compared to 2.1 in 1991. The incidence rates of cancer have increased over the years since the Norwegian Cancer Registry began reporting in 1953 (Figure 1).[2] The five-year relative survival of cancer has increased from 32 per cent in 1970-74 to 66 per cent in 2005-09. Between 30 to 40% of all cancer patients will develop metastatic disease, which in most cases is incurable.

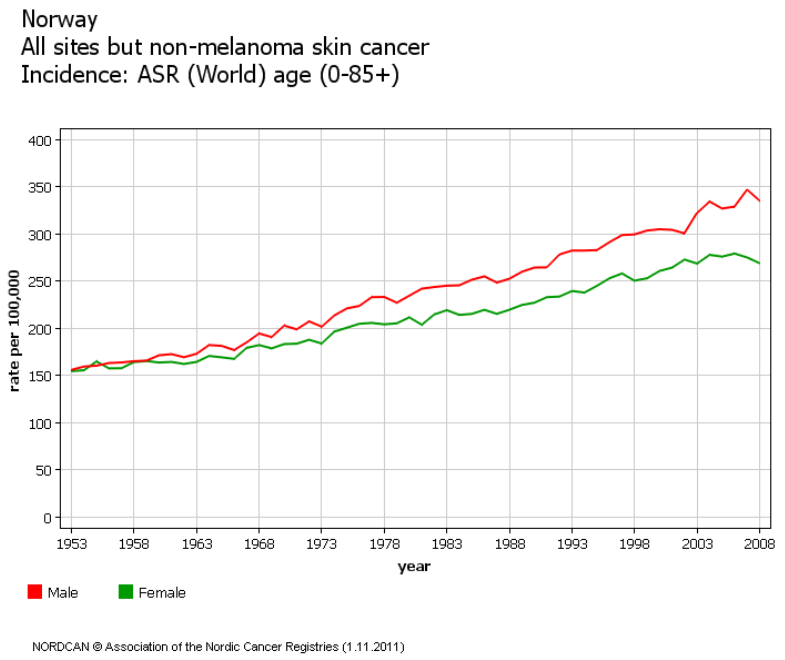


Figure 1. Incidence rate of cancer in Norway.

Incidence and survival of colorectal cancer

Considering both genders together, colorectal cancer (CRC) is the most frequent malignant disease. The incidence of CRC is increasing more in Norway than in other Nordic countries (Figure 2). In 2009, 2,405 new cases of carcinoma in the colon and 1,219 new cases of the rectum were reported. Based on TNM-classification CRC is divided into four stages (stage I, IIA, IIB, IIIA, IIIB, IIIC and IV). According to the earlier classification of Dukes, Dukes' A represents stage I, Dukes' B represents stage IIA and IIB, Dukes' C represents all stage III and Dukes' D stage IV of distant metastatic CRC.

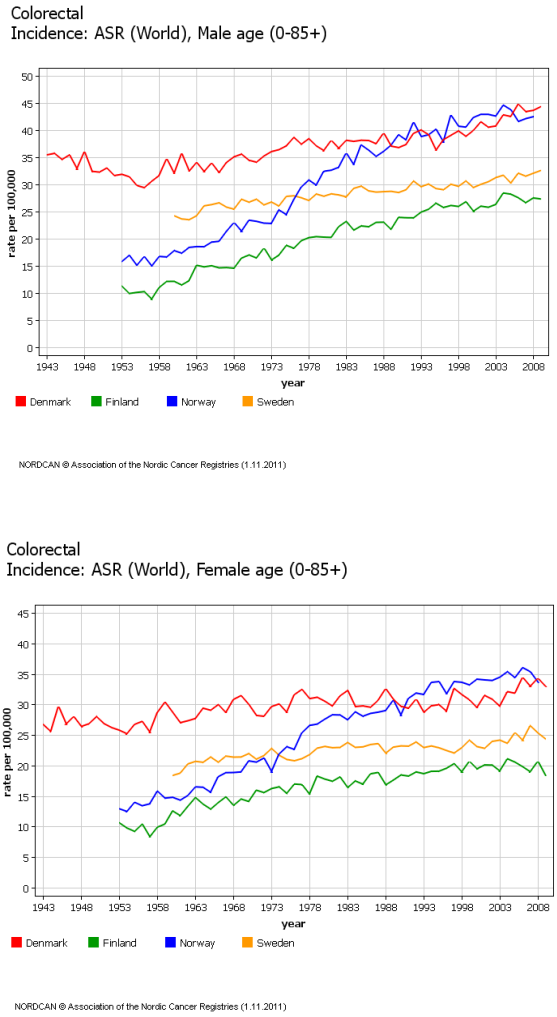
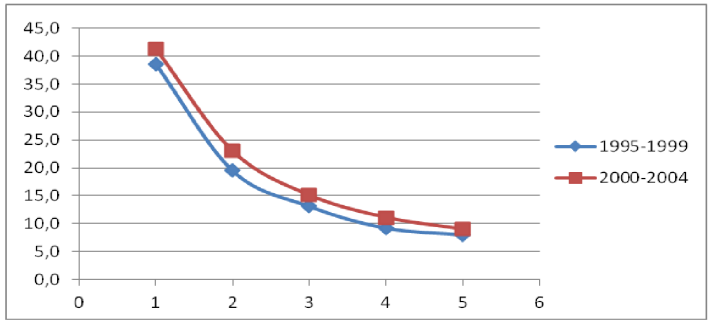


Figure 2. Incidence rates of CRC in males and females in Denmark, Finland, Norway and Sweden.

During 2005 to 2009 667 cases (20%) of the patients were primarily diagnosed at the advanced stage, of them 70% were cancer in the colon and 30% cancer in the rectum. In addition, 25-35% of the CRC patients will be diagnosed with metastases to the liver and in 10% with metastases to the lung. In Norway there will be about 1,600 patients diagnosed with metastatic colorectal cancer (mCRC) annually.[3]

The relative survival has increased about 6% in CRC when comparing 2000-2004 with 2005-2009 and is approximately 62%. Figure 3 shows the relative survival in mCRC. The five-year relative survival in 2005-2009 was around 12%. Patients median survival has increased from 6 months in the 1980s to 18-19 months in 2008 in patients given palliative chemotherapy.[3] Median survival for mCRC patients not receiving chemotherapy but best supportive care only was found to be 2.8 months.[4]



(X-axis is years and y-axis is percent of patients alive. Source; Data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the author.)

Figure 3. Relative survival of patients with mCRC.

Treatment of metastatic CRC

The treatment of mCRC is, with few exceptions, of palliative character. Thus, not many cases can be cured. Palliative chemotherapy and surgical interventions are intended to prolong progression free survival, overall survival and to provide better quality of life (QoL).[3, 5] Until recently, 5-fluorouracil (5-FU) was the standard first-line treatment for mCRC.[3, 6] Today 5-FU is given to older patients (>75 years) and patients who would not tolerate the toxicity of combination chemotherapy.[4] First-line chemotherapy of choice for patients <75 years are 5-FU intravenously or orally (capecitabin) combined with folinate, oxaliplatin (FLOX,

FOLFOX, XELOX)) or irinotecan (FLIRI). The effect of bevacizumab, a target therapy against the VEGF receptor will be investigated in ongoing protocols. In a subgroup of patients with carcinomas showing the KRAS gene of wild type, a new target therapy can be provided.

The most common side effects of combination chemotherapy are bone marrow suppression, nausea, diarrhoea, and neurosensoric toxicity. All oxaliplatin containing regimes may give dysesthesia commonly occurring in the extremities and triggered by exposure to cold. Toxicities of capecitabin are hand foot syndrome, hypertension and proteinuria. Irinotecan may cause diarrhoea and hair loss.[3]

Surgical removal of metastatic liver lesions is an increasing option. About 20% of the patients may be candidates for surgical interventions. Several procedures can be considered, as resection, embolisation, radioablation or combinations of these different options.[3]

In conclusion, the incidence of CRC is still increasing, but more patients with CRC can be cured and patients with mCRC are living longer. Today novel treatment options are rapidly introduced in the clinic. In cancer treatment, important clinical endpoints are survival or progression free survival.[7] For patients treated with palliative intention it is also especially important to maintain their QoL.[8-11]

Nutrition decline

During recent decades weight loss in cancer patients has been considered as a challenge. It is most frequently observed in patients with carcinoma of the head and neck, oesophagus, stomach and pancreas.[12-14]

The frequency of weight loss in cancer patients is shown ranging from 31% in patients with favourable non-Hodgkin's lymphoma up to 87% in patients with gastric cancer.[15] In this study a total of 32% of the patients had lost more than 5% of their body weight, with the highest rates of weight loss in patients with lung, pancreatic and gastric cancer. Weight loss has also been shown to be more pronounced as the disease progresses in advanced stages.[12, 16, 17] The prevalence of weight loss was reported in 46% of cancer patients from 17 studies including 13,167 patients and increased to 86% during the last two weeks of life.[18]

The consequences of weight loss in cancer patients have been investigated in several studies. The results indicate increased complications after surgical procedures,[19, 20] increased length of hospital stay,[21] increased treatment toxicity,[22, 23] and reduced survival.[15, 22-24] In malnourished cancer patients it has also been shown that their immune-competent cells are reduced.[25]

Colorectal cancer

Weight loss, nutrition risk or malnutrition has been assessed in different settings in patients with CRC. In one study of 101 patients it has been described that, before start of neoadjuvant radiotherapy, five out of 14 with stage I/II CRC had lost >10% of their usual body weight, whereas 61 out of 86 patients with stage III/IV CRC had lost >10% of their body weight.[26] At the end of radiotherapy 46 out of the 86 patients with stage III/IV had lost >10% of their baseline body weight.

In another study investigating CRC patients prior to surgery, 35 patients out of 85 were malnourished as assessed by SGA, 18 patients had unintended weight loss of >10% of their body weight and 40 patients had lost up to 10% of their body weight.[27]

In a Swedish study investigating CRC patients, 39 out of 75 patients had lost body weight over 6 months prior to surgery.[21] Six of the patients had lost between 5-10% and nine patients had lost >10%. During hospital stay as many as 67 of the patients had lost a mean of 4.7 ±4.4% of their body weight.

An additional study investigating the nutrition risk in 186 patients prior to surgery found weight loss in 102 patients (55%).[28] Two different tools for nutrition risk were used. Using NRS-2002, 39% of the patients were at risk, while 32% were at risk according to Reilly's NRS. All patients had CRC of stage III/IV.

A retrospective study evaluated the prognostic significance of malnutrition defined by SGA in 217 patients with stage III/IV CRC. All patients were treated at one Medical Centre and as many as 113 (52%) patients were found to be malnourished.[29]

In an additional study of 781 patients with locally advanced or metastatic CRC weight loss was reported to occur in 246 patients (34%) before referral to an oncology unit and start of chemotherapy.[23] The magnitude of weight loss was not described.

A review of 464 patients with mCRC receiving palliative chemotherapy showed that 13% of the patients had lost >10% of body weight and 28% had lost between 5 and 10%.[4]

The SGA questionnaire was evaluated in 87 patients with various malignant neoplastic diseases in an Out-patients Unit. A subgroup of 31 patients had CRC.[30] According to SGA, 5 out of 13 patients with CRC Dukes' B+C, and 6 out of 18 patients with CRC Dukes' D were malnourished.

Of 51 patients with advanced CRC attending a clinic for palliative treatment, 28 patients were malnourished according to SGA. Eighteen patients had lost >10% of their body weight during the last 6 months.[31]

Overall these studies show, despite different settings and stages of the disease, a prevalence of weight loss in CRC patients between 41 and 71%. Studies investigating nutrition risk or nutritional status show a prevalence between 30 and 55% for patients to be at nutrition risk or malnourished.

Survival

Weight loss at diagnosis has a significant impact on survival in CRC.[15, 23, 32] Without weight loss patients survived on average 43 weeks compared to 21 weeks for those with weight loss.[15] Also for patients with mCRC, weight loss has a negative prognostic impact on survival.[32, 33]

Malnutrition defined by SGA has shown to be of prognostic significance for survival in patients with ovarian cancer,[34] mCRC,[29, 31] and in patients with various gastrointestinal carcinomas.[30] Well-nourished patients have been shown to attain a significantly longer survival.

The reason for the reduced survival for cancer patients that have lost weight is thought to be the increased toxicity of chemotherapy, resulting in a lower total dose intensity of chemotherapy given.[22, 23]

In three randomised studies the effect of improving nutritional status of cancer patients by parenteral nutrition has been investigated. All three studies found a prolonged survival.[35-37]

Quality of Life

The WHO has defined QoL as a state of complete physical, mental and social well-being, and not merely the absence of disease.[38] The concept of QoL describes health in terms that capture aspects of coping, flexibility, pleasure, and independence, among others. It refers commonly to a broad range of physical and psychological characteristics that express a person's capability and pleasure to function.[39] QoL is an imprecise term that means different things to different people and the term is under continuing debate. One aspect is the referral to those things that give a person worth, meaning, purpose and satisfaction to life.[40] To distinguish between QoL in its more general sense from the requirements of clinical medicine and trials, the term "health-related quality of life" (HR-QoL) is frequently used.

Assessment of QoL becomes crucial in situations in which a patient's treatment is likely to cause distressing symptoms or disturbances in physical functioning, work, family and social roles, cognition, or emotional adaption.[41] EORTC developed a cancer specific health-related QoL, HR-QoL, questionnaire measuring functional, global health status, single- and multi-item symptoms.[42]

HR-QoL is a multidimensional concept which quantifies the physical and psychosocial effects of an illness and its therapy.[43, 44] In cancer patients, health status is well reflected on the measured QoL, which is largely influenced by nutritional aspects.[44-46] Nutrition care should be integrated into overall oncology care because of its significant contribution to QoL. In patients with advanced colorectal cancer maintenance of HR-QoL is an important aim of treatment besides delaying disease progression.[5] Fatigue, pain, lack of energy, weakness and appetite loss occurred in more than 50% of patients with incurable malignant disease in whom a total of 37 symptoms have been identified.[18]

Nutrition care

Proper nutrition in hospital is regarded as a human right.[47] It is emphasized as an essential component of high quality health care with a team working to achieve this.[48, 49] The Council of Europe's Resolution on food and nutrition care in hospitals states that hospital management, physicians, pharmacists, nurses, dietitians and food service staff should work together in providing nutrition care.[50] Cancer patients often have a significant number of symptoms that reduce food intake. To relieve the symptoms pharmacological options should be chosen on an individual basis.[51] Symptom assessment followed by dietary advice and pharmacological prescription has been proved to reduce the overall symptoms in patients with advanced cancer.[52]

Nutrition care is defined as interventions and counselling of individuals on appropriate nutrition intake through the integration of information from the nutrition assessment.[53] In all, 44 tools for assessing nutritional status or identifying a person at risk of malnutrition are identified in the literature.[54] A validation of the tools for nutrition assessment is essential.[55-57] The screening tools developed for adults have been evaluated for validity, reliability, sensitivity and specificity, ease of use and cost-effectiveness.[58] Concerning outcome measurement, the American Society of Parenteral and Enteral Nutrition (ASPEN) stated in their guidelines from 2002 that only SGA had been validated with respect to clinical outcome.[58]

When different assessment tools are compared in the same group of patients, wide discrepancies are found in the prevalence of malnutrition.[59-63] Due to the lack of a gold-standard for nutrition assessment, a number of different tools are used. Diverse clinical outcomes such as the patients' mortality, survival, physiological measure, QoL or other clinical end-point should be assessed when evaluating the assessment tools.[64-66]

The nutrition care process (NCP) was introduced by the American Dietetic Association (ADA) in 2003 and updated in 2008.[48, 67, 68] The NCP aims to provide high-quality nutrition care, implicating doing the right thing at the right time, in the right way for the right person to provide the best possible results. The NCP consists of four distinct steps; (1) nutrition assessment, (2) nutrition diagnosis, (3) nutrition intervention, and (4) nutrition monitoring and evaluation (Figure 4).

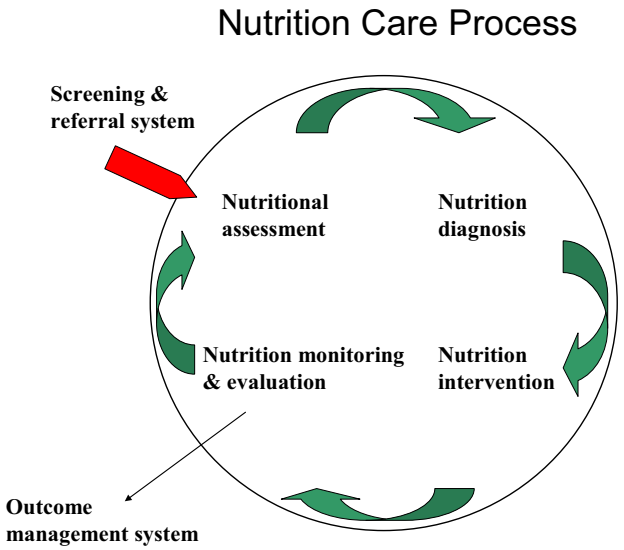


Figure 4. The nutrition care process.

Screening and Nutrition Assessment

Nutrition screening intends to identify patients at risk of nutrition deficit before it progresses to malnutrition.[69] The nutrition screening tool should be rapid to use, easy and sensitive.[70] Malnutrition is both under-recognised and under-treated.[71] Internationally there is an agreement that nutrition screening is essential for identifying those patients needing appropriate nutrition assessment and intervention.[72-76] Early identification of nutrition deficit allows for early intervention and may improve clinical outcomes.[70] In patients with advanced cancer nutrition intervention may at best only achieve weight stabilisation, suggesting early intervention is more beneficial to the patient.[77]

Best practice, as stated by NICE Guidelines requires that patients shown to be at nutrition risk should undergo nutrition assessment and be considered for treatment.[78] Nutrition assessment is a comprehensive evaluation completed by the clinical dietitian or health care professional with a speciality in nutrition and includes:

i. Food/Nutrition-Related History
ii. Anthropometric Measurements
iii. Biochemical Data, Medical Tests, and Procedures
iv. Nutrition-Focused Physical Findings
v. Client History

A complete nutrition assessment usually gathers information obtained by different health care professionals such as physicians, nurses, speech therapists as well as from biochemical and microbiological analyses, and is thus a multidisciplinary task.[78]

Sarcopenia

Loss of skeletal muscle is age-associated and termed sarcopenia.[79] Sarcopenia is derived from the Greek words "sarx" meaning flesh and "penia" meaning poverty. In 1989 Rosenberg suggested naming the decline of lean body mass seen in elderly people as sarcomalacia or sarcopenia.[80] Originally sarcopenia was described by Evans and Campbell in 1993.[81] Sarcopenia was associated with decreased muscle strength and functional capacity in elderly people.[82] The diagnosis of sarcopenia is generally based on a combination of percentage of muscle mass $\geq$ 2 standard deviations below the mean obtained in a reference population plus walking speed below 0.8 m/s in the 4-m walking test.[83] Several conditions other than aging may lead to the development of sarcopenia, namely immobilisation, nutrition deficiencies of protein and vitamin D, malabsorption, endocrine disorders and cachexia.[79]

Computed tomography (CT) and magnetic resonance imaging (MRI) are considered to be the most accurate imaging methods available for *in vivo* quantification of skeletal muscle.[84] In 1979 CT was introduced for quantifying undernutrition in hospitalised patients.[85] The use of CT for diagnostic purpose in cancer patients has raised the possibility of measuring muscle mass in this population.[84, 86-93]

Skeletal muscle components consistent with sarcopenia may be assessed by mid upper-arm muscle area by anthropometry, appendicular skeletal muscle index determined by Dual-energy X-ray Absorptiometry (DXA) or whole body fat-free mass index without bone

determined by bioelectrical impedance.[94] As a general rule the cut-off value for muscle mass is set below the 5th percentile.

Malnutrition

Malnutrition literally means bad nutrition. Generally there is no accepted definition of malnutrition. The term is used variously, and encompasses both undernutrition, overnutrition and imbalance in macronutrients and micronutrients.[13] Most commonly, malnutrition is denoted as undernutrition. The following definition of malnutrition is proposed of The British Association for Parenteral and Enteral Nutrition (BAPEN);

> "Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome."

The American Dietetic Association defines malnutrition as:

> "Inadequate intake of protein and/or energy over prolonged periods of time resulting in loss of fat stores and/or muscle wasting including starvation-related malnutrition, chronic disease-related malnutrition and acute disease or injury-related malnutrition."

Some authors also highlight the defective assimilation of food in the definition of malnutrition.[95, 96] The malnutrition/undernutrition concept therefore comprises food intake, digestion and nutrient requirement.

The criteria used to define malnutrition in malignancy vary widely and make comparison between studies difficult and may underestimate the size of the problem. In a cohort of 5,628 patients with neoplastic malignant disease, 7% of the patients were classified as malnourished based solely on BMI <20.[97]

Cachexia

The term cachexia is derived from the Greek words *kakòs* (bad) and *héxis* (condition). As long ago as 400 BC, Hippocrates wrote "the flesh is consumed and becomes water,… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest, and thighs melt away… The illness is fatal."[98] Cachexia is associated with several chronic diseases and accounts for about 20% of cancer deaths.[99] Patients suffering from cachexia lose lean body

mass, predominantly skeletal muscles, resulting in weakness and immobilisation. Cachexia is not solely a nutrition deficit, but a catabolic condition with complex metabolic changes leading to loss of adipose tissue and skeletal muscle.[100] Adipose tissue wasting is not as well established as loss of skeletal muscle. The importance of agreement about definition and classification of cancer cachexia is warranted and underlined in several publications.[101-104]

In 2007, a cachexia consensus working group met and agreed upon the following definition of cachexia;

> "Cachexia, is a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism and is associated with increased morbidity".[101]

The group recommended the following diagnostic criteria for cachexia:

Weight loss of at least 5% in 12 months or less in the presence of underlying illness,

PLUS THREE of the following criteria:

I. Decreased muscle strength (lowest tertile)
II. Fatigue
III. Anorexia
IV. Low fat-free mass index
V. Abnormal biochemistry
a) Increased inflammatory markers C-reactive protein (CRP) >5.0 mg/L, Interleukin-6 >4.0 pg/ml
b) Anaemia (Haemoglobin <12 g/dl)
c) Low serum albumin (<3.2 g/dl)

Based on a study of 170 weight-losing patients with advanced pancreatic cancer, the Cancer Cachexia Study Group (CCSG) proposed on that cancer cachexia is characterized by three main factors: body weight loss ≥10%, nutrient intake ≤1,500 kcal/day, and a level of CRP ≥10 mg/L.[105] Patients defined with cachexia according to these criteria had a shorter survival than patients without cachexia.

Later on, the SCRINIO (Screening Nutritional Risk in Oncology) Working Group[106] proposed a definition of cancer cachexia as follows:

> "cachexia is a complex syndrome characterized by a severe, chronic, unintentional and progressive weight loss, which is poorly responsive to the usual nutritional support, and may be associated with anorexia, asthenia and early satiation"

They proposed also a classification of precachexia and cachexia based on the absence or presence of weight loss >10%, anorexia, fatigue and early satiation.

Further, a group of experts in clinical cancer cachexia research took part in a consensus process involving two focus groups and two Delphi rounds ending up with the following definition of cancer cachexia, published in 2011;[94]

> "cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment."

Cancer cachexia was divided into three stages; precachexia, cachexia and refractory cachexia. At present there is no method described to identify precachexia. The criteria for cachexia were weight loss >5% over the past 6 months (in absence of simple starvation); or BMI <20 and any degree of weight loss >2%; or an appendicular skeletal muscle index consistent with sarcopenia and any degree of weight loss >2%.

Simple starvation in the general meaning is frequently defined as secondary nutrition impact symptoms or as secondary cachexia. It involves all causes of reduced dietary intake that can be corrected.[107, 108] Studies that examine the relationship between interventions toward nutrition impact symptoms and nutritional status are limited. One study of the prevalence of nutrition impact symptoms and their relationship to QoL and performance status highlights the importance of early identification and management of nutrition impact symptoms in order to provide optimal care for patients with cancer.[109]

To distinguish between malnutrition and cachexia is challenging. Both declines appear with loss of body weight and wasting. Malnutrition is proposed as reversible when adequate amounts of nutrients are provided; while cachexia is not treatable by this approach.[98]

Nutrition Diagnoses

Setting nutrition diagnoses challenges the clinical dietitian to critically consider the likely cause(s) of the nutrition problem and how it can be solved.[67, 110] Initially 62 nutrition diagnostic terms were identified for the dietetics' profession.[111] Later on, two diagnoses were deleted, namely hypermetabolism and hypometabolism. The reason for this was that dietetic practitioners are unable to treat these patients within their scope of practice. Of the 60 nutrition diagnostic terms, 22 commonly occurring diagnoses in oncological patients were content validated by members of the Oncology Nutrition Dietetic Practice group.[111] The diagnoses are divided into three domains; 1) Intake domain, 11 diagnoses, 2) Clinical domain, six diagnoses, and 3) Behavioural-Environmental domain, five diagnoses. Malnutrition belongs to the intake domain while unintended weight loss is one of the diagnoses in the clinical domain. Further, increased energy expenditure is one of the 60 diagnoses in the NCP but not incorporated into the terms validated by the Oncology Nutrition Practice Group.

Nutrition Intervention

Nutrition intervention is defined as "a purposefully planned action(s) designed with the intent of changing nutrition-related behaviour, risk factor, environmental condition, or aspect of health status". The nutrition intervention is typically directed towards resolving the nutrition diagnoses but may also be targeted at reducing the signs or symptoms of the nutrition diagnoses.[110] Ideally, the nutrition support should involve a team approach including clinical dietitians, nurses and physicians.[112]

Nutrition: Monitoring and Evaluation

The purpose of monitoring and evaluation is to determine if progress has been made and the goal(s) or desired outcome of nutrition care has been met. Monitoring and evaluation require active commitment to measure and record outcome indicators relevant for the nutrition diagnosis and intervention. The major goal of outcome management is to utilize collected data to further improve the quality of nutrition care rendered.

Recently the International Confederation of Dietetic Associations (ICDA) and the European Federation of the Associations of Dietitians (EFAD) decided to recommend their members to implement the NCP and the International Dietetics & Nutrition Terminology (IDNT) within the clinical dietitian professions.[113]

In conclusion, the NCP is a systematic problem-solving method developed to reflect current practice. The model intends to be used by food and nutrition professionals delivering nutrition care. The NCP is regularly reviewed and updated.

The Role of the Clinical Dietitian

According to the Council of Europe, clinical dietitians should assume a more central role in nutrition support.[50] In 2010, the Norwegian Directorate of Health published guidelines for palliation in oncology where among others competence requirements for clinical dietitians were set.[114] According to these guidelines, the clinical dietitian requires not only basic knowledge in oncology and nutrition care, but also knowledge about evidence based diet therapy. The clinical dietitian has to interact in the multidisciplinary team when decisions are made with focus on enteral or parenteral nutrition. Another issue for the dietitian is to initiate research. In all, these tasks require knowledge in several areas, including palliation, psychosocial behaviour and communication. Knowledge in ethics is of particular importance when deciding to give or not to give artificial nutrition support to patients with advanced cancer.[115] Use of enteral and parenteral nutrition in palliative care is controversial. It is mainly recommended in patients with a dysfunctional gastrointestinal tract to avoid dying of starvation.[116, 117] However, it has recently been described that home parenteral nutrition among patients enrolled in palliative home care services was used to supplement oral intake and not only in patients with dysfunctional gastrointestinal tract.[118]

One particular challenge for the majority of clinical dietitians working in hospital within several specialities is to gain sufficient experience to become professional and reliable.

> "*I met the wee dietician, but sure the stuff was for them you know, wanting to lose weight. Well I, said to her about that, [that] I was losing the weight and she said 'Oh well' she says, 'you don't have to stick to that diet, you don't need a diet'. You know, she was a young girl, you know, although well I'm saying to you she was a young girl, maybe she was a real dietician, you know I'm not taking that away from her… but this business of the weight loss, it's a rare commodity that anybody knows all about it*."[119]

The above statement describes the experience of a patient referred to a clinical dietitian for counselling. Being an effective counsellor involves nutrition knowledge and good communication skills but also the ability to develop a therapeutic relationship with the patients where exchange of information and dialogue is approached.[120, 121] As shown in one study, patients and their families wanted the weight loss acknowledged and information about why it was happening.[119] Their experience of weight loss and its impact on everyday life emphasises that more attention has to be paid to it in order to break the taboo that exists in clinical practice.[122, 123] When health carers avoid initiating discussion about symptoms in their belief that little could be done to help patients with weight loss, new approaches within this field have to be found.[123]

Aims of the Thesis

During the last two decades malnutrition in cancer patients has been of growing interest. The aetiology of malnutrition is complex. Today, there exists an increasing bulk of knowledge that nutrition interventions are beneficial in cancer patients. The overall goal within nutrition oncology is to prevent malnutrition.

Several conditions can influence the outcome of reaching this goal;

» Of major importance can be the health care system, responsible for focussing on the field of malnutrition.

» Applying different methods for assessing nutritional status and cachexia, not appropriately validated, can contribute to being unsuccessful in this context.

Therefore, the fundamental aims of this study were to obtain further knowledge about

- the focus of health care workers on clinical nutrition
- the criteria for assessing the patients nutritional status
- which methods classify patients with malnutrition and cachexia most appropriately with regards to clinical outcome.

The specific aims were

1. to investigate whether doctors and nurses on hospital units with greater access to clinical dietitians had a better awareness and focus on clinical nutrition (Paper I)

2. to describe the nutritional status of a group of patients with different types of advanced malignant neoplastic diseases in a palliative unit, and to validate the SGA questionnaire in these patients (Paper II)

3. to investigate the prevalence of nutritionally depleted patients by different nutrition assessment criteria in a cohort of patients with mCRC, and to examine whether the results obtained correlate with the overall survival and QoL (Paper III and IV)

4. to investigate the association between body weight changes and QoL after a follow-up period of three months (Paper IV)

Materials and Methods

Study populations and design are shown in Table 1.

Table 1. Study population

	Paper I	Paper II	Paper III	Paper IV
Population (N)	12,678 health care professionals (physicians/nurses /dietitians)	80 patients with miscellaneous malignant neoplasm of advanced stages	77 patients with mCRC	152 patients with mCRC
Setting	Working in Scandinavian Hospitals	Palliative in-patients ward	Oncology out-patients clinic	Oncology out-patients clinic
Country/ places	Denmark, Norway, Sweden	Trondheim	Edmonton, Trondheim	Trondheim
Included (N)	4,871 (1,753 / 2,759 / 359)	46	Edmonton: 27 Trondheim: 50	50
Design	A questionnaire based cohort study	A consecutive prospective study	A prospective cohort study	A prospective cohort study

Reference Populations

The reference data on QoL was obtained from a randomly selected population of Norwegians above 18 years.[124] A newer publication has shown that HR-QoL in the general Norwegian population appears to be stable over the 8 year period from 1996 to 2004.[125] The latter publication separated results by gender. For that reason the reference data from 1996 have been used.

The cohort of 50 mCRC patients included in Trondheim has been compared with a total of 760 mCRC patients referred to their first oncological consultation between 2003 and 2006 at three different hospitals in Scandinavia, namely Odense University Hospital in Denmark, Haukeland University Hospital in Norway and Uppsala University Hospital in Sweden.[4] The reference patients revealed an unselected patient cohort considered for palliative therapy. Terminally ill patients, older patients and those with low performance status may not have been referred for oncological consideration.

Methods

Dietary Intake

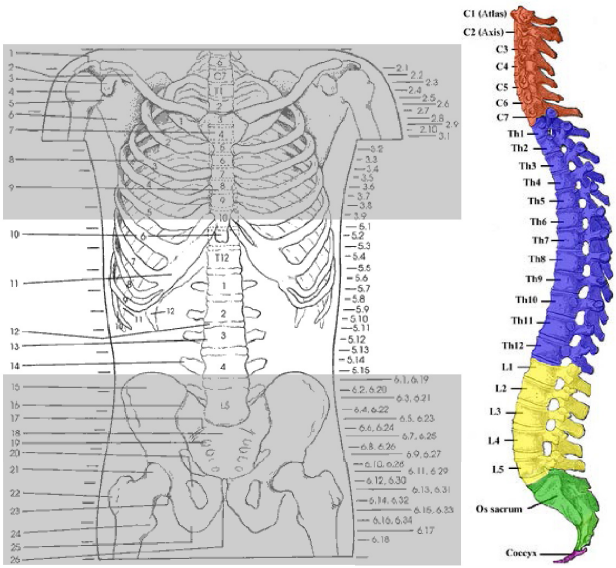
A dietary history was performed in one study (Paper 2). The patients were asked to describe their meal pattern, to quantify their meals in household terms and describe their food choice with emphasis on food of high or low energy content. The dietary intake was dichotomized as "frequent meals" defined as four meals or more, and "few meals" defined as three meals or less.

A dietary record was performed for four days (Norwegian population) and three days (Canadian population) in two studies (Paper III and IV). Food and beverages were recorded over consecutive days, including one weekend day. The quantity of food and beverages was described in household measures. Diet records were reviewed by a registered dietitian for completeness and were analyzed using the FoodProcessorII© nutrient analysis software (ESHA Research, Salem OR) in the Canadian cohort. In the Norwegian cohort the diet record was not reviewed for completeness. The energy intake was calculated by means of the software Diet 32 using the Norwegian National Food Composition Tables.

CT Image

CT images distinguish different tissue types *in vivo* based on attenuation characteristics.[126] Attenuation is a function of tissue density and chemical composition i.e. the electron per unit mass.[127] Tissue is mainly made up of carbon, nitrogen, oxygen, and hydrogen. The ratio of electron-to-mass for carbon, nitrogen and oxygen is 0.5, whereas the ratio for hydrogen is 1.0. Thus, the higher quantity of hydrogen in adipose tissue separates it clearly from other types of tissue and fluids. The attenuation values determined by CT are expressed in Hounsfield units (HU), based on a linear scale using water as reference (0 HU). CT distinguishes fat from muscle because fat displays negative attenuation values (-190 to -30 HU), while the attenuation values for muscle are within the range of -29 to +150 HU.[128] On the image, the adipose tissue is indicated by a darker area and the muscle by a lighter area. The cross-sectional area (cm^2) of the skeletal muscle can thus be calculated from a single CT image.[89]

CT estimates of adipose tissue-free skeletal muscle area are shown to correlate highly with corresponding cadaver values (R=0.99, standard error of estimate = 3.8 cm^2, $p<0.001$).[128] Further, CT estimates of muscle area at the 3rd lumbar vertebra (L3) (Figure 5) in patients with lung cancer or CRC correlate well with fat-free mass by DXA both at the L3 level (R=0.84, $p<0.001$) and in the whole-body (R=0.83, $p<0.001$).[89]



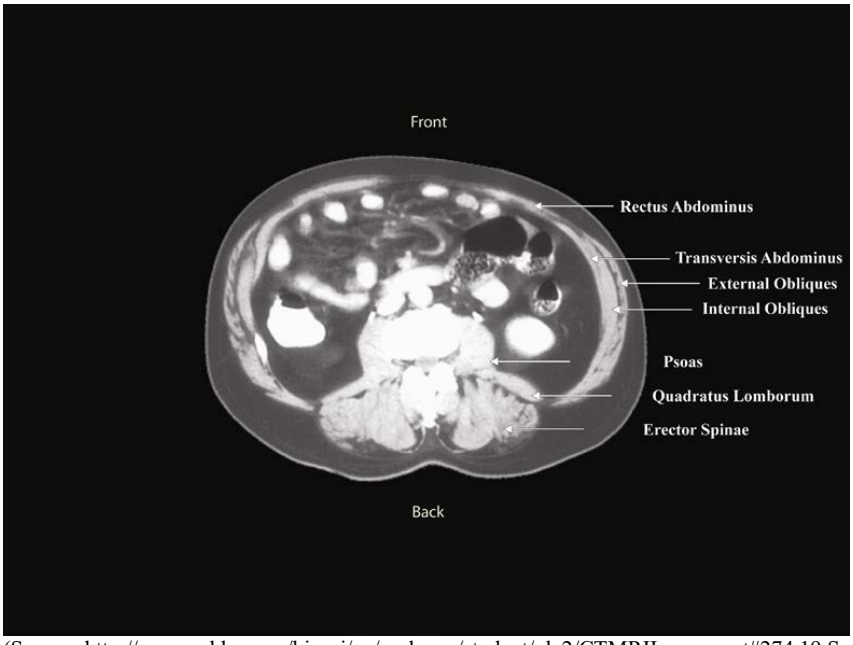
(Source: http://www.anatomyatlases.org/HumanAnatomy/5Section/Top.shtml and Wikipedia/Human vertebral column)

Figure 5. Lower Thorax (Lungs) and Abdomen.

The skeletal muscle area at a single slice 5 cm above L4-L5 correlated significantly (R^2=0.855) with the whole body volumes of skeletal muscle in healthy adults where the total body skeletal muscle volume was calculated by means of multi-slice MRI.[129] The area at L3 is therefore chosen as a landmark for CT images. Thus, whole body store of appendicular skeletal muscle seems to be calculated using the skeletal muscle area at L3. The muscles at this level involve psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, as well as rectus abdominus (Figure 6).

Different cut-off points for sarcopenia defined by CT image have been proposed. Cut-off points for sarcopenia obtained by CT images were described as gender-specific cut-off levels. There has been found an association between the occurrence of sarcopenia and mortality in 250 patients with malignant neoplastic diseases in the lung and gastrointestinal tract.[86] Cut-

offs were set at 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women. These cut-off levels are somewhat lower than the reference cut-off values (55.4 cm^2/m^2 for men and 38.9 cm^2/m^2 for women)[89] derived from the New Mexico Elder Health Survey[130] used in other studies.[93, 131]



(Source: http://www.mhhe.com/biosci/ap/seeleyap/student/olc2/CTMRIImages.ppt#274,19,Section 19)

Figure 6. CT image at the L3 level.

NRS-2002

The NRS-2002 is a system for screening of nutrition risk taking into consideration degrees of severity of disease and undernutrition.[132] The patients are scored according to each of the two components whether they are absent (score 0), mild (score 1), moderate (score 2) or severe (score 3). Finally one score for age >70 is added, giving a total score between 0 and 7. The screening system was validated in RCTs. The main goal was to find out whether NRS could distinguish between patients with positive clinical outcome and patients without an effect on clinical outcome. Of a total of 128 RCTs thirty studies were performed in cancer patients. The NRS-2002 is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) in the hospital setting.[69] Cancer patients in general are given the score of 1 for

severity of disease while patients with haematologic malignant disease are given the score of 2.

SGA

The SGA is an assessment of nutritional status classifying patients in groups to be well-nourished (SGA-A), moderately or suspected malnourished (SGA-B) or severely malnourished (SGA-C).[133] SGA have been translated into various languages. A scored patient-generated version (PG-SGA) has been developed were the patients fill in weight history, food intake, symptoms and activities. The health care professionals classify the disease, metabolic demand, physical examination and make the global scoring. The PG-SGA has been evaluated against SGA and had been found to have a sensitivity of 98% and a specificity of 82% in predicting SGA classification.[134]

The SGA was translated to Norwegian from a Swedish version which has been translated from English to Swedish, back-translated and retranslated again.[30] The Norwegian SGA questionnaire was used for the Norwegian patients in Paper 2, 3 and 4. The form was filled in by the clinical dietitian. The Canadian patients filled in the 1st page of the PG-SGA questionnaire.

The categorization in SGA classes was done as follows: Well-nourished implied stable body weight or increasing body weight and "no problems with eating" while Malnourished implied weight loss and decrease in nutrient intake with presence of nutrition impact symptoms.

Cachexia

The criteria set for cachexia by CCSG and EPCRC were a part of the baseline characteristics allowing characterisation of cachexia in the patients with mCRC included in the two studies. The association with respect to patients' survival and QoL was investigated.

Cachexia (CCSG)

Cachexia (CCSG) was defined as present when two of the following factors were fulfilled: CRP $\geq$10 mg/L, body weight loss $\geq$10% or energy intake $\leq$1500 kcal/d.[105]

Cachexia (EPCRC)

Cachexia (EPCRC) was defined as present when the patients either showed a weight loss ≥5% during the last 6 months, or a weight loss 2% - 5% in combination with a BMI <20, or a weight loss of 2% - 5%, together with the presence of sarcopenia.[94] Sarcopenia was defined using the cut-off point for the lumbar skeletal muscle index calculated from CT images.[86]

Cachexia (EPCRC-SGA)

The analyses in Paper 3 revealed a high proportion of the patients as having cachexia (EPCRC) at the same time as a high proportion of them were defined as well-nourished by SGA. This caused the idea of further defining cachexia (EPCRC) and only including those patients having ongoing weight loss. Cachexia (EPCRC-SGA) was therefore defined as present when patients fulfilled the criteria of cachexia (EPCRC) as well as being malnourished by SGA.

EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item questionnaire validated as reliable and a valid measure of QoL of cancer patients in multicultural clinical settings.[42] The 28 items measuring physical, role, emotional, cognitive, social functioning, symptoms and financial difficulties have a four-grade scale: Not at All, A little, Quite a Bit and Very Much. The two items concerning global QoL have a seven-grade scale of 1 Very Poor to 7 Excellent. The item scales are transformed to a 0-100 grade scale (Not at All = 0, A little = 33.3, Quite a Bit = 66.6 and Very Much = 100) (1 = 0, 2 = 16.6, 3 = 33.2 and so on to 7 = 100). For the multi-items scale the mean value of items was calculated. A high score on the functional scales and the QoL scale indicate a high level of health, whereas a high score on a single symptom or symptom scale represents a high level of symptoms. Differences in QoL score between groups of patients with or without nutrition decline and changes in QoL score over time were investigated for signs of statistical significance or clinical importance.[135]

Statistics

SPSS was used for statistical analyses. Two-sided P-values <0.05 were considered significant. The level was set at 0.01 in some analyses with multiple hypotheses.

Group comparisons

Group differences were explored using Pearson's chi-squared test and Fisher's exact test for categorical variables. For numerical variables Student's t-test and Mann-Whitney U test were used. Kruskal Wallis ANOVA was used when more than two groups were compared.

Survival analyses

Kaplan-Meier survival curves were used to visualise the cumulative survival percentage of patients with or without the different nutrition declines during 60 months follow up. The curves start at date of assessing nutrition status or date for CT image (Paper 3).

Regression analysis

Log-rank test

Group differences in survival time in the different nutrition decline groups were tested with the Log-rank test (Paper 3).

Cox proportional hazard regression

To analyze the effect of nation, age and gender on the hazard ratio for the different nutrition declines, Cox proportional hazard regression was used (Paper 3).

Linear regression analysis, adjusted age and gender

To test whether age and gender were confounders for differences in the mean QoL scores with the different nutrition declines, linear regression analyses were performed (Paper 4).

Summary of Papers

Paper I: Doctors and nurses on wards with greater access to clinical dietitians have better focus on clinical nutrition.

In this questionnaire based study about clinical nutrition practice in Scandinavian hospitals, 6,000 physicians and 6,000 nurses working in hospital units where under-nutrition of patients was documented to be common were invited to participate. Data from 2,759 nurses, 1,753 physicians and 359 clinical dietitians were stratified according to whether the clinical dietitians were visiting the units "frequently" ($\geq$3 times a week) or "rarely" ($\leq$2 times a week).

Nurses and physicians who met a clinical dietitian frequently versus those who met clinical dietitians rarely found it more seldom difficult to identify undernourished patients (16% vs. 25%). They claimed more rarely to lack techniques for identifying undernourished patients (21% vs. 38%), and more seldom that nutrition had a low priority in their department (14% vs. 30%). They had more often nutrition as a component of the continuous education program (58% vs. 39%). Sixty percent of those who met clinical dietitians frequently stated that there was no shortage of clinical dietitians whereas the group who met clinical dietitians rarely 60% stated that there was a shortage.

Of the clinical dietitians, 28% were working within one specific specialty. Of these, 67% visited their collaboration units frequently. They were mainly collaborating with medical gastroenterology, general medicine and medical oncology, respectively. Those clinical dietitians visiting their collaborative units frequently also referred more undernourished patients and more often took part in multi-disciplinary conferences at the units. There was no statistical difference between the opinion on sufficient clinical dietitian resources in the units between those clinical dietitians visiting their collaborative units frequently or rarely. The percentage of dietitians that stated there were sufficient resources was 11% and 5% respectively ($P = 0.096$).

In conclusion, the present study showed that physicians and nurses meeting clinical dietitians $\geq$3 times a week in hospital wards had better focus on clinical nutrition.

Paper II: Nutritional status of patients with advanced cancer: the value of using the subjective global assessment of nutritional status as a screening tool.

In this paper nutritional status was assessed in 46 patients with advanced neoplastic malignant diseases admitted to an in-patient palliative unit during a 3-months period. A total of 80 patients were admitted. The reasons for exclusion were readmission (16 patients), not able to carry out an interview (6 patients), moribund (3 patients) and other reasons (9 patients). Nutritional status was assessed by using objective criteria and by means of the SGA questionnaire. According to the objective criteria (body weight loss, BMI, TSF, MAMC, S-Albumin and S-Pre-albumin), 28 patients were estimated to be malnourished. By SGA, 30 patients were assessed to be malnourished as SGA-B and SGA-C.

The SGA classes correlated significantly with all the objective nutrition variables. The SGA-A patients showed (all results given as mean values) BMI of 28, weight loss of 4%, a TSF of 18 mm and MAMC of 26 mm, S-Albumin of 36 g/L and S-Pre-albumin of 0.23 g/L. The SGA-C patients showed BMI of 19, weight loss of 26%, TSF 8 mm, MAMC of 21 mm, S-Albumin of 31 g/L and S-Pre-albumin of 0.10 g/L. The moderately malnourished patients (SGA-B) showed mean values for all the objective nutrition variables in between the values for SGA-A and SGA-C groups.

Distribution of patients	Malnourished	Well nourished	Total number
SGA-B and SGA-C	27	3	30
SGA-A	1	15	16
Total number	28	18	46

The sensitivity of SGA was 96% and the specificity was 83%.
The food intake differed between well-nourished and malnourished patients. Malnourished patients ate small portions more often. The mean amount of symptoms affecting food intake was 3.7 and the most frequent symptoms were loss of appetite followed by early satiety. SGA-C patients had on average 5.7 symptoms affecting dietary intake.

In conclusion, we found that two thirds of the patients assessed were malnourished. The SGA questionnaire seems to be valid in assessing malnutrition in patients with different kind of advanced malignant neoplastic diseases.

Paper III: Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results.

In this paper, nutritional status and cachexia were assessed by different assessment criteria in 77 patients from Norway and Canada diagnosed with CRC stage IV and referred to an oncology clinic for treatment with chemotherapy. The nutrition assessment methods applied were NRS-2002, SGA questionnaire, sarcopenia and cachexia according to definitions from CCSG and EPCRC.

The number of patients defined as having nutrition decline varied considerably according to the nutrition assessment method used. Seven patients were underweight defined by BMI <20, 32 patients were at nutrition risk by NRS-2002, 26 patients were malnourished by SGA, 16 patients had cachexia according to CCSG criteria and 41 patients out of 75 patients had cachexia according to EPCRC criteria. Sarcopenia was defined in 28 patients out of 71. The large variation in the number of patients defined as having nutrition decline led to an investigation of the overlapping results obtained by the different nutrition assessment tools. A comparison between the results obtained by NRS-2002, SGA and cachexia (CCSG) revealed 14 patients being at risk by NRS-2002 without being detected by the two other methods. Seven patients were detected by SGA only, and two patients had cachexia (CCSG) without being detected by NRS-2002 or SGA. Similar overlaps between cachexia (CCSG), malnutrition (SGA) and sarcopenia have also been found. In the cohort where CT images were taken within 30 days from inclusion, eight patients were defined with sarcopenia without being detected by the CCSG cachexia criteria or SGA.

Regarding survival as clinical outcome, patients with cachexia (CCSG) had shorter survival in an unadjusted analysis, HR 2.43; 95% CI 1.32 to 4.47 (P = 0.005). When adjusted for nation, age and gender cachexia (CCSG), HR 2.26; 95% CI 1.18 to 4.32 (P = 0.014) and malnutrition (SGA); HR 1.83; 95% CI 1.06 to 3.13 (P = 0.029) remained significant predictors of survival.

In conclusion, the study showed a high prevalence of sarcopenia, malnutrition and cachexia among patients with CRC stage IV and a lack of concordance between the nutrition assessment tools used. A group of patients that fulfilled the CCSG cachexia criteria or had malnutrition (SGA) showed increased risk of death.

Paper IV: The association of different criteria for nutritional assessment with health-related quality of life in patients with advanced colorectal carcinoma.

In this paper, nutritional status and cachexia were assessed by different assessment criteria in 50 patients from Norway diagnosed with CRC stage IV. The assessment tools used were the same as in paper III but a third cachexia criterion was added, viz. the EPCRC-SGA. The criteria of EPCRC include weight loss $\geq$5% during the last 6 months but does not consider weight gain prior to assessment. Therefore, a new cachexia criterion, EPCRC-SGA were created in which patients with newly measured weight gain or stabilisation were defined to have no cachexia despite overall weight loss during the last 6 months.

The number of patients defined as having nutrition decline varied considerably depending on the nutrition assessment method used. Twenty-five patients were at nutrition risk by NRS-2002, 16 patients were malnourished by SGA, 14 patients had cachexia according to CCSG criteria, 31 patients had cachexia according to EPCRC criteria and 11 patients had cachexia according to EPCRC-SGA criteria. Sarcopenia was found in 10 patients out of 28.

The clinical outcome in this paper was health-related QoL. At baseline, the patients showed, compared to a healthy population, worse scores in physical, role, social function and global health status. They showed lower appetite, more constipation, diarrhoea and insomnia.

Appraised statistically, cachexia (EPCRC-SGA) and malnutrition (SGA) differentiated groups of patients had worse or better QoL scores on eight and seven scores. Appraised clinically, cachexia (EPCRS-SGA) differed on 14 scales, malnutrition (SGA) on 13 scales and cachexia (CCSG) on 10 scales.

At 3-months follow-up, 43 patients were alive. Of these 13 had gained $\geq$5% body weight, 7 had lost $\geq$5% body weight and 23 had stable weight. The patients with weight gain improved their QoL clinically with respect to role functioning, global health status, insomnia and appetite, whereas constipation worsened. In patients with weight loss, QoL worsened clinically on physical, role, emotional and social functioning as well as on the global health status, on pain and dyspnoea, while diarrhoea improved. Patients with stable body weight had unchanged QoL scores except for clinical worsening on diarrhoea.

In conclusion, the study showed a high prevalence of nutrition decline among patients with CRC stage IV. A group of patients that fulfilled the EPCRC-SGA cachexia criteria or had malnutrition (SGA) could be distinguished with clinically significant worse QoL. After the follow-up period of 3 months, only seven patients showed significant loss of their body weight. These patients also showed a significant worsening of a number of their QoL scores.

Discussion

The Role of the Clinical Dietitian

As shown in Figure 4 the nutritional care process starts with screening for nutritional risk and referral of patients at risk to nutritional assessment. Better focus on nutrition among health care professionals is assumed to be an important premise to start this process and to implement good nutritional care. In Paper I it has been found that health care workers with access to clinical dietitians in hospital units had better focus on clinical nutrition compared to those without.

Clinical dietitians have gained scientific knowledge in nutrition during their education and have the skills to translate this knowledge into useful dietary advice. Of the responding clinical dietitians in Paper I, only 28% were working within only one specific specialty and medical oncology was rated as the third common specialty. The majority of the clinical dietitians in Scandinavian Hospitals therefore work with patients with malignant neoplastic diagnoses as a part of several medical diagnoses they have to keep updated on. Those clinical dietitians working in one specific specialty visited the hospital units more often than dietitians working within two or more specialties. Thus enabling clinical dietitians to specialise within nutritional oncology may increase the awareness of nutrition care among cancer patients.

Similar results were found in a study where two thirds of a group of trainees in oncology rated nutritional status especially important for the patients' clinical outcome.[136] As many as 95% of the respondents stated that nutritional intervention would play a role for the QoL in a patient with significant weight loss. As many as 91% assumed that nutritional intervention could influence the patient's morbidity. A large number, 78%, claimed that nutritional intervention also influences the side effects due to anticancer treatment. Eighty percent of the trainees in oncology expressed uncertainty in their ability to identify patients with malnutrition. Major barriers to including patients in nutritional care processes were the lack of guidelines (69%), knowledge (60%) and time (56%). Lack of evidence obtained by means of RCT's was only looked upon as a barrier in one fifth of the respondents.

The clinical dietitian is responsible for educating other health care professions about their competency and to clarify their role in the management of the overall treatment of cancer

patients. In a questionnaire study of nurses' and doctors' understanding of cachexia and handling of associated symptoms, 62% and 21% of the respondents, respectively, mentioned referral to a dietitian as the most common management strategy for poor appetite and early satiety in patients with advanced malignancies.[137] The clinical dietitian may in different clinical situations advise the patient about which food to eat. However, several distressing symptoms should be treated pharmacologically.[51] Thus, a multidisciplinary approach seems to be essential. The clinical dietitian can perform nutrition assessment and support the multidisciplinary team with strategies to improve nutritional status. In an observational study of 116 elderly patients with cancer, nutrition intake was maintained in 92% of the patients until they died.[138] The most important interventions were treatment of distressing symptoms as pain, constipation, nausea, vomiting and heartburn, as well as dietary adaptation suggested by the clinical dietitian. Combined intervention of pharmacological treatment and dietary counselling resulted in increased appetite and body weight in a study with a mixed group of cancer patients with advanced disease.[139] The most common symptoms treated were early satiety, constipation, nausea and depression. No description of the dietary counselling was available in this publication.

The questionnaire study in Paper I has several limitations and the results must be interpreted with caution. The questionnaires were sent not only to physicians and nurses working with cancer patients but also to health care workers within specialties where undernutrition is common. It is not known how many of the respondents were seeing cancer patients regularly. However cancer patients are treated within several specialties, not only in oncology units. It is likely that the respondents from medical and surgical units have experience with cancer patients. It is not known whether the health care workers distinguish patients with malignant neoplastic diseases from patients with other diagnoses with regards to referral to clinical dietitians. Several studies published in the 1980s and 1990s have contributed to the view that nutritional counselling has no benefit on the nutritional status of cancer patients.[140-144] A systematic review published in 2004 claimed that there is a lack of evidence to support dietary advice in the management of disease-related malnutrition.[145] Moreover, the questionnaire was not developed primarily to explore the role of the clinical dietitians and its reliability was not tested for that purpose. Overall, the survey gave some indications that clinical dietitians play an important role when physicians and nurses collaborate more frequently with them. They found it also simpler to identify undernourished patients and experienced higher priority of nutrition in their department than those seeing the dietitian rarely.

Methodological terminology

One of the challenges during the course of this thesis was to find out which of the methodological terminologies strictly describe the different aspects of nutritional assessment. Terms like *cachexia*, *anorexia, sarcopenia*, *malnutrition* and *hypercatabolism* are frequently used as synonyms in earlier scientific reports.[103] *Protein calorie malnutrition*, *under-nutrition*, *wasting disease* are other common terms. W*eight loss* has been used as a substitute for *cachexia, caloric deficit*, *starvation* or *dehydration*.[102, 146, 147] Thus, more standardised concepts seem to be urgently needed. They would be of great value in clinical communication and they would also let to describe scientific work more clear-cut.[48]

The importance of agreement of what cachexia is has been pointed out.[137] However, researchers and healthcare professionals may use the assessment and management differently. It can be difficult to develop intervention strategies to improve a clinical condition when the terminology is interpreted differently.

In this thesis different nutritional assessments have been explored. We have investigated a population of patients with regard to *sarcopenia*, where the patients muscle mass index has been assessed by means of CT images. The patients' *nutritional risk* has been defined by means of criteria set by NRS-2002. The term *malnutrition* has been used according to the SGA questionnaire, in which the patients were defined as being well-nourished, moderately malnourished or severely malnourished, respectively. When *cachexia* was examined different criteria for cachexia has been applied and the results were described as cachexia (CCSG), cachexia (EPCRC) or cachexia (EPCRC-SGA), respectively. In this thesis, the broad term *nutritional decline* implicates any of the conditions referred to as malnutrition, cachexia, nutritional risk or sarcopenia.

Assessments and Clinical Outcome

Sample and Patient Characteristics

In Paper I, 6,000 physicians were randomly chosen from national databases of physicians, 6,000 questionnaires were sent to lead nurses at the same departments as the selected physicians. The lead nurse was asked to complete one questionnaire and give the remaining 4-9 questionnaires to the first nurses she/he met in the unit on a particular day. Clinical dietitians were found by means of companies offering nutritional supplements. In total, 678 clinical dietitians working in Scandinavian hospitals were identified. The questionnaire was sent to all these dietitians. The questionnaire consisted of 12 pages with 29 main questions and several sub-questions. The response rate of physicians, nurses and clinical dietitians were 29%, 46% and 53%, respectively. Due to the length of the questionnaire it can be anticipated that those who answered were more interested in nutrition than non-responders. Non-responders can of course introduce a study bias. A non-responder analysis was therefore performed among the Swedish physicians. The analysis revealed that non-responders were older, less interested in nutrition and found nutrition to be less relevant for their work.[148] The results from the questionnaire study must thus be interpreted with this in mind.

In Paper II, the patients were recruited from an in-patient palliative unit. During the recruitment period a total of 80 patients were admitted, only 46 of them were included in the study. Readmission was an exclusion criterion of 16 patients. The remaining 18 patients were excluded for several reasons; three were moribund, six were judged as not able to carry out an interview and nine patients were excluded of other reasons (psychiatric inconvenience, aphasia, not willing, amnesia, non-native-speaking, spouse' anxiety, intoxication). The 46 patients included in the study could be looked upon as a strongly selected group. Thus, the high prevalence of nutritional decline described in the results may not be representative for a general population of in-patients in palliative units.

The study of dietary intervention in mCRC patients was aimed at investigating the effect of individualised nutrition counselling according to the principle targeted nutrition care. The patients were randomised to dietary intervention or control. All patients were followed up every 3 months with assessment of body weight, bioelectrical impedance assessment, QoL questionnaire and diet history. The intervention group was offered consultation of the clinical

dietitian in between the ordinary follow-ups date. The patients were asked to call if they experienced weight loss. However, after the inclusion of 50 patients it was clear that control patients were referred to the dietary department for dietary counselling and intervention patients failed to make contact when their body weight declined. The inclusion was thereafter stopped and all patients were followed-up according to the protocol. There was no significant difference in the number of dietetic consultations between intervention patients and controls.

The Norwegian patients (Paper III and IV) were mainly recruited from the out-patient clinic. The intention was to ask all patients with mCRC referred to the Oncology Clinic with mCRC to participate in the study. However, when the patients not included in the study were checked further on, we found that 16 patients had not wanted to participate and 98 patients were living outside Trondheim. There were 38 patients living in Trondheim but it is not known how many of them were invited to participate. Barriers to study recruitment can be patient related or physician related. Important areas identified for recruiting patients in RCT, are trial specific factors, practical considerations, patient factors and anticipated outcome.[149] In cancer-related trials it is well-known that older adults, rural residents and individuals of low socioeconomic status are underrepresented.[150] During the recruitment period of our study, an additional study of chemotherapy in mCRC patients was initiated. In fact, the patients should have been able to participate in both studies. However, the inclusion of patients in our study was reduced, maybe due to the large amount of information demanded.

Patient characteristics of our study cohort and of the 760 mCRC[4] patients referred for their first oncological consideration at three hospitals in Scandinavia during 2003 to 2006 are shown in Table 2. The figures can at least give some information about how representative our small cohort is compared to a larger population with mCRC. The most striking differences were the number of metastases and the patients' weight loss. Our study included more patients with metastases to only one site as well as more patients with weight loss >10%. Age, gender, performance status and site of metastases were, however, similar in the two cohorts. Our patients were not consecutively included, as it was in the large study. Thus, despite similarities in most characteristics, our cohort may not be representative for the general population of mCRC patients referred for oncological consideration.

Table 2. Patient characteristics

	N	Age, year median	Gender, Men percentage	WHO status 0-3 percentage	Metastases, Number percentage	Metastases, Sites percentage	Weight loss percentage
Trondheim study	50	63	53	0: 40 1: 47 2: 13 3: 0	1: 65 2: 25 3+: 10	Liver 65 Lung 29 Lymph node 17	5-10:18 >10: 34
Scandinavian references	760	64	53	0: 50 1: 32 2: 14 3: 3	1: 35 2: 39 3+: 26	Liver 60 Lung 28 Lymph node 29	5-10: 28 >10: 13

Sarcopenia in Patients with mCRC

The prevalence of sarcopenia in the patients with mCRC in our study was high; about two out of five patients had such decline (Table 3). Sarcopenia was found in all strata of BMI classes except within BMI >30. Somewhat unexpectedly only two out of 23 patients with BMI >25 were sarcopenic (Paper III). We have not found any studies solely investigating prevalence of sarcopenia in colorectal cancer patients in the literature. In one study >50% of the patients were found to be sarcopenic, but this was in a mixed group of non-small cell lung cancer and CRC patients.[89] Another study analysing sarcopenic obesity (BMI >30) among cancer patients with mixed diagnoses revealed 38 patients out of 250 to be obese and sarcopenic, giving a prevalence of 15% for sarcopenia.[86] In pancreatic cancer patients sarcopenia was found in 56% of all investigated patients and in 41% of those with BMI >25.[93] In our study we used the cut-off value for sarcopenia from a study where skeletal muscle index defined by means of CT images were associated with mortality.[86] These cut-off values were lower than cut-off values derived from DXA where the cut-off was set by two standard deviations below the mean of healthy people.[89] Thus, the prevalence of sarcopenia found in our cohort could have been higher if the two standard deviation limit would have been used. Due to the small number of patients in our study the prevalence of sarcopenia found should not be considered as ultimate for patients with mCRC in general.

Interpreting the impact of having sarcopenia in mCRC patients we found the hazard ratio for risk of death to be 1.74 (95% CI = 0.99 to 3.03, p=0.053) after adjusting for nation, age and gender. It was not significant, but it can be argued that the trend was toward increased risk of death. Sarcopenia in overweight and obese patients has been found to be an independent

predictor of survival among cancer patients with mixed diagnoses (hazard ratio, 4.2; 95% CI = 2.4 to 7.2, P<0.0001) [86] and in pancreatic cancer patients (hazard ratio, 2.1; 95% CI = 1.2 to 3.5, P=0.006).[93] Before conclusions about the influence of sarcopenia on mCRC patients survival can be drawn, future studies are needed.

Table 3. Results from Paper II, III and IV.

Nutrition assessment	**Number of patients having nutrition decline**			**Clinical outcomes**		
				Survival	**QoL**	
	Mixed cancer diagnoses	Colorectal cancer		Colorectal cancer		
	N=46	N=77 Norway and Canada	N=50 Norway	N=77 Norway and Canada	N=50 Norway	
				Hazard ratio, 1) Median survival months	Number of QoL scales differing statistic significant	Number of QoL scales differing clinical significant
Malnourished by combination of criteria (body weight loss, BMI, TSF, MAMC, S-alb, S-pre-albumin	28					
Sarcopenia		28	10	HR 1.74 **15.3** vs. 17.3	0	4
Nutritional risk (NRS-2002)		32	25	HR 1.42 **15.8** vs. 19.1	0	2
Malnourished (SGA)	30	26	16	HR 1.83 **12.4** vs. 19.5	7	13
Cachexia (CCSG)		16	14	HR 2.26 **13.3** vs. 21.4	3	10
Cachexia (EPCRC)		41	31	HR 1.54 **15.8** vs. 19.5	0	5
Cachexia (EPCRC-SGA)			11	HR 1.82, 2) **13.7** vs. 19.1	8	14

1) adjusted for nation, age and gender, 2) not published

Some unexpected sarcopenia did not show significant statistical separation of QoL scales. This finding should not be overemphasised. The subgroups investigated were small with only 28 patients totally. Appraised clinically,[151] those patients having sarcopenia had lower scores on physical, role and social scales. We compared QoL measures with sarcopenia data obtained from CT images taken ± 30 days from the date were the patients replied to the QoL questionnaire. One can not assume that the skeletal muscle mass has been unchanged in this period. Ideally both measures should be taken on the same day. It would reduce the bias that can arise from changes in body composition during the two measures.

The high prevalence of sarcopenia in our cohort of mCRC patients raises the question of whether there can be an association between vitamin D and sarcopenia in this population of patients. Low serum of 25-OH vitamin D is shown to be related to low muscle mass and low muscle strength.[152] Results from several studies support the hypothesis that vitamin D is inversely related to colorectal cancer risk.[153] In a recent dose-response meta-analyses, it was found inverse associations between dietary vitamin D and CRC risk.[154] Further, in a cohort of 515 patients with mCRC it was found that 50% of the patients were vitamin D deficient (<20 ng/mL), and 82% were vitamin D insufficient (<30ng/mL).[155] Thus, future supplementation of vitamin D to depleted patients would easy to be performed. A screening for vitamin D deficiency should also be discussed, especially in a group of CRC patients.

Nutritional risk in Patients with mCRC

The NRS-2002 identified 32 out of 77 of the mCRC patients to be at nutritional risk. We have not found any publication in the literature investigating the NRS-2002 in a clinically defined cohort of mCRC patients. One study reported nutritional risk from NRS-2002 in CRC patients before elective surgery to be 39%, which is a similar finding compared to ours.[28]

When exploring the overlaps between nutritional risk, malnutrition and cachexia (CCSG) in the 73 patients in the cachexia (CCSG) cohort, 14 patients were detected at nutritional risk but they were not diagnosed as malnourished or having cachexia (CCSG). Twelve patients were not detected at nutritional risk but were malnourished and/or had cachexia (CCSG) (Paper III). NRS-2002 are suggested to be used within 48 hours after the patients hospital admission.[63] Those patients detected by NRS-2002 having nutritional risk should be further assessed for malnutrition. However, if NRS-2002 doesn't detect the malnourished patients

found by SGA, some patients will be lost for further interventions. As the most appropriate tool for nutritional screening that tool which best predicts clinical outcomes, has been proposed. When classifications of nutritional decline differ, the identification of the tool most effectively predicting outcome may be one useful indicator.[156] However, in our cohort of mCRC patients, NRS-2002 did not significantly predict the patients reduced survival or worse QoL. Thus, NRS-2002 is not the most appropriate tool in this population of patients.

Malnutrition in Patients with mCRC

The SGA questionnaire used has been proposed on two occasions during treatment and follow-up. When starting chemotherapy for mCRC, one third of the patients were defined as malnourished. In the group of patients with miscellaneous neoplastic malignant diseases admitted to a palliative unit, two thirds of the patients were malnourished. The SGA questionnaire has been validated and interpreted as the gold-standard for nutritional assessment in hospital settings.[63] Though it should be commented that the SGA does not cover the broad evaluation for nutritional assessment recommended in the NCP.

In the literature malnutrition in patients with CRC assessed by SGA has shown a prevalence of malnutrition between 30% and 55%,[29-31] with the exception of one study where only four patients out of 75 were defined as malnourished (SGA B/C)[21]. In another investigation 29% of newly diagnosed CRC patients were found to be malnourished.[157] Further, during chemotherapy in a small cohort of 33 CRC patients with two third of the patients at stage IV, almost half of them were defined as malnourished.[158] In general, the prevalence of malnutrition in patients with CRC is high as described in the literature. Our results investigating a clinically well-defined cohort of patients with mCRC showed that one third of them were malnourished. These findings seem to be in good concordance with the literature. Our cohort showed more than twice the number of patients who had experienced weight loss >10% compared to the mCRC reference population. The intention for participating in our study may, for some patients, have been their own experience of weight loss. Thus, the cohort studied could have been biased. However, the prevalence of malnutrition recently found is not greater than in comparable studies.

The median survival of well-nourished mCRC patients was 19.4 months compared to 12.4 months in the malnourished patients. Two other studies have explored survival in mCRC

patients using the SGA. One study found a median survival of 12.8 months in well-nourished patients, 8.8 months in moderately malnourished and 6 months in severely malnourished patients.[29] The second study found a median survival of 18.4 months in well-nourished and 10.3 months in the malnourished patients.[31] Overall, the significance of being well-nourished for prolonged survival in mCRC is notable.

Separation by SGA of patients in to groups of better and worse QoL was statistically significant on seven scores and clinically significant on 13 out of 15 scores. Thus, malnutrition has been found to be of great importance for QoL. A retrospective study in CRC, where half of the patients had mCRC, found similar statistical differences in QoL scores on global health score, role function, fatigue, pain, insomnia, and appetite loss.[159] Twenty six percent of the variation of change in QoL has been explained by changes in PG-SGA in a mixed group of cancer patients.[160] A study made on pancreatic cancer patients showed that weight stabilisation over 8 weeks was associated with improved QoL.[161] Not only the association between malnutrition and QoL has been established. There is growing evidence that nutritional interventions improve patients' nutritional status and QoL. Studies has been undertaken on dietary counselling in CRC patients,[162] in patients with mixed cancer diagnoses[163, 164] and of supplementation of parenteral nutrition in mCRC patients.[36]

Cachexia in Patients with mCRC

The prevalence of cachexia (Paper III, IV) has been investigated using the diagnostic criteria set by CCSG and EPCRC, see above. The results showed that 16 out of the 77 patients had cachexia according to CCSG, whereas as many as 41 had cachexia according to EPCRC.
It became evident that several patients had experienced weight loss, most often temporary. At inclusion, for 51 of the 77 patients either stable weight or recent weight gain were documented. These observations lead to the establishment of a new set of cachexia criteria where those patients with cachexia according to EPCRC but with recent weight stabilisation or weight gain were ultimately defined as having no cachexia. Thus, by means of the new cachexia criteria, entitled EPCRC-SGA, only 11 out of the 50 patients investigated were defined as having cachexia.

The prevalence of cachexia using these three different criteria varies threefold. The highest prevalence has been found using the criteria of EPCRC. Thus, it raises the question "which of

the definitions most accurately diagnoses cachexia?" With the lack of a gold-standard for diagnosing cachexia this has to be a question for future research. A recent publication requested universal collaboration to develop a diagnostic tool for assessing cachexia. There, one refer to the area of cancer pain where about 50 different tools are available.[165]

Cachexia (CCSG) was the tool that best distinguished patients in groups with better or worse overall survival. Median survival in the group without cachexia (CCSG) was 21.4 months compared to 13.3 months in those having cachexia (CCSG). Thus the difference in survival between the groups was found to be 8 months.

As well-known one main difference between cachexia (CCSG) and the other criteria of cachexia investigated is the inclusion of CRP. The CRP value is used as a surrogate marker for the assessment of cytokines. CRP is known to be synthesised in the liver in response to soluble cytokines, interleukin (IL)-1, IL-6, IL-11, tumour necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β).[166] Cytokines are mediating tissue catabolism in animal models. In humans their effect is more uncertain.[99] CRP elevation is found to be of prognostic significance in CRC patients previous to elective tumour surgery,[167-173] in metastatic CRC patients,[32, 174] in CRC patients with peritoneal carcinomatosis,[175] and in patients who are aimed to undergo surgical procedures of CRC liver metastases.[176] The cut-off value for CRP elevation has in these studies has been set at different levels (CRP > 5 mg/L,[32, 167, 168, 170] CRP > 8 mg/L,[171] CRP > 10 mg/L,[169, 173, 174, 176] CRP >35 mg/L.[175] In one study four different strata of CRP levels were investigated[172]). CRP elevation >1.8 mg/L was in one study not found to demonstrate significance differences with regard to overall survival in patients undergoing curative resection for CRC.[177] The cut-off level of CRP $\geq$10 mg/L in our study showed a hazard ratio, 2.56 for death; 95% CI = 1.4 to 4.6, P<0.002.

Of the three cachexia assessments investigated, the cachexia (EPCRC-SGA) differentiated most superior between the groups of patients with better or worse QoL. As EPCRC-SGA has been derived from the cachexia (EPCRC) excluding the number of patients being well-nourished by SGA, we would expect that the number of patients identified by the two assessments should be nearly identical. Nevertheless, 11 patients were defined having cachexia (EPCRC-SGA) and five more patients were malnourished by SGA. Further, the two assessments identified groups of patients differing in characteristics of worse QoL, in that

patients with cachexia (EPCRC-SGA) scored significantly on emotional and cognitive function scales while the malnourished patients scored significantly on role function.

Survival

Overall survival was best predicted of having cachexia (CCSG), secondly of being malnourished (SGA). The two nutritional declines are partly overlapping, 12 patients had both declines while four patients had only cachexia (CCSG) and 13 out of 73 patients were only malnourished (Paper III). The two assessment tools were thus distinguishing different cohorts of patients and seem to be not interchangeable.

One of the specific aims of this thesis was to investigate whether the different nutritional decline will be able to predict survival in a clinically defined cohort of mCRC patients. In the literature several prognostic factors for CRC patients have been published. Negative prognostic factors for CRC patients are as follow; more than one metastatic site, S-albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), white blood cell count (WBC), reduced haemoglobin level, low energy intake, anorexia, impaired physical function, low performance status, advanced age and low QoL.[31-33, 141, 178-184] Phase angle, determined by bioelectrical impedance analysis, in mCRC patients has been shown to be a prognostic factor.[185] Phase angle correlates with malnutrition (SGA) in CRC patients (stage III and IV) and thus may be a marker of nutritional status.[186] Also marital status has been shown to be of predictive value. Higher mortality has been found among patients who had lost their partners previous to surgery[187] and in widowed women.[188] In our study only a number of the known predictive factors were investigated. Our intention was not to sort out which factor finally should be used to predict survival in mCRC patients. Such a study has to be planned especially with this intention. Identification of prognostic factors is important for planning nutritional intervention and overall clinical management of cancer patients in general, especially for patients in advanced stages. Our study intended to compare different diagnostic tools for nutritional decline in mCRC patients and to find out whether they showed an input on clinical outcome. For this purpose we selected survival and QoL.

Quality of Life

We have studied the association between the patients QoL and several nutritional declines. Both cachexia (EPCRC-SGA) and malnutrition (SGA) distinguished most superior between groups of patients as having better or worse QoL. To maintain good QoL in patients with mCRC it seems to be important to know the aspects which affect QoL and be familiar with the relation between nutrition and QoL. Gender-associated differences in QoL in CRC patients were found. Women indicate more fatigue, nausea/vomiting, pain, dyspnoea, sleeping disturbances and appetite loss compared to men.[189] High levels of distress were found among unmarried and male patients.[190, 191] Other factors that may affect QoL in CRC patients were depression[192] and having a stoma.[193]

Dietary counselling in CRC patients undergoing radiotherapy increased dietary intake, maintained or improved nutritional status and improved all QoL function scales in a prospective, randomised, controlled trial.[162] Single symptoms and symptom scales deteriorated at the end of treatment. Nevertheless, this decline was transient and after three months the scores were reversed to basic level. In a mixed group of patients with CRC and gastric cancer, the patients who managed to gain weight had a higher score for global QoL and lower scores for fatigue and appetite loss, while no statistical difference was seen in QoL scores between the randomised groups.[194] A third study of nutrition intervention showed similar results with minimising weight loss, better global QoL and physical function in patients receiving dietary counselling during radiotherapy for malignant tumours in the gastrointestinal tract and the head neck area.[164]

Parenteral nutrition is a controversial topic and has not been established as nutrition treatment except when the patients suffer from a dysfunctional gastrointestinal tract and will, without adequate nutrition, die of starvation.[195] A randomised study on mCRC patients where one group was supplied with parenteral nutrition containing 675 kcal/day ha shown, that these patients experienced less chemotherapy-related side effects such as mucositis and diarrhoea. They also reported fewer symptoms such as early satiety, constipation, nausea, vomiting and abdominal pain. QoL improved most in the parenteral group in whom a significant increase in appetite was seen. The energy intakes in both groups were equal.
During the 3 months follow-up we found that the majority of the patients had stable body weight, seven patients lost and 13 patients gained body weight. Those patients losing weight

had a statistically significant worsening in physical, role and social functioning while diarrhoea improved. The reason for the improvement of diarrhoea was not obvious, may be it was a side effects of chemotherapy; induced when given and improved when it was stopped. It has been suggested that weight gain could be a marker of tumour response to chemotherapy.[196] On the contrary weight loss could indicate no response and ending chemotherapy. Another possibility is that less diarrhoea indicates dehydration of the patient. The patients gaining body weight had clinical improvement in role functioning, global health status, insomnia and appetite, whereas constipation worsened. In patients with stable body weight the QoL scores remained constant except for clinical worsening of diarrhoea. The improvement in QoL in the patients gaining body weight could indicate that weight gain is an improvement in nutritional status and not merely accumulation of water.

Conclusions and Future Directions

In the present thesis we have studied the focus of health care professionals on clinical nutrition, studied criteria for assessing nutritional status in cancer patients and evaluated methods for classifying malnutrition and cachexia regarding patients' survival and QoL as clinical outcomes.

The results from the papers can be summarised as follows:

- We found an association between increased focus on clinical nutrition and frequent visits of clinical dietitians in hospital units where undernourished patients were common. Physicians and nurses seeing clinical dietitians $\geq$3 times a week had a higher priority on nutrition, found it less difficult to identify undernourished patients and had more often nutrition on their educational programme.
- The frequency of malnutrition found was high (65% or two out of three) among patients with advanced malignant neoplastic diseases.
- Subjective global assessment of nutritional status was found to be a valid assessment tool for use in patients with advanced malignant neoplastic diseases. Patients have been categorized into three distinct groups of nutritional status; well nourished, moderately malnourished and severely malnourished.
- Two out of five mCRC patients were diagnosed with sarcopenia.
- Two out of five mCRC patients were at nutritional risk.
- One out of three mCRC patients was malnourished.
- Cachexia was present in between one and three out of five mCRC patients depending on the criteria used for assessing cachexia.
- The mCRC patients fulfilling the criteria for cachexia proposed by the Cancer Cachexia Study Group or malnourished according to (SGA) could be distinguished by a significantly shorter survival.
- There was overlap between cachexia (CCSG) and SGA, but four patients had cachexia (CCSG) without having malnutrition (SGA) and 13 patients were malnourished (SGA) without having cachexia (CCSG). Thus both tools dispartate patients that were not detected by the other tools.

- The mCRC patients fulfilling the criteria for cachexia defined by EPCRC, and adjusted for weight stabilisation or weight gain, could be distinguished with significantly worse statistical and clinical QoL. The same was found for malnourished (SGA) mCRC patients.
- A 3 months follow-up of mCRC patients referred to an Oncology Out-patient Clinic revealed that a high number of the patients remained weight stable or gained body weight. Only a minor part of the patients lost significant body weight. These patients also showed significant worsening of a number of their QoL scores. The patients gaining weight had a moderate clinical improvement in some QoL scores (role, global health status, insomnia, appetite).

The high prevalence of nutritional decline found in mCRC patients entering chemotherapy calls for more focus on nutrition at an earlier occasion in time in the patient's course of the disease. There are urgent needs to agree consent on how to define cachexia and make clear distinctions of undernutrition. Weight loss does not discriminate cachexia from undernutrition or vice versa. The mechanisms behind the muscle loss seen in cancer patients need to be explored. A longitudinal study investigating changes in body weight and body composition during the course of disease from initial diagnosis, during surgery, radiation and chemotherapy may bring more insight into the natural course of fluctuations in body composition. In such a study it would be crucial to measure muscle mass, muscle strength and include measures of physical activity, QoL and dietary intake.

In planning nutritional intervention it is essential to have an adequate diagnosis of the nutritional problem. Plain weight loss does not call for a particular intervention but calls for an investigation about the causes of the weight loss and most likely for interventions targeting the specific problem. For that reason the clinical dietitians need to sub-specialise in nutritional oncology to yield good quality advice and guide patients in nutrition during the course and varying stages of the disease.

A more in-depth understanding of the association between symptoms and dietary intake is warranted. Last, but not least, more knowledge about the impact of symptom management on dietary intake and nutritional status should be achieved.

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Paper I

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Paper II

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Paper III

Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results.

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Short title
Nutritional status and survival in colorectal carcinoma

Keywords
Advanced colorectal carcinoma, nutritional risk, cachexia, sarcopenia, malnutrition, survival

Abstract

Background & Aims

Different nutrition assessment tools and definitions are proposed for cancer-associated malnutrition and wasting (cachexia). We studied the associations between these assessments and overall survival in stage IV colorectal carcinoma patients.

Methods

Anthropometric measures, energy intake, biochemical variables, nutritional risk screening, assessment of malnutrition, cachexia and body composition from computed tomography images were analyzed, in 77 patients from Norway and Canada. Results were dichotomised into presence or absence of nutritional risk, malnutrition, cachexia and sarcopenia (low muscle mass) and associated with survival.

Results

Overall, 22% up to 55% of the patients had cachexia according to different cachexia criteria: 34% were malnourished, 42% were at nutritional risk, and 39% were sarcopenic. Forty-four percent of the patients did not meet criteria for any of these conditions. Patients with cachexia defined by Cancer Cachexia Study Group (CCSG) had shorter survival in an unadjusted analysis, [Hazard ratio (HR) = 2.43; 95% confidence interval (CI) 1.32 to 4.47; P = 0.005]. After adjusting for nation, age and gender, cachexia (HR = 2.26; CI 1.18 to 4.32; P = 0.014) and malnutrition (HR = 1.83; CI 1.06 to 3.13; P = 0.029) remained significant predictors of survival.

Conclusions

Nutritional depletion in up to 55% of the patients was found. The lack of concordance between the results obtained by different assessment criteria was obvious. CCSG's cachexia score was the best prognostic factor for overall survival.

1. Introduction

Malnutrition and weight loss is a frequent problem in patients with malignant neoplastic disease, affecting prognosis, length of hospital stay, health-care costs, quality of life and survival.[1] The prevalence of malnutrition varies among tumour types and sites, and the stage of the neoplastic disease. There is, however, also a variation between the criteria used for assessing malnutrition. In fact, screening for nutritional risk and referral for nutrition assessment are the fundamental first steps in the nutritional care pathway.[2] Identification of patients at risk of malnutrition allows an appropriate nutritional assessment and nutritional intervention with the aim of improving clinical outcomes and quality of life.[3] Nonetheless, there is no consensus on which method to use for assessing nutritional status in patients with malignant neoplastic diseases.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline recommendation for nutrition screening in the hospital setting is the Nutritional Risk Screening (NRS-2002).[4] NRS-2002 has not yet been validated in cohorts of patients with advanced malignant neoplastic disease. We previously reported that the Subjective Global Assessment (SGA) is a valid tool in assessing nutritional status in patients with advanced cancer [5] and several studies have confirmed this finding.[6-10]

Recent interest in cancer cachexia has led to the development of new diagnostic tools to better understand this syndrome. It is understood that the pathophysiology of cachexia-related weight loss in cancer patients consists of a mixture of reduced food intake (undernutrition) and abnormal metabolism, leading to muscle degradation.[11] Recently, the Cancer Cachexia Study Group (CCSG) suggested to apply three diagnostic criteria for cancer cachexia, (weight loss $\geq$10%, intake $\leq$1500 kcal / day, C-reactive protein (CRP) $\geq$ 10 mg/L), incorporating the sign of systemic inflammation related to the wasting process.[12] Another distinct process mentioned in the current literature is the wasting of lean body mass, particularly the loss of skeletal muscle, indicating cachexia in cancer patients. Several studies have demonstrated the utility of computed tomography (CT) images for the assessment of skeletal muscle wasting in cancer patients, and its association with reduced survival.[13-15] In a recently published review from the European Palliative Care Research Collaborative (EPCRC) concerning definition and classification of cancer cachexia, the incorporation of sarcopenia as a diagnostic criterion of cachexia together with weight loss and body mass index was suggested.[16]

At present, with the lack of consensus on which method to use for assessing nutritional status, an evaluation of nutritional screening and assessment tools is urgently needed. Thus, the aims of the present study were

1. to investigate the prevalence of patients identified to be nutritionally depleted by different nutritional assessment criteria in a cohort of patients with advanced colorectal carcinoma, and
2. to examine whether the results obtained correlate with the patients' overall survival.

2. Materials and methods

2.1. Patients

Fifty patients with stage IV colorectal cancer referred to the Department of Oncology, St.Olav´s University Hospital, Trondheim, were invited to participate in a randomised study comparing dietary counselling to standard practice. Recruitment spanned from March, 2004 to June, 2006. Inclusion criteria were histopathologically or cytodiagnostically confirmed adenocarcinoma of the colon and rectum at stage IV. Patients too confused to fill in the questionnaires were excluded.

At the Cross Cancer Institute, Edmonton, Alberta, 27 patients were recruited as part of a comprehensive cross-sectional evaluation in which nutritional, biochemical, and functional variables of the patients were assessed. Recruitment spanned from January, 2005 to October, 2006. Inclusion criteria were: Histopathologically or cytodiagnostically confirmed colorectal adenocarcinoma of the colon and rectum at stage IV, over 18 years of age, and able to communicate freely in English. Individuals who were pregnant, had a pace-maker, or were HIV+ were excluded.

Informed consent was obtained from all participants in both centers.

2.2 Clinical data

After inclusion, relevant clinical characteristics (age, sex, mode of diagnosis, metastatic sites, previous cancer treatment, and performance status according to the World Health Organization (WHO) scale) were recorded. In Trondheim, blood samples were analysed at the Biochemical laboratory, St. Olav's Hospital, for haemoglobin (Hb), albumin and C-reactive protein (CRP). CRP was analysed by means of an immunoturbidimetric method, (Roche Diagnostics, coefficients of variance (CV) = 2.9%). Blood samples from the Canadian cohort were analysed at the Alberta Provincial Clinical Laboratory, Edmonton, Canada. CRP was analysed by means of Rate Nephelometry on Beckman Image (CV=10%). All patients in the Norwegian cohort were followed up at the Department of Oncology clinically and with assessments of the nutritional status every 3 months during 2 years from inclusion or until death. In Canada patients were invited to come back for a second nutritional assessment after 2 months from initial visit.

2.3 Nutritional assessments

Anthropometric measurements

Patients were weighed without shoes, in light clothes or hospital gown, using a Seca digital scale, graduation 0.1 kg. Body height was measured to the nearest 1.0 cm with a mechanical wall-tape or stadiometer; graduation 1 mm. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Energy intake

Patients recorded their consumption of food and beverages for four (Norway) or three (Canada) consecutive days, including one weekend day. The quantities of food and beverages were described in household measures. Energy intake of the Norwegian cohort was calculated by means of the software Diet 32 (Aivo, Trondheim) using the Norwegian National Food Composition Tables. The energy intake of the Canadian cohort was calculated by means of the FoodProcessorII© nutrient analysis software (ESHA Research, Salem OR) using the Canadian Nutrient database. Energy intake (EI) was reported in absolute amounts (kcal), as well as divided by basal metabolic rate (EI/BMR) calculated using Harris Benedict equation, and per kilogram body weight (kcal/kg).

Sarcopenia

The skeletal muscle mass cross-sectional area (cm^2) was calculated using CT images. The level of the third lumbar vertebra (L3) was chosen as standard landmark in which two consecutive transverse images were assessed for each patient. The first image selected was that in which both vertebral transverse processes clearly were visible. The muscles at the L3 level comprise psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus. The CT images were analysed by using the Slice-O-matic software, version 4.3 (Tomovision, Montreal, QC). The mass of skeletal muscles was identified and assessed by means of the quantitative scale, measuring radiodensity in Hounsfield units (HU) with thresholds -29 to + 150.[17] The mean value of the HU in the two images was computed for each patient. The muscle mass index was calculated as skeletal muscle mass area (cm^2)/height^2 (m^2). Sarcopenia was defined using the cut-off point for lumbar skeletal muscle index of $\leq$38.5 cm^2/m^2 for women and $\leq$52.5 cm^2/m^2 for men.[13]

The actual CT images were acquired for the purposes of routine medical care and not only for body composition analysis. As the dates for CT scan did not always coincide with the date for initial visit and nutritional assessment, comparison between sarcopenia and nutritional assessment was done only for patients who had an abdominal CT examination within 30 days of the initial assessment (average ± SE = 15 ± 9.7 d).

NRS-2002

NRS-2002 consists of an initial and a final screening of the patients based on a score for impaired nutritional status (score 0 – 3), severity of disease (score 0 – 3) and age adjustment for patients aged >70 years (score 1) with a total maximum score of 7.[18] The nutritional scores are: **0** = normal nutritional status, **1** = weight loss >5% within 3 months, or food intake of 50-75% of the normal requirement during the preceding week, **2** = weight loss >5% within 2 months or BMI 18.5 – 20.5 kg/m^2 and impaired general condition or food intake of 25-50% of the normal requirement during the preceding week, **3** = weight loss >5% within 1 month (>15% in 3 months) or BMI <18.5 kg/m^2, and

impaired general condition or food intake of 0-25% of the normal requirement during the preceding week. The severity of disease was for all patients scored to 1 due to their diagnosis of advanced malignant neoplastic disease.

SGA

The SGA questionnaire used in Norway was a modified version translated to Norwegian. The SGA classification is consistent with the original of Detsky.[19] In Canada, the scored Patient-Generated SGA (PG-SGA) was used.[20] The two versions of the SGA questionnaires have been validated and the results obtained were judged essentially to be the same. PG-SGA had a sensitivity of 98% and a specificity of 82% when predicting the SGA classification related to Detsky.[20] Therefore, all patients could be classified according to the three categories: SGA-A "well-nourished", SGA-B "moderately malnourished" or SGA-C "severely malnourished".

Cachexia

Cachexia was defined by means of two different classifications. The first one was based on the CCSG criteria, in which the patients are defined as suffering from cachexia when two of the following factors were fulfilled: CRP $\geq$10 mg/L, weight loss $\geq$10%, or energy intake $\leq$1500 kcal/d.[12] The second one was based on the criteria recently published in an EPCRC review.[16] Here, the patients are defined as having cachexia, either when they show a weight loss $\geq$5% during the last 6 months, or, a weight loss 2% - 5% in combination with a BMI <20, or a weight loss of 2% - 5%, together with the presence of sarcopenia.

2.4 Statistical analyses

PASW Statistic 18 was used for the statistical analyses. Two-sided p-values < 0.05 were considered significant. In the survival analyses, all covariates except age were dichotomized. Kaplan-Meier survival curves and the Log-rank test were used to describe survival for the different nutritional status groups. In addition, we used Cox proportional hazards regression, unadjusted and adjusted for nation, age and gender. Patients' survival were determined from the date of nutritional assessment until death or the censor date in the survival analysis for NRS-2002, SGA and cachexia, in the survival analysis for sarcopenia from the date of CT image until death or the censor date. Date of censoring was set as the 13th of May 2009 in Norway and the 16th of April 2009 in Canada. The Mann-Whitney U test was used to analyze differences between BMI with or without sarcopenia.

2.5 Ethics

This study was approved by the Regional Committee of Medical Ethics at the Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, and by the Alberta Cancer Research Ethics Committee, Edmonton, Alberta, Canada.

3. Results

The clinical data for all of the 77 patients are shown in Table 1a. There were 41 males and 36 females with a median age of 63 years (22-85). Only 12 patients went through preoperative radiotherapy. Most of the patients, 65 out of 77, had been through surgical interventions. Metastatic tumour load was mainly found in the liver and 50 out of 77 patients had metastases only to one site. Many patients showed a high performance status according to WHO, and some patients, 10 out of 77, presented with performance status 2. Their good performance is also reflected by the fact that most of the patients, 66 out of 77, were considered to achieve chemotherapy.

Nutritional and blood parameters for all 77 patients are shown in Table 1b. Three patients in the Norwegian cohort did not answer the food diary. Twenty-one patients had CRP $\geq$10 mg/L.

Table 2 shows the association between the patients' dichotomized baseline values obtained by the different nutritional assessment tools and their risk of death (hazard ratio). At censoring time May, 2009, 60 out of the 77 patients had died. Eight and 9 patients were alive in the Norwegian and in the Canadian cohort, respectively. Follow-up was at least 2.5 years for patients alive at censoring time. Median survival was 15.8 months in the Norwegian cohort and 20.6 months in the Canadian cohort (p=0.15, Log rank test).

The number of patients defined as having nutritional decline varied considerably according to the different nutritional assessment methods used.

By means of the BMI, only 7 out of the 77 patients were considered to be underweight. Twenty-five patients had lost more than 10% of their body weight when entering the study and 20 of them had lost all within 6 months (not shown in table).

The assessment of sarcopenia, could not be done in six patients due to missing CT images at the L3 level. Of the remaining 71 patients in whom the muscle cross-sectional area measurements were made 28 patients were defined as sarcopenic.

According to the NRS-2002 method, 32 out of 77 patients were defined to be at nutritional risk, whereas only 26 out of the 77 were defined as malnourished by means of the SGA method.

Data for energy intake were missing in three patients and for CRP in one patient. In the remaining 73 patients, 16 were defined as having cachexia according to the CCSG criteria.

The EPCRC's definitions of cachexia were possible to apply in 75 patients, and 41 of them were defined as having cachexia.

As seen in Table 2, having cachexia, defined by the CCSG criteria, increases the risk of death to 2.43 (2.26) in the unadjusted (adjusted) analysis. The single items weight loss and CRP had significant prognostic value in the unadjusted analysis, as well as cachexia defined by EPCRC. The changes in hazard ratio for all nutritional variables were minor after adjusting for covariates.

Table 1a. Clinical baseline data of all patients (N = 77)

	Norway N	Canada N
	50	27
Male/Female	26 / 24	15 / 12
Diagnosis		
Ca. coli	27	20
Ca. recti	23	7
Radiation pre-surgery		
Yes	5	7
No	45	20
Surgery		
Yes	43	22
No	7	5
Metastasis		
Lymph nodes	11	2
Peritoneum	4	2
Liver	32	18
Lung	12	10
Brain	1	0
Carcinomatosis (peritoneal/pleural)	5	0
Skeletal	1	1
Other	2	3
Metastasis		
One organ	31	19
Two organs	15	4
Three or more organs	4	4
WHO performance status		
0	16	15
1	27	9
2	7	3
Intended to be treated with chemotherapy		
Yes	48	18
No	2	9

Table 1b. Nutritional and blood parameters of all patients (N = 77)

	Norway N 50	Canada N 27
Nutritional characteristics		
Height (m), mean (SD)	1.72 (0.08)	1.69 (0.08)
Weight (kg), mean (SD)	74.1 (12.6)	80.1 (23.2)
BMI (kg/m^2), mean (SD)	25.1 (3.5)	27.9 (7.4)
Nutritional intake		
Energy intake, kcal, median (range)	1792¤ (639-2902)	2352 (1119-3870)
Energy intake, EI/BMR**, median (range)	1.31¤ (0.47-2.09)	1.46 (0.89-2.32)
Energy intake, kcal/kg median (range)	25.9¤ (9-42)	28.5 (14-55)
Blood analyses		
Hb (g/L), median (range)	13.0 (8.5-15.7)	12.8 (9.4-15.4)
CRP (mg/L), median (range)	5.0 (<5-136)	4.2 (<1-18)
Albumin (g/L), median (range)	40 (29-47)	37 (23-43)

¤n=47, three of the Norwegian patients did not fill in the food diary.

** Energy intake, EI/Basal metabolic rate, BMR

Table 2. Nutritional characteristics at baseline obtained by means of the different nutritional assessments and their Hazard Ratio for risk of death in patients with colorectal carcinoma stage IV (N = 77)[1]

		Dichotomised			Unadjusted analysis			Adjusted for nation, age and gender		
					Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
	N		N	Alive[2] N						
BMI										
<20	7	<20	7	2	0.99	0.39 to 2.48	0.975	0.96	0.38 to 2.42	0.925
20.0-24.9	29	≥20	70	15	1.00			1.00		
25.0-29.9	25									
>30	16									
Weight loss ≥10%		No	52	14	1.00			1.00		
		Yes	25	3	1.83	1.07 to 3.11	0.027	1.67	0.95 to 2.94	0.078
Energy intake ≤1500 kcal		No	62	16	1.00			1.00		
		Yes	12	1	1.80	0.92 to 3.50	0.085	1.65	0.83 to 3.26	0.403
CRP ≥10 mg/L		No	55	17	1.00			1.00		
		Yes	21	0	2.70	1.56 to 4.66	<0.001	2.56	1.41 to 4.64	0.002
Sarcopenia[3]		No	43	11	1.00			1.00		
		Yes	28	3	1.67	0.98 to 2.85	0.061	1.74	0.99 to 3.03	0.053
NRS-2002										
Score 1	23									
Score 2	22	No risk	45	13	1.00			1.00		
Score 3	18	At risk	32	4	1.55	0.92 to 2.59	0.098	1.42	0.84 to 2.41	0.19
Score 4	11									
Score 5	3									
SGA										
SGA-A	51	Well-nourished	51	13	1.00			1.00		
SGA-B	20	Malnourished	26	4	1.67	0.98 to 2.83	0.058	1.83	1.06 to 3.13	0.029
SGA-C	6									
Cachexia (CCSG)[4]										
Score 0	37									
Score 1	20	No cachexia	57	16	1.00			1.00		
Score 2	12	Cachexia	16	1	2.43	1.32 to 4.47	0.005	2.26	1.18 to 4.32	0.014
Score 3	4									
Cachexia (EPCRC) [5]		No	34	10	1.00			1.00		
		Yes	41	5	1.71	1.01 to 2.90	0.046	1.54	0.88 to 2.71	0.133

[1] Survival was determined from the date of nutritional assessment until death or the censor date in the analysis for BMI, cachexia, SGA and NRS-2002, and from the date of CT image until death or the censor date in the analysis for sarcopenia. [2] At date of censoring. [3] Number patients with accessible L3 in CT images (N=71). [4] Cancer cachexia study group. [5] European Palliative Care Research Collaborative

Table 3 shows the relation between BMI and sarcopenia in those 49 patients in whom the CT images at the L3 level were prepared within 30 days from study baseline. Mean BMI of patients with sarcopenia was 22.4 kg/m^2. In patients without sarcopenia (p=0.001) it was 27.5 kg/m^2. Rather surprisingly, two patients with BMI > 25 kg/m^2 were considered to have sarcopenia.

Table 3. Relation between BMI classes and sarcopenia in patients with colorectal carcinoma stage IV (N = 49[#])

	Sarcopenia	
BMI	Yes	No
<18.5	2	0
18.6-19.9	2	1
20-24.9	11	10
25-29.9	2	10
>30	0	11

[#]Number of patients with CT images within 30 days from baseline, p<0.001 (Mann–Whitney U test).

Overlaps between the various assessments are shown in Figure 1. Out of 73 patients, 32 (44%) showed no nutritional decline by any of the methods used. Only nine patients were identified as nutritionally deranged by means of all the various assessments. The lack of concordance between the results obtained by means of the different nutritional assessment tools was striking. With the NRS-2002 method, quite a large number of patients (14) were identified as having nutritional risk whereas none of the other two methods used were able to detect these patients. Almost all of the 16 cachectic patients defined according to the CCSG criteria (CRP ≥10 mg/L, weight loss ≥10%, or a dietary intake ≤1500 kcal/d) were identified by means of the NRS-2002 or by the SGA methods. However, four patients with these rather obvious indices of malnutrition were not identified by means of the SGA criteria.

The overlaps between sarcopenia, SGA, and cachexia (CCSG), are shown in Figure 2 for those 49 patients in whom the CT images at the L3 level were taken within 30 days from study baseline. Notably, eight patients classified as sarcopenic were not identified as being malnourished or as having cachexia.

Overall survival according to the presence or absence of sarcopenia, nutritional risk (NRS-2002), malnutrition (SGA), CCSG cachexia, and EPCRC cachexia is shown in Figs 3 a-e. Median survival for patients in the non-sarcopenia and that for the sarcopenia group were 17.3 and 15.3 months, respectively (Log rank test, p=0.058). Median survival for patients with the absence or presence of nutritional risk (NRS-2002) was 19.1 and 15.8 months, respectively (Log rank test, p=0.095). Statistically, there were no significant differences in survival between the patients in the SGA-groups A, B and C. Median survival for patients belonging to the SGA-A group was 19.5, compared to 12.4 months in the SGA-B and C groups (Log rank test, p=0.055). There was a significant difference in survival in favour of the group without cachexia (CCSG) with a median survival of 21.4, compared to 13.3 months in the group with cachexia (Log rank test, p=0.003). Median survival for the patients defined according to cachexia (EPCRC) was 19.5 months without cachexia, compared to 15.8 months with cachexia (Log rank test, p=0.043).

4. Discussion

Patients with malignant neoplastic diseases are considered at risk for sarcopenia, malnutrition, and cachexia. Owing to the lack of a clear-cut concept of the criteria defining these conditions in cancer patients, different nutritional assessment tools have been used. In the present study, the results obtained by means of these assessment tools in a relatively homogenous group of patients reveal a high degree of inconsistency in the classification of nutritional decline of individual patients.

Sarcopenia

The prevalence of sarcopenia was high and sarcopenia was found in all BMI classes except the obese ones. Five times more patients were overweight/obese than underweight. The normal and overweight/obese patients may appear well nourished despite loss of significant amount of body weight or muscle mass. In earlier studies, the prevalence of sarcopenia in overweight/obese patients with advanced pancreatic carcinoma, and in a mixed group of patients with lung and colorectal carcinomas is reported to be present in 16% and 22%, respectively.[14, 21] In the present study, only two out of 23 overweight patients had

Fig. 1. Overlaps between Cachexia as defined by the Cancer Cachexia Study Group (CCSG), Malnutrition by Subjective Global Assessment (SGA) and Nutritional Risk by Nutritional Risk Screening 2002 (NRS-2002) in patients with colorectal carcinoma stage IV (N=73). Forty three patients out of 73 were diagnosed with nutritional depletion by means of one, two or three of the nutritional assessment tools used, whereas the remaining 30 patients were noted to be without.

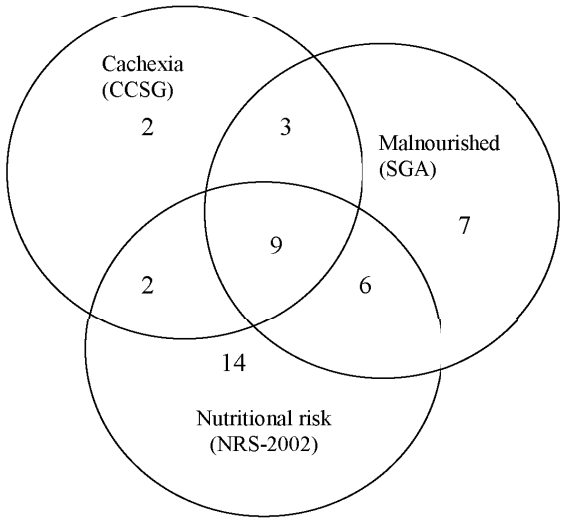
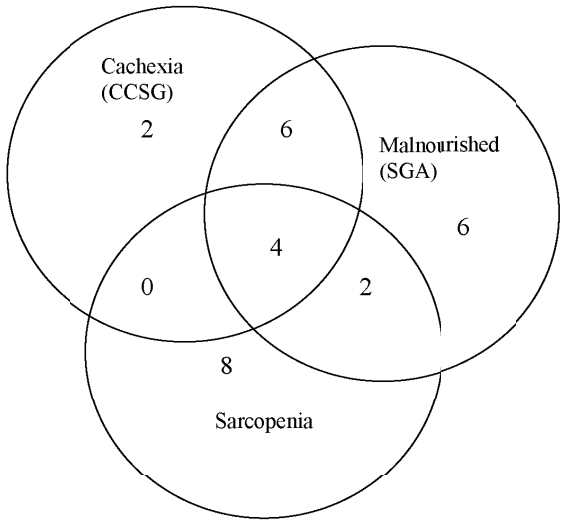


Fig. 2. Overlaps between Cachexia as defined by the Cancer Cachexia Study Group (CCSG), Malnutrition by Subjective Global Assessment (SGA) and Sarcopenia in patients with colorectal carcinoma stage IV. Subgroups of patients having CT images taken within 30 days from inclusion(N=49).



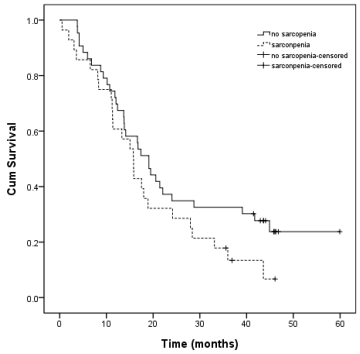


Fig. 3a. Overall survival of patients with colorectal carcinoma stage IV (N=71) with respect to the presence (dotted line, N=28) or absence (solid line, N=43) of sarcopenia.

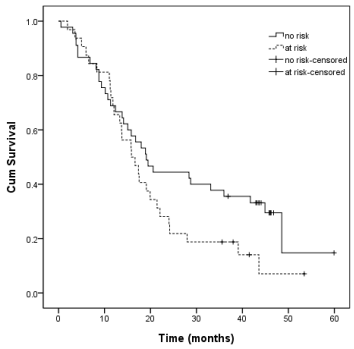


Fig. 3b. Overall survival of patients with colorectal carcinoma stage IV (N=77) with respect to the presence (dotted line, N=32) or absence (solid line, N=45) of nutritional risk (NRS-2002).

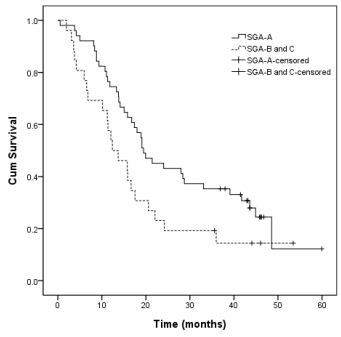


Fig. 3c. Overall survival of patients with colorectal carcinoma stage IV (N=77) with respect to the presence (dotted line, N=26) or absence (solid line, N=51) of malnutrition (SGA).

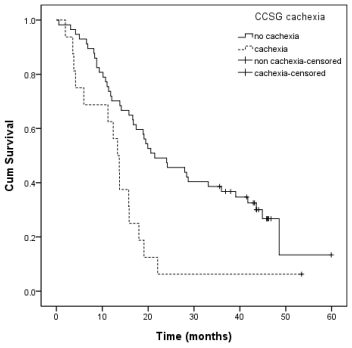


Fig. 3d. Overall survival of patients with colorectal carcinoma stage IV (N=73) with respect to the presence (dotted line, N=16) or absence (solid line, N=57) of cachexia defined by the Cancer Cachexia Study Group.

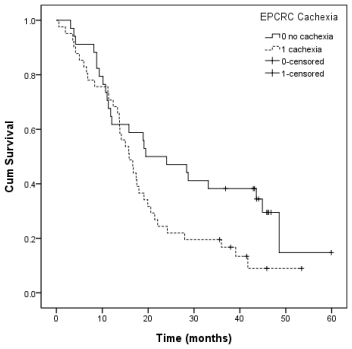


Fig. 3e. Overall survival of patients with colorectal carcinoma stage IV (N=75) with respect to the presence (dotted line, N=41) or absence (solid line, N=34) of cachexia defined by the European Palliative Care Research Collaborative.

signs of sarcopenia. The prevalence of sarcopenia in patients with different malignant neoplastic diseases has not been thoroughly investigated so far.

There was almost statistical significance for reduced survival in the patients with sarcopenia and the hazard ratio was similar to that found for SGA in the unadjusted analysis. The importance of sarcopenia for survival has until now mainly been studied in older people in whom muscle mass decrease has been related to functional impairment and loss of autonomy.[22] In cancer patients, diagnostic and follow-up CT images can be used to assess the

occurrence of sarcopenia and to establish its importance for survival. It is important to point out that sarcopenia in the present study was found in 8 patients who did not have cachexia or malnutrition.

The aetiology of sarcopenia is multifactorial.[23] Whether, or not sarcopenia is a result of immobilization and reduced physical activity or a consequence of metabolic components is a question that still remains unanswered.

NRS-2002

The NRS-2002 identified 42% of the patients to be at nutritional risk. Almost half of them were not identified as being malnourished by SGA and did not fulfil the criteria for cachexia (CCSG). The NRS-2002 considers patients at risk when the score is 3 or higher. Patients with an advanced malignant disease will easily accumulate 3 points; one point for the presence of cancer, one for age >70 years, and one for weight loss. As surgery is often the primary treatment in colorectal carcinoma it is probably the reason for some weight loss as well. Actually, in this group of patients, NRS-2002 may identify a falsely large proportion of patients at nutritional risk and seems, therefore, to be less useful for nutritional screening.

According to the Venn-diagram, NRS-2002 was missing patients which by SGA were identified as malnourished. Although, SGA may not represent a golden standard, it has been previously found to have both high sensitivity and specificity when evaluated against objective nutritional variables.[5]

SGA

In this study about one third of the patients were classified as malnourished according to the SGA. To the best of our knowledge, this is the first study made on a fairly homogeneous group of patients with stage IV colorectal carcinoma. Nutritional status measured preoperatively in patients with colorectal carcinoma with different stages of the disease revealed 41% of the patients as malnourished according to SGA.[24] Here, only 8% of the patients were at stage IV. Another study of colorectal carcinoma patients prior to radiotherapy showed a prevalence of 38% malnutrition assessed by the SGA tool.[25] In the present study, 59% of the patients were at stage III/IV. Despite different stages of the disease and different oncological treatments, a prevalence of malnutrition of 30-40% must be considered to be quite substantial.

Cachexia

The CCSG definition of cachexia is one of several proposals in this field. It was introduced in a study of patients with pancreatic carcinoma in which cachexia was found to be related to the patients´ survival.[12] In that study, 60% of the patients had cachexia. HR for overall survival was 2.23, a HR value close to that of our findings. These observations suggest that the CCSG definition of cachexia used should be applicable also in advanced colorectal carcinoma. According to the EPCRC's newly published definition and classification of cancer cachexia[16] a greater number of our patients were classified as having cachexia. As mentioned above, by means of the EPCRC's criteria, cachexia is diagnosed with weight loss >5% over the past 6 months or any degree of weight loss >2%, and BMI <20 or an appendicular skeletal muscle index consistent with sarcopenia. Using these EPCRC criteria, the prevalence of cachexia in the present study was found to be more than 50%, because as much as 39 of them had a weight loss of > 5%. As a matter of fact, 20 of these patients were classified as well-nourished by means of the SGA criteria and had stabilized or gained weight during the last month before baseline.

Another aspect is the use of CRP as a criterion for cachexia. EPCRC's criteria do not include CRP in the definition of cachexia, obviously due to the fact that cachexia can exist without overt systemic inflammation.[16] CRP can be elevated for reasons other than cachexia; its levels can rise dramatically during an inflammatory process in the body. The patients in our study, recruited from outpatient clinics, showed a rather good performance status. Their elevated CRP probably is caused by the malignant disease itself and not by an incidental infection. Therefore, CRP may be a relevant parameter in cachexia. Having cachexia (CCSG definition) was the only variable that reached statistical significance in both unadjusted and adjusted survival analyses and was the most powerful predictor of survival in this study.

The patients included showed also, as expected, a highly functional performance

status according to the WHO criteria. As we did not perform an analysis of the patients excluded, there could be a selection bias. Patients who reject participation in studies have been shown to be older and more seriously ill.[26] The prevalence of malnutrition is reported to be higher in patients of advanced age.[27] Therefore, the occurrence of nutritional decline in an unselected cohort of patients with metastatic colorectal carcinoma may also be higher. Thus, the results should not be generalized applicable to an unselected population of patients with advanced colorectal carcinoma.

The observed lack of concordance among the different nutritional assessment tools used in the present study highlights the need for more specific nutritional assessment tools for screening of patients with malignant neoplastic disease. A high proportion of the patients were identified by one tool only. It can be argued that a combination of CCSG cachexia and SGA can be a possible tool since both remained significant after adjusting for covariates. An important task will also be to investigate how the results obtained by such assessment tools can be linked to a nutritional intervention.

The different nutritional assessment tools were compared with regard to the patients overall survival. Since the majority of them received chemotherapy, it can be claimed that the survival data obtained have been influenced by treatment response, a possibility which has not been investigated in the present study. It has previously been shown that patients with weight loss at the time of initiating chemotherapy receive lower chemotherapy doses, develop more severe toxicity, and receive less antineoplastic treatment.[28] Therefor, the reduced survival in nutritionally depleted patients shown in the present study may be associated with a lack of treatment response.

In conclusion, the results of the present study show a high prevalence of sarcopenia, malnutrition, and cachexia among patients with advanced colorectal carcinoma and a lack of concordance between the nutritional assessments tools used. However, using the CCSG cachexia criteria, a group of patients with short survival was significantly distinguished.

Conflict of interest statement
The authors have no conflict of interest to declare.

Statement of authorship
Author's contributions to the manuscript are as follows: LT carried out the study and data analysis and drafted the manuscript. GF was responsible for recruitment of patients, data collection, samples and data analysis. SL contributed with statistical analysis and interpretation of the results. HU calculated energy intake and contributed with data analysis. VB contributed to the presentation of the results and writing of manuscript. CP was responsible for recruitment of patients, data collection and writing of manuscript. LB analyzed the CT images and contributed with the data analysis. UF conceived the study, and participated in its design, data analysis and writing of manuscript. All authors read and approved the final manuscript.

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Paper IV

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