Malnutrition has detrimental effect on patient’s quality of life and survival. In patients with head and neck cancer (HNC) the tumor itself, its location, surgical procedures, and oncological therapies cause significant symptoms and side effects, which interfere with eating and expose to malnutrition. This thesis focuses on different nutritional status assessment methods and nutrition intervention strategies, which may be applied in the development of novel nutrition support strategies among HNC patients.
Nutritional Status and Effect of Nutritional Counseling in Patients with Head and Neck Cancer
HELENA ORELL

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To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in the Department of Oncology, Helsinki University Hospital, Haartmaninkatu 4, Helsinki, on Thursday, June 14th 2018, at 12 noon

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Departments of Otorhinolaryngology – Head and Neck Surgery, and Oncology
Helsinki University Hospital and University of Helsinki, Helsinki, Finland

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To my dear father
Viljo Orell
1921-2004
"If you do something do it well, or don’t do it at all."
To my dear father

Viljo Orell
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“If you do something do it well, or don’t do it at all.”
ABSTRACT:
In patients with head and neck cancer (HNC) the tumor itself, its location, surgery, and oncological therapies may cause significant symptoms such as pain, mucositis, nausea, dysphagia, and dryness of mouth, which interfere with eating and give rise to malnutrition. Furthermore, at a more advanced stage of disease, cachexia is prevalent and associated with poor survival. Nutritional status and nutrition intervention have not been studied earlier in a Finnish HNC population.

The aim of the randomised and controlled study was to assess the effect of pre-planned nutritional counselling during chemoradiotherapy (CRT), given by a dietitian either in an intensive manner or on-demand (Study IV). Furthermore, we evaluated prevalence of malnutrition, cachexia, nutritional risk and vitamin D (serum 25-hydroxyvitamin D, S-25-OHD) status prior to diagnosis.

Between November 2007 and December 2009 altogether 65 patients participated in the study, out of which 58 patients participated in the intervention study. Prior to diagnosis 34% of all patients were malnourished, and 28% were at nutritional risk (Study II). Low handgrip strength (HGS) was seen in 43% and cachexia in 31% of the patients (Study III). Vitamin D deficiency was seen in almost half of all patients (Study I) and lower concentrations were seen in patients with malnutrition and cachexia. The intervention study showed that both intensive and on-demand nutritional counseling could stabilize weight loss in patients with pre-treatment weight loss (Study IV). Nutritional status and weight loss did not differ in the two study groups. Baseline malnutrition and cachexia decreased the overall survival and the disease-free survival, whereas treatment-induced weight loss was not associated with survival.

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TIIVISTELMÄ:
Pään ja kaulan alueen syöpäpotilaill e voi kehittyä kasvaimen sijainnin, leikkauksen ja syöpähoitojen takia merkittäviä syömistä haittaavia oireita kuten kipua, suun limakalvon tulehdusta, pahoinvointia, nielemisvaikeuksia ja suun kuivumista. Nämä altistavat potilaan vajaaravitsemuksen kehittymiselle. Lisäksi kaakeksian yleisyys kasvaa taudin edetessä ja on yhteydessä heikentyneeseen elossa oloaikaan. Tämän potilasryhmän ravitsemustilaa ja ravitsemushoitoa ei ole aiemmin tutkittu Suomessa.

Tämän satunnaistetun ja kontrolloidun tutkimuksen tavoitteena oli verrata ravitsemusterapeutin antamaa intensiivistä ravitsemusohjausta tarpeen mukaan annettuun ohjaukseen. Lisäksi selvitettiin vajaaravitsemuksen, kaakeksian ja ravitsemusriskin yleisyys sekä D-vitamiinistatus diagnoosihetkellä.


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I am thankful to my dear colleagues Anne, Jetta, and Pia for their constant understanding and patience during past years. I am grateful to my dear friends Helena, Sari-Sofia, Tuija and Päivi as well as the sewing gang for the many joyful moments that gave indispensable breaks during these long research project years. I owe my warmest gratitude to my dear cousins Pertti, Martti and Markku and their families for the peace of mind and support that they gave to me.

I want to thank all the patients who participated in the study. It would not have been possible to conduct this study without them. I am also grateful for the Finnish Cultural Foundation for providing me financial support for this work. Financial support was also provided by Meilahti and Veritas säätiö.

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Helsinki, 5. April 2018

Helena Orell
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Helsinki, 5. April 2018
Helena Orell
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List of the original publications

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Abbreviations

ADA American Dietetic Association
AUC area under curve
BCM body cell mass
BEE basal energy expenditure
BIA bioimpedance analysis
BIVA bioimpedance vector analysis
BMI body mass index
BW body weight
CAMA corrected arm muscle area
CRP C-reactive protein
CRT chemoradiotherapy
(C)RT (chemo)radiotherapy
CT computed tomography
CTx chemotherapy
DHA docosahexaenoic acid
DFS disease-free survival
DSS disease-specific survival
DXA dual energy x-ray absorptiometry
ECM extracellular mass
ECW extracellular water
EPA eicosapentaenoic acid
ESPEN The European Association for Clinical Nutrition and Metabolism
EWGSOP The European Working Group on Sarcopenia in Older People
FFM fat-free mass
FFMI fat-free mass index
FM fat mass
GI gastrointestinal
HBE Harris-Benedict equation
HGS handgrip strength
HNC head and neck cancer
HNSCC head and neck squamous cell carcinoma
HPV human papillomavirus
HUH Helsinki University Hospital
IBW ideal body weight
IC indirect calorimetry
ICU intensive care unit
ICW intracellular water
IL-1 interleukin-1
IL-6 interleukin-6
IMRT intensity-modulated radiotherapy
IQ range interquartile range
LOS length of stay
LST lean soft tissue
MAC mid-arm circumference
MAMA mid-arm muscle area
MAMC mid-arm muscle circumference
MF-BIA multiple-frequency bioimpedance analysis
MRI magnetic resonance imaging
NRS-2002 nutritional risk screening 2002
ONS oral nutritional supplement
OPSCC oropharyngeal squamous cell cancer
In patients with head and neck cancer (HNC) the disease itself and its treatment may compromise nutritional status and thus also survival (1,2). The localization of the tumor is critical because it may cause obstruction, swallowing difficulties (dysphagia), painful swallowing (odynophagia), and loss of appetite, thus requiring enteral nutrition already prior to diagnosis in many cases. The management of HNC includes either definitive chemoradiotherapy (CRT), or combined treatment consisting of surgery and postoperative concomitant radiotherapy (RT) or CRT (3,4). These oncological treatments may cause severe side-effects (5). Malnutrition is prevalent already at diagnosis in this patient population, and this risk increases further during surgery and oncological treatment modalities (6-9). It has been reported that prior to diagnosis 30%–60% of the HNC patients are malnourished (10-15), and at the end of treatment malnutrition increases up to 88% (13,16,17). This is due to the physiological condition deteriorating through wasting, cancer-related catabolic effects, and abnormal metabolism of nutrients (18-20). The situation may further lead to cachexia, with a prevalence varying from 6% to 37% among HNC patients depending on the criteria used (21).

The primary factors that increase the risk of malnutrition among HNC patients are age (>50 y), Stages III and IV, oropharyngeal site, CRT, and duration of disease (1,22-25). CRT-induced morbidity such as mucositis, dysphagia, dry mouth (xerostomia), taste changes, odynophagia, nausea, and anorexia, further contribute to muscle loss in this patient population (26-29). Treatment-induced adverse events in combination with malnutrition compromise functional ability, inflammatory response, and quality of life (QoL) (30). Furthermore, patients with HNC malignancies present additional nutritional problems due to a common history of dietary indiscretion, excessive smoking, and alcohol abuse, which cause a risk of developing deficiencies of energy, protein, and many other nutrients (11,31). It can be even stated that these patients are more likely to experience malnutrition than patients with any other cancer in any phase of the treatment.

Disease-related malnutrition is a prevalent and poorly recognized phenomenon in hospitals (32), while in majority of cases nutritional status further deteriorates during hospitalization (33). Even modest decrease in the nutritional status is known to adversely affect disease outcome, and physical, as well as psychological health (34). Malnutrition is associated with increased complications and mortality rates, longer length of stay (LOS) in hospital and increased overall cost of care. Thus, nutritional care should be an integral part of treatment, as it improves QoL, decreases the likelihood of secondary malnutrition, and increases the tolerance to CRT among cancer patients. Still, only 40% of malnourished hospitalized patients receive nutritional support (35).

There is Level 2 evidence that patients identified as being at nutritional risk by the Nutritional Risk Screening tool (NRS-2002) have a 12-fold higher risk of dying compared with non-risk patients (36). It is well accepted that cachexia is the immediate cause of death in 20% of all cancer-related deaths (37-39), and mortality is a typical consequence after weight loss below 70% of normal body weight (37,40). Therefore, early detection of patients at nutritional risk or having malnutrition should be one of the priorities in the treatment of HNC patients. The recently published study by Sulo et al. (41) showed that nutritional-focused quality improvement project could reduce readmission, LOS, and costs of care among malnourished hospitalized patients. In general, adverse clinical consequences of malnutrition are widely known, although the awareness of the patient’s nutritional status is often neglected, and nutritional care abandoned in many cases. The problem is global and presumably similar in Finland and in other European countries (36). Furthermore, knowledge on how to assess nutritional status is sparse and this...
1 Introduction

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In general, adverse clinical consequences of malnutrition are widely known, although the awareness of the patient’s nutritional status is often neglected, and nutritional care abandoned in many cases. The problem is global and presumably similar in Finland and in other European countries (36). Furthermore, knowledge on how to assess nutritional status is sparse and this
issue remains rarely reported in patient charts. The nutritional risk screening is mandatory in some European countries, like Denmark and Norway, but not routinely performed in all Finnish hospitals.

There is still a lack of a universally accepted screening method, which would detect patients, who might benefit clinically from nutritional support. Criteria and methods used to define and describe malnutrition vary between studies, and this causes discrepancies in the results of the prevalence of malnutrition and in the effects seen in nutrition intervention studies (42). Intervention studies are demonstrating clinical benefit and cost effectiveness of nutritional support, but they are often criticized of having a small sample size and inadequate methodology (43).

A constant need remains for improved nutritional status assessment methods and systematic nutritional care, as well as for an appreciation of the treatment of nutrition related complications especially among HNC patients. A growing body of research suggests that nutritional support and patients’ good nutritional status are crucial for patients’ outcome and morbidity. This current study highlights the importance to recognize nutritional status, increase awareness of nutritional status assessment methods, and to show the challenges of nutritional care in patients with HNC.

The aim of this study was to compare intensive and on-demand nutritional counseling on nutritional status and body weight loss. Furthermore, prevalence of nutritional risk, malnutrition, and cachexia were evaluated. Also, vitamin D status was assessed prior to diagnosis. We analysed also the value of NRS-2002 as a clinical risk screening method and handgrip strength (HGS) with mid-arm muscle area (MAMA) as a cachexia diagnosing method and their relationship with survival was assessed. Nutritional status and its assessment methods have not been previously studied to this extent in Finnish HNC patients.
2 Review of the literature

2.1 HEAD AND NECK CANCER

2.1.1 Aetiology
Head and neck cancer is an entity including malignancies originating within the mouth (oral cavity), throat (nasopharynx, oropharynx, and hypopharynx), larynx, nose, sinuses, or salivary glands (44). Majority of the cancers (95%) of head and neck region are squamous cell carcinomas (HNSCC). The anatomical sites and diagnosis of HNC that are included in the current thesis are shown in Table 1 and Figure 1.

Head and neck cancer is considered the 5th most common cancer in the world with 686,000 new cases annually (45). In Europe HNC is estimated to account for 1% of all cancers, with 140,000 new cases and 63,500 deaths annually (46). Oropharyngeal squamous cell cancer (OPSCC) is the most common site, followed by oral cavity and laryngeal cancers (44). HNCs are seen most in the age group of 50-70 years and among men (47,48). The epidemiology has changed during last 10 years with oropharyngeal cancer incidence rising among young adults (<45 y) due to human papillomavirus (HPV) -related cancers (49,50).

HNCs in Finland account for 2% of all cancers. There were 800 new cases in the year 2017, of which 292 (37%) cases in Helsinki and Uusimaa Hospital district (HUS) (51). The incidence of oral cavity cancer and oropharyngeal cancer are increasing in Finland (51) and Scandinavia (52,53). Yet, the five most common cancers in Finland are prostate, breast, lung, colon, and skin melanoma, accounting for 54% of all cancer cases in the Nordic countries (48).

Table 1. The HNSCC sites and diagnosis according to ICD-10.

<table>
<thead>
<tr>
<th>Site</th>
<th>Diagnosis (ICD-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>C02-04, C05.0, C06</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>C01, C05.1-9, C09, C10.0, C10.2-9</td>
</tr>
<tr>
<td>Larynx</td>
<td>C32+C10.1</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>C11</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>C12-13</td>
</tr>
<tr>
<td>Pharynx, undefined</td>
<td>C14</td>
</tr>
</tbody>
</table>

The two major lifestyle risk factors for HNSSC are smoking and excessive alcohol consumption. The risk is even higher in people who simultaneously smoke and are heavy drinkers. This implies particularly to the cancers of the oral cavity, oropharynx, hypopharynx, and larynx (54-56). Smoking is observed in 53% and high alcohol consumption in 67% of HNC patients, while 46% of the patients have both risk factors (57,58).

The evidence that smoking is one of the major risk factors for oral and pharyngeal cancer has been established in many studies (59,60). Snuff has been found to have a strong association with oral leucoplakia (61), except Swedish moist snuff due to its lower level of tobacco-specific N-nitrosamines compared with others (62).

Human papillomavirus is a rather new emerging etiological factor for the development of oropharyngeal squamous cell carcinomas and its prevalence has increased significantly from 40% to 72% over the past 10 years in Europe and North America (63-65). In tonsillar squamous cell carcinoma HPV positivity was 62% in a Danish study and 93% in a Swedish study (66,67). Patients with a HPV-related HNSCC are often younger (<55 years) and have a mostly tonsillar tumor.
origin and better survival than HPV-negative cancers (68-70). In Finland 58% of OPSCC patients are HPV-positive, with higher prevalence among men (71).

Figure 1. The anatomy of the head and neck area.

2.1.2 Symptoms and diagnostic evaluation
The most typical symptoms of HNC are a lump or mass in the head and neck area, a non-healing ulcer in the oral cavity, leukoplakia, erthroplasia, odynophagia, dysphagia, and a change or hoarseness of the voice (72). Typically, HNC metastasizes first to cervical lymph nodes Level I to V (i.e. nodal metastasis) and further to mediastinal nodes, lungs, bone, liver, skin, and bone marrow (i.e. distant metastasis). Disease stage is based on tumor size (T0 to T4), regional lymph node metastasis (N0 to N3), and distant metastasis (M0 to M1) (73). Zero means there is no evidence of primary tumor (T0), regional lymph nodes (N0), or distant metastasis (M0), numbers from 1 to 4 indicate the size and local extent of the primary tumor (T1 to T4) and involvement of regional lymph nodes (N1 to N3), while M1 indicates that there is distant metastasis (73). Extracapsular growth, nerve, and vein invasion, depth of invasion, and HPV positivity also have an influence on TNM staging (73).

Clinical head and neck examination with fine-needle aspiration (often ultra-sound guided) or tissue biopsy samples of any suspicious lesions forms basis for HNC diagnostics (72). Magnetic resonance imaging (MRI) is used to elucidate the nodal status, extent of soft tissue, perineural, and bone invasions. Other available diagnostic methods include panendoscopy and chest computed tomography (CT). Distant metastases and certain small tumors might also be seen by positron emission tomography (74). TNM staging is determined according to the clinical examination and imaging results. In Finland, treatment will be planned according to existing national guidelines of the Finnish Head and Neck Oncology Working Group, and at a university hospital by a multidisciplinary tumor meeting.

2.1.3 Oncological treatment
Oncological treatment options with curative intent in patients with HNSCC include surgery, RT, CRT, or a combination thereof. The general strategy for advanced cancer treatment is radical surgical resection with soft-tissue and osseous reconstructions (75-77) followed by RT or CRT (74,78). Small tumors without nodal metastases (i.e. Stage I and II cancers) are treated either by
surgery or RT depending on their site and patient-related factors. Large tumors (i.e. Stage III and IV), nodal involvement, extracapsular spread, perineural or lymph vascular invasion, or remaining malignancy in surgical margins are indications for combination therapy with postoperative CRT or solely by definitive CRT.

Extensive surgery aiming at radicality may warrant tracheostomy, partial or total glossectomy, floor of mouth resections, mandibulectomy, partial or total pharyngectomy, total laryngectomy, soft or hard palate resections, or surgery of the skull base, and reconstruction of these defects (76,77). Resection of the tumor located in these sites is often combined with unilateral or bilateral neck dissection. Reconstruction is performed by pedicle or free flap reconstruction. Several vascularized osteocutaneous, musculocutaneous, and fasciocutaneous flap techniques are available for reconstruction of tissue defects (77,79).

The incidence of postoperative complications is high at 20-50% (80,81). Risk factors for developing wound complications after HNC surgery are co-morbidities, malnutrition, alcohol withdrawal syndrome, anemia, hypoalbuminemia and hypoproteinemia, advanced stage of tumor, preoperative RT, tracheostomy, and extent of surgery (82-86), with hospital admission rate of 20% (87). Preoperative nutritional support may correct nutrient deficiencies, minimize malnutrition-related morbidity and mortality, reduce the LOS and hospital costs and prevent alcohol withdrawal syndrome (80,88,89). Bertrand et al. (89) noticed that nutritional support received preoperatively for 7-10 days for patients with HNC was efficient in preventing postoperative complications by 10%.

Surgery is often followed by RT or CRT. At the Helsinki University Hospital (HUH) intensity-modulated radiotherapy (IMRT) is used for all HNC patients if oncological treatment is warranted. This technique allows better adjustment of the dose to the tumor and reduced exposure of healthy tissue (90). RT is commenced usually as an outpatient’s treatment with a daily radiation dose of 2 Gray (Gy) received five times a week up to 6 or 7 weeks, resulting in total amount of 60-70 Gy. The effects of RT are seen in cells dividing rapidly such as cancer cells, but also in healthy tissues such as mucous membranes and salivary glands (parotic, sublingual, and submandibular glands). In advanced Stage III and IV HNSCC the postoperative treatment is 6 to 7 weeks RT or CRT usually with cisplatin as a radiation sensitizer. The CTx is usually commenced once a week in a 6-week period with cisplatin 40 mg/m², and in nasopharyngeal carcinoma first once a week in a 6-week period and then 3 times every 3 weeks with cisplatin 100 mg/m². The prevalence of mucositis, odynophagia, dysphagia, and nausea increases during the third week of CRT. In OPSCC treatment modality has changed from surgery to definitive CRT, which has resulted in better functional outcome (91), however it is expected that the rate of surgeries may increase in the HPV-associated HNC patients (92).

### 2.1.4 Survival in head and neck cancer

The site of the tumor, TNM stage, HPV-positivity, keratinizing histology, treatment modality, and smoking among other factors have an impact on survival rates. The five-year overall survival (OS) rate is 63% in cancers of oral cavity, 63% for laryngeal cancers, 60% for oropharyngeal cancers, and 57% for nasopharyngeal cancer, with the majority of the patients undergoing treatment with a curative intent (71,93-95).

Mortality among HNC patients can be explained by direct effect of the disease, comorbidities, or the treatment itself (96). Comorbidities such as cardiovascular diseases and stroke, tumor-dependent factors (e.g. lymphosytenia, high platelet counts, tumor volume), patients-related comorbidities (e.g. poor performance status, malnutrition, depression), and treatment-related complications (e.g. prolonged surgery time, ) have a significant negative effect on patients prognosis.

The HNSCC survival has mainly improved during past decades due to the development of treatment modalities. The tumor site with the most unfavorable prognosis has been hypopharynx, but the five-year survival rate in North America has improved since 1990 from 38% to 41%, due to the change in treatment protocols to favor definitive oncological approach
(97). In patients with anterior wall OPSCC tumors the five-year disease-specific survival (DSS) has improved from 47% to 65%, while with lateral tumors slightly from 73% to 75% (71,98). Laryngeal cancers have had the most favorable prognosis, but the change from surgery to nonsurgical treatment has slightly decreased the five-year DSS rate from 55% to 51% (99). The recurrence-free survival of oral tongue cancer has improved from 47% to 65% in Finland, but higher number of recurrence has been seen among Stage I and II disease compared with Stage III and IV (100). Also, patients with laryngeal T2 tumors have reduced survival compared with T1 and T3-4 tumors indicating the need to develop new treatment modalities (94).

Human papilloma virus-positive OPSCC patients have better survival compared with HPV-negative (69,70), which has seen even among Stage III-IV patients with the five-year OS of 80% in HPV-positive and 40% in HPV-negative (101). This same trend has been seen also among Finnish OPSCC patient population, with the five-year DSS of 81% in HPV-positive and 57% in HPV-negative tumors (71).

The survival decreases with advanced stage. The DSS is 61% for patients with advanced HNC and the major cause of death is locoregional recurrence, with a three-year OS of 47% for men and 76% for women, DSS 55% and 76%, respectively (102). The five-year OS rate is 85% in localized, 59% in regionally metastasized, and 36% in distantly metastasized oral cavity and pharyngeal carcinomas (93). OS has increased due to improvement of treatment modalities. Postoperative concurrent CRT over RT have increased OS from 45% to 53% during the last 30 years with the highest increase of 10% in patients with regional or distant metastases (103).

2.1.5 Effects of nutritional status on the survival
In patients with head and neck malignancies the association of weight loss and malnutrition with prognosis have been shown in several studies (2,12,102,104-108). The association of severe weight loss (<10%) and survival was already shown in 1985 (109) and since then it has been shown that survival decreases with preoperative weight loss exceeding 5% (102), CTX-induced weight loss exceeding 20% (107), and RT-induced weight loss exceeding 5% (108). Symptoms affecting nutrition intake such as swallowing difficulties and pain increases weight loss and thus have negative impact on mortality (2). Furthermore, smoking and to a lesser extent alcohol use prior to diagnosis have been associated with poorer prognosis, while high intakes of vegetables, dietary fibers, and vitamin C favors survival (110,111).

Malianourished cancer patients have a decreased two-year OS rate (35%) compared with well-nourished (64%) patients (105). In patients with recurrent oral cavity or oropharyngeal carcinomas one-year survival rate of 54% was reported in patients without weight loss and 12% with weight loss (106). Furthermore, malnutrition is associated with infections, which contribute to 44% of deaths (112). Weight loss is a common primary cause of death in patients with cancer, accounting 20% to 40% of cancer-related deaths secondary to impaired nutritional status (106,113,114). In patients with HNC 10% of deaths are due to cachexia (115,116), and in all cancers 20% (38).

2.1.6 Role of vitamin D in cancer management
The role of dietary factors on the development of upper digestive tract squamous cell carcinoma has been widely studied. A large body of evidence has supported that a diet with plenty of fruit, vegetables, olive oil, and dietary fiber reduces risk of HNC, whereas meat, sugar, and low flavonoid intake may increase the risk (117-125). The observation of low vitamin D levels in many cancer patients has recently drawn attention of the medical community. Several in vitro studies provide evidence for vitamin D having an important role in head and neck carcinogenesis (126-128) and etiology (129).

Vitamin D and its active form, 1,25-hydroxy-vitamin D (1,25-OHD, calcitriol) have an important role in calcium and bone metabolism (130). Epidemiological, molecular, and cellular studies have implicated a role for vitamin D in differentiation, proliferation, apoptosis, and angiogenesis in many tumor types, and consequently in the development and progression of
several cancers (131). Low concentrations of vitamin D have been associated with an increased risk of colorectal (132,133), breast (134), prostate (135), oral cavity, and oesophageal cancers (136), while the association is not so clear with ovarian and endometrial cancers (137). On the other hand, high vitamin D in concentrations ≥80 nmol/l may improve prognosis in breast, colon, prostate, and lung cancer (138,139). A meta-analysis by Yin et al. (140) showed that an increase of serum 25-hydroxyvitamin D (S-25-OHD) by 50 nmol/l was associated with a risk reduction of 59% for rectal cancer and 22% for colon cancer. Furthermore, an intervention study showed that an increase of 25 nmol/l in S-25-OHD was associated with a 17% reduction in total cancer incidence, and a 29% reduction in total cancer mortality in men (141), but there are studies showing that high vitamin D concentrations (≥100 nmol/l) are associated with higher risk of developing pancreatic and prostatic cancer (142,143).

2.2 NUTRITIONAL STATUS TERMINOLOGY

2.2.1 Body composition

Body fat mass (FM, adipose tissue) and fat-free mass (FFM, adipose-tissue free mass) are the two major components of body weight (Figure 2). Indices of body composition can be used to identify malnutrition, and to monitor long-term changes in body composition during nutritional support. The FFM compartment includes lean soft tissue (LST, previously lean body mass) and bones. LST is a sum of body water, total body protein, carbohydrates, soft tissue minerals (electrolytes), and non-fat lipids (i.e. lipids that are not in FM) (144).

About 60% of the body weight is water, with the hydration fraction for lean tissue of 73% (145,146). Intracellular water is directly associated with body cell mass, which is the metabolically active, energy-consuming component of body (147). Muscle solids are mainly proteins and thus skeletal muscle depletion reflects the protein status of the body. A muscle reserve becomes depleted during chronic malnutrition and during severe acute illness or injury.

Adipose tissue is the main storage of energy and alterations in body fat content provide indirect estimates of changes in energy balance. Body fat is dependent of sex; the normal fat mass range is 12-20% for men and 20-30% for women (148). Over one-third of total body fat is estimated to be subcutaneous fat. A change in adipose tissue is sensitive to acute malnutrition with large and rapid loss of adipose tissue indicating severe energy malnutrition.

![Figure 2. Body composition of a 70-kg reference man according to Heymsfield (149). FFM fat-free mass, TBW total body water, ICW intracellular water, ECW extra cellular water, LST lean soft tissue.](image)
2.2.2 Malnutrition, sarcopenia and cachexia

Malnutrition. The European Society for Clinical Nutrition and Metabolism (ESPEN) has defined malnutrition as a state of nutritional status, in which a deficiency, excess, or imbalance of energy, protein, and other nutrients causes measurable adverse effects on body size, composition, function, and clinical outcome (150). Systemic inflammation is considered an important underlying factor in the progression of disease-related malnutrition (151), with especially cytokines promoting muscle catabolism and inhibiting protein synthesis and thus compromising muscle repair (152). The general conception is that body composition analysis should be integrated in routine clinical practice, since muscle loss associates with morbidity and mortality in many clinical conditions (153).

Malnutrition occurs along continuum of inadequate energy, protein, and micronutrient intake, impaired absorption, and altered utilization together with increased requirements (154). In this regard, disease-related malnutrition means specifically protein-energy malnutrition (PEM) that leads to a loss of FFM and FM. It is noteworthy that also non-gastrointestinal cancers cause malnutrition, malabsorption, and delayed gastric emptying mainly due to release of inflammatory cytokines including interleukins-1 and -6 (IL-1, IL-6) and tumor necrosis factor alpha (TNF-\(\alpha\)) (155,156).

Sarcopenia. Sarcopenia is defined as any loss of muscle mass (fat-free mass, FFM) and muscle function due to aging, chronic disease, and inactivity (157,158). Wasting is used as a term for disease-, and cancer-related muscle loss (159). According to the present understanding of malnutrition the focus is on muscle-mass loss rather than solely on weight loss or body mass index (BMI).

Sarcopenia can be diagnosed by the assessment of muscle mass and strength, and physical performance as shown in Table 2 (177). According to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria sarcopenia requires the presence of both low muscle mass and low HGS or physical performance (Table 2).

Table 2. Diagnostic criteria for sarcopenia (177).

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Assessment method</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass</td>
<td>CAMA by anthropometry</td>
<td>≤24.1 cm(^2)</td>
<td>≤21.6 cm(^2)</td>
</tr>
<tr>
<td></td>
<td>FFMI by BIA</td>
<td>≤17 kg/m(^2)</td>
<td>≤15 kg/m(^2)</td>
</tr>
<tr>
<td></td>
<td>SMI by BIA</td>
<td>&lt;8.87 kg/m(^2)</td>
<td>&lt;6.42 kg/m(^2)</td>
</tr>
<tr>
<td></td>
<td>Lumbar skeletal muscle index by CT</td>
<td>&lt;55 cm(^2)/kg(^2)</td>
<td>&lt;39 cm(^2)/kg(^2)</td>
</tr>
<tr>
<td></td>
<td>Appendicular skeletal muscle index by dual energy X-ray absorptiometry(^a)</td>
<td>&lt;7.26 kg/m(^2)</td>
<td>&lt;5.45 kg/m(^2)</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>HGS adjusted for BMI</td>
<td>BMI ≤24: ≤29 kg</td>
<td>BMI ≤23: ≤17 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI 24.1-26: ≤30 kg</td>
<td>BMI 23.1-26: ≤17.3 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI 26.1-28: ≤30 kg</td>
<td>BMI 26.1-29: ≤18 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI &gt;28: ≤32 kg</td>
<td>BMI &gt;29: ≤21 kg</td>
</tr>
<tr>
<td>Physical performance</td>
<td>Gait speed (4-m walk test)</td>
<td>≤0.8 m/s</td>
<td>≤0.8 m/s</td>
</tr>
<tr>
<td></td>
<td>Get-up-and-go (TUG) time(^b)</td>
<td>&gt;10 s</td>
<td>&gt;10 s</td>
</tr>
</tbody>
</table>

CAMA corrected arm muscle area, FFMI fat-free mass index, SMI skeletal muscle index, CT computed tomography, HGS handgrip strength, BMI body mass index, TUG timed up and go time

\(^a\) Measured at 3rd lumbar vertebral

\(^b\) Time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down.
Diagnosing sarcopenia is of utmost importance in cancer because it increases CTx-related toxicity and is associated with physical decline and decreased survival (160-162). Furthermore, muscle mass predicts risk of toxicity better than body surface area, which is used for CTx dosing (161). It is justified to assume that in the future sarcopenic obesity is increasing in chronic diseases such as cancer (153). HNC patients have followed the general phenomenon of increasing number of overweight. More than ten years ago 42% of the patients had BMI <20 prior to RT (163), while nowadays half of the cancer patients are overweight (58).

**Cachexia.** Cachexia is defined as a condition with unintentional body weight loss and systemic inflammation, and classified in three stages: pre-cachexia, cachexia, and refractory cachexia (164-166). Evans et al. (164) published the non-disease-specific general framework for cachexia (Table 3). A few years later a consensus-based cancer-specific framework for pre-cachexia was published by Muscaritoli et al. (157) and a framework for cachexia and refractory cachexia by Fearon et al. (165) (Table 4).

The pathogenesis of cancer cachexia is complex and multifactorial, with strong involvement of several inflammatory cytokines (e.g. IL-1, IL-6, TNF-α) and cachexia-specific proteins such as lipid-mobilizing factor and proteolysis-inducing factor, which contribute to muscle-mass loss (20). In conjunction with this, the anabolic mediators (i.e. growth hormone, insulin, insulin-like growth factor, testosterone) are downregulated, and thus inhibiting lean body mass synthesis (20). Furthermore, severe fat depletion is followed by hypogonadism, which is associated with low levels of leptin and, among other things, a higher incidence of anorexia (18,19).

**Table 3. Diagnostic criteria for cachexia by Evans et al. (164).**

1. **Presence of a chronic disease AND**

2. **Loss of body weight ≥5% in 12 months or less (or BMI <20.0 kg/m²) AND**

3. **Presence of at least three of the following:**
   - Reduced muscle strength (HGS lowest tertile)
   - Fatigue
   - Anorexia (total caloric intake less than 20 kcal/kg body weight/d; <70% of usual food intake) or poor appetite by The Simplified Nutritional Assessment Questionnaire (176)
   - Low FFMI: <17 kg/m² (M), <15 kg/m² (W); MAMC: <25 cm (M), <19 cm (W)
   - Abnormal biochemistry:
     - Inflammation (CRP >5 mg/l, IL-6 >4 pg/ml)
     - Anemia (Hb <120 mg/l)
     - Low albumin concentration (<32 g/l)

HGS handgrip strength, FFMI fat-free mass index, M men, W women, MAMC mid-arm muscle circumference, CRP C-reactive protein, IL-6 interleukin 6, Hb Hemoglobin

Typical symptoms of cachexia are anorexia, reduced food intake, metabolic changes, weight loss, sarcopenia, and fatigue associated with reduced physical function, QoL, reduced tolerance to anticancer therapy, and reduced survival (157,166-169).

The presence of cachexia prior to any oncological treatment is a poor prognostic sign and related to postoperative complications (167). In patients with newly diagnosed HNSCC cachexia was seen in 42% ad pre-cachexia in 15% of the patients (170). Furthermore, as the literature demonstrates, cachexia is the immediate cause of death in 10% of patients with HNC (115,116), and in 20% to 30% of all cancer cases (38,115,171).
during past 6 months, >15% of pre-diagnosis weight, BMI <20 kg/m² circumference (MAMC), serum albumin and prealbumin. Patients are classified as malnourished status II cancer. Method includes body weight loss, BMI, triceps skinfold (TSF), mid-arm muscle anthropometric and biological objective parameters, which have been used to classify nutritional strength, and physical performance in addition to weight loss in cachexia (164,177). (154). Criteria to diagnose sarcopenia and cachexia include estimation of muscle mass, muscle functional status, decreased muscle mass, decreased subcutaneous fat, and fluid accumulation (154).

Table 4. Diagnostic criteria for cancer pre-cachexia and cachexia.

### Pre-cachexia (157)
- Weight loss ≤5% during previous 6 months
- Anorexia (total caloric intake less than 20 kcal/kg body weight/d, <70% of TEE, or poor appetite (VAS <5 cm)
- Inflammation (CRP ≥8 mg/l)

### Cachexia (165)
- Weight loss >5% during the previous 6 months or BMI <20 kg/m² and weight loss >2% or sarcopenia (FFM index <5th percentile of age and sex-specific reference values (34)), and weight loss >2%
- Anorexia (total caloric intake less than 20 kcal/kg body weight/d; <70% of TEE, or poor appetite (VAS <5 cm))
- Inflammation (CRP >8 mg/l)

VAS visual assessment scale, TEE total energy expenditure, CRP C-reactive protein, FFM fat-free mass

Identification of the etiology of weight loss in patients with HNC is central because appropriate treatment for malnutrition and cachexia has important differences. Weight loss due to dysphagia (i.e. malnutrition) can be reversed by nutrition intervention, while weight loss due cachexia cannot unless the primary disease is cured (165).

In pre-cachexia nutrition intervention should be started as soon as possible to prevent progression to cachexia. Tube feeding does not improve signs of cachexia, but can be used to treat malnutrition, fluid, and drug administration. It is noteworthy that nutritional advice with or without ONS may improve weight gain, body composition, and HGS, but not survival (172). Corticosteroids and synthetic progestogens (e.g. medroxyprogesterone acetate or megestrol acetate) are recommended to stimulate appetite in Europe (173). There is also some evidence that HNSCC patients may benefit from progressive resistance training (174,175).

#### 2.2.3 Nutritional status

The aim of nutritional status assessment is to discriminate malnourished, sarcopenic, and cachectic patients from well-nourished ones. Currently there is no international consensus of a single, universally accepted method or criteria for the recognition of disease-related malnutrition (154). Nevertheless, some guidelines for nutritional status assessment (154), and criteria to diagnose sarcopenia (177), and cachexia (164) have been published. Currently more attention is focused specifically to muscle-mass estimation, which is considered as a central part of nutritional status assessment (144). Therefore, several methods are usually used in parallel to discriminate malnourished patients from well-nourished (154).

In ESPEN guidelines severe nutritional risk is defined as the presence of at least one of the following criteria, including weight loss (>10-15% within 6 months), BMI <18.5 kg/m², SGA Grade C, NRS-2002 ≥3, and serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction) (150). Meanwhile, the American Society for Parenteral and Enteral Nutrition (ASPSN) and the Academy of Nutrition and Dietetics (ADA) suggested using six criteria, of which two or more are needed to diagnose malnutrition, including insufficient energy intake, weight loss, decreased functional status, decreased muscle mass, decreased subcutaneous fat, and fluid accumulation (154). Criteria to diagnose sarcopenia and cachexia include estimation of muscle mass, muscle strength, and physical performance in addition to weight loss in cachexia (164,177).

Criteria published by Thoresen et al. (178) are derived from combination of both anthropometric and biological objective parameters, which have been used to classify nutritional status Ii cancer. Method includes body weight loss, BMI, triceps skinfold (TSF), mid-arm muscle circumference (MAMC), serum albumin and prealbumin. Patients are classified as malnourished if two or more of the following criteria are fulfilled: weight loss >5% during past month, or >10% during past 6 months, >15% of pre-diagnosis weight, BMI <20 kg/m², TSF ≤5th and MAMC ≤5th
percentile of reference values, serum albumin ≤30 g/l, and serum prealbumin ≤210 mg/l.

2.3 NUTRITIONAL STATUS ASSESSMENT METHODS

Body composition can be estimated by anthropometric measurements, bioimpedance analysis (BIA), or specific imaging techniques. In the early years of nutritional status assessment anthropometric measurements including body weight, BMI, TSF, mid-arm circumference (MAC), MAMC, MAMA, the percentage of body weight loss, and the scored Patient-generated Subjective Global Assessment (PG-SGA) tool have been widely used (118). Anthropometry means “the measurement of man”, and includes body size measurements, such as body weight, height, skinfold thicknesses, and circumferences. Anthropometry is non-invasive, easily obtained, and inexpensive, but relatively insensitive for small changes (179).

The golden standard and criterion method for the assessment of body composition is a combination of measurement techniques used in 4-compartment models including hydrodensitometry or air displacement plethysmography, total body water (TBW) dilution, and dual energy x-ray absorptiometry (DXA), but they are limited mainly to research settings (144). On the other hand, CT scans, MRI, and ultrasound have gained ground among researchers (144). The majority of the cancer patients are followed regularly by abdominal CT scans, thus giving an opportunity to quantify body composition with high specificity and precision. Skeletal muscle area from third lumbar region (L3) is strongly associated with total body muscle volume (144). Since diagnostic CT scans are not routinely performed in patients with HNC at L3 level, the third cervical vertebra (C3 with paravertebral and sternocleidomastoid muscles) have been used, which correlates well with L3 level (180,181). Severe muscle-mass depletion is defined as absolute muscle mass below the 5th percentile, which has a strong association with complications of cancer surgery, dose-limiting toxicity, and mortality (182). Muscle mass can be assessed by MAMA, appendicular muscle index, lumbar skeletal index, or whole body FFMI without bone. Cut-off values are shown in Table 5.

HGS is a measure of muscle function, which reacts earlier to nutritional depletion than other methods, and thus is a potential non-invasive assessment method (183-187). Subjective methods, such as NRS-2002 (188) and PG-SGA (189) lean on BMI, weight loss and changes in food intake thus being much less accurate methods, but regarded practical in daily clinical use (42,190).

Table 5. The criteria for severe muscle-mass depletion determined by different methods (182).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Assessment method</th>
<th>5th percentile Males</th>
<th>5th percentile Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAMA</td>
<td>Antropometry</td>
<td>&lt;32 cm²</td>
<td>&lt;18 cm²</td>
</tr>
<tr>
<td>Appendicular skeletal muscle index</td>
<td>DEXA</td>
<td>&lt;7.26 kg/m²</td>
<td>&lt;5.45 kg/m²</td>
</tr>
<tr>
<td>Lumbar skeletal muscle index</td>
<td>CT imaging</td>
<td>&lt;55 cm²/m²</td>
<td>&lt;39 cm²/m²</td>
</tr>
<tr>
<td>Whole body FFM index without bone</td>
<td>BIA</td>
<td>&lt;14.6 kg/m²</td>
<td>&lt;11.4 kg/m²</td>
</tr>
</tbody>
</table>

MAMA mid-arm muscle area, FFM fat-free mass, DEXA dual energy x-ray absorptiometry, CT computed tomography, BIA bioimpedance

2.3.1 Body weight and BMI

Daily variation in body weight is generally small (i.e. less than ± 0.5 kg) in healthy persons, but in conditions like acute severe or chronic illness, body weight may decline due to negative energy-nitrogen balance. Short-term changes reflect the fluid balance, and longer-term changes reflect net changes in real tissue mass. Nonetheless, body weight is a poor measure of energy-nitrogen reserves in disease conditions, in which edema, ascites, dehydration, diuresis or massive
tumor growth occurs. An increase in total body water or massive tumor growth may mask actual weight loss that results from losses of fat and muscle mass. Most of the fat mass (90%) is available as an energy source, while a loss of 50% of FFM (i.e. 30% of body weight) leads to death (37,40).

Body weight change and BMI have a long history as health status indices (144), and weight loss have been widely used to discriminate malnourished patients from well-nourished (191). The Blackburn et al. (192) criteria for severe weight loss are widely used (Table 6). Estimation of body weight loss in clinical practice is often undetermined due to unknown usual weight or relying on patient’s own reported weight (193). In a small study by van den Berg et al. (194) 68% of patients reported weight loss within 2 kg. Body weight is usually measured in light indoor clothes without shoes. Weight should be corrected for clothing by deducting 1.4 kg in summer and 1.8 kg in winter for men, and 0.9 kg and 1.1 kg for women, respectively (195).

Table 6. Evaluation of percentage of weight changes by Blackburn et al. (192).

<table>
<thead>
<tr>
<th>Duration</th>
<th>Significant weight loss, %</th>
<th>Severe weight loss, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>1-2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>1 month</td>
<td>5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>3 months</td>
<td>7.5</td>
<td>&gt;7.5</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

A body weight loss exceeding 10% of the usual body weight has been shown to be prominent predictive parameter for the occurrence of major postoperative complications in patients with HNC (23,167). A study of Nguyen et al. (106) demonstrated that weight loss had more prognostic power than the TNM staging system. Moreover, body weight loss of ≥5% in one month and ≥10% in previous six months are well-accepted criteria for malnutrition also among HNC patients (106,167,196). Weight loss is a marker of either low nutritional intake or cachexia, but lacks accuracy to detect muscle-mass loss.

BMI is a very rough method to assess body composition since patients with equal BMI may have very different body composition, and large fat mass may mask severe muscle wasting (i.e. sarcopenic obesity) (197). While BMI is easy to perform, it does not permit determination of the proportions of FFM and FM. BMI underestimates nutritional risk in obese patient, hence it is not concerned as a sensitive and specific tool to detect nutritional risk effectively (23,198). BMI is usually categorized by the WHO criteria for adults, with <18.5 kg/m² indicating underweight. For elderly (≥65 y), <23 kg/m² is suggested (140, 141).

In a recently published study by Martin et al. (199) a combination of BMI categories and weight loss percent were used to create a screening system for the assessment of survival reduction among cancer patients. For example, in this screening system patients with BMI between 25 and 28 kg/m² with weight loss more than 16% were graded to have similar survival as patients with BMI less than 20 kg/m² and weight loss more than 6%.

### 2.3.2 Upper-arm anthropometry

Upper-arm anthropometry includes measures of MAC and TSF, which can be used to calculate MAMC and MAMA (200). While body weight and height are relatively quick and easy measurements, upper-arm anthropometry requires more training and has a substantial degree of intra- and interobserver measurement errors (201,202).

MAMC and MAMA are derived from measurements MAC and TSF thickness, and calculated using the equations MAMC = MAC_{nm} – (π x TSF_{nm}) (203) and MAMA = [MAC_{nm} – (0.3142 x TSF_{nm})]^2 / (4 x 3.142). Measurement of TSF provides an estimate of body fat reserves while MAC, MAMC and MAMA correlates with measures of total muscle mass, but they do not detect small changes in protein status (179). MAC measures total upper-arm tissue including bone, muscle, fluid, and fat, while MAMA reflects more adequately the magnitude of arm muscle tissue.
changes (204). The MAC is a one-dimensional measurement, whereas MAMA is two-dimensional.

A decrease in MAC reflects reduction in muscle mass, subcutaneous tissue, or both. In the interpretation of the measurements it should be considered that, if the volume of the mid-arm muscle changes, the change in MAMC will be proportionally smaller than the change in the MAMA. Therefore, MAC is insensitive to small changes (205). In general, during a short-term nutritional support or deprivation the upper-arm anthropology is not able to detect small changes (179). Still, MAMA reflects the magnitude of muscle tissue changes more accurately than MAC, and hence MAMA is regarded more accurate than MAC as an index of body muscle mass (204). MAMA was recently suggested as a criterion for diagnosing sarcopenia (177). It is noteworthy that MAMA is an approximation (±8%) of the actual MAMA, and this should be considered when interpreting results (205). Furthermore, the accuracy of MAMA in obese and lean subjects has been criticized (206).

Values are compared with age- and sex-specific reference values (200, 207), with a cut-off point of <5th percentile indicating muscle or fat mass wasting (204). Cut-off points either <5th or <15th percentile have been used in patients with advanced cancer or (208, 209) lung cancer (210), in palliative care (211), and in other clinical conditions (212-215). Sex-specific MAC values corresponding BMI 10, 13 and 16 (216) can be used (Table 7) as well as fixed cut-offs such as MAC <20.2 cm in men and <18.6 cm in women; TSF <5.2 in mm in men and <9.7 mm in women (217). The reference percentile values for TSF, MAC, and MAMA are shown in Appendix 2.

Upper-arm anthropometry is a non-invasive method and correlates with survival in COPD (218), cirrhosis (219), and HIV infection (220). In elderly HNC patients low MAC (≤25 cm) was an independent predictor of increased postoperative length of hospital stay (221). Anthropometry has been used to assess nutritional status in clinical conditions where hydration states may be altered such as in liver and renal diseases (213-215), and among intensive care unit (ICU) patients (222). Low MAC and TSF values have been demonstrated also in cachectic hospitalized patients (223).

Table 7. Sex-specific mid-arm circumference (MAC) values in cm corresponding BMI in severe wasting (216).

<table>
<thead>
<tr>
<th>Malnutrition grade</th>
<th>BMI, kg/m²</th>
<th>MAC, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Extreme wasting</td>
<td>&lt;10</td>
<td>&lt;17</td>
</tr>
<tr>
<td>Severe wasting</td>
<td>&lt;13</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Undernourished</td>
<td>&lt;16</td>
<td>&lt;23</td>
</tr>
</tbody>
</table>

MAC mid-arm circumference, BMI body mass index

2.3.3 Bioelectrical impedance analysis (BIA)

Bioelectric impedance analysis (BIA) is the most commonly used method to assess body composition in clinical settings and in research. BIA is used for indirect measurement of body compartments: FM, FFM and TBW (224). The electrical current with either single frequency (SF-BIA, 50 kHz) or multiple frequencies (MF-BIA, 5-1000 kHz) is passed between two electrodes, usually located on the ankles and wrists of an individual. MF-BIA and bioimpedance spectroscopy approaches are superior to SF-BIA.

The BIA measures the body tissue resistance (R) and reactance (Xc). The resistance is the conductive characteristic of body fluids, whereas the reactance is a frequency-dependent reactive component of cell membranes (225). The impedance (Z) is the frequency-dependent opposition by the body (i.e. conductor) to the flow of electric current and is derived from the resistance and reactance by the equation $Z = \sqrt{R^2 + X_c^2}$ (225). It is estimated that each arm is approx. 4% and each leg 17% of body weight, and contributing approx. 47 to 50% of whole body resistance, while the
trunk contains 50% of the body mass and contributes only 5-12% of whole body resistance (226,227).

The electric current passes well in tissues with high water and electrolyte concentrations (i.e. skeletal muscle and blood) and poorly in fat, bones and air-filled spaces (225). In low frequencies, the current passes through the extracellular water (ECW), while in higher frequencies it allows to quantify total body water \( (TBW = \frac{\text{height}^2}{R_{50}} \text{or height}^2/Z_{50}) \) (225). Intracellular water (ICW) is the difference between TBW and ECW. TBW is used for estimation of FFM according to the assumption that the hydration status of FFM is 73% (228,229), while ICW is used for estimation of body cell mass (BCM) according to the assumption that the hydration status of cell is 70% (230).

Impedance, resistance and reactance values are used further to calculate the FFM and TBW of the subject with standardized prediction equations including one or more other variables, such as age, weight, menopause status, recent physical activity and consumption of food or beverages. Body posture has an effect on the redistribution of body fluids. Fluids shifts from arms and legs to the trunk if posture changes from standing to supine. Therefore, to minimize this effect the recommended equilibrium time before BIA measurement should be 10 to 15 min (235). Eating, drinking, alcohol use, and exercise should be avoided for over eight hours before BIA measurement. Measurements should always be performed on the same body side, and at the same time of the day with standardized procedures for longitudinal follow-ups, and appropriate population, age, or pathology-specific BIA equations. It is noteworthy that BIA may be inaccurate due to abnormal tissue conductivity in the extremes of BMI as in severe underweight (BMI <16 kg/m²) and severe obesity (BMI >34 kg/m²) (236). BIA is a non-invasive method that relies on population-specific regression equations, but overestimates FFM in severely obese patients (BMI >34 kg/m²) (237).

The effect of nutritional support on body composition has been assessed with BIA in HNC patients (238). Jager-Wittenaar et al. (239) compared BIA to DXA and showed that FFM can be reliably assessed by BIA. The resistance increases after surgery in patients with HNC probably due to increase of ECW (15).

Other applications of BIA are measurement of the phase angle (PA) (240-245) and body cell mass-extra cellular mass ratio (BCM/ECM ratio) and vector analysis (14,246,247). PA is a highly prognostic index of cell membrane integrity and survival (240-245) and can be calculated according to the equation \( \frac{\pi}{2} \times (X_c/R) \) (248). Worse survival is associated with PA values less than 5th percentile of the reference values (249). ECM/BCM ratio values higher than 1.2 indicate malnutrition (15,250). BIA vector analysis has been used in assessment of body hydration and mass in cancer patients, including HNC (14,246,247).

### 2.3.4 Handgrip strength

HGS is a valid non-invasive and easy method to perform in clinical and hospital settings to measure the patient’s functional status, which correlates with total body protein (251-253), body cell mass (183), mid-arm anthropometry (254-256), and FFM (254,257). Furthermore, several studies have shown that muscle function reacts earlier to nutrition deprivation than changes in body weight or composition (183-187). In addition, several studies have shown an association between HGS and inflammation in non-critically ill and surgical patients (257-259).

Already in 1996 Guo et al. (256) published the first study on the association of HGS and nutritional status in patients with oral and maxillofacial cancers. The study showed that HGS was a useful indicator of MAMC, and low HGS was associated with a higher risk of postoperative complications. A more recent study showed that low HGS was a predictor of five-year survival in patients with HNC (260). Association between HGS and nutritional status has been studied also in patients with colorectal (261), lung (262), and mixed group of cancers (263). A prospective
study by Norman et al. (263) confirmed that malnutrition was an independent determinant of HGS in cancer patients.

Several authors have reported decreased HGS in malnourished patients (183,262-264), especially in hospitalized patients (264,265). The measured HGS in patients with HN SCC has been reported to vary between 26-40 kg (266-268). The reference values for females aged 50-69 years are 25-28 kg and for males 43-47 kg, respectively (269). Low HGS is associated with increased LOS (265,270) and a higher complication risk in surgical patients (253,268,271,272). Furthermore, HGS has been shown to be a short- and long-term predictor of mortality, including mortality from all-causes (254,273), in HNC (260), in advanced lung and gastrointestinal cancers (274), in surgical and medical hospitalized patients (265,275). Indeed, HGS may be a valuable tool in the assessment of nutritional status (154,177, 264,265,276,277).

Various reference values for HGS (268,269,278-280), and cut-off points for decreased muscle function and muscle depletion have been used, including a <85% from the mean value (253,256), <10th percentile (274), and <5th percentile (269,281) below normal age and sex specific values (Appendix 2). In addition, either measured values are compared with predicted values (276) or study sample sex-specific tertile or quartile are used (264,265). To diagnose sarcopenia with standardized HGS values they should be stratified by BMI and sex as shown in Table 2 (177).

In healthy people, age and gender are the strongest influencing factors for HGS (273), while a recent large British study with 8 441 subjects showed that in healthy adults HGS was 2.7 kg higher in men and 1.5 kg higher in women in those in the upper quartile of BMI (282). HGS improved in non-oncological gastroenterological patients during a 3-month nutritional intervention in oral nutritional support (ONS) group (283).

2.3.5 Biochemistry

Albumin and prealbumin concentrations have been used traditionally as indicators of malnutrition (Table 8), but they should be interpreted with caution as it has been suggested in recently published ASPEN guideline for detection of malnutrition (154). It has been shown that albumin is more a sign of severity of disease than a measure of malnutrition (284,285). Several studies have shown that hypoalbuminemia correlates with medical complications (286-288), surgical site infections (81), LOS (289,290), and mortality (291-293). A low prealbumin concentration has been shown to be a risk factor for microvascular free flap failures in patients with HNC (84). In a study of Guo et al. (294) patients with several cancers was shown that the prealbumin concentration of patients was related to functional status.

**Albumin** Over 40% of body pool of albumin (120 g) is present in the vascular space and 60% (180 g) in extravascular space (295,296). Albumin has a long half-life of 20 days (297) and is synthesized in the liver from amino acids, which are derived either from intestinal absorption or muscle catabolism (295). Albumin is a main regulator of oncotic (i.e. colloid osmotic pressure), but it has a central role in the transportation and metabolism of several substances and drugs.

Variety of conditions affect albumin levels (298). Hypoalbuminemia may be generated by loss of protein due to gastrointestinal and renal diseases, by reduced protein synthesis due to liver disease and hypothyroidism, by increases in plasma volume e.g. due to congestive heart failure or by hemodilution due to pregnancy. Furthermore, infections and zinc depletion are associated also with hypalbuminemia. Serum albumin concentrations decrease in the presence of traumatic injury or with ongoing stress because of shift of albumin from the intravascular to the extravascular space. Patients are defined to have hypoalbuminemia if serum albumin is <30-35 g/l (299).

Albumin levels may be maintained during chronic malnutrition because of compensatory reduction in albumin catabolism and redistribution of extravascular albumin to the intravascular space (299). Hyperalbuminemia may occur in semistarvation due to a shift of albumin from the extravascular space to the intravascular space. Serum albumin concentrations may be elevated also in patients with dehydration.
Prealbumin (transthyretin). Prealbumin, known also as transthyretin or thyroxin-binding prealbumin, serves as a carrier protein for serum retinol-binding protein and as a transport protein for thyroxine. It has shorter half-time (i.e. 2 days) than albumin (297). Thus, it might be more sensitive marker of recent protein intake, protein deprivation, and effect of nutritional interventions. Due to its high content of tryptophan and proportion of essential to nonessential amino acids it can be used as an indicator of the availability of essential amino acids in the body (300). Ramsey et al. (301) suggested already at 1992 that prealbumin does not reflect the risk of protein malnutrition, but it reflects acute protein intake.

Prealbumin concentrations are altered in several clinical situations such as variation in inflammatory status, infections and surgical stress, and hepatic, kidney and gastrointestinal diseases, and with specific medications such as anti-inflammatory medications and oestrogen replacement therapy, (299). The reference values vary by age and sex.

Serum transferrin. Transferrin is a serum β-globulin protein with a half-life of 8-19 days used for iron transport. The liver synthesizes transferrin and it is located mainly intravascularly in the body. Transferrin concentrations are lower in liver, gastrointestinal and renal diseases, congestive heart failure, cancer, and inflammation, while concentrations are elevated by iron deficiency, pregnancy, oestrogen therapy, and during acute hepatitis (299).

Table 8. Concentration of albumin, prealbumin and transferrin according to Gibson (246).

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Albumin g/l</th>
<th>Prealbumin mg/l</th>
<th>Transferrin g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;35</td>
<td>150-290</td>
<td>2.5-3.0</td>
</tr>
<tr>
<td>Slight depletion</td>
<td>28-35</td>
<td>100-150</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Medium depletion</td>
<td>21-27</td>
<td>50-100</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>Severe Depletion</td>
<td>&lt;21</td>
<td>&lt;50</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

2.3.6 Nutritional risk screening 2002 (NRS-2002)

NRS-2002 method is based on an analysis of previous randomized controlled trials (RCTs) of nutritional interventions (188). It has been shown to have high validity to identify correctly those patients who will benefit from nutritional support (302). The consequences of malnutrition are severe and often irreversible if the primary disease condition is not cured. For this reason, ESPEN recommends to screen all hospital patients within 48 h of admission to identify risk patients and to start nutrition intervention as soon as possible (42). NRS-2002 is not validated for psychiatric, pediatric, or pregnant patients.

The NRS-2002 tool is widely used for screening malnutrition, and it is rapid, simple and easy to perform in all health care settings and specialities (188). In addition, it is suitable for preoperative screening and for screening elderly patients (303-305). In general, 30% of all hospital patients (36,306,307) are at nutritional risk on admission. HNC patients are one of the highest risk groups among all cancer patients (307). It is noteworthy that nutritional risk is seen mostly among elderly patients with BMI in the normal or overweight range, but is also seen among younger patients with overweight (306).

The NRS-2002 method includes two steps, initial (Step 1) and final screening (Step 2). Step 1 addresses BMI, weight loss, alterations in food intake and the illness, while the step 2 includes impaired nutritional status, the metabolic effect of disease or trauma, and age 70 years and older. Nutritional status is evaluated by BMI, recent weight loss and changes in dietary intake during the previous week before admission. The severity of disease is determined by how a clinical condition or disease affects nitrogen (i.e. protein) need (188).

Nutritional status and disease severity are scored from 0 to 3 separately. In addition, extra point is added in patients 70 years or older. After addition of scores, a score from 0 to 7 is possible, and a patient with score equal or higher than 3 is considered to be at nutritional risk, and nutrition
intervention should be initiated (188). The NRS-2002 screening tool has been found to be suitable to identify patients who will benefit clinically from nutritional intervention. For scores indicating the absence of malnutrition or risk of malnutrition, nutritional support is less likely to be of benefit (302). However, preoperative nutritional support should be allocated for all patients with major gastrointestinal (GI) surgery irrespective of NRS-2002 score.

The prevalence of nutritional risk by NRS-2002 is generally varying from 28% to 30% in hospitalized patients (36,306,308) and from 28% to 44% in cancer patients (36,306,307,309), with higher prevalence 36-65% seen among gastric (310,311), gynaecological (312), and head and neck (307,313) cancers as well as in patients in palliative care (314). Moreover, nutritional risk is high in intensive care unit patients (74%), in patients with infections (51%) as well as during emergency admission (35%) (306). Patients with upper GI tumors presenting with both fatigue and anorexia are in high risk developing malnutrition detectable by high NRS-2002 score (309). NRS-2002 status has been shown to predict postoperative complications and length of hospital stay in patients with gastric and gynaecological cancers (310,312), and anastomotic leakage and wound infections in colorectal cancer surgery (315). In addition, NRS-2002 has been shown to predict outcome in elderly patients equally to Mini Nutritional Assessment short form and better than Malnutrition Universal Screening Tool in hospitalized patients (316).

NRS-2002 tool has been compared against the PG-SGA (Chapter 2.3.7) instrument (308,311,313,317). In a study with 705 hospitalized patients 28% were at nutritional risk by NRS-2002 and 39% were malnourished by SGA (308). NRS-2002 has shown moderate agreement (kappa 0.56) with SGA in predicting poor clinical outcomes. Furthermore, NRS-2002 has been shown to be a strong predictor for postoperative death, while malnutrition by SGA was a predictor for very long hospital LOS (308). In a study by Ryu et al. (311) malnutrition was seen in 43% as measured by NRS-2002 and 31% by PG-SGA in 80 patients with gastric cancer at admission with NRS-2002, showing 80% sensitivity and 98% specificity with PG-SGA as the standard method. In a study of 300 surgical patients by Almeida et al. (317), 66% were at nutritional risk as determined by NRS-2002, and 64% were malnourished as determined by SGA. NRS-2002 showing good agreement (kappa 0.85), with 80% sensitivity and 89% specificity with SGA. In a study of 30 HNC patients, 43% were at nutritional risk as measured by NRS-2002 and 53% were malnourished as measured by PG-SGA. NRS-2002, BMI and anthropometry have shown a good correlation up to six months after surgery, but a year after surgery both NRS-2002 and SGA had normalized to the preoperative status, while body weight and anthropometry still showed malnutrition (311). In a review by Bokhorst et al. (318) the authors concluded that NRS-2002 shows inconsistent validity in screening malnutrition among hospitalized patients compared with PG-SGA.

2.3.7 Patients-generated subjective global assessment (PG-SGA)

PG-SGA was developed from SGA and validated specifically for cancer patients, and has been considered a golden standard for assessment of nutritional status in patients with cancer (23,319,320). It is based on a combination of weight loss, dietary intake, nutrition impact symptoms, performance status, the metabolic effect of the disease and estimation of body composition (189). It has been translated to Swedish (321). SGA has also been used previously in Finland in patients with colorectal cancer (322). PG-SGA is a combination of subjective and objective variables.

The PG-SGA provides subjective information about changes in body weight, dietary intake, gastrointestinal symptoms and functional capacity. In addition, it considers loss of subcutaneous fat, muscle wasting, edema, ad ascites and the metabolic effects of the disease.

The tool has been developed so that the first four sections of PG-SGA are completed by the patient, while the disease and its stage, age, metabolic stress, and body composition are evaluated by a clinician. The metabolic stress includes neutropenic fevers, sepsis, and use of corticosteroids.
Table 9. Guidelines for nutritional status assessment modified by PG-SGA (189).

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B Modestly (or suspected of being) malnourished</th>
<th>Stage C Severely malnourished</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well nourished</td>
<td>• Recent non-fluid weight gain or no weight loss</td>
<td>Clear and convincing evidence of weight loss.</td>
</tr>
<tr>
<td></td>
<td>• Definite decrease in food intake</td>
<td>Definite decrease in food intake</td>
</tr>
<tr>
<td></td>
<td>• Increase in nutrition impact symptoms</td>
<td>Increase in nutrition impact symptoms</td>
</tr>
<tr>
<td></td>
<td>• Reduced performance status</td>
<td>Severe loss of subcutaneous tissue, possible peripheral oedema</td>
</tr>
<tr>
<td></td>
<td>• No weight stabilization or weight gain</td>
<td>Decreased performance status</td>
</tr>
</tbody>
</table>

The physical examination includes assessment of loss of subcutaneous fat (triceps region and midaxillary line at the level of the lower ribs), muscle wasting (temporal areas, deltoids, and quadriceps with a loss of bulk and tone by palpation), and edema (ankle or sacral) or ascites. Patients are classified according to weight loss, dietary intake, nutrition impact symptoms, body composition, and performance status in three groups of nutritional status (Table 9); well-nourished (Stage A), moderately or suspected malnourished (Stage B), or severely malnourished (Stage C).

The PG-SGA is completed as described by Ottery (189). A numerical score is calculated from percentage of body weight loss, changes in dietary intake, gastrointestinal symptoms, functional capacity according to performance status, metabolic effect of disease, and loss of fat mass and muscle depletion. For each component of the PG-SGA points (0–4) are assigned depending on the impact of the symptom on nutritional status and a total score is summed (323). The scored PG-SGA is an easy nutrition assessment tool that allows quick identification and triage of need for nutritional support in hospitalized patients with cancer (320,324). PG-SGA has showed 98% sensitivity and 82% specificity at predicting SGA classification in patients with mixed group of cancers (320).

The PG-SGA is used in conjunction with the nutritional risk of planned cancer therapy to define a standardized interventional approach in oncology patients as well as in clinical practice, cooperative oncology group protocols, and clinical trials of nutritional intervention regimens (325). Furthermore, PG-SGA can be used also among cancer patients in palliative care (211).

2.4 RISK FACTORS FOR WEIGHT LOSS AND MALNUTRITION

Severe weight loss is a central feature of HNC, which is frequently observed especially among males, alcohol users, elderly, and in those with advanced stage (1,22-25,326). This is partly due to cachexia, which is often present in metastatic disease as well as in patients with locally advanced HNC (83). Mastication difficulties are common (34%) due to high prevalence of dentures and dental extractions done before RT to reduce risk of osteonecrosis of the jaws (196).

Surgery in the head and neck area can cause severe problems with mastication, swallowing, speech, and breathing. RT has a negative impact in many critical tissues such as major blood vessels, salivary glands, and nerves causing deterioration in swallowing, mastication and respiration (327). CTX-induced side-effects such as loss of appetite and nausea compromise nutritional status and limit oral intake exposing patients to high risk of malnutrition. Furthermore, it has been shown that CRT and severe pre-treatment weight loss (>10%) are risk factors for further weight loss during postoperative therapy (22,328).
2.4.1 Surgery, radiotherapy and chemotherapy

The consequences of the surgical resections are dysphagia and risk of aspiration, which are caused by disruption of the anatomical structures of swallowing. If a tongue resection has been performed with portions of the floor of the mouth removed, the patient will experience impaired tongue mobility and difficulties in managing the oral phase of swallowing (329). The oral phase of swallowing can also be affected due to resection of the hard and soft palate. Patients with oropharyngaeal malignancies are more likely to have more surgical defects that interfere swallowing than other sites of head and neck area (330).

RT induces early adverse side-effects including mucositis, dysphagia, pain in the mouth and throat, reduction in saliva production, mouth dryness, and bacterial and fungal infections, which cause taste changes, anorexia, and weight loss. At the onset of RT anorexia is seen in 7% and nausea in 10% of patients, while at the end of RT the prevalence is 57% and 20%, respectively (12).

The acute reactions associated with RT usually occur in 10 to 17 days. Late side-effects may develop months or even years after treatment (331-333). The use of IMRT has decreased grade ≥3 acute toxicity from 70% to 45% compared with 3-dimensional conformal RT (334). With IMRT, dose reduction is allocated to the critical organs at the tumor site such as salivary glands, oral cavity, swallowing muscles, larynx, brain stem, spinal cord and cochlea. Still the most commonly reported side-effects at the end of IMRT are tube feeding-dependent dysphagia (37%) and mucosis (41%) (334).

CRT is associated with a better progression-free survival and OS than RT alone but combined therapy also doubles the amount of severe acute adverse events compared with RT alone (335). The adverse events are dependent on the type of cytostatic drugs used, as well as the dose and frequency of the treatment. Adding cisplatin-based chemotherapy to RT induces nausea, anorexia, taste changes, and other severe toxicity such as nephrotoxicity and bone marrow depression (336), which are seen in up to 30% of patients (337). In general, CRT-induced mucositis and dysphagia at oral, pharyngeal, and laryngeal sites begins within 15 days from the start of CRT (338). For patients with recurrent or metastatic HNSCC progressing on cisplatin based CTx, new immunotherapy (e.g. nivolumab and pembrolizumab) are available with different toxicity profiles than cisplatin-based CTx. Cetuximab is a biologic drug that is used as a radiosensitizer or in combination with chemotherapy (339,340).

The accumulation of acute adverse events during CRT predisposes to increased weight loss (341). Mucositis and dysphagia are seen in 87% of patients treated with CRT, leading to an additional 10% of weight loss (342,343). Moreover, sarcopenia increases dose-limiting toxicity from chemotherapy, and patients with low body muscle-mass experience toxicity in 44% compared with 14% in patients with normal muscle mass (181). This is explained by accumulation of cisplatin in muscles and other tissues.

Therefore, many protocols formerly favored the insertion of a percutaneous endoscopic gastrostomy (PEG) for patients planned to undergo CRT to ensure adequate nutritional intake and to prevent malnutrition, although currently it is recommended to a lesser extent. There has been concern that prophylactic gastrostomy insertion would increase gastrostomy dependency, dysphagia due to muscle disuse and atrophy, as well as procedure complications such as pain, tube migration, bowel perforation, peritonitis, abscess, and fistula (344), whereas others disagree (345). A recent study by Alterio et al. (346) showed that the absorbed radiation dose at the cervical esophagus and cricopharyngeal muscle might be responsible for dysphagia. Several studies in patients with HNC, however, favor either PEG or nasogastric tube insertion before CRT with recommendations to use radiologically inserted gastrostomy instead of PEG to prevent potential metastatic seeding (347-350).

2.4.2 Dysphagia

Dysphagia and odynophagia are common symptoms of HNC treatment due to the disease itself, its treatment, and its side-effects, which predispose patients to malnutrition, dehydration, and
aspiration (351,352). Even though the use of IMRT allows to spare organs, and thus to reduce toxicity, RT-induced adverse effects are still considerable among HNC patients (353,354). Before commencing any treatment, already 22-37% of the patients have dysphagia (12,29,196,355), while at the end of RT almost all patients (82-91%) suffer from this condition (12,355). The ability to swallow recovers slowly and is still one of the major aspects affecting patients’ QoL during the first year after RT (353). Late dysphagia has decreased from 31% to 10% with the IMRT technique, which has had propitious effects decreasing the need for tube feeding by 13% (from 50% to 37%) during CRT in patients with oropharyngeal carcinoma (334). A retrospective study showed no differences in weight change or need for tube feeding following either IMRT or three-dimensional conformal RT (356). The median weight loss in both groups was more than 5%, and the need for PEG varied from 86% to 92%.

2.4.3 Mucositis
Inflammation of mucosa (mucositis) is a general term to describe a state of mucosal irritation that can include erythema, inflammation, ulceration and infection (352). The addition of CTx to RT increases the prevalence of mucositis and Candida or other oral microbial infections (357). Radiation-induced mucositis begins 10 to 14 days after the commencement of RT and decreases 4 to 6 weeks after ending of radiation (358). Mucositis increases risk for unplanned RT breaks and for hospitalization (357,359).

The prevalence of mucositis in patients with HNC during RT with or without CTx is reported to be around 80% (305). At baseline 0-2% of the patients have mucositis; by the end of RT 76-91% develop mucositis, and one month after the completion of RT or CRT 55-76% of patients have significant mucositis (5,29,342,357). In 29-66% of cases it is severe, grade III-IV mucositis (5,357). The incidence of mucositis decreases during follow up, but still one year after cessation of the treatment approximately 16% of patients have mucositis (29).

2.4.5 Xerostomia
Major salivary glands (parotid, submandibular and sublingual glands) are usually part of the irradiation field, which results in xerostomia, including reduced salivary output and increased viscosity (360). Patients suffer from oral discomfort and have difficulties to chew, swallow and speak and have greater risk for oral infections. After RT caries develops in 11% of patients and candidiasis in 21% of patients (361). In patients with oropharyngeal carcinoma IMRT has decreased severe xerostomia from 37% to 13% (334). However, others have reported higher prevalences (40%) with parotid-sparing IMRT (362). One earlier study reported that the problem is low during the first 18 months after RT, but increases gradually at 24 months (353). Xerostomia is also often underestimated by health care professionals compared with patient-reported outcomes (363).

2.4.6 Taste alterations
Taste alterations (dysgeusia) due to the disease itself, surgery, RT, and CTx can lead to food aversions, nausea, and loss of appetite (364). Taste changes may also be related to opioid medication or secondary infections. Patients often describe taste changes as food tasting metallic, like cardboard or sandpaper, sensitivity or insensitivity to sweetness, saltiness, sourness, or intolerance to bitterness, or a total loss of taste (365). The changes begin at around day 10 to 14 and resolve in 14 to 21 days after last RT session (366). Prior to RT 22-28% (12,196) and after RT 63% have dysgeusia (367). Loss of taste and appetite are more frequently associated with cancer Stages III and IV than Stages I and II (23).

Taste alterations can arise either from tumor cells secreting amino acid-like substances (365) or CTx drug (cisplatin) diffusion from the blood to the bottom of taste buds, giving a bitter taste (368), which can last for a few hours or even 3 weeks (369). RT damages taste buds, resulting a metallic taste. It has been suggested that zinc deficiency could be linked to hypogeusia (370), but zinc sulphate supplementation was not able to prevent taste changes in oropharynx carcinoma during RT (371).
2.5 CONSEQUENCES OF MALNUTRITION

2.5.1 In cancer patients in general
Cancer-related body weight loss and malnutrition have multifactorial effects on patient’s health. Weight loss more than 15% associates with major complications in a mixed group of cancer patients (372), while in general weight loss more than 10% during previous six months is regarded as severe. Weight loss and malnutrition decreases patients’ resistance to infections (112,373,374), weaken respiratory and immune system function (375-378), and enhance susceptibility to postoperative complications (167,379-383), CTx derived toxicity (37,160-162,384-387), and treatment-induced complications and interruptions (107,388). Altogether, the consequences for patients and healthcare are detrimental, because patients’ QoL (24,389-391) is decreased and mortality (12,37,320,392-398) is increased, LOS (399,400) and overall hospital costs (41,395,400-404) are increased.

Advanced cancer patients with sarcopenic obesity have worse survival than patients without sarcopenia (162,405,406). In a study performed by Prago et al. (162) median survival rate was 11 months in the presence of sarcopenic obesity compared with 22 months without sarcopenia independently of cancer site, stage and performance status. Three-year follow-up results of the van Bokhorst et al. (102) study showed that a high nodal (N) classification and male gender combined with preoperative weight loss of 5% or more were found to be the most prominent risk factors for increased mortality.

A recent study by Leandro-Merhi et al. (407) investigated the relationship between nutritional status and outcome. They found that among cancer patients low mid-arm anthropometry, BMI, and nutritional intake (<75%), malnutrition, nutritional risk, age over 60 years, and male gender were associated with increased complications, LOS, and mortality. Ravasco et al. (408) showed that nutritional counseling by a dietitian compared with either oral nutrition supplements only or normal diet ad libitum, improved both QoL function and symptom scores in colorectal cancer during RT. In this regard it is surprising that nearly 60% of the malnourished patients still do not receive any nutritional treatment during hospitalization as was shown in recent study in Norway (35).

2.5.3 In head and neck cancer
Body weight loss is a significant and early phenomenon among HNC patients. The highest (>30%) prevalence of severe body weight loss is seen among oral cavity, oropharynx, hypopharynx, nasopharynx, and supraglottic larynx cancer patients, while in cancers of subglottic and transglottic larynx cancers the prevalence is 20% (1). The lowest (10%) prevalence is seen in carcinomas of the glottis and other squamous cell cancers of the head and neck (e.g. salivary glands, nasal cavity, and thyroid).

During RT and CRT malnutrition has been found to impair immune function (107,409) and decrease tolerance to treatment (107,109,355). Half of HNC patients have toxicity-related delays during CRT (336) and tumor control is decreased by 1.4% per day of RT interruptions (410). In patients with HNC malnutrition decreases QoL and increases morbidity and mortality. The role of malnutrition decreasing QoL in patients with HNC has been long recognized (24,102,105,114,194,411-414). Ravasco et al. (24) reported that nutrition intake and weight loss were associated with low QoL function scores, while tumor location and stage affected QoL symptom scores.

Preoperative weight loss exceeding 10% of the usual body weight during past 6 months correlates with major postoperative complications in patients with HNC (167,404). Malnutrition increases the risk of post-surgical infections (107,373), and delays wound healing (415). Matthews et al. (10) were not able to confirm the association between nutritional parameters and incidence of complications, while a more recent study showed relationship between weight loss (>10% in previous 6 months) and post-surgery complications (167). Malnutrition increases hospital readmissions of HNC patients (107) with dysphagia being the strongest predictor for prolonged LOS (416).
2.6 NUTRITIONAL STATUS IN HEAD AND NECK CANCER

A review of nutritional status assessment in patients with HNC showed that 24 different definitions for malnutrition have been used, with percentual weight loss in the previous month or six months and the Patient-generated Subjective Global Assessment (PG-SGA) method being the most common (191). One study assessed malnutrition in a HNC patient cohort with six different methods and malnutrition varied from 20% to 67% depending on the method (167). This loose terminology and differences in used nutritional status assessment methods explain the wide variability in the prevalence of malnutrition that has been seen in HNC studies.

Weight loss affects patients already prior to treatment and becomes aggravated in a more advanced stage of disease and during oncological treatment. Body weight loss is reported to affect 30% to 58% of patients with HNC at diagnosis (102,355), while malnutrition is seen in 40% of patients (15).

2.6.1 Prior to the diagnosis

Weight loss. The incidence of significant weight loss (5-10% during previous 6 months) at the time of diagnosis and before any cancer treatment (i.e. surgery, RT, or CRT) has been reported in 13% to 57% (1,10,167,194,196,417-420). In a retrospective study one third of patients were assessed to be nutritionally deficient by weight loss criteria (112). Highest risk (34% to 43%) for severe weight loss was among patients with hypopharynx, oropharynx, oral cavity, and supraglottic larynx cancers (1). The main reasons for decreased nutrition intake were dysphagia, loss of taste and appetite, all of which were seen more in patients with tumor T stages three to four than stages one to two. In cancer Stages III and IV weight loss was seen in 15-34% of patients, while in Stages I and II only in 3-7% (1,24).

Malnutrition. Malnutrition prior to diagnosis has been reported to range from 19% to 75% (25,196,342,421) and before operation or postoperative treatment from 35% to 64% (14,109,379,422-425). In these studies, nutritional status has been assessed by weight loss, nutritional assessment score, prognostic nutritional index, general nutrition score or by protein energy malnutrition scale. In a study where a combination of malnutrition criteria was used, 48% of patients were malnourished prior to diagnosis (25). In more recent studies PG-SGA has been used as a golden standard for nutritional status assessment, with the prevalence of malnutrition ranging from 40% to 60% (11,12,14,15).

2.6.2 During postoperative therapies

The prevalence of severe weight loss during, either chemoradiotherapy (CRT) or radiotherapy, has been reported to be 16-89% (22,196,355,413,417,419,426). Silver et al. (30) observed that weight loss began one week after initiation of the concurrent CRT and continued for one month during the follow up period.

In a study by van den Berg et al. (417) severe weight loss was seen in 32% of patients at the end of (C)RT (>10% during the previous 6 months) while in a more recent study by Jager-Wittenaar et al. (413) the prevalence was only 16%. Forty-four percent of Stage I-II laryngeal cancer patients had weight loss exceeding 5%, while 15% had weight loss exceeding 10% at the end of RT (13). Due to the high incidence of severe weight loss a higher incidence of dehydration (11%) and prophylactic feeding gastrostomy tube placement (32%) have also been reported (22).

Patients start to lose weight early during RT and the situation tends to worsen during first year of follow up. Moreover, nutritional status deteriorates during the postoperative period even if appropriate enteral nutrition has been administered (427). In a study by Larsson et al. (29) the mean percentage weight loss was 3% after two weeks of RT, 4% after three weeks, 7% at the end of RT, 11% a one month after RT, 14% after six months and 17% a year after RT. In another study patients lost 5% of weight with substantial lean weight loss (62%) during RT or CTx even in patients with sufficient nutrient intake (267). Patients may lose an additional 10% to 12% of body...
weight during RT and CRT (30,428,429). The mean muscle loss varies from 7 to 11 kg (30,417,430), and can make up 72% of the total body mass loss (30). A high dose of RT received at larynx level accentuates the weight loss (431). Malnutrition is seen in 44% to 88% at the end of (C)RT (13,16,17).

2.7 NUTRITIONAL SUPPORT IN CANCER

The most recent guidelines and recommendations on nutrition care in cancer and surgery were published by ESPEN (182,432,433), and they are in accordance with the earlier recommendations (434-436). Currently regular screening to detect nutritional risk or the presence of malnutrition and nutritional support are recommended to all cancer patients (182). A wide range of nutritional support options, including volitional and non-volitional feeding (348), are available for the treatment of malnutrition in patients with HNC undergoing RT or CRT. Volitional feeding includes diet counseling, diet consistency modification of regular food, and ONS. Non-volitional feeding includes enteral tube feeding (PEG or nasogastric tube), and parenteral nutrition support. Usually a combination of these are needed (32). Moreover, resistance and aerobic exercise training should be part of the nutritional treatment in addition to pharmacologic agents in severely malnourished patients with advanced disease (182).

In patients with HNC, weight loss in the early stages of disease often results from simple starvation, which is potentially reversible with appropriate nutritional support, while in more advanced stages weight loss and muscle mass depletion result from poor nutritional intake and cachexia, which are refractory to the nutritional support. In a study of 47 HNC patients, energy intake decreased on the average by 122 kcal/day during radiotherapy, and increased by 326 kcal/day during follow up (417). Nutritional intake is considered inadequate if a patient is not able to swallow for more than a week or if estimated energy intake is less than 60% of requirement for more than 1-2 weeks (434-436). Also, partial daily reduction in nutrition intake (i.e. energy and protein) should be taken into consideration, because it can result in large energy and protein deficits causing severe muscle and fat mass depletion over time.

Ravasco et al. (437) reported that nutritional intervention improved long-term prognosis in colorectal cancer patients, while preoperative intensive physician-requested nutritional counseling was effective in preventing postoperative major complications in patients with esophageal cancer (438). Nutritional counseling improved patients’ outcome among colorectal cancer (408), and improved weight maintenance among gynecologic, gastric, and esophageal cancer patients (439). Moreover, intensive, individual dietary counseling received by a dietitian together with provision of ONS was more effective than counseling received by a nurse without any supplements (439).

2.7.1 Nutritional support in patients with head and neck cancer

Currently in patients with HNC nutrition support is considered, at least partially, efficient and to improve outcome (182). ESPEN recommends that especially during RT of the head and neck site, an adequate nutritional intake is ensured primarily by individualized nutritional counseling by a trained professional with or without ONS (182). There are two reviews regarding the effects of nutritional interventions among HNC patients receiving (C)RT (440,441), with five studies between years 1992 and 2005 during RT (12,355,442-444), three between years 2007 and 2012 during (C)RT (17,445,446), of which three studies (four publications) were RCTs (12,443-445).

The medical nutritional therapy protocol launched by the American Dietetic Association (ADA) (434,447) has been found to be effective both in physiological, and clinically relevant outcomes in HNSCC patients undergoing RT (12,443-445). Isenring et al. (443,445) among the first, showed already a decade ago that nutrition intervention according to the ADA protocol was efficient to decrease body weight loss, increase QoL, and physical function during RT in patients with GI-cancer or HNC. Furthermore, the implementation of nutritional guidelines has been shown to be beneficial in stabilizing weight during RT in patients with HNC (448), while in
general, oncologic patients are more satisfied with nutrition intervention than without it (449). Capuano et al. (107) demonstrated that nutritional-program compliant patients were weight stable, whereas non-compliant HNC patients lost a median 11% of body weight during CRT. It is noteworthy that 84% of these non-compliant patients lost more than 20% of body weight, which was associated with poor survival.

Four randomized studies in patients with HNC compared individualized nutritional dietitian-delivered counseling with no counseling and standard nutritional advice by a nurse. The results of these studies underlined the necessity of nutritional interventions given by a dietitian (12,443-445). Intensive nutritional counseling administered by a registered clinical dietitian has been shown to increase dietary intake, prevent therapy-associated weight loss, and interruption of RT and CTx (12,443-445). Ravasco et al. (12) showed that nutritional counseling was more effective in decreasing RT induced morbidity than ONS only or ad libitum diet. Nutritional deterioration was seen at the end of RT in 20% of individualized dietary counseling group compared with 76% in ONS, and 96% in the ad libitum diet group (12). Furthermore, during follow-up the patients in nutritional counseling group gained weight while none of the ONS, or ad libitum group patients did (12). A retrospective study by Paccagnella et al. (17) compared early nutritional counseling by a dietitian with late nutritional counseling during CRT. Patients in the early counseling group lost less weight and had fewer RT breaks due to toxicity than patients in the late counseling group. In a more recent randomized HNC study, dietitian-based counseling with ONS resulted in better protein-calorie intake, weight maintenance, QOL, and treatment tolerance than without ONS (450).

Two studies compared ONS with no supplements during RT (12,355). In the study by Nauyel et al. (355) the intervention group had weight gain and no treatment interruptions, while 42% of patients in control group lost weight and had treatment interruptions. In a study by Ravasco et al. (12) use of ONS increased protein and energy intake without any effect on weight gain or to QoL, in contrast to dietary counseling. Lee et al. (451) reported that ONS reduced need for PEG tube placement. Early insertion of PEG reduced hospitalization due to dehyration by 18% in 45 patients with oropharyngeal cancer receiving RT (452).

It is noteworthy that some of the nutrition intervention studies with positive outcome results compared nutrition support to usual care or a free ad libitum diet (i.e. patients were without appropriate nutrition treatment) (12,443-445). A study by Goncalves Diaz et al. (442) showed that nutritional support regardless of the method used (diet, ONS, or tube feeding) increase both energy and protein intake in patients with HNC during RT. The hallmark of the nutrition support is to ensure that energy, protein, and nutrient requirements are met for all cancer patients, preferably by the enteral route with regular food and ONS, or by tube feeding, excluding patients with end of life care (182).

**Immunonutrition**

Immunonutrients such as the amino acid arginine and glutamine, dietary nucleotides, and omega-3 fatty acids provided perioperatively may modulate the immune and inflammatory response. In a recent meta-analysis, arginine-enriched enteral nutrition was shown to decrease fistulas and LOS in patients undergoing HNC surgery (453). Arginine promotes collagen formation, stimulates growth hormone production, serves as a substrate for the synthesis of nitric oxide, and regulates immune function, thus enhancing wound healing and reducing infections (454).

Five studies on patients with HNC reported the effect of arginine on immune response and postoperative complications (455-459). In early studies, an arginine-enhanced diet did not decrease either IL-6 or CRP levels, and had no effect on outcome compared with standard formula (456,457). In two studies with oral and laryngeal cancer, de Luis et al. (458,459) showed that high dose-arginine was associated with reduced incidence of fistulas and shorter LOS but not with incidence of infections. Riso et al. (455) showed that arginine reduced postoperative infections and wound complications especially in malnourished patients, contrary to a previous study by van Bokhorst et al. (456).
Eight studies in patients with HNC compared preoperatively administered immunonutrition with standard formula (57,418,456,459-462), one compared two immune-enhanced enteral formulas (i.e. arginine-rich and Impact® with standard formula (463), one study compared preoperative and perioperative immunonutrition (464), and two studies were performed during CRT (465,466). The enteral formula was specified (Impact®, Nestle Healthcare Nutrition, Switzerland) in three studies (418,460,462) and not specified in three studies (456,459,461).

Immunonutrition (Impact®) reduced the incidence of infections and LOS in a study with 136 HNC patients (460) and postoperative complications in a study with 40 HNC patients (418). In a very small (n=8) pilot study, immunonutrition was shown to improve inflammatory status and decrease LOS (462). Casa-Rodera et al. (463) compared two immuno-enhanced enteral formulas with a control diet and demonstrated that immunonutrition decreased infection rates but not fistula rates in patients with oral and laryngeal cancer. Pre- and postoperative immunonutrition compared with isocaloric nutritional support did not improve wound healing in a small study with 15 HNC patients (57), nor in a larger double-blind RCT (464). In the latter study, majority of the patients were well-nourished prior to surgery, both energy and protein intake (1500 kcal and 84 to 105 g of protein) were rather low and the compliance for nutrition care was poor, all of which may have biased the results. During CRT immunonutrition has been shown to improve functional capacity and weight gain in HNC and oesophageal cancer (465), as well as prevent severe mucositis (466).

High-fat enteral nutrition formula containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improved both nutritional and functional parameters compared with a standard high-carbohydrate formula in patients with HNC and esophageal cancer undergoing CTx (467). Moreover, in a more recent study in patients with advanced non-small cell lung cancer, ONS including EPA improved appetite, nutritional intake, quality of life, and body composition and decreased fatigue and neuropathy during CTx (468).

2.7.2 Energy requirement
Determination of energy need is a central part of nutritional support. The energy need of the body depends on the amount of metabolically active tissue mass (i.e. LST), physical activity, diet-induced thermogenesis, and illness-induced hypermetabolism. In healthy normally active adults resting energy expenditure (REE) accounts for two thirds of the total energy expenditure (TEE). Callaghan et al. (469) showed that brain, liver, heart, and kidneys constitute 6% of total body weight and comprise 58% of basal metabolic rate (BMR) in normal-weight adult. Muscle represents 50% of FFM and is responsible for about 23% of BMR while adipose tissue comprises about 20% of body weight but accounts only 4% of BMR.

Cancer patients can have varying energy needs due to hypometabolic, normometabolic, or hypermetabolic REE (470-474). Cao et al. (475) found that 47% of cancer patients were hypermetabolic, 44% normometabolic, and 10% hypometabolic at diagnosis compared with 25%, 56% and 18% in healthy controls, respectively. It has been calculated that an elevation of 12% in the metabolic rate could account for the loss of 1-2 kg of body weight per month (470).

The tumor type appears to play an essential role in determining whether an elevation of REE is observed. Patients with lung (476) and pancreatic cancer (472,477) have been reported to have increased REE. In a small study (n=24) with cachectic pancreatic cancer patients, REE was approximately 100 kcal higher and TEE was 200 kcal lower than in healthy subjects (477). The explanation for the difference in TEE was a result of lower physical activity level in cachetic cancer patients (1.24 vs. 1.5) (171,477). An approximately 10% higher REE has been shown in patients with lung cancer compared with healthy controls (476,478), while in colorectal and gastric cancer such association has not been found (471,479).

Weight loss in colorectal cancer patients is a result of decreased food intake, whereas in lung cancer it is due to combination of both increased REE and low food intake (480). Furthermore, it seems that inflammation increases REE as was reported by Johnson et al. (481). In this study of weight losing patients with miscellaneous group of cancers, those with high CRP concentration
had 200 kcal higher REE compared with the ones with low CRP concentration. Moses et al. (477) showed that in patients with cancer cachexia, anorexia reduced energy supply by 300-500 kcal/day whilst enhanced metabolism increased the energy need by 100-200 kcal/day. The wasting syndrome is in part explained by elevated cardiovascular activity due to anemia and loss of cardiac contractile capacity (482).

Duration of disease and oncological treatments increase energy expenditure. In colorectal cancer, the patients were normometabolic at 4.5 months, hypometabolic at 10 months, and hypermetabolic at 14 months (474). It is assumed that surgery increases REE, but the effect is less than presumed. Major elective gastrointestinal cancer surgery increased REE only about 100 kcal, and patients receiving preoperative total parenteral nutrition or suffering postoperative complications showed a 10% increase in REE (483). Reeves and co-workers (484) found an overall 10% increase in REE in patients with solid tumors undergoing anticancer therapy. Silver et al. (30) found a mildly hypermetabolic state one month after CRT when REE was adjusted for FFM in patients with HNC. In contrast, in an earlier study REE was 100 kcal higher at the beginning of therapy and 2 weeks after treatment, but not during treatment among HNC patients (429).

REE can be measured more accurately by indirect calorimetry (IC), which is regarded as the most recommended method. IC is not usually available in everyday clinical practice, and thus estimation equations or a fixed number of calories per kg of body weight are used. Differences between measured and estimated REE can be more than 10% or 250 kcal, which has been considered clinically unacceptable (485).

It has been shown that REE estimation may vary from 40% below up to 30% above measured REE (484). REE is estimated by gender, weight, height and age (Table 10). Weight is either current, ideal or adjusted body weight. Anthropometric measures may improve the predictability of basal metabolic rate in adult subjects (486).

The most popular equation for REE estimation is the Harris-Benedict formula (HBE), which is corrected by a disease-related stress factor, varying from 1.2 to 1.6 (e.g. in cancer 1.3) (487,488). HBE underestimates REE when compared with indirect calorimetry in several cancers including HNC (429) and pancreas cancer (489). In patients with lung cancer measured REE was 20% and in cachectic patients 10% higher than predicted by HBE (481,490). Thus, it has been recommended that rather a stress factor 1.1 instead of 1.3 (484) should be used with HBE in patients with cancer (481). Furthermore, the HBE without an added stress and activity factor is more accurate than the clinically estimated resting energy expenditure also in critically ill cancer patients (491). In hospitalized patients HBE and Mifflin St Jeor equations (492) were equally accurate at a group level while at an individual level considerable differences were seen (493). HBE is accurate in 55-62% of hospitalized patients when actual weight is used (485). In contrast, Schofield (494) equations have been shown to estimate REE more accurately than HBE (495), which overestimates REE by 10%.

In a review by Miles et al. (496) it was suggested that the majority of patients can be fed adequately by supplying 100% to 120% of the estimated REE, while others suggest that a minimum of 30 kcal/kg/day is needed to maintain body weight (445,497,498). As a rule-of-thumb, ESPEN recommends for non-obese ambulant patients 30-35 kcal/kg/day and for bedridden patients 20-25 kcal/kg/day using the actual body weight (499).

In studies with HNC including nutritional support the energy intake target has varied from 30 to 35 kcal/actual BW/day (413), 1.5 x the basal energy expenditure (BEE) estimated by the HBE based on actual body weight (500). BEE has been estimated for patients aged 18-60 years by the WHO formula (494) and for patients >60 years by the formula by Owen et al. (501,502) in two studies (11,12). Also, the Schofield equation has been used previously to calculate energy need in cancer patients (16). An energy intake ≥35 kcal/kg/day and protein intake ≥1.5 g/kg/day have been considered sufficient (267,499,503).
Table 10. Basal metabolic rate (BMR) and resting energy expenditure (REE) estimation equations.

<table>
<thead>
<tr>
<th>Estimation equation (Kcal)</th>
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<tbody>
<tr>
<td><strong>Harris-Benedict (BMR)</strong></td>
</tr>
<tr>
<td>M: 66 + 13.7 x weight (kg) + 5 x height (cm) - 6.8 x age (y)</td>
</tr>
<tr>
<td>W: 665 + 9.6 x weight (kg) + 1.8 x height (cm) - 4.7 x age (y)</td>
</tr>
<tr>
<td><strong>Mifflin-St Jeor (REE)</strong></td>
</tr>
<tr>
<td>M: 10 x weight (kg) + 6.25 x height (cm) - 5 x age (y) + 5</td>
</tr>
<tr>
<td>W: 10 x weight (kg) + 6.25 x height (cm) - 5 x age (y) - 161</td>
</tr>
<tr>
<td><strong>Schofield by weight and height</strong></td>
</tr>
<tr>
<td>(BMR, 30-60 years)</td>
</tr>
<tr>
<td>M: 11.5 x weight (kg) - 2.6 x height (m) + 877</td>
</tr>
<tr>
<td>W: 11.6 x weight (kg) - 1.4 x height (m) + 844</td>
</tr>
<tr>
<td><strong>Owen (&gt;60 y, REE)</strong></td>
</tr>
<tr>
<td>M: 10.2 x weight (kg) + 879</td>
</tr>
<tr>
<td>W: 7.18 x weight (kg) + 795</td>
</tr>
</tbody>
</table>

BMR basal metabolic rate, REE resting energy expenditure, M men, W women

2.7.3 Protein requirement

In addition to sufficient energy intake, optimal protein intake is crucial for wellbeing, as a 30% loss of body protein results in death (504). Protein turnover is well balanced in the normal state, but easily altered during illness, resulting in negative nitrogen balance and muscle-mass depletion.

As an optimal protein intake, ESPEN recommends 1.2-2 g/kg/day for oncological patients (505), and for surgical patients 1.2 to 1.9 g/kg/day depending on the severity of illness (506,507). Optimal nitrogen requirement has not yet been determined (508). Furthermore, 1.9 g/kg/day is recommended for severely underweight patients (505). Ishibashi et al. (507) suggested that protein intake of 1.5-1.7 g/kg/day is too high for septic ICU patients.

In a study by Isenring et al. (445) concluded that for oncology patients in RT protein intake of 1.3 g/kg/day was beneficial compared with 1.1 g/kg/day. The authors were concerned that for some patients, attaining protein intake of 1.5 g/kg/day is unrealistic and a more appropriate goal would be 1.1-1.2 g/kg/day. On contrary, Sauerwein and colleagues suggested a higher protein intake of 1.5-1.7 g/kg/day (503). In studies with HNC including nutritional support the protein intake target has been from 1.0 to 1.5 g/actual body weight/day (413). High intake of protein (25-35% of total energy) may induce a sense of early satiety, with vegetal proteins having higher satiety effect than animal proteins (509).

2.7.4 Enteral nutrition by PEG

Since its introduction in 1980, PEG has become more common in the management of patients with HNC (510). Enteral nutrition is the treatment of choice for patients with functioning gastrointestinal tract. In patients with HNC, tube feeding is used in 4% to 57% of patients (22,511). To be successful, this requires appropriate dietetic support and follow up to the patient, family and health professionals involved in their care (512). In a study with 79 HNC patients Lee et al. (419) showed that patients with PEG lost on the average 3 kg compared with 7 kg in patients without PEG. It was also noted that a weight loss of 4.5 kg or more during treatment was an identifiable predictive factor of the need for a PEG. Patients with prophylactic PEG had significantly reduced rate of hospitalization for dehydration and complications of mucositis during high-intensity RT.

Patients with HNC show benefit from the insertion of PEG during RT (419,452,513). Treatment-induced grade 3-4 mucositis is usually observed by the end of fourth week of CRT, which requires either a liquid diet or tube feeding (352,514). Factors associated with the need for PEG include primary tumor location in the hypopharynx, oral cavity, or oropharynx (515), supraglottic larynx (1), or nasopharynx (513), severe weight loss (22,342,347,516), female gender (342), increased age
(347), heavy alcohol use (517), and smoking (518). In addition, patients with Stage IV disease needed prolonged tube feeding because normalization of the diet was slow (342,419,515,519). Prophylactic PEG placement reduces the incidence of severe weight loss and hospitalization due to dehydration, maintains nutritional status, and reduces treatment interruptions during CRT (520). Thus, it has been recommended that PEG is needed in patients with recent weight loss >10% of the usual weight, BMI <20 kg/m² and age >70 years. Other indicators for PEG placement (419,452), include WHO performance status 2-3, albumin <40 g/l, and smoking >20 cigarettes/day (518). Preoperative risk factors for long-term nutritional support and need for PEG are heavy alcohol use, tongue base involvement, surgery, pharyngectomy, composite resection, reconstruction with a myocutaneous flap, RT, tumor size, and moderately-to-poorly differentiated histology (518).

The placement of a PEG tube is a safe method for providing non-oral nutritional support to patients with HNC with a complication rate of 11% (521). In another study by Chandu et al. (522) minor complications were reported in 10% of patients and major complications in 8% of patients. In a study by Hujala et al. (523) the incidence of acute complications was 1.3% and late complications 15%, while in a more recent study by Ruohoalho et al. (524) major complications were observed in 3%.

There is a small, but definite risk for tumor implantation in the gastrostomy site when the pull technique is used in patients with HNC, especially oropharyngeal or hypopharyngeal cancers, before cancer treatment (525,526). In a Finnish study with 127 HNC patients one metastasis developed at the PEG site, while in another study with 304 HNC patients two such cases were seen (524,527).
3 Aims of the study

The primary aim of this study was to study the effect of intensive nutritional counseling on nutritional status, body weight, and treatment-related adverse events in HNSCC patients. We studied nutritional status at diagnosis, prior to any cancer treatment and during (C)RT. The general objective was to improve nutritional care in patients with primary HNSCC and to find suitable nutritional status assessment methods to be integrated in routine medical care.

The specific aims of this thesis were as follows:

1. To assess vitamin D (S-25-OHD) status in Finnish HNSCC patients (I).
2. To evaluate nutritional status and the prevalence of malnutrition prior to diagnosis in HNSCC patients (II).
3. To analyse the potential relationship of NRS-2002 with nutritional status, anthropometry and HGS to assess its value as a clinical risk screening method in HNSCC patients (II).
4. To analyse the relationship of cachexia measured by HGS and mid-arm anthropometry with survival in HNSCC patients (III).
5. To assess the effect of a pre-planned patient-adjusted intensive nutritional counseling received by a dietitian several times during (C)RT vs. individualized nutritional counseling received by a dietitian once in the beginning of (C)RT and thereafter on-demand during the treatment, on nutritional status and survival in HNSCC patients (IV).
Subjects and methods

4.1 SUBJECTS

Patients were recruited between November 2007 and September 2009 from cancer patients referred to the Head and Neck Surgery branch of HUH Department of Otorhinolaryngology. Patients were recruited for the study at their first outpatient visit after the multidisciplinary tumor board meeting at the Department of Otorhinolaryngology – Head and Neck Surgery of the Helsinki University Hospital (HUS). Patients received either definitive CRT or combined treatment consisting of surgery and postoperative RT or CRT after the diagnosis.

Patients were included in the study if they had a locally advanced histologically verified diagnosis of squamous cell cancer of oral cavity, oropharynx, hypopharynx, larynx or nasopharynx. Patients aged 18-80 years were eligible for inclusion. Cancers of the ear, salivary gland, nose or paranasal cavity, esophagus, thyroid gland, skin, eye, and lymphomas were excluded. Also, patients with moderate-to-severe kidney failure (serum creatinine >1.5 times the upper limit of normal), hepatic failure (serum bilirubin >1.5 times the upper limit of normal), heart failure, COPD, or cognitive impairment were excluded. Patients were also excluded if they had had a previous cancer in any location or if they were recommended to receive treatment with palliative intent.

Altogether 195 patients were assessed. Inclusion criteria were not met in 107 patients (55%). Of the 88 (45%) eligible patients seven refused, two participated in another clinical trial, and 14 were not included due to logistic reasons.

Sixty-five (74%) of the eligible 88 patients gave their written informed consent to participate in the study including 50 men (77%) and 15 women (23%) with primary HNSCC. Baseline characteristics of the patients are shown in Table 10. The median age was 61 years (range, 33 - 73) and 25% were 65 years or older. Most the patients had oropharyngeal carcinoma (35%) and Stage IV (65%) disease. Most patients had normal body weight (41%) or were overweight (49%) and median BMI was 23.7 kg/m² (interquartile [IQ] range, 21-27). All patients were assessed prior to any therapeutic intervention.

Inclusion of subjects in the substudies was as follows:

- Studies 1-3: Vitamin D status, prevalence of malnutrition, nutritional risk, and cachexia were assessed in 65 patients; 50 males and 15 females.
- Study 4: In the nutrition intervention study all 65 participants were included; 32 (21 males, 11 females) were randomly assigned to receive intensive individualized nutritional counseling (INC) and 33 (25 males, eight females) received individualized on-demand counseling (ODC). Fifty-eight (89%) patients completed the treatment and were included in the analyses, one patient withdrew his consent, three died and three had their treatment discontinued due to disease progression.
- In addition, we determined the validity of HGS as a method to diagnose sarcopenia in 50 male patients were included in the analyses. Women were excluded due to their small number (n=15).
4 Subjects and methods

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Table 11. Baseline clinical characteristics of the 65 patients.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;39</td>
<td>2 (3)</td>
</tr>
<tr>
<td>40-64</td>
<td>47 (72)</td>
</tr>
<tr>
<td>≥65</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>50 (77)</td>
</tr>
<tr>
<td>BMI, n (%)</td>
<td>23.7 (21-27)</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>6 (9)</td>
</tr>
<tr>
<td>18.5-24.0</td>
<td>27 (41)</td>
</tr>
<tr>
<td>24.1-30.0</td>
<td>24 (37)</td>
</tr>
<tr>
<td>&gt;30.0</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Larynx</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>11 (17)</td>
</tr>
<tr>
<td>III-IV</td>
<td>53 (82)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Surgery and RT</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Surgery and CRT</td>
<td>10 (15)</td>
</tr>
<tr>
<td>CRT</td>
<td>42 (65)</td>
</tr>
<tr>
<td>RT</td>
<td>6 (9)</td>
</tr>
<tr>
<td>PEG, n (%)</td>
<td>54 (83)</td>
</tr>
<tr>
<td>Alcohol use, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Current</td>
<td>61 (94)</td>
</tr>
<tr>
<td>Former</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Current</td>
<td>42 (65)</td>
</tr>
<tr>
<td>Former</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Alcohol use and smoking currently, n (%)</td>
<td>32 (49)</td>
</tr>
<tr>
<td>Nutritional parameters, median (IQ range)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.7 (60-87)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174.0 (168-180)</td>
</tr>
<tr>
<td>Weight loss during previous 6 months, %</td>
<td>1.3 (0.2-7)</td>
</tr>
<tr>
<td>TSF, mm</td>
<td>13.0 (10-18)</td>
</tr>
<tr>
<td>MAC, cm</td>
<td>28.5 (25-31)</td>
</tr>
<tr>
<td>MAMA, cm²</td>
<td>47.6 (26-57)</td>
</tr>
<tr>
<td>HGS, kg</td>
<td>36 (26-47)</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>58.8 (47-65)</td>
</tr>
<tr>
<td>FM, kg</td>
<td>15.0 (10-21)</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>6 (3-21)</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>39.0 (36-42)</td>
</tr>
<tr>
<td>Prealbumin, mg/l</td>
<td>237 (184-292)</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>139 (130-148)</td>
</tr>
</tbody>
</table>

IQ interquartile, BMI body mass index, PEG percutaneous endoscopic gastrostomy, TSF triceps skin fold, MAC mid-arm circumference, MAMA mid-arm muscle area, HGS handgrip strength, FFM fat-free mass, FM fat mass. Data are shown as median (IQ range) or number (%).
4.2 ETHICAL CONSIDERATIONS

The study design followed the guidelines laid down in the Declaration of Helsinki (as revised in 2008). The study proposals and procedures involving human patients were approved by the Institutional Research Ethics Committee of the Helsinki University Hospital. All patients received both oral and written information about the study. After having received the information, all patients signed a written informed consent to participate in the study. It was judged not ethical to perform a nutritional intervention study with a control group without on-demand nutritional counseling.

4.3 STUDY DESIGN

Studies I to III were prospective and cross-sectional cohort studies and Study IV was a RCT. The study was registered at the US National Institutes of Health (reference number NCT02159508).

All patients visited the outpatient clinic at the Department of Otorhinolaryngology – Head and Neck Surgery prior to diagnosis and at the Department of Oncology to undergo definitive CRT, postoperative RT or CRT. The baseline nutritional status, anthropometry, body composition, HGS, and blood samples were obtained before surgery or at the onset of RT or CRT. The study schedule is shown in Table 12. Nutritional status assessment (PG-SGA), risk screening (NRS-2002), anthropometry, HGS measurements, and BIA analysis were performed by the same research dietitian (HO) for all patients during the whole study. The research dietitian also calculated energy and protein requirements for all patients and planned and guided nutrition care including tube feeding.

Table 12. Schedule for nutritional status assessment and nutrition intervention.

<table>
<thead>
<tr>
<th>Method</th>
<th>Baseline*</th>
<th>CRT, week</th>
<th>Follow-up, month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1**</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NRS-2002</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PG-SGA</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anthropometry</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bioimpedance</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Handgrip strength</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Energy and protein need</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy and protein intake</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nutrition intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INC</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ODC</td>
<td>X</td>
<td>(x)</td>
<td>(x)</td>
</tr>
</tbody>
</table>

NRS Nutritional risk screening, PG-SGA patient-generated subjective global assessment, INC Intensive nutritional counseling, ODC On-demand counseling, CRT chemoradiotherapy

* Before surgery or first radiotherapy or chemoradiotherapy
** For postoperative patients in addition to baseline assessment

Randomization was performed by the minimization procedure (528) with the Minim Program®. The allocation was done by the following criteria: 1) Stage I-II vs. Stage III-IV; 2) age
<65 vs. ≥65 years; 3) BMI <20 vs. ≥20 kg/m² and 4) tumor location (oral cavity- oropharynx-tonsils vs. hypopharynx-larynx vs. nasopharynx). The allocation ratio was 1:1.

4.4 METHODS

4.4.1 Nutritional Risk Screening 2002 (NRS-2002)
The nutritional risk was assessed by the NRS-2002 method. The final screening (Step 2) was performed for all study patients according to Kondrup et al. (188). This step included evaluation of impaired nutritional status, severity of disease and age >70 years. In all patients, the disease severity was classified as mild (score 1). Patients who had age-adjusted total score equal to or greater than 3 were categorized to be at nutritional risk.

4.4.2 Patient-generated Subjective Global Assessment (PG-SGA)
The patients’ stage of malnutrition (SGA A to C) was assessed by PG-SGA and the PG-SGA score was calculated (189,320). If the patient was categorized to be on the borderline between A and B, A was chosen; and if between B and C, B was chosen. Due to the small number of severely malnourished patients, moderately (PG-SGA B or Stage B) and severely (PG-SGA C, Stage C) malnourished categories were combined and referred to as “malnourished” (PG-SGA BC).

For the PG-SGA score, all values from each section of the PG-SGA were summed with scores ranging between 0–35. A score ≥24 was used to categorize patients as “risk patients” and score ≥29 was used to categorize patients as “critical need for nutrition intervention” from non-critical patients. Scored PG-SGA with cut-off points 4 and 9 were used in this study.

Permission for the full form of scored PG-SGA© was received from Pt-Global (http://pt-global.org/). The English PG-SGA version 2001 was translated into Finnish and was used only for the current study. The Finnish version is in Appendix 5.

4.4.3 Anthropometry
Anthropometric data included body weight, height, BMI, mid-arm circumference (MAC), TSF, and MAMA. Height was documented from hospital charts, measured without shoes, or by recall. Actual body weight was measured to the nearest 0.1 kg with a portable calibrated digital scale (Tanita, Illinois, USA). Patients were weighed in indoor clothing without shoes, and 1.0–1.5 kg was deducted from the scale reading. Body weights at 6 months and at one month before the study measurements were documented by recall.

Body mass index (BMI) was calculated and a patient was classified underweight if BMI was <18.5 kg/m², normal if BMI was 18.5–24.9 kg/m², overweight if was BMI 25.0–29.9 kg/m², or obese if BMI was ≥30 kg/m². Clinically significant weight loss before diagnosis was determined as >10% during previous 6 months or >5% during previous month and referred as “critical weight loss”, which is a well-accepted criterion for malnutrition in HNC patients (106,167,196). During (C)RT weight loss >5% was determined as significant or severe.

MAC and TSF were measured on the dominant arm using a non-stretchable tape measure and the Harpenden skinfold calliper (Baty International, West Sussex, UK) by Frisancho principles (200). MAC was measured at the midpoint between the acromion processes and tip of the olecranon. The subject was standing sideways to the measurer, arms hanging loosely by the side, with the palm facing inward. Three measurements were taken, and the mean of the three measurements was used.

MAMA in cm² was calculated using MAC and TSF values, by the following equation: MAMA (cm²) = [MAC (in cm) – 0.3142 x TSF (in mm)]² / (4 x 3.142). For all anthropometric measures, reference tables, standardized for age and sex and validated for normal subjects (See Appendix 1-3) were used to classify individual values (200). MAMA <10th percentile was considered as indicator for muscle depletion and referred as “low MAMA” or “muscle depletion”.

4.4.4 Handgrip strength
Muscle function was measured with a Jamar® handgrip dynamometer (Sammons Preston Rolyan, Chicago, USA). HGS for both hands was measured with the same handgrip (left hand for the dominant hand, the non-dominant hand was used. To compare the HGS values with reference values, the dominant hand were used for the analysis. If a patient was unable to perform HGS with the dominant hand, the non-dominant hand was used. HGS was performed for all study patients according to Kondrup et al. (188). This step included evaluation of impaired muscle strength, severity of disease and age >70 years. In all patients, the disease severity was classified as mild (score 1). Patients who had age-adjusted total score equal to or greater than 3 were categorized to be at nutritional risk.

4.4.6 Bioimpedance
Body composition was assessed by bioimpedance using a single frequency (50 kHz) two-terminal impedance meter (TANITA BC-418, Tanita Corporation, Tokyo, Japan). Total body water was calculated by the Kotler equation (Table 13) (530). The theoretical hydration of fat-free tissue was calculated as 0.73 (145) and MAMA = (MAC – 0.3142 x TSF) / 3.142. For all anthropometric measures, reference tables, standardized for age and sex and validated for normal subjects (See Appendix 1-3) were used to classify individual values (200). MAMA <10th percentile was considered as indicator for muscle depletion and referred as “low MAMA” or “muscle depletion”.

4.4.7 Biochemical measurements
Blood samples for assessment of concentrations of albumin, prealbumin, C-reactive protein (CRP) and blood cells were usually taken between 8 am and 2 pm. Laboratory methods, and values were compared with the reference values of Hospital District of Helsinki and Uusimaa (HUS) laboratory. Serum albumin and prealbumin were measured with standard laboratory methods (518, 519), and values were compared with the reference values of HUS laboratory. Albumin was measured with the standard laboratory method (518). Serum prealbumin was measured with the standard laboratory method (519). CRP was measured with the standard laboratory method (518). Heparinized whole blood samples were used for assessment of the concentrations of albumin, prealbumin, C-reactive protein (CRP) and blood cells. Blood samples were separated from the plasma and serum using a centrifuge. Serum albumin and prealbumin were measured with standard laboratory methods (518, 519), and values were compared with the reference values of HUS laboratory. Albumin was measured with the standard laboratory method (518). Serum prealbumin was measured with the standard laboratory method (519). CRP was measured with the standard laboratory method (518). Heparinized whole blood samples were used for assessment of the concentrations of albumin, prealbumin, C-reactive protein (CRP) and blood cells. Blood samples were separated from the plasma and serum using a centrifuge. Serum albumin and prealbumin were measured with standard laboratory methods (518, 519), and values were compared with the reference values of HUS laboratory. Albumin was measured with the standard laboratory method (518). Serum prealbumin was measured with the standard laboratory method (519). CRP was measured with the standard laboratory method (518).
4.4.4 Handgrip strength
Muscle function was measured with a Jamar® handgrip dynamometer (Sammons Preston Rolyan, Chicago, USA). HGS for both hands was measured with the same handgrip dynamometer for all. Patients performed the test while sitting with shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in neutral position. The width of handle was adjusted so that when the subject held the dynamometer, the second phalanx was against the inner stirrup. The hand dynamometer was adjusted for hand size; position three was used for men, and position two for women. Patient performed a maximal isometric contraction three times with 30 second intervals, and the mean of three test values for the dominant hand were used for the analysis. If a patient was unable to perform HGS with the dominant hand, the non-dominant hand was used. To compare the HGS values with reference values (269), the reference values were converted from lb to kg (conversion factor = 0.45). Values <5th percentile were classified as a marker of severe muscle depletion and <85% of the normal median value was considered as an indicator for low muscle mass (See appendix 4) (183).

4.4.5 Cachexia and sarcopenia
Cachexia was defined by low HGS and MAMA. HGS values were compared with age-appropriate reference values for healthy males and females. The HGS value less than 85% of normal median value was considered an indicator for low muscle function (269). MAMA less than 10th percentile was considered an indicator for muscle depletion. Patients with both low-MAMA and low-HGS were categorized as cachectic. Sarcopenia was defined as low MAMA (<10th percentile).

4.4.6 Bioimpedance
Body composition was assessed by bioimpedance using a single frequency (50 kHz) two-terminal bioimpedance meter (Bodystat® Ltd, Isle of Man, UK), and performed according to the standard procedure (529). Patients were in supine position with no body parts touching the torso. Electrodes were placed on the patient's right hand and foot using a four-surface standard electrode technique. A single frequency current of 800 μA; 50 KHz was used. Arms were separated from the trunk by approximately 30° and legs 45° to avoid thigh contact. All metal objects were removed. The patient was in supine position for 5-10 min.

Table 13. Kotler equation for total body water (530).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Kotler equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.58 x (Height^{1.03/Z0.7} x 1.0/1.35) + 0.32 x Weight (kg) – 3.66</td>
</tr>
<tr>
<td>Women</td>
<td>0.76 x (Height^{1.09/Z0.58} x 1.0/18.91) + 0.14 x Weight (kg) – 0.86</td>
</tr>
<tr>
<td>Z Impedance</td>
<td></td>
</tr>
</tbody>
</table>

The measured impedance values were used, and total body water was calculated by the Kotler equation (Table 13) (530). The theoretical hydration of fat-free tissue was calculated as 0.73 (145) and fat mass (FM) was calculated as the difference between body weight and FFM. Percental FM and FFM were also calculated.

4.4.7 Biochemical measurements
Blood samples for assessment of concentrations of albumin, prealbumin, C-reactive protein (CRP), hemoglobin, S-25-OHD, calcium and phosphate were obtained. Serum 25-OHD was assessed by liquid chromatography and other laboratory analyses were measured by standard laboratory methods, and values were compared with the reference values of Hospital District of Helsinki and Uusimaa Laboratory (HUSLAB). Because of the time constraints of the patients, the blood samples were usually taken between 8 am and 2 pm.
Hypocalcemia was defined as plasma Ca < 2.15 mmol/l and hypophosphatemia as P-Pi < 0.76 mmol/l (women) or < 0.71 mmol/l (men). Vitamin D deficiency was defined as S-25-OHD < 37.5 nmol/l (531), and hypovitaminosis D as 37.5 - 50 nmol/l (532). S-25-OHD between 50 and 79.9 nmol/l was considered sufficient, and values 80-100 nmol/l were considered optimal (533,534).

4.4.8 Acute adverse events of RT
Acute adverse events were assessed either by a research dietitian (HO) or an oncologist (KS) (535). For all patients, a treatment break was defined as an interruption of RT longer than 3 days (419). Hospital admissions for dehydration or malnutrition were considered nutrition related and were analysed as a separate endpoint as well as admissions for infection.

4.4.9 Alcohol use and smoking
Alcohol consumption and smoking for all patients was determined at baseline by asking about alcohol consumption per week and the cigarettes smoked per day. Alcohol consumption was reported as drinks per week. One drink was equivalent to 12 g of ethanol. Patients were categorized as heavy drinkers if they consumed > 24 drinks per week for men and > 16 drinks per week for women.

Smoking was reported as the number of cigarettes smoked per day and smoking years. Smoking was recorded as pack years and calculated according to the equation [(number of cigarettes smoked per day x number of years smoked)/20]. One pack of cigarettes was equivalent to 20 cigarettes. Patients were categorized as heavy smokers when they had smoked ≥ 20 pack years.

4.4.10 PEG placement
All the PEGs were placed via an endoscopic approach at the Department of Otorhinolaryngology – Head and neck Surgery of HUS. The PEG was routinely placed to all patients who were going to have a RT or CRT for the site of nasopharynx, oral cavity, and oropharynx. The PEG was placed under moderate sedation using intravenous midazolam and fentanyl, along with local anaesthesia (i.e. lidocaine) at the site of tube placement. If patient required deeper sedation, propofol was used. For some patients PEG was inserted under general anesthesia for cancer surgery.

4.4.11 Nutritional requirements, dietary assessment and counseling
Nutritional requirements. Daily estimated energy requirement was calculated from the basal energy requirement according to the WHO equation (Table 14), and multiplied by a 1.5 activity factor (30-35 kcal/kg) corresponding to sedentary or light activity lifestyle (494). Ideal body weight (IBW, defined as BMI 22) was used. Protein requirement was estimated by multiplying IBW (kg) by a 1.2-1.5 factor. Fluid need was calculated as 30-35 ml/kg of actual body weight/day and for patients with BMI > 30 according to adjusted body weight (i.e. BMI 25).

Table 14. Basal energy requirement equation (kcal) for men and women by Schofield used in the current study.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-60 years</td>
<td>11.5 x weight (kg) – 2.6 x height (m) +877</td>
<td>8.1 x weight (kg) – 1.4 x height (m) +844</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>9.1 x weight (kg) + 972 x height (m) – 834</td>
<td>7.9 x weight (kg) + 458 x height (m) + 17.1</td>
</tr>
</tbody>
</table>

Nutritional counseling. Nutritional counseling considered each patient’s actual nutritional status, current food habits, known food aversions, existing diet, capability to chew and swallow and other symptoms that had an impact on the patient’s diet. Individualized dietary advice was based
on current foodstuffs, nutritional supplements and enteral tube feeding, depending on the symptoms affecting the patient’s eating. Individual nutritional support program was planned for every patient with per os feeding; the diet by mouth consisted of texture modified energy dense meals accounting for 2000-2500 kcal per day, supplemented or replaced by enteral tube feeding as needed. Enteral formulas containing 1 kcal/ml and 1.5 kcal/ml energy, and 0.3 g/ml and 0.6 g/ml protein (Nutrison® Multi Fibre and Nutrison® Energy Multi Fibre, Nutricia, N.V. Nutricia, Zoetermeer, Holland) were used and delivered through PEG. Nutritional counseling was performed by research dietitian (HO) for all study patients.

The two study groups (intensive individualized nutritional counseling, INC and on-demand nutritional counseling, ODC) differed in the number of nutritional consultations during treatment. The INC consisted of pre-programmed counseling given by a dietitian once at baseline and on the 2nd and 4th week of the treatment and at the end of CRT (Table 12). The INC group had more visits if clinically needed. The ODC group received baseline nutritional counseling, which consisted of one dietetic consultation before (C)RT. During (C)RT ODC patients received further counseling only on-demand and referral by a physician.

At baseline, nutritional counseling included guidance on a texture-modified energy- and protein-dense diet according to the study protocol. Every patient got an individualized meal plan at the specific energy and protein target. In addition, an individualized enteral tube feeding plan was carried out. For all patients, the practical guidance on how to carry out enteral tube feeding at home was instructed. Tube feeding was suggested to be performed as bolus feeding. Physicians prescribed the enteral formula for patients by a dietitian’s instructions. The ODC group was instructed to start enteral tube feeding on the third week of RT at the latest. All patients with CRT were instructed to use antiemetics by physician’s order.

In the INC group, the realization of enteral nutrition plan was followed regularly during (C)RT, and in 20 patients (78%) enteral nutrition by PEG was started gradually as eating per mouth was decreased. Those ODC group patients who were referred to a dietitian by a physician received appropriate nutritional support according to the clinical situation, including modification of the oral diet or enteral tube feeding by PEG, which was in 31 patients (97%).

Nutritional intake was assessed by the 24-hour diet recall at every dietitian visit during CRT.

4.4.12 Statistical analysis
The normality was assessed by Shapiro-Wilk’s test (p>0.05). HGS, weight, MAMA, S-25-OHD, plasma Ca and plasma Pi were normally distributed. BMI, age, plasma Alb, plasma CRP and PG-SGA score were not, and non-parametric analysis were performed. The missing laboratory values (less than 5%) were replaced by group mean.

Descriptive data was reported as medians and IQ range, or as numbers and percent. Between-comparisons were analysed for continuous variables with the non-parametric Mann-Whitney U test or Kruskal-Wallis test, as appropriate. Categorial variables were compared by the Pearson’s X² test and nominal variables by the Fisher’s exact test.

Correlation was analysed by the non-parametric Spearman correlation test or Kendal’s tau correlation tests, as appropriate. Agreement analysis between two variables was performed using the Kappa (K) and Spearman correlation coefficients (r). A correlation was weak when the correlation coefficient was ≤0.35, moderate 0.36 to 0.67, and strong ≥0.68. Kappa value 1 indicated perfect agreement, while value <0.4 indicated that chance alone accounted for the observed agreement.

The receiver operating characteristics (ROC) analysis was performed to study the concordance between two variables. The accuracy was measured by the area under (AUC) the ROC curve. The ROC AUC of 1.0 suggests perfect, >0.9 high, 0.7 to 0.9 moderate, and 0.5 to 0.69 low accuracy, and <0.5 suggests that the test is not better than chance. The true-positive rate (sensitivity) was plotted against the false-positive rate (1-specificity) across the values of the study variables, with 45° line representing the ROC AUC of 0.5.

A contingency table was used to determine the sensitivity, specificity, positive and negative
predictive values, which were calculated against the reference method. Sensitivity is the proportion of persons with diagnosis who are detected positive by the test. Specificity is the proportion of persons without diagnosis who are detected negative by the test. Positive predictive value refers to the proportion of positive test results that are true positives, and negative predictive value refers to the proportion of negative test results that are true negatives. The cut-off points of the diagnostic values are: 90–100% excellent; 80–89% good; 70–79% fair; 60–69% insufficient and <60% poor (The Academical Point System, http://gim.unmc.edu/dx/tests).

The Kaplan-Meier analysis and the log-rank test statistic was used to evaluate the equality of survival distributions across different strata. Cox regression analysis were performed to calculate hazard ratio.

Statistical analyses were carried out using SPSS Versions 19 to 21.0 (IBM corp., Armonk, NY). Confidence intervals, sensitivity, specificity and Kappa values were calculated using Confidence Interval Analysis (CIA) software (version 2.2.0; University of Southampton, Southampton, England). Confidence intervals, sensitivity, specificity and Kappa values were calculated using Confidence Interval Analysis (CIA) software (version 2.2.0; University of Southampton, Southampton, England). A p-value less than 0.05 was considered statistically significant.

Study I: BMI was transformed (natural log) to normalize distribution. The difference between group means was analysed by t Test and between medians by Mann-Whitney U test or Kruskal-Wallis test, as appropriate.

Study II: Descriptive data were expressed as median (IQ range) analysed by non-parametric tests. The ROC analysis was performed between NRS-2002 (≥2 and ≥3) and PG-SGA score (≥4 and ≥9). The sensitivity, specificity, positive and negative predictive values were calculated for NRS-2002 cut-off ≥2 and ≥3 against reference method PG-SGA category (BC) and score (≥4 and ≥9).

Study III: Descriptive data were expressed as median (IQ range) and analysed by non-parametric tests. The ROC analysis was performed between cachectic, dead and alive patients. The Kaplan-Meir analysis, the log-rank test statistic and Cox regression analysis were performed.

Study IV: Descriptive data were expressed as median (IQ range) analysed by non-parametric tests. Repeated measures were analysed by Sign test or Wilcoxon signed-rank test, and categorical variables by relates samples McNemar test. The Kaplan-Meir analysis, the log-rank test statistic and Cox regression analysis were performed.

The ROC analysis was also performed between PG-SGA (A and BC), MAMA (low and normal) and HGS. To determine whether other nutritional assessment tools could predict HGS, a proportion of variation-explained statistics was calculated by using simple linear regression for continuous variables. Sensitivity, specificity and predictive values were calculated to appraise the value of the HGS in predicting nutritional risk (NRS-2002) and status (PG-SGA).

Power analysis was performed before the beginning of the study. A sample size of 102 patients was identified to achieve 30% reduction in the prevalence of malnutrition at the end of treatment (50% to 20%), with a significance value of 5% (p < 0.05), 90% power. The second calculation was for a sample size of 88 patients for 30% reduction in prevalence of malnutrition at the end of treatment (50% to 20%) with the significance value 5% (p<0.05), 85% power and effect size 70%. Based on these numbers, the aim was to recruit 100 patients, with the assumption that 12% of patients would be lost during follow up. Sixty-five patients were recruited, maintaining a significance value of 5% (p<0.05) with 60% power. The sample size calculations assumed a 60% relative reduction and 30% absolute reduction (20% vs. 50%) in malnutrition when the treatment group was compared to the control group.
5 Results

5.1 VITAMIN D STATUS PRIOR TO DIAGNOSIS (STUDY I)

Subnormal serum 25-OHD concentration was found in a significant proportion of the patients already prior to diagnosis of HNC, but no seasonal variation was observed. Two patients had vitamin levels <10 nmol/l, vitamin D deficiency (S-25-OHD <37.5 nmol/l) was seen in 45% of patients, and hypovitaminosis (S-25-OHD 37.5-50.0 nmol/l) in 20%. Only three female patients had optimal values (80-100 nmol/l). Thirty-five percent of the patients had sufficient S-25-OHD concentrations (≥50 nmol/l). Tumor location was not associated with vitamin D concentrations. The median value was 28 nmol/l in Stage I-III and 46 nmol/l in Stage IV disease.

Malnourished patients (PG-SGA BC) had significantly lower vitamin D values than well-nourished patients (Figure 3). This was seen in both men and women. Underweight patients (BMI <18.5 kg/m²) had significantly lower vitamin D levels than patients with higher BMI (p=0.034). The mean S-25-OHD concentration was 24.2 (SD 13.0) nmol/l in underweight patients and 43.9 (SD 21.8) nmol/l in normal weight and obese patients. All three patients with optimal 25-OHD concentrations (80-100 nmol/l) had oropharyngeal Stage IV carcinoma and normal BMI.

![Figure 3. Vitamin D (S-25-OHD) status between well-nourished and malnourished HNC patients. PG-SGA patient-generated subjective global assessment. The horizontal line is a S-25-OHD concentration of 50 nmol/l.](image-url)
5.2 ALCOHOL USE AND SMOKING HABITS (STUDY I)

Alcohol and smoking history was evaluated in 65 patients. Eighty-five percent (n=55/65) of patients had a history of smoking, and 65% (n=42/65) were current smokers, 20% (n=13/65) former smokers, and 15% (n=10/65) had never smoked. Current smokers had smoked for a median (IQ range) of 40.5 (range 22-52) pack years and former smokers for 4.5 (1-24; p<0.001). Fifty-eight percent of current and ex-smokers were heavy smokers (≥20 pack years). Sixty-one (94%) of the patients were current alcohol users, while three had quit. In this patient cohort, ten patients (16%) were heavy alcohol users (≥24 drinks or ≥16 drinks per week), of whom two were women. The rest of the women consumed ≤5 drinks/week. Nine (14%) patients were both heavy smokers and alcohol users.

Well-nourished (PG-SGA A) patients had smoked less (median 20, IQ range 1-36) than malnourished (PG-SGA BC; median 40, IQ range 16-55) pack years; p=0.008). Heavy smokers were more often malnourished than those who smoked less (15% vs. 7%, p=0.045) according to PG-SGA, but the association was not as clear between heavy drinkers and those who drank less (6% vs. 16%, p=0.057). Alcohol drinking and smoking stratified by nutritional status is illustrated in Figure 4. In heavy male smokers, weight (74 vs. 86 kg, p=0.034), HGS (36.7 vs. 47.3 kg, p=0.011), MAC (28.2 vs. 31.2 cm, p=0.011) and MAMA (47.6 vs. 59.9 cm², p=0.006) were significantly lower than in those who had smoked <20 pack years. Such an association was not seen among women. Alcohol consumption was not different between well-nourished and malnourished patients according to PG-SGA, but in heavy male alcohol users HGS (47.3 vs. 36.7 kg, p=0.011), MAMA (55.8 vs. 49.6 cm², p=0.026), and MAC (31.1 vs. 28.5 cm, p=0.048) were significantly lower than in those who consumed alcohol less than 24 drinks per week. Such an association was not seen among women.

![Image](image.png)

Figure 4. Alcohol drinking and smoking stratified by nutritional status according to PG-SGA in 50 men and 15 women.

5.3 NUTRITIONAL RISK ASSESSED BY NRS-2002 (STUDY II)

The prevalence of malnutrition in all 65 patients prior to diagnosis was 28% when determined as the NRS-2002 score ≥3. The prevalence of nutritional risk was 49% when determined as the NRS-2002 score of 2.
All variables (BMI, MAC, MAMA, HGS, albumin, prealbumin, C-reactive protein) except TSF and albumin, were significantly lower in malnourished patients (NRS-2002 ≥3) than in well-nourished patients. NRS-2002 had positive correlation between PG-SGA category and PG-SGA score both in men (n=50, r=0.72, p<0.001, r=0.81, p=0.001, respectively) and women (n=15, r=0.72, p=0.002, r=0.94, p<0.001, respectively). In men, BMI (r=-0.51, p<0.001), MAC (r=-0.51, p<0.001) and MAMA (r= -0.56, p<0.001) had negative correlation with NRS-2002, whereas in women such correlation was not seen. HGS had negative correlation with NRS-2002 in women (r=-0.70, p=0.003) and in men (r=-0.32, p=0.022). Albumin, prealbumin, and hemoglobin were inversely correlated with NRS-2002 in men (r = -0.40 - -0.47 (p=0.001-0.004) but not in women. CRP had positive correlation with NRS-2002 in women (r = 0.66, p=0.007) and men (r = 0.34, p=0.014).

Sensitivity, specificity, and kappa coefficient of NRS-2002 were calculated, assuming the following classifications as standard methods: nutritional status (PG-SGA BC), and need for nutrition intervention (PG-SGA score ≥4 or ≥9). Sensitivity, specificity and accuracy between PG-SGA category and NRS-2002 with cut-off 3 were 77%, 98%, and K = 0.78, respectively. To evaluate the validity of NRS-2002 as a screening tool in this patient cohort we compared score 2 to PG-SGA scores 4 and NRS-2002 score 3 to PG-SGA score 9. Sensitivity, specificity and accuracy were 97%, 79% and K=0.75 for NRS-2002 score 2, and 89%, 90%, and K=0.72 for score 3, respectively.

ROC-curve analysis for NRS-2002 score ≥2 and ≥3, against PG-SGA scores ≥4 and ≥9 were performed. The ROC AUCs for NRS-2002 with score ≥3 was 0.883 (95% CI: 0.772, 0.995, p<0.001), and for NRS-2002 score ≥2 0.889 (95% CI: 0.804, 0.975, p<0.001).

### 5.4 Nutritional Status Assessed by PG-SGA (Study II)

Prior to diagnosis 34% of the patients were malnourished by PG-SGA, 15/50 (30%) were men and 7/15 (47%) women. Six (9%) patients were severely (PG-SGA C) and 16 (25%) moderately malnourished or suspected of being malnourished (PG-SGA B). The median (IQ range) PG-SGA score for all patients was 5.0 (1-8), for men 4.5 (1-8) and for women 6 (2.5-8). PG-SGA score ≥9 was seen in 15 (23%) of all patients indicating critical need for nutritional intervention, and score ≥4 in 38 (58%) patients indicating some need for nutritional intervention.

Low HGS (<85% of median reference value) was seen in 28 patients (43%) with 22/50 (44%) men and 6/15 (40%) women. Muscle-mass depletion indicated by low MAMA (<10th percentile) was seen in 46% of all patients, with 22/50 (44%) men and 8/15 (53%) women.

Forty-four (68%) patients had lost weight during previous six months, but only 7 (11%) had severe weight loss (≥10% of usual weight). Forty-two percent of all patients were overweight (BMI ≥25), and the prevalence was higher (50%) in men than in women (13%, p=0.010). Underweight (BMI <18.5) was seen in 6 (9%) patients only. The proportion of nutritional risk, malnutrition, low HGS and MAMA are illustrated in Figure 5. The differences observed between sexes were not statistically significant. Nutritional characteristics (n=65) by nutritional status (PG-SGA), HGS category, MAMA category, and nutritional risk (NRS-2002), stratified by sex are shown in Table 15. Four patients (6%) fullfilled nutritional risk, malnutrition, and low HGS criteria.
Figure 5. Proportion of baseline nutritional risk, malnutrition, low HGS, and low MAMA in all 65 patients. Nutritional risk (NRS-2002 ≥3), Malnutrition (PG-SGA BC), Low HGS (<85% of the median reference value), Low MAMA (<10th percentile). HGS handgrip strength, MAMA mid-arm muscle area.
Table 15. Nutritional variables (median, IQ range) according to nutritional status, handgrip strength, and nutritional risk in all 65 patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nutritional status&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Handgrip strength&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Nutritional risk&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-nourished&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Malnourished&lt;sup&gt;d&lt;/sup&gt;</td>
<td>p-value&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>n = 43</td>
<td>61 (33-73)</td>
<td>60 (54-75)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>n = 22</td>
<td>80.0 (69-90)</td>
<td>63.1 (55-71)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 (23-28)</td>
<td>21.4 (18-23)</td>
<td>0.001</td>
</tr>
<tr>
<td>TSF, mm</td>
<td>14.0 (10-19)</td>
<td>11.0 (9-15)</td>
<td>0.116</td>
</tr>
<tr>
<td>MAC, cm</td>
<td>31.0 (27-33)</td>
<td>25.0 (23-28)</td>
<td>0.005</td>
</tr>
<tr>
<td>MAMC, cm</td>
<td>26.1 (23-28)</td>
<td>21.3 (20-24)</td>
<td>0.001</td>
</tr>
<tr>
<td>MAMA, cm²</td>
<td>54.1 (43-62)</td>
<td>36.1 (33-44)</td>
<td>0.001</td>
</tr>
<tr>
<td>FFMI, kg/m²</td>
<td>17.5 (16-19)</td>
<td>15.2 (14-16)</td>
<td>0.001</td>
</tr>
<tr>
<td>HGS, kg</td>
<td>38.7 (32-50)</td>
<td>25.2 (21-36)</td>
<td>0.05</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>40.2 (38-42)</td>
<td>36.1 (32-40)</td>
<td>0.023</td>
</tr>
<tr>
<td>Prealb, mg/l</td>
<td>269.0 (216-304)</td>
<td>180.0 (117-233)</td>
<td>0.005</td>
</tr>
<tr>
<td>Crp, mg/l</td>
<td>4.0 (3-10)</td>
<td>20.0 (6-53)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>141.0 (133-151)</td>
<td>132.5 (122-145)</td>
<td>0.116</td>
</tr>
<tr>
<td>D-25, nmol/l</td>
<td>49.0 (32-62)</td>
<td>23.0 (13-38)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

IQ Interquartile, BMI body mass index, TSF triceps skinfold, MAC mid-arm circumference, MAMC mid-arm muscle circumference, MAMA mid-arm muscle area, FFMI fat-free mass index, HGS handgrip strength, Prealb prealbumin, Crp C-reactive protein, Hb Hemoglobin, D-25 25-hydroxyvitamin D, PG-SGA patient-generated subjective global assessment

a. PG-SGA A vs. PG-SGA BC
b. Normal HGS (≥ 85% of the median reference value) vs. low handgrip strength (<85% of the median reference value).
c. NRS-2002 <3 vs. NRS-2002 ≥3
d. The Mann-Whitney’s U-test was used to compare medians of groups
5.5 THE PREVALENCE OF CACHEXIA AND ITS ASSOCIATION WITH SURVIVAL (STUDY III)

Cachexia was seen in 31% of the patients, and there were no differences between sexes. Survival was significantly lower in patients with cachexia. The median (IQ range) disease-free survival was 15 (3-66) month in cachectic patients and 66 (30-78) months in non-cachectic patients (DFS) (p=0.004). The median (IQ range) OS was 21 (13-69) months in cachectic patients and 70 (66-81) months in non-cachectic patients (p=0.004). The Kaplan-Meier analysis supported these findings, showing that cachexia was associated with both shorter OS (p=0.001) and DFS (p=0.003). The hazard ratio for DFS was 2.8 (95% CI, 1.38-8.82, p=0.004) and for OS 3.4 (95% CI, 1.58-7.10, p=0.002, Figure 6). The five-year survival rate was 30% in cachectic patients and 69% in non-cachectic patients. The five-year DSS (disease specific survival) rate for all patients was 68% and OS rate 57% with a median (IQ range) DFS time of 64 months (4-73) and OS time of 68 months (17-78).

![Overall Survival](chart.png)

Figure 6. Kaplan-Meier survival and Cox regression analysis for overall survival in cachectic (n=20) and non-cachectic (n=45) patients.
5.6 THE EFFECT OF DIETARY COUNSELING ON NUTRITIONAL STATUS DURING (C)RT (STUDY IV)

There were 26 patients (21 men, 5 women) in the intensive nutritional counseling group (INC) and 32 patients (25 men, 7 women) in the on-demand counseling group (ODC). In the ODC group was significantly more patients with T4 stage (p=0.022), and PEG-dependence at baseline (p = 0.002), and they more often received CRT (p=0.036) than patients in the INC group. In terms of age, sex, and tumor location the two groups were comparable and homogenous. There were some differences in nutritional variables. In the INC group MAC was significantly lower than in the ODC group (p=0.029), and malnutrition was more prevalent in the ODC group than in the INC group (p=0.039).

During (C)RT all nutritional variables decreased significantly in both groups, and there were no significant differences between the two study groups (Table 17). Treatment-induced critical weight loss (>5%) was seen equally in both groups at the end of treatment: 77% in the INC and 67% in the ODC group (NS) with median weight loss 8% and 7% (NS), respectively.

The median weight change as a function of time stratified by three treatment-induced weight loss groups (<5%, 5-10%, ≥10%) is illustrated in Figure 7. Patients who were losing weight at baseline (median 8.3%, IQ range 5-11) maintained MAMA (p=0.075) and lost weight significantly less than baseline weight stable patients (<0.001, Table 16).

The prevalence of malnutrition by PG-SGA increased significantly during treatment in both study groups; in the INC group from 27% to 85% (p<0.001), and in the ODC group from 44% to 75% (p=0.007). Even though both HGS and upper-arm anthropometry decreased significantly in patients with baseline BMI <25 and BMI ≥25, overweight patients had still higher HGS (p<0.001), MAMA (p<0.001), and TSF (p<0.001) at the end of the treatment.

Table 16. The change of MAMA and HGS values from baseline to end of treatment between patients that were weight-losing (n=31) or weight-stable (n=27) at baseline.

<table>
<thead>
<tr>
<th>Anthropometry, median (IQ range)</th>
<th>Weight losinga</th>
<th>Baseline p-valueb</th>
<th>Weight stable p-valueb</th>
<th>p-valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAMA, cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>41.8 (35-53)</td>
<td>54.2 (42-62)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>End</td>
<td>40.0 (35-51)</td>
<td>48.3 (38-53)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Change baseline-end, %</td>
<td>2.4 (12-2)</td>
<td>11.5 (14-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGS, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>33.3 (25-40)</td>
<td>41.0 (30-49)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>End</td>
<td>29.3 (24-39)</td>
<td>36.0 (25-47)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Change baseline-end, %</td>
<td>4.2 (12-15)</td>
<td>8.9 (14-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>5.5 (8-1)</td>
<td>7.7 (7-11)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

MAMA mid-arm muscle area, IQ interquartile, HGS handgrip strength
a. Weight loss ≥1 kg during previous 6 months before diagnosis
b. The Wilcoxon Signed Rank Test was used for comparison for related median values between baseline and end.
c. The Mann-Whitney’s U-test was used for comparison of medians between losing weight and weight stable patients at the end of treatment

The median HGS (22 kg) was stable in women and decreased in men from 39 kg to 35 kg (p<0.001) during (C)RT. The prevalence of low HGS (<5th percentile) increased significantly from 17% to 31% (p=0.008) during treatment. Low HGS was seen equally in all three weight losing groups (24%, 41% and 21%, respectively) as well as in both nutritional counseling groups (NS).

Patients with baseline malnutrition (Table 18) could prevent FFM loss (p=0.033) despite of
weight loss during the treatment. Baseline overweight and well-nourished patients had significantly higher FFM (p<0.001, p=0.005) and HGS (p<0.001, p=0.001) despite treatment-induced severe loss of body weight and FFM.

Despite body weight loss patients could complete scheduled CTx and RT equally in both study groups: 61% and 92% in the INC group and 60% and 91% in the ODC group (NS), respectively. There were five patients in both groups who were admitted to the hospital during CTx, and one patient had a break in RT for >5 days in the INC group. In patients with >10% weight loss, 86% completed CTx and all patients RT while, in patients with ≤10% weight loss 48% managed to complete CTx and 89% RT (p<0.001).

Most patients (69%) were not able to carry out their planned nutrition treatment. The main patient-related difficulties in nutrition intake were nausea (22%), early satiety (12%), loss of motivation (9%) or other miscellaneous reasons (21%, e.g. PEG-related causes, exhaustion, cachexia, financial issues and severe diarrhea). Percentual weight loss and severity of anorexia had significant linear correlation (r = −0.34; p<0.01) explaining 11% of variation in weight loss. Severe nausea was more prevalent (29% vs. 5%) in patients with >10% weight loss as compared with ≤10% weight loss (p=0.01).

Figure 7. Median weight as a function of time in three weight loss groups, weight loss during treatment less than 5% (—), 5 to 10% (— —) and equal or more than 10% (...).

OS and DFS were not significantly different between the two study groups: 46 and 42 months in the INC group and 42 and 40 months in the ODC group, respectively (NS). The 3-year OS, DFS and DSS rates were in the INC group: 73%, 69%, and 76%, respectively, and in the ODC group 59%, 50% and 73%, respectively.

Baseline low HGS (<5th percentile) and pre-treatment malnutrition (SGA BC) were associated with poor survival (Figure 8). Patients with normal HGS had a median (IQ range) OS of 45 (35-54) months and DFS of 41 (9-52) months, and in patients with low HGS 21 (14-42) months (p=0.018) and 15 (5-40) months (p=0.047), respectively. The DFS was significantly shorter (42 vs. 17 months) among patients with pre-treatment malnutrition (SGA BC) than in patients with normal nutritional status (p=0.014).
weight loss during the treatment. Baseline overweight and well-nourished patients had significantly higher FFM (p<0.001, p=0.005) and HGS (p<0.001, p=0.001) despite treatment-induced severe loss of body weight and FFM.

Despite body weight loss patients could complete scheduled CTx and RT equally in both study groups: 61% and 92% in the INC group and 60% and 91% in the ODC group (NS), respectively. There were five patients in both groups who were admitted to the hospital during CTx, and one patient had a break in RT for >5 days in the INC group. In patients with >10% weight loss, 86% completed CTx and all patients RT while, in patients with ≤10% weight loss 48% managed to complete CTx and 89% RT (p<0.001).

Most patients (69%) were not able to carry out their planned nutrition treatment. The main patient-related difficulties in nutrition intake were nausea (22%), early satiety (12%), loss of motivation (9%) or other miscellaneous reasons (21%, e.g. PEG-related causes, exhaustion, cachexia, financial issues and severe diarrhea). Percentual weight loss and severity of anorexia had significant linear correlation (r = -0.34; p<0.01) explaining 11% of variation in weight loss.

Severe nausea was more prevalent (29% vs. 5%) in patients with >10% weight loss as compared with ≤10% weight loss (p=0.01).

Figure 7. Median weight as a function of time in three weight loss groups, weight loss during treatment less than 5% (−−−), 5 to 10% (−−−−) and equal or more than 10% (…).

OS and DFS were not significantly different between the two study groups: 46 and 42 months in the INC group and 42 and 40 months in the ODC group, respectively (NS). The 3-year OS, DFS and DSS rates were in the INC group: 73%, 69%, and 76%, respectively, and in the ODC group 59%, 50% and 73%, respectively.

Baseline low HGS (<5th percentile) and pre-treatment malnutrition (SGA BC) were associated with poor survival (Figure 8). Patients with normal HGS had a median (IQ range) OS of 45 (35-54) months and DFS of 41 (9-52) months, and in patients with low HGS 21 (14-42) months (p=0.018) and 15 (5-40) months (p=0.047), respectively. The DFS was significantly shorter (42 vs. 17 months) among patients with pre-treatment malnutrition (SGA BC) than in patients with normal nutritional status (p=0.014).

Figure 8. Kaplan Meier analysis for overall survival and disease-free survival in 58 patients according to handgrip strength and nutritional status. Low HGS <5th percentile, Normal HGS ≥5th percentile. HGS handgrip strength, PG-SGA patient-generated subjective global assessment.
Table 17. Clinical characteristics in the 58 patients randomized to intensive nutritional counselling and on-demand nutritional counselling.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients, median (IQ range)</th>
<th>INC, median (IQ range)</th>
<th>ODC, median (IQ range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=58)</td>
<td>End (n=58)</td>
<td>p-value&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.5 (61-86)</td>
<td>70.0 (57-79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>24.0 (21-27)</td>
<td>22.8 (20-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>19.3 (16-21)</td>
<td>18.3 (16-20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>59.7 (47-65)</td>
<td>55.3 (46-64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FM, kg</td>
<td>14.1 (11-21)</td>
<td>12.4 (10-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAC, cm</td>
<td>29.1 (25-31)</td>
<td>27.6 (25-31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAMA, cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>48.5 (36-57)</td>
<td>45.8 (35-52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HGS, kg</td>
<td>36.7 (27-46)</td>
<td>30.7 (25-42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WL, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.2 (1-9)</td>
<td>6.8 (4-9)</td>
<td>0.088</td>
</tr>
<tr>
<td>Alb, g/l</td>
<td>38.8 (46-42)</td>
<td>36.4 (34-39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prealb, mg/l</td>
<td>238.5 (186-296)</td>
<td>193.0 (158-232)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crp, mg/l</td>
<td>5 (3-19)</td>
<td>9.5 (4-19)</td>
<td>0.866</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>139.0 (130-146)</td>
<td>113.5 (104-123)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PG-SGA, score</td>
<td>6.0 (2-9)</td>
<td>12 (7-16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Energy kcal/kg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32.4 (31-35)</td>
<td>28.5 (24-31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein, g&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100 (93-106)</td>
<td>72 (59-82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein, g/kg</td>
<td>1.4 (1.2-1.5)</td>
<td>1.0 (0.9-1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as median, IQ interquartile, BMI body mass index, FFMI fat-free mass index, FFM fat-free mass, FM fat mass, MAC mid-arm circumference, MAMA mid-arm muscle area, HGS handgrip strength, WL weight loss, Alb albumin, Prealb prealbumin, Crp C-reactive protein, Hb Hemoglobin, PS-SGA subjective-global assessment, INC intensive nutritional counselling, ODC on-demand nutritional counseling

b. Energy requirement at baseline and energy intake at the end of treatment.
c. Protein requirement at baseline and protein intake at the end of treatment.
d. The Wilcoxon Signed Rank Test was used for comparison for related median values between baseline and end
Table 17. Clinical characteristics in the 58 patients randomized to intensive nutritional counselling and on-demand nutritional counselling.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline nutritional status (PG-SGA), median (IQ range)</th>
<th>Baseline BMI, kg/m², median (IQ range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-nourished</td>
<td>Malnourished</td>
</tr>
<tr>
<td>N, %</td>
<td>37 (64)</td>
<td>21 (36)</td>
</tr>
<tr>
<td><strong>Weight loss, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.3 (2 - 1)</td>
<td>3.6 (6 - 1)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>7.0 (11 - 5)</td>
<td>6.6 (8- 1)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>FFM, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.3 (54-68)</td>
<td>47.2 (42-61)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>58.6 (50-64)</td>
<td>47.4 (42-56)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>FFMI, kg/m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>19.9 (19-22)</td>
<td>16.9 (14-20)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>19.3 (17-20)</td>
<td>16.3 (16-18)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>MAMA, cm²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54.2 (42-62)</td>
<td>35.8 (32-45)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>49.3 (39-54)</td>
<td>36.9 (31-46)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.322</td>
</tr>
<tr>
<td><strong>HGS, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39.3 (33-49)</td>
<td>28.0 (22-37)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>38.0 (29-47)</td>
<td>27.3 (20-31)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>PG-SGA, score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (1-6)</td>
<td>11 (8-15)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>13 (8-17)</td>
<td>10 (7-14)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.627</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS, month</td>
<td>44 (40-56)</td>
<td>42 (16-48)</td>
</tr>
<tr>
<td>DFS, month</td>
<td>42 (37-54)</td>
<td>17 (4-43)</td>
</tr>
</tbody>
</table>

a The Mann-Whitney’s U-test was used for comparison of medians between nutritional status and BMI categories.

b The Wilcoxon Signed Rank Test was used for comparison for related median values between baseline and end.
5.7 THE CLINICAL VALUE OF HGS AND MAMA IN 50 MALE PATIENTS
(UNPUBLISHED DATA)

The median (IQ range) age was 61 (56-65) years. Twenty-two (44%) male patients had sarcopenia (i.e. low MAMA) and 15 (30%) were malnourished as determined by PG-SGA. Twenty-two (44%) patients had low HGS according to the cut-off <85% of median reference value. The median (IQ range) MAMA was 52 (41-62) cm², and HGS was 39 (31-49) kg. There were no significant differences in HGS between the dominant and non-dominant hand (Figure 9). Most patients (70%) had lost weight during the previous 6 months and 52% during the previous month before diagnosis, with a median (IQ range) weight loss of 5% (9-1) and 3% (5-1), respectively. Nine (18%) patients had lost weight both during the previous month and during the previous six months.

The median (IQ range) HGS was 48 (42-54) kg among normal HGS patients and 31 (25-35) kg among low HGS patients. Patients with low HGS had significantly lower body weight, BMI, FFM, FFMI, FM, MAMA, and prealbumin, but no differences were seen in age, height, albumin, or Crp, as shown in Table 19. OS was almost two times longer in patients with normal-HGS than in low-HGS patients, but it was not statistically significant due to low statistical power. The distribution of Stage I-III vs. IV disease in two HGS groups was not statistically significantly different (p=0.384): Stage IV disease was seen in 75% of normal HGS patients and 64% in low HGS patients.

Malnourished patients had significantly lower HGS (31 vs. 42 kg) than well-nourished patients (p=0.005). A significantly higher proportion of malnourished patients exhibited low HGS (73% vs. 31%, p<0.001) and low MAMA values (87% vs. 26%, p<0.001) vs. well-nourished patients. Patients with severe weight loss (>10% within 6 months) had significantly lower HGS than patients with ≤10% weight loss (31 vs. 41 kg, p=0.036).

A positive correlation was obtained between HGS and MAMA (r=0.707, p<0.001), explaining 50% of the variation in HGS. Correlation coefficient was significant with HGS and PG-SGA (r = -0.387, p=0.007), with weight loss during the previous 6 months (r = -0.39, p=0.005), and one-month weight loss (r = -0.29, p=0.044). Six-month weight loss explained 15% and one-month weight loss
8% of the HGS variation, and 25% and 41% of the variation of MAMA, respectively. FFM ($r=0.699$), BMI ($r=0.586$), and FFMI ($r=0.589$) had positive correlation with HGS ($p<0.001$).

The scatter plot shows the association between HGS and FFM stratified by MAMA (Figure 10). The regression line shows that every increment that HGS goes up one kg, the FFM goes up by 0.5 kg.

Table 19. Median (IQ range) values of 50 male patients between normal and low HGS.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal HGS, n=28</th>
<th>Low HGS, n=22</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>61.5 (56-65)</td>
<td>60.0 (57-63)</td>
<td>0.335</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.4 (77-94)</td>
<td>68.2 (57-77)</td>
<td>0.001</td>
</tr>
<tr>
<td>6-month weight loss, %</td>
<td>0.2 (3-1)</td>
<td>6.0 (9-1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178.0 (174-180)</td>
<td>174.5 (170-179)</td>
<td>0.087</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (24-29)</td>
<td>22.6 (21-25)</td>
<td>0.004</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>66.1 (61-72)</td>
<td>56.2 (48-61)</td>
<td>0.001</td>
</tr>
<tr>
<td>FM, kg</td>
<td>20.3 (15-23)</td>
<td>11.8 (9-15)</td>
<td>0.001</td>
</tr>
<tr>
<td>FFMI, kg/m²</td>
<td>18.1 (17-20)</td>
<td>16.0 (16-17)</td>
<td>0.001</td>
</tr>
<tr>
<td>MAMA, cm²</td>
<td>57.1 (52-64)</td>
<td>41.2 (36-50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>39.7 (37-41)</td>
<td>38.4 (33-42)</td>
<td>0.569</td>
</tr>
<tr>
<td>Prealbumin, ml/l</td>
<td>269.0 (208-308)</td>
<td>199.0 (137-238)</td>
<td>0.023</td>
</tr>
<tr>
<td>Crp, mg/l</td>
<td>7.5 (3-20)</td>
<td>10.0 (3-31)</td>
<td>1.000</td>
</tr>
<tr>
<td>Overall survival, months</td>
<td>68.5 (38-80)</td>
<td>32.0 (16-73)</td>
<td>0.144</td>
</tr>
</tbody>
</table>

HGS handgrip strength, 6-month six-month weight loss before diagnosis, BMI body mass index, FFM fat-free mass, FM fat mass, FFMI fat-free mass index, MAMA mid-arm muscle area, Crp C-reactive protein

The Mann-Whitney’s U-test was used for comparison of medians between HGS groups.
The ROC AUC for observed HGS (Figure 11) as a measure of muscle-mass depletion by low-MAMA was good, 0.85 (95% CI: 0.74, 0.96; p<0.001) and as a measure of nutritional status by PG-SGA (Figure 12) it was fair, 0.755 (95% CI: 0.613, 0.897; p=0.005). The agreement between HGS, MAMA, and PG-SGA was poor for PG-SGA ($K = 0.37$) and fair for MAMA ($K = 0.59$).

Figure 11. ROC curve for observed HGS (HGS in kg) as a measure of body muscle mass according to mid-arm muscle area in 50 males. The area under the curve is 0.85 (95% CI: 0.74, 0.96; p<0.001). The 45° line represents a curve for a receiver operating characteristics area of 0.5.

Figure 12. ROC curve for observed HGS as a measure of nutritional status according to PG-SGA in 50 males. The area under the curve is 0.76 (95% CI: 0.613, 0.897; p=0.005). The 45° line represents a curve for a receiver operating characteristics area of 0.5.

**5.8 SUMMARY OF THE RESULTS**

Vitamin D deficiency (S-25-OHD <37.5 nmol/l) was seen in 45% and hypovitaminosis (S-25-OHD 37.5-50.0 nmol/l) in 20% of all patients. Low levels of vitamin D had an association with malnutrition, cachexia, underweight, male gender, and Stage IV disease. Smoking, but not alcohol consumption, was associated with malnutrition, and both were associated with muscle depletion.

Prior to diagnosis 34% of all patients were malnourished as measured by PG-SGA, and 23% had a critical need for nutritional intervention according to a PG-SGA score ≥9. Low HGS (<85% of the median reference value) was seen in 28 patients (43%) and muscle depletion as measured by low MAMA in 46% of all 65 patients. Severe weight loss was seen only in 11% of patients during the 6 months before the diagnosis of cancer.

Malnourished patients had significantly lower values than well-nourished patients for all nutritional variables except TSF and hemoglobin. Patients with low HGS had significantly lower values for all variables except TSF, albumin, CRP, and hemoglobin than those with normal strength. Patients at nutritional risk differed from others in all but TSF and albumin levels (Table 15).

Prior to diagnosis 28% of patients were categorized as malnourished according to a NRS-2002 score ≥3 and 49% as at nutritional risk with a score of 2. The validity of NRS-2002 cut-off of 2 as a screening tool was compared with a PG-SGA score of 4 and an NRS-2002 cut-off of 3 as a marker of malnutrition compared with a PG-SGA score 9. Sensitivity, specificity and accuracy was 97%,
79% and $K=0.75$ for an NRS-2002 score of 2 (i.e. nutritional risk) and 89%, 90%, and $K=0.72$ for a cut-off of 3 (i.e. malnutrition), respectively.

Thirty-one per cent of the patients were cachectic at baseline, and as compared with, their DFS (15 vs. 66 months) and OS (21 vs. 70 months) were significantly shorter ($p=0.004$) than non-cachectic patients.

During postoperative therapy, all nutritional variables decreased significantly in both dietary counseling groups, and there were no significant differences between the two study groups (Table 17). Critical weight loss ($>5\%$) was equally seen in both groups: 77% in the INC and 67% in the ODC, with a median weight loss of 8%. According to the PG-SGA malnutrition increased significantly during treatment in the INC group from 27% to 85% ($p<0.001$) and in ODC group from 44% to 75% ($p=0.007$). There was no difference between the two study groups.

Patients with low or normal body weight at baseline (BMI $<25$) lost significantly less weight during their treatment than overweight patients ($p=0.013$). The median (IQ range) of body weight loss was 5.6 (1-5) % vs. 7.7 (5-9) %, respectively. Patients with baseline weight loss maintained body weight and MAMA during treatment, while overweight and weight stable patients lost weight, HGS and MAMA during postoperative therapy. At the end of treatment baseline well-nourished and overweight patients had significantly higher FFM ($p<0.001$, $p=0.005$) and HGS ($p=0.001$, $p<0.001$) than those with low body weight. Weight loss had no association with survival or treatment interruption, but baseline malnutrition was associated with poor survival.

Forty-four percent of the 50 male patients had sarcopenia (i.e., low MAMA) prior diagnosis. Low HGS had an association with malnutrition and severe weight loss in a subgroup of 50 men. Patients with low HGS had lower body weight, BMI, FFM, FFMI, FM, MAMA, and prealbumin as well as more severe body weight loss than those with normal HGS. Malnourished patients had also significantly lower HGS than well-nourished patients ($p=0.005$). A positive correlation was obtained between HGS and MAMA, FFM, FFMI and BMI, but not with age. MAMA explained 50% of the variation in HGS. HGS was found to be a useful measure of muscle-mass depletion according to ROC AUC (0.85, 95% CI: 0.74, 0.96; $p<0.001$) and to be a fair measure of nutritional status ROC AUC (0.755, 95% CI: 0.613, 0.897; $p=0.005$), respectively.
Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Subjects

In the present study, only patients with histologically verified diagnosis of primary HNSCC planned to receive either definitive CRT or combined treatment of surgery and postoperative RT or CRT were included. The subjects were well characterized for the study and were recruited at the first hospital outpatient visit after diagnosis of HNSCC was confirmed, i.e. prior to any cancer therapy. The strength of our study is that it was prospective, and the intervention part was randomized. In addition, the patient cohort was homogenous, including only primary HNSCC patients with curative intent of treatment. Two previous nutrition intervention studies have been conducted with an HNC patient population similar to ours (12,443), while other intervention studies included both HNC and GI cancer patients (443), colon cancer patients (408), and mixed groups of patients (408, 439). Furthermore, the study was performed within a normal clinical framework, and therefore the results can be applied to daily clinical work. Nutritional status was assessed with several validated methods, allowing comparisons between different methods.

Recruiting of patients was done mainly on the same day when the cancer diagnosis was confirmed, and cancer treatment was scheduled for the patient. The original target was to enrol 100 patients. We managed to recruit 65 patients during the recruitment period representing 74% of the eligible patients (n=88), and 33% of the overall HNSCC population in the HUS area (n=195). In the previous nutrition intervention studies the sample size has varied from 38 to 111 (12,408, 439, 443-445).

Twenty-three eligible patients were excluded due to consent to another study. In general, the situation was stressful for patients, for which reason some patients denied participating in the study. For some patients scheduled for surgery, the timeline was too tight to consider participation in the study and have time to perform preoperative nutritional status assessment. Fourteen patients with oral cavity cancer had an operation in another hospital. For these patients, preoperative nutritional assessment was logistically unfeasible, and they were excluded from the study. Among the non-participants were significantly more patients older than 65 years (p=0.03), with oral cavity cancer (p<0.001), and who underwent surgery either with CRT (p=0.014) or RT (<0.001) (See Appendix 3).

Most of patients in the current study had oropharyngeal cancer (54%), followed by hypopharynx and laryngeal cancers. In this study 17% had Stage I-II and 82% Stage III-IV, which is in accordance with Ravasco et al. (23) study. Age and sex distribution was also representative. Altogether, the study cohort was homogenous and was representative of HNSCC patients in the Helsinki and Uusimaa hospital district.

6.1.2 Study design

For the randomization the minimization method was used. The stratification was done by stage, age, BMI, and tumor location. These characteristics were chosen to allow quick randomization directly after written informed consent was received. In hindsight, better stratification by nutritional status could have been achieved by using weight loss during previous 6 months instead of BMI, and this would have resulted in better PG-SGA agreement between ODC and INC groups. In previous studies allocation has been done by stage, diagnose, patients' postal code or has not been specified (12,408, 439, 443-445).
6 Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Subjects
In the present study, only patients with histologically verified diagnosis of primary HNSCC planned to receive either definitive CRT or combined treatment of surgery and postoperative RT or CRT were included. The subjects were well characterized for the study and were recruited at the first hospital outpatient visit after diagnosis of HNSCC was confirmed, i.e. prior to any cancer therapy. The strength of our study is that it was prospective, and the intervention part was randomized. In addition, the patient cohort was homogenous, including only primary HNSCC patients with curative intent of treatment. Two previous nutrition intervention studies have been conducted with an HNC patient population similar to ours (12,444), while other intervention studies included both HNC and GI cancer patients (443), colon cancer patients (408), and mixed groups of patients (408,439). Furthermore, the study was performed within a normal clinical framework, and therefore the results can be applied to daily clinical work. Nutritional status was assessed with several validated methods, allowing comparisons between different methods.

Recruiting of patients was done mainly on the same day when the cancer diagnosis was confirmed, and cancer treatment was scheduled for the patient. The original target was to enrol 100 patients. We managed to recruit 65 patients during the recruitment period representing 74% of the eligible patients (n=88), and 33% of the overall HNSCC population in the HUS area (n=195). In the previous nutrition intervention studies the sample size has varied from 38 to 111 (12,408,439,443-445).

Twenty-three eligible patients were excluded due to consent to another study. In general, the situation was stressful for patients, for which reason some patients denied participating in the study. For some patients scheduled for surgery, the timeline was too tight to consider participation in the study and have time to perform preoperative nutritional status assessment. Fourteen patients with oral cavity cancer had an operation in another hospital. For these patients, preoperative nutritional assessment was logistically unfeasible, and they were excluded from the study. Among the non-participants were significantly more patients older than 65 years (p=0.03), with oral cavity cancer (p<0.001), and who underwent surgery either with CRT (p=0.014) or RT (<0.001) (See Appendix 3).

Most of patients in the current study had oropharyngeal cancer (54%), followed by hypopharynx and laryngeal cancers. In this study 17% had Stage I-II and 82% Stage III-IV, which is in accordance with Ravasco et al. (23) study. Age and sex distribution was also representative. Altogether, the study cohort was homogenous and was representative of HNSCC patients in the Helsinki and Uusimaa hospital district.

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Patients were randomized to receive either intensive nutritional counseling (i.e. intervention group, INC) or on-demand nutritional counseling (i.e. control group, ODC) to assess the effect of
the number of nutritional counseling sessions. Previous studies have compared nutritional counseling received by a dietician vs. by a nurse (439,443,445), oral nutritional counseling with ONS vs. free ad libitum diet (12). Before the current study HNC patients were referred to a dietician only occasionally in our institution. There is strong evidence that dietician based counseling is effective (12,408,439,443-445) and that nutritional support should be integral part of cancer treatment (319,448). We decided that it was not ethical to compare counseling received by dietician to either nurse-based counseling or without any counseling (i.e. free ad libitum diet). Moreover, dietician resources are limited in our institution and therefore, it was important to assess if intensive counseling would give a better outcome than on-demand counseling. To the best of our knowledge such study protocol has not been used before.

The nutritional status assessment, anthropometry, and biochemistry were planned according to the scheduled appointments, before the initiation of surgery, RT, or CRT, to cause as little inconvenience for the patients. Study blood samples were obtained with regular CRT-related blood samples day before CRT. For patients with RT only, blood samples were scheduled separately for the study protocol, causing some inconvenience for patients.

The study protocol was logistically cumbersome. The original plan was that recruitment would take a year, but due to the slow accumulation of patients it was continued for another year. Performing full nutritional assessment and nutritional counseling and managing all appointments and blood samples on schedule in conjunction to a normal dietician’s clinical work was hectic. This might have caused some negative effect on dietary counseling during the second study year. It is justified to presume that patients in the ODC group were “contaminated” at least to some extent during the study. The ODC group saw the research dietician as often as the INC group when the nutritional status assessment was performed at regular intervals throughout the study period, even though no dietary counseling was performed. Also, the fact that patients were participating in a nutritional clinical trial may have motivated patients as well as nurses and physicians to carry out the nutrition care plan more carefully also in the ODC group.

6.1.3 Anthropometry and body composition
All anthropometric measurements were performed by standardized procedures by the same research dietician (HO). Height was documented from hospital charts. Weight 6 months before the oncology diagnosis was documented by recall, which may have increased the prevalence of normal weight and overweight (BMI 25·0-29·9 kg/m²) underestimated underweight (BMI <18·5 kg/m²) and obesity (BMI ≥30·0 kg/m²) (536). But this was not considered to be significant because BMI was not used as a measure of nutritional status in the current study.

Body weight was measured with the same scale through the whole study period and was measured in light indoor clothes without shoes and corrected for weight of clothes by subtracting 1.5 kg in men and 1 kg in women, which was the current standard in our clinic. This is in line with a previous study (195), which suggests that weight should be corrected for clothing by deducting 1.4 kg (summer) and 1.8 kg (winter) for men, 0.9 kg and 1.1 kg for women, respectively (195).

The baseline body weight was measured and nutritional status assessed within seven days before surgery and seven days before RT in those patients who first had surgery and and then postoperative RT or CRT. Patients who had only RT or CRT the body weight was measured within 14 days before the first RT. The weight loss may increase in the period between diagnosis and start of the treatment, especially in those patients with dysphagia (1), thus causing some bias in current study. During CTx, the weight was measured before infusion to prevent bias of the fluid accumulation caused by CTx.

There is some concern that MAMA is overestimated in overweight patients (206). In our study cohort only 12% of the patients had BMI >30, and overweight was not regarded as a significant source of error. Keeping in mind that none of the anthropometric methods are currently regarded as golden standards, MAMA was a practical method during the study period and superior to MAMC as suggested by Frisancho (204). Recently, corrected MAMA was suggested as a criterion for diagnosing sarcopenia (117). In the current study MAMA was used instead of corrected MAMA as suggested by Frisancho (204).
6.1.4 Weight loss
For the weight loss assessment, recalled weight six months before the diagnosis was used as the normal weight. The accuracy of recalled weight is influenced by age, current BMI, weight gain, weight loss, and weight variability, with a trend for overestimation in patients with current BMI less than 28.6 kg/m², and underestimation with BMI 28.6 kg/m² or over (193). Most patients in the current study cohort had BMI <26 kg/m², and only 11% had severe weight loss, which is less than previously reported (1,10,167,196,417).

Weight loss is currently thought to be a rough method to assess nutritional status even though it is widely used and often referred to as a valid method (106,167,196). Nevertheless, weight loss is a marker of low energy intake or cachexia. We used a generally accepted criterion by Blackburn et al. (192) for severe weight loss, which has been used also in patients with HNC (106,167,196). Severe or significant weight loss was defined as body weight loss of ≥5% in one month or ≥10% in the previous six months. Weight loss is a marker of either low nutritional intake or cachexia, but it lacks accuracy to detect muscle-mass loss. For these reasons, it was used in the current study more as a measure of inadequate energy intake than nutritional status.

6.1.5 Body composition
FFM and TBW were estimated by measuring impedance by a single-frequency 50 kHz bio-impedance analysis (BIA). BIA is convenient for patients, but it has some confounding factors that should be considered. BIA has been criticized that it does not assess body composition accurately in patients with fluid accumulation or altered distribution of extra- and intra-cellular water such as in obesity, liver cirrhosis, and cardiac insufficiency (237,537). The suggested optimal BMI range for BIA analysis is 16-34 kg/m² (237). Most our patients (95%) fell within this range. Furthermore, none of the patients had liver cirrhosis, renal diseases or cardiac insufficiency due to the exclusion criteria used. All patients in the current study were to have curative treatment. It was therefore considered unlikely that there would be fluid accumulation due to cancer cachexia to a considerable extent.

We used the Kotler equation (145) for total body water calculation, which is valid also in situations where there might be alterations in the distribution of water compartments such as in HIV infections (145). Furthermore, BIA can detect a ≥5% change in FFM in 89% of cases (145). The standard frequency for BIA, 50 kHz, has been shown to be high enough to estimate TBW, with 2-8% standard error compared with isotope dilution (530). In healthy adults, hydration of fat-free tissue is 73%, while in severely underweight subjects FFM hydration varies from 73% to 76% (538). In a study by Bokhorst et al. (167) a hydration fraction of 0.723 was used. Due to the small number of severely underweight patients in the current study we used the tissue hydration of 73% in our analysis, even though if there were a 3% increase in cell hydration it would result an overestimation of 0.7 kg in FFM (538). BIA was regarded as a valid indirect method to assess body composition when age- and sex-specific Kotler equations were applied, even though there was one severely malnourished patient with severe fluid accumulation at baseline. In previous studies Lukaski equations (232) have been used among cancer patients. We chose to use the Kotler equation, which uses impedance, because a measure of resistance, applied in Lukaski equations, was not available in our study (232,234).

During previous years, phase angle and bioelectrical impedance vector analysis (BIVA) have gained more attention as a more precise measure of nutritional status and disease severity (539). Currently CTx, MRI, and dual energy X-ray absorptiometry (DEXA) scans are considered golden standards, which were not accessible at the time of initiation of this study. In the future, it would be tempting to use CTx for muscle-mass assessment in patients with HNSCC, as has been reported recently (540).

6.1.6 Handgrip strength
HGS has been widely used as a measure of muscle function. Recent studies have shown that it is also a valuable method to assess nutritional status in various clinical settings, but there is wide variety of reference values, and cut-off points used for assessment of low muscle function and
6.1.7 Cachexia
Cancer cachexia is characterized by decreased muscle mass and function, which together are associated with poor prognosis (543). In the current study, we chose to analyse muscle-mass loss by MAMA and muscle function by HGS due to convenience and low costs of these two methods. Previous studies have shown that muscle depletion and low HGS have a strong association with OS (544). Sarcopenia and skeletal mass depletion have been shown to be independent predictors of survival among patients with HNSCC (540).

We combined these two objective methods instead of weight loss or anorexia and food intake assessment preceding weight loss. Our hypothesis was that by classifying patients as cachectic we would be able to find patients who have a poor prognosis (540). Further, it is important to note that food intake assessment needs expertise and recalled weight can be somewhat biased. Therefore, new methods are needed for clinical practice.

6.1.8 Sarcopenia
In the current study sarcopenia was assessed by MAMA. We were fully aware that dual energy X-ray absorptiometry (DXA) and CT scans are more precise and generally accepted methods for body composition assessment, but they were not available at the time of the current study. Instead, we decided to use MAC and MAMA, because they are non-invasive, relatively easy to perform, and inexpensive in daily dietitian practice. It has been shown that HGS has a strong correlation with upper-arm anthropometry especially in male patients (183). We decided to perform the analysis only in 50 men, because of the low number of women (n=15).

6.1.9 Nutrition intervention
Patients with HNSCC should be routinely screened for malnutrition risk and referred to a dietitian both perioperatively and during curative intention (C)RT (191). At the time of the current study the standard practice was that patients with HNC were referred to a dietitian according to the physician’s judgement. Referral was often quite late, during postoperative treatment rather than prior to diagnosis.

The aim was to create a protocol where HNSCC patients would be regularly referred to a dietitian in the very beginning of (C)RT and thus establish nutrition treatment and nutritional status assessment as an integral part of medical treatment in this patient group according to ADA Medical Nutrition Therapy Protocol (434).

Clinical dietitians are the only healthcare profession in Finland with a master’s degree in clinical nutrition and expertise in both clinical nutrition therapy and support, whereas physicians are responsible for the implementation of the nutritional support. Taking into consideration the limited dietitian resources and efforts to improve efficiency in our institution, it was justified to compare two different nutritional counseling models given by a dietitian instead of a nurse as in previous studies in patients with HNC.

To the best of our knowledge, there are no previous comparisons of two different ways of nutritional counseling. In our study, the treatment group had nutritional support counseling by a dietitian at least four times during (C)RT. The ODC group had nutritional support counseling once before (C)RT, and on demand according to the physician’s judgement if the patient’s clinical condition deteriorated. It is noteworthy that during the study period all healthcare professionals treating the study patients were aware of the open label intervention with nutritional support.
This was apparent among those patients who were either excluded or declined to participate in the study. Half of these patients were referred to a dietitian during (C)RT.

6.2 GENERAL DISCUSSION

6.2.1 Vitamin D status

Epidemiological studies have suggested an important role for vitamin D in cancer incidence, prevention, survival and treatment in several cancers (141,546-548). Although the significance of poor vitamin D status in the development of HNC is not known, it might have some consequences in the treatment outcome, including occurrence of complications. As the literature demonstrates, high vitamin D intake is associated with better survival in patients with cancer (549). Furthermore, it has been shown that underweight, obesity, and smoking are associated with lower vitamin D status (550).

In the current patient cohort, most patients had hypovitaminosis, and almost 50% vitamin D deficiency, while 35% of the patients were regarded as having sufficient vitamin D levels. The number of patients with hypovitaminosis was much higher (67%) compared with the general Finnish population (21%) (551), but it was well in line with Finnish middle-aged smokers (62-75%) (552), and with Finnish internal medicine patients (66%) (553).

The mean S-25-OHD concentration levels in our study (42 nmol/l) was in line with a subgroup of 44 Danish HNC patients (48 nmol/l) (550) and Finnish prostate cancer patient cohorts (41 nmol/l) (554,555). Higher values have been reported in patients with Stage I-II HNSCC (64 nmol/l) (556), colorectal (54 nmol/l) (557), lung (52 nmol/l) (558), and breast cancer (69 nmol/l) (559,560), and lower values in one colorectal cancer study (31 nmol/l) (133).

HNC patients in the current study had significantly lower S-25-OHD concentrations than values reported for the general Finnish population in men aged older than 35 years and women aged equal or less than 60 years. The mean S-25-OHD concentration for men was 41 (SD 20.7) nmol/l and for women, 46 (SD 25.6) nmol/l. In HNC patients both hypovitaminosis and deficiency was seen more often, 65% vs. 21% (p<0.001) and optimal 25-OHD concentrations (80-100 nmol/l) more rarely, 5% vs. 42% (p<0.001), than in the general Finnish population. It is noteworthy that vitamin D levels may vary according to season and between laboratories.

In the present study, we observed low serum S-25-OHD concentrations especially in patients with low BMI, malnutrition, cachexia, among males, and in patients younger than 65 years of age in contrast with previous studies, where older age, female gender and obesity have been associated with an increased risk of being vitamin D deficient (561). In a Danish study with 12 200 cancer patients by Skaaby et al. (550) low vitamin D concentrations were reported in both underweight and overweight patients. In the same study, lower S-25-OHD concentrations were seen in abistent patients and among current smokers, however the clinical meaning of this finding is not clear, and it might suggest that poor vitamin D status associates with overall poor nutritional status also among HNC patients. It has been shown that higher socioeconomic status and education as well being married are associated with higher vitamin D status (562). This can be one explanation for high prevalence of hypovitaminosis in our study due to high alcohol consumption associated with lower socioeconomic status also in the current study (data not shown).

In our cohort, the location of tumor or stage was not associated with S-25-OHD concentrations. In contrast, patients with Stage IV cancer had higher S-25-OHD than those with Stage I-III disease. Our study was not designed and powered, however, to evaluate the role of vitamin D in cancer development. It therefore remains unknown whether the suboptimal vitamin D status may have played a role in cancer development or is it the result of concomitant malnutrition.

The extremely low levels of vitamin D indicate that HNC patients might need a high dose of vitamin D substitution at the beginning of cancer treatment to bring the S-25-OHD concentrations to the optimal level. Some pre-clinical in vitro and phase II studies show promising results with the use of vitamin D analogues, i.e.1,25-OHD analogues, as anticancer drugs in colon, prostate,
and hepatocellular cancer (563-565). Furthermore, there is some evidence that 1,25-OHD and its analogues combined with docetaxel have synergistic antitumor effects in a small randomized prostate cancer study (566). To best of our knowledge there are no data about vitamin D or vitamin D analogues used as a supplement during the treatment of head and neck carcinoma. On the other hand, Zhou et al. (139) has shown that patients with non-small-cell lung cancer had improved overall and recurrence-free survival with high baseline S-25-OHD concentrations (>39 nmol/l) and slightly lower vitamin D intake (>371 IU/day) than recommended (400 IU/day). In this study patients who had surgery in summer and thus satisfactory vitamin D levels had a 3-fold better recurrence-free survival and a 4-fold better OS (OS) than those with surgery in winter and low vitamin D status.

So far there are no recommendations for optimal S-25-OHD concentration for cancer patients. According to Giovannucci et al. (141) optimal S-25-OHD concentration in cancer prevention might be ≥80 nmol/l and should not exceed 100 nmol/l (142). According to a transcriptomics, some people are regular responders to vitamin D supplements while others are irregular responders (567). For this reason, S-25-OHD levels should be monitored, with some patients needing more supplementation than others.

6.2.2 Nutritional risk screening (NRS-2002)

In this study nutritional risk as defined by a NRS-2002 score of 2 was seen in 49% (n=32) of all 65 patients. A NRS-2002 score ≥3 indicated malnutrition and was seen in 28% of patients. This finding is concordant with a subgroup of 116 oral cavity cancer outpatients in a large oncological study by Bozzetti et al. (545) where 28% of oral cavity cancer patients had a NRS-2002 score ≥3. Higher values have been reported (42%) in hospitalized HNC patients (25), and after RT (60%) (12). The prevalence of malnutrition in the current study was slightly lower than previously reported (35% to 43%) in patients with HNC (307,313), but in line (30%) with overall cancer outpatients (309). The lower prevalence of malnutrition (NRS-2002 score ≥3) in the current study is likely due to the timing of nutritional status assessment, which was performed before any oncological treatments. The higher prevalence in previous studies can also be due to the small number of HNC patients, causing some overestimation of nutritional risk.

We found a moderate correlation between NRS-2002, anthropometry and HGS. Our results showed that NRS-2002 with a score ≥3 had high sensitivity and specificity compared with PG-SGA category BC (K = 0.78, 77% and 98%, respectively) and score ≥9 (K = 0.72, 89% and 90%, respectively). NRS-2002 with a cut-off ≥2 showed high sensitivity and specificity with PG-SGA score ≥4 (K=0.75, 97% and 79%, respectively). These results are in line with studies in gastric cancer (80% sensitivity and 98% specificity) (311) and surgical patients (K = 0.85, 80% and 89%) (317) indicating that NRS-2002 with a cut-off point ≥3 indicates malnutrition. On the other hand, in patients with gastric cancer, NRS-2002 (43%) showed a higher prevalence of malnutrition than PG-SGA (31%) (311).

The agreement between the methods was high, indicating that the same patients were identified by both methods as malnourished or at nutritional risk. When comparing NRS-2002 scores with PG-SGA scores even higher sensitivity and specificity was found in patients critically needing nutrition intervention. These findings indicate that HNSCC patients are already malnourished prior to initiation of any treatment if a NRS-2002 cut-off value of ≥3 is used. This finding is supported in patients with gastric cancer and surgical patients (311,317). In contrast, the Raslan et al. (308) study showed that NRS-2002 underestimated the incidence of patients at risk (28%) compared with those who were classified as malnourished (39%) by SGA in a mixed group of 705 hospitalized patients. This might be due to the difference between NRS-2002 and SGA detecting slightly different patients with SGA indicating more chronic type of malnutrition, and NRS-2002 indicating more recent changes in nutritional status. Hospitalized patients might be more severely ill, and thus the prevalence of chronic malnutrition can be expected to be higher than in an outpatient cohort.
6.2.3 Nutritional status
In the current study, severe weight loss (≥10% of usual weight) was seen only in 11% of the
patients and 48% had lost weight during previous month of diagnosis. In a study by Lees et al.
(196) 57% were losing weight prior to commencing RT with mean weight loss of 10%. Several
studies have shown wide variations in the prevalence of severe weight loss, from 19% to 57%
(1,167,194,417,419). Our lower prevalence can be partly explained by timing of measurement,
stage and location of tumor. Furthermore, all our patients were assigned curative care.

A study (n=407) performed by Jager-Wittenaar et al. (1) and a smaller study (n=47) by van den
Berg et al. (194) reported severe weight loss (≥5% in 1 month or ≥10% in 6 months) in 19% of
patients prior to diagnosis, which is in line with our results. Jager-Wittenaar et al. (1) study
showed that severe weight loss was more frequent in patients with Stage III and IV (43%) than
Stages I and II (7%). In a retrospective study with majority of patients with Stage III and IV disease
57% of patients had weight loss ≥5%, but the data of weight loss was available only in 28 (32%)
patients (419). In our study Stage III and IV patients were more prevalent (82% vs. 26-38%) than
in the Jager-Wittenaar (1) and van den Berg studies (194). Thus, it would have been expected that
there should have been more patients with severe weight loss in our study than there was.

Other studies have also reported higher prevalence of severe weight loss at diagnosis. In a
study by van den Berg et al. (417) 28% had severe weight loss (5-10% of usual body weight). Most
of the patients (89%) had oral cavity and oropharyngeal cancer, compared with 54% in our study.
It has been shown that oral cavity, oropharynx, and hypopharyngeal cancers are associated with
a higher risk of weight loss due to dysphagia and loss of appetite (1,12).

In a Bokhorst et al. (167) study with 64 patients, severe weight loss was seen in 30% of patients
with primary tumor and 35% in patients with previous RT. All patients were to have major HNC
surgery, while in our study surgery was performed only in 17 (26%) patients. Furthermore, all
our patients were previously untreated. One explanation for the higher prevalence of severe
weight loss prior to commencing RT or CRT could be the fact that weight loss may increase in the
period between diagnosis and surgery, start of the RT or CRT, especially if dysphagia is present.
The most logical explanation might be simply the overestimation of usual weight six months
before diagnosis and thus giving higher values for weight loss.

It has been shown that patients with BMI ≥29 kg/m² tend to underestimate recalled weight
(193). This has possibly happened also in the current study, where 42% of all patients were
overweight (BMI ≥25) at diagnosis. The prevalence of overweight or obesity is in line with
previous studies; 32% in the van den Berg et al. (417) study, 33% in the Bokhorst et al. (167) study,
and 53% in the van den Berg et al. (194) study.

At the time of diagnosis 34% of the patients were malnourished according to PG-SGA. This is
well in line with previous studies, in which malnourishment ranged from 40% to 60%
(11,12,14,15). This finding is concordant with a subgroup of oral cavity cancer outpatients (29%)
in a large oncology study with a mixed group of cancers by Bozzetti et al. (545), but lower than
the values reported in the study by Righini et al. (25) in hospitalized HNC patients (42%) and in
patients receiving RT after CRT (60%) (12).

6.2.4 Cachexia
The prevalence of pre-treatment cachexia in patients with HNC has reportedly been 20% to 32%,
which is well in line with our finding (31%) (166), but also higher (42%) (170) and lower
prevalences (6-15%) have been reported (568,569). Furthermore, pre-cachexia (2-5% weight loss
during previous 6 months) has been found in 15% of patients, which is in line with current study
finding of 9% (170). In study by Jager-Wittenaar et al. (170), the appendicular skeletal muscle
index was measured by DEXA, which is a more accurate method to assess muscle mass than
anthropometry, which was used in our study. In the study by Stegel et al. (569) multiple
frequencies BIA was used. This is one possible reason to explain this difference.

Inflammatory activity is an essential part of cachexia, even though it has been suggested that
cachexia can exist without systemic inflammatory activity (165). In the current study median (IQ
range) CRP concentration in cachetic patients was 13 (4-42) mg/l and in non-cachetic patients 5
also influenced the
that early use of PEG resulted in better feeding management. This could be one explanation why
immediately after PEG placement with a dose of 400 ml/day (i.e. (control group). In the intervention group, the supplemental tube feeding was commenced
supplemental tube feeding (intervention group) with tube feeding started later during CRT
61% of patients in the study group needed enteral nutrition (nasogastric tube or PEG) , and 39%
study performed in 66 patients with HNC compared early nutritional intervention (study group)
Cachexia was associated with poor survival. Severe weight loss, muscle mass depletion and decrease of muscle function are explanatory factors for cachexia-induced death. Pre-treatment weight loss was seen in 40% of our study population, which was higher than previously reported (20-32%) (166). It is noteworthy that severe weight loss during treatment was not associated with mortality. The OS rate (30%) among cachectic patients in our study was much lower than previously reported (62%) in muscle mass-depleted HNSSC patients (540).
Since cachexia is prevalent already in early phase of HNSCC and the prevalence rises to 60-80% in advanced states, cachexia should be distinguished from simple malnutrition and reduced energy intake. Moreover, cancers of the head and neck area carry a higher risk of cachexia than tumors of other organs (166).

6.2.5 Nutrition intervention
In this present randomized clinical trial, we compared two protocols of nutritional counseling. The INC group received nutritional counseling regularly during (C)RT along with nutritional status assessment. The ODC group received nutritional counseling once at the beginning of adjuvant therapy and on-demand by physician referral followed by regular nutritional status assessment (12,444,445,449). Previous studies have clearly shown that nutritional counseling received from a dietitian is more effective than no counseling or counseling received from a nurse (12,443-445). To the best of our knowledge, there are no comparisons of two types of counseling received from same dietitian.

We did not find any significant differences in clinical values of nutritional status between two study groups contrary to earlier studies, probably due to timely consultation referrals to the dietitian by physicians in the on-demand group (12,443-445). Another difference between current and the previous RCT studies was that most patients in our study had CRT on the oral cavity, oropharyngeal and hypopharyngeal location, which cause more severe mucositis than RT alone. In contrast, in previous studies, most patients underwent RT (12,443-445). Furthermore, due to high number of patients with CRT, PEG was inserted in most patients, whereas PEG was not used in previous studies. These differences make comparison between earlier studies and the current study difficult.

There are few non-randomized studies with CRT and enteral nutrition care. One retrospective study performed in 66 patients with HNC compared early nutritional intervention (study group) with no-counseling (control group) during CRT (17). Patients at the study group had less weight loss, RT breaks and unplanned hospital admissions than control group. At the end of the study, 61% of patients in the study group needed enteral nutrition (nasogastric tube or PEG), and 39% ONS due to dysphagia. In the current study, enteral nutrition was seen in much higher number of patients; 78% of INC and 97% of ODC patients, respectively.

A RCT by Brown et al. (570) with 108 locally advanced HNC patients compared early supplemental tube feeding (intervention group) with tube feeding started later during CRT (control group). In the intervention group, the supplemental tube feeding was commenced immediately after PEG placement with a dose of 400 ml/day (i.e. 600 kcal), and further increased during CRT. Both groups lost weight similarly; 6% in the intervention group and 7% in the control group, which is in line with the current study. Furthermore, the Brown et al. (570) study showed that early use of PEG resulted in better feeding management. This could be one explanation why the ODC group managed as well as the INC group, because the ODC group had more malnourished patients and thus more patients needing PEG already at baseline than the INC group. Because both groups received nutritional counseling by a dietitian, it is possible that this also influenced the on-demand group in the enteral nutrition management. It has been shown earlier that compliant patients (90%) could maintain weight during CRT, whereas non-compliant patients (10%) lost 9 kg of weight during CRT (107). Enteral nutrition was performed by nasogastric tube.
Although nutritional care was planned according to the ADA Medical Nutrition Therapy Protocol, most patients (69%) were not able to achieve energy and protein intake goal, which is in line with previous studies among HNC patients during CRT (107,570). In the Paccagnella et al. (17) study, the mean energy intake infused was 1800 kcal in females and 2100 in males, which is in accordance with our study. The energy requirement was calculated by 30-35 kcal/kg and protein requirement by 1-1.5 g/kg corresponding our energy and protein estimations. The control group lost weight twice as much as the study group, but the nutrition care plan for the control group was not reported. In the current study nutrition need was planned similarly, explaining the equal weight loss in both study groups.

In the current study, the REE was multiplied by an activity factor of 1.5 and protein requirement (g/day) was calculated by multiplying ideal body weight (IBW, defined as BMI 22) by 1.2 to 1.5. A protein goal of 1.5-1.7 g/IBW or even higher (267,503) has been suggested to preserve muscle mass due to elevated inflammatory activity during CRT (30). In a study with 29 HNC patients, patients with sufficient nutrition intake (≥35 kcal/kg and ≥1.5 g protein/kg) lost less body weight (1 kg) and muscle mass (0.3 kg) than patients with insufficient intake (7 kg and 3 kg, respectively), but could still not fully preserve muscle mass (267). One explanation could be that muscle loss accelerates despite adequate nutrition intake because of physical inactivity due to treatment-induced fatigue or inflammatory mediators, since they both reduce protein anabolism (30,571).

Adherence to dietary counseling, defined as consuming ≥75% of recommended energy, and protein intake, has been associated with favorable outcomes on body composition (572). Instead, we found that patients who lost more than 5% of weight during CRT received median of 77% of the estimated energy need compared with 91% among patients with less than 5% of weight loss. The protein intake was slightly less, accounting for 70-73% of the estimated need, which could be one explanation for muscle-mass loss seen in the current study.

The practice during intervention was to use an enteral product with 1.5 kcal/ml energy and 0.6 g/ml protein in a combination with 1.0 kcal/ml and 0.3 g/ml product, respectively. It seemed that an energy intake of 2000 kcal with total volume of 1400 ml/day enterally was achievable for the majority of the patients, but it was insufficient especially for overweight patients. One solution would be the use of a more energy and protein dense enteral product (2.0 kcal/ml and 1.0 g protein/ml), in which a total daily volume of 1400 ml would provide 2800 kcal and 140 g protein, which would be enough also for overweight patients.

The main barriers managing tube feeding in the current study were nausea and early satiety, which was in line with a previous study (570). These problems were more pronounced among overweight patients, as reported earlier (573,574). In the retrospective study by Grossberg et al. (540) in 2840 HNSCC patients, overweight patients lost twice as much muscle and fat mass as normal weight patients. Furthermore, those patients in the current study who were losing weight before oncological treatment were weight stable during CRT, which was opposite to a previous study (107). It seems that in the current study patients with higher pre-treatment BMI had more nausea and anorexia, and thus greater weight loss. Sarcopenic obesity may increase CRT-related adverse events (162). Overweight patients may have more cytokines from adipose tissue, delaying gastric emptying and inducing nausea and anorexia (575). On the other hand, the energy target and the total enteral feed volume for overweight patients are higher than in normal weight patients and thus may be harder to achieve during CRT. Moreover, it can be assumed that overweight patients may need more opioids for symptom management, which delays gastric emptying and leads to impaired nutrition through PEG. We cannot completely exclude the possibility that patients with lower BMI were heavy alcohol users, and therefore had less CRT-related adverse events such as nausea, vomiting and anorexia (576).

Malnutrition prior to diagnosis and during treatment (102,577) and weight loss of more than 20% during CRT have been regarded to predict poorer survival in HNSCC (107,108). In the current study, such an association was not seen, even though overweight patients lost weight significantly. This can be because none of the patients lost more than 15% of weight, and the median weight loss in all patients was less than 10%. Grossberg et al. (540) reported that even
though overweight HNSCC patients lost significantly muscle mass they had better survival than non-obese patients, which is in line with our results.

Most patients (84%) in the current study had oropharyngeal cancer, which has better survival in patients with HPV-positive disease (71). Thus, it is possible that HPV-positivity may have influenced survival, which could not be ruled out in the current study because we did not assay HPV-positivity at that time.

6.2.6 Handgrip strength and sarcopenia
Low HGS was seen in 44% of male patients. Malnourished patients had 26% lower HGS than well-nourished patients (p=0.002), which is in line with previous studies (183,262,263). Furthermore, HGS showed a strong correlation with MAMA (p<0.001; r 0.70), which agrees with a study by Norman et al. (183). HGS showed 77% specificity and 82% sensitivity (K=0.59) to detect low MAMA, which indicates that HGS is an important measure of upper-arm anthropometry. In a previous study by Kilgour et al. (274) in advanced cancer patients HGS was linked to poor survival. This was also seen in the current study with OS and DFS, but the differences were not statistically significant. These discrepant results may be caused by the small sample size.

The European Working Group on Sarcopenia (EWGSOP) has stated that sarcopenia requires both presence of low muscle mass and low HGS (158), which is part of the recently launched ESPEN criterion for diagnosing sarcopenia (177). In 50 male patient sarcopenia was seen in 34% of patients before any oncological treatments, which was in line with previous studies (15-50%) regarding lung and gastrointestinal cancers (162,387,543). Sarcopenia had an association with lower OS (p=0.031) and DFS (p=0.009).
6.3 CONCLUDING REMARKS

The specific conclusions of this thesis were as follows:

1. A considerably high number of patients has vitamin D hypovitaminosis and deficiency at the beginning of oncological treatments.

2. At diagnosis one third of the HNC patients were malnourished.

3. NRS-2002 with a cut-off point of 3 seems to reflect existing malnutrition and thus a cut-off point 2 would be more appropriate for starting nutritional care to prevent impairment of nutritional status.

4. A substantially high number of patients had cachexia already at diagnosis, which was associated with poor OS. HGS together with MAMA seems to be a useful method for integration into the assessment of cachexia.

5. The outcome of the INC group was not different from the ODC group. Nutrition intervention can stabilize nutritional status in those patients who are losing weight prior to diagnosis, but not in overweight patients. Even a significant weight loss of overweight patients is not associated with poor survival if FFM and HGS are in normal range at the end of (C)RT.
Summary

Malnutrition is characterized by depletion of FFM and FM, which have a detrimental effects on a patient's quality of life and survival. The aim of nutritional status assessment is to reliably screen malnourished from well-nourished and to detect patients with FFM loss (i.e. sarcopenia). The relatively high number of overweight HNC patients along with several findings of detrimental changes in body composition and survival suggests that nutritional status assessment requires more attention in the future than today.

In the current study, several objective and subjective methods that were available at the time were used for the nutritional status assessment. Currently, growing evidence suggests that more precise methods should be used to assess changes in body composition (i.e. DXA and CT), some of which are more useful than others in clinical practice. The aim was to use nutritional status assessment methods that could be easily applied in clinical practice by dietitians and physicians. The choice of a specific method or combination of methods in clinical setting depends on various considerations, including availability, cost, convenience, subject acceptability, accuracy, and radiation exposure, often in this order.

Even though body weight loss is a rough nutritional status assessment method that has many confounding factors, weighing is easy to perform in clinical practice. It is therefore a suitable screening and follow-up method. In addition, HGS and mid-arm anthropometry are practical and easy to perform. By combining these two methods it is possible to distinguish cachectic patients from non-cachectic patients, and thus these methods should be included in the HNC patient care management in combination with the PG-SGA method.

HNC patients can be assumed to be at nutritional risk, depending on the location of tumor and its oncological treatments, which seriously hamper the patients' food intake especially in patients with oropharyngeal and hypopharyngeal cancers. If nutritional risk screening (NRS-2002) is performed in all HNC patients already at diagnosis, a cut-off of 2 would be more appropriate to start preventive nutrition care and to assess the need for prophylactic PEG insertion.

A substantially high number of HNSCC patients had low vitamin D values prior to diagnosis compared with values of the healthy Finnish population. This highlights the importance of diagnosing hypovitaminosis and evaluating the need for supplementation.

No differences in nutritional outcomes were seen between the two types of nutritional counseling. Achieving adequate energy and protein intake was challenging due to treatment-induced severe side-effects, which were seen especially among overweight patients. High-risk and malnourished patients were more likely to succeed in planned nutrition care. Contrary to previous studies weight loss was not associated with poor survival.
7 Summary

Malnutrition is characterized by depletion of FFM and FM, which have a detrimental effects on a patient’s quality of life and survival. The aim of nutritional status assessment is to reliably screen malnourished from well-nourished and to detect patients with FFM loss (i.e. sarcopenia). The relatively high number of overweight HNC patients along with several findings of detrimental changes in body composition and survival suggests that nutritional status assessment requires more attention in the future than today.

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FUTURE RESEARCH

In the current study we were not able to show clearly the effect of intensive nutrition counseling and nutrition support on nutritional status and body composition. In the future, more studies should be performed in patients at risk for disease-related malnutrition to find out the ideal protein requirement for muscle-mass maintenance. One interesting research aim would be to test the effect of nutrition support including energy 35 kcal/kg and protein 1.5-1.7 g/kg on FFM, HGS, and weight loss during CRT. We had not anticipated the substantially high prevalence of cachexia seen already prior diagnosis. This draws attention to study the effect of anti-cachectic treatment (i.e. non-steroidal anti-inflammatory drugs, EPA fatty-acid and physical exercise) in combination with an energy- and protein-dense diet on body composition and survival in HNSCC patients. The methods we used to examine body composition were not as robust as those currently recommended. It would be interesting to use CT scan at the C3 level for muscle-mass assessment and to compare its association with HGS and PA. In this study we did not study the association of nutritional status and QoL. One subject for future study should be to clarify the role of nutrition support on QoL, especially among patients in palliative care. In general, controversy still exists on the effect of nutritional support to decrease surgical complications, infections, and health care costs as well as to increase survival and QoL. Therefore, research on these issues should continue in all patient groups, also including critically ill patients such as ICU patients and patients waiting for transplant.
FUTURE RESEARCH
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APPENDICES

Appendix 1. Review of literature: Search String

[head and neck cancer (head and neck neoplasms OR head OR neck OR oropharyn OR pharyn OR laryn OR throat OR glotti OR nasopharyn OR hypopharyn)] AND [cancer (carcinom OR tumor OR tumor OR neoplasm OR malignan OR metasta)]
[nutrition (nutrition therapy OR nutrition processes OR nutrition disorders OR nutrition assessment OR nutritional status OR nutrition requirements OR food OR feeding behavior)]
[anthropometry (body weight OR upper-arm OR mid-arm muscle area OR MAMA OR mid-arm muscle circumference OR MAC OR bioimpedance OR BIA OR fat-free mass OR FFM OR handgrip strength OR HGS)]
[nutrition risk (nutritional risk screening OR NRS-2002)]
[nutritional status (nutritional status OR nutritional status assessment OR patient-generated subjective global assessment OR PG-SGA)]
cachexia
[survival (overall survival OR disease-free survival OR disease-specific survival)]
Appendix 2. Anthropometric percentiles and handgrip strength reference values for females and males

Table 1. The 5th and the 10th percentile of triceps skinfold (TSF) in millimeters (mm) by age for women and men aged 18 to 90 years.

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<thead>
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Table 2. The 5th and 10th percentile of mid-arm circumference (MAC) in centimeters (cm) by age for women and men aged 18 to 90 years.

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Table 3. The 5th and 10th percentile of mid-arm muscle area (MAMA) in square centimeters (cm²) by age for women and men aged 18 to 90 years.

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Table 4. The 5th and 10th percentile bone free mid-upper arm muscle area (bfAMA) in square centimeters (cm²) by age for women and men aged 18 to 74 years.

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Table 5. The reference values of handgrip strength (HGS) in kilograms (kg) by age for women and men aged 20 to 80 years (269).

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Appendix 3: Baseline characteristics between the nutrition intervention study participants and non-participants

Table 1. Baseline characteristics of the nutrition intervention study participants and non–participants.

<table>
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<td>58</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age y, median (IQ range)</td>
<td>60 (55-61)</td>
<td>60 (50-69)</td>
<td>0.550</td>
</tr>
<tr>
<td>≥65 y, n (%)</td>
<td>13 (22)</td>
<td>9 (39)</td>
<td>0.03</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>46 (79)</td>
<td>18 (78)</td>
<td>0.348</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>6 (10)</td>
<td>10 (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>24 (41)</td>
<td>6 (26)</td>
<td>0.821</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9 (16)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>12 (21)</td>
<td>5 (22)</td>
<td>0.275</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>6 (10)</td>
<td>1 (4)</td>
<td>0.568</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0.048</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6 (10)</td>
<td>4 (17)</td>
<td>0.087</td>
</tr>
<tr>
<td>III</td>
<td>12 (21)</td>
<td>1 (4)</td>
<td>0.952</td>
</tr>
<tr>
<td>IV</td>
<td>37 (64)</td>
<td>17 (75)</td>
<td>0.087</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0.048</td>
</tr>
<tr>
<td>Stage III-IV, n (%)</td>
<td>49 (84)</td>
<td>18 (78)</td>
<td>0.549</td>
</tr>
<tr>
<td>T Class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>11 (19)</td>
<td>4 (17)</td>
<td>0.358</td>
</tr>
<tr>
<td>T2</td>
<td>15 (26)</td>
<td>7 (30)</td>
<td>0.196</td>
</tr>
<tr>
<td>T3</td>
<td>14 (24)</td>
<td>1 (4)</td>
<td>0.982</td>
</tr>
<tr>
<td>T4</td>
<td>17 (29)</td>
<td>10 (44)</td>
<td>0.054</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0.048</td>
</tr>
<tr>
<td>N Class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>20 (34)</td>
<td>8 (35)</td>
<td>0.326</td>
</tr>
<tr>
<td>N1</td>
<td>6 (10)</td>
<td>3 (13)</td>
<td>0.170</td>
</tr>
<tr>
<td>N2</td>
<td>31 (53)</td>
<td>11 (48)</td>
<td>0.520</td>
</tr>
<tr>
<td>N3</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0.048</td>
</tr>
<tr>
<td>PEG, n (%)</td>
<td>51 (88)</td>
<td>17 (74)</td>
<td>0.814</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + CRT</td>
<td>11 (19)</td>
<td>9 (39)</td>
<td>0.014</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>2 (3)</td>
<td>11 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRT</td>
<td>41 (71)</td>
<td>3 (13)</td>
<td>1.000</td>
</tr>
<tr>
<td>RT</td>
<td>4 (7)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

IQ Interquartile, T tumor, N node, PEG percutaneous gastrostomy, CRT chemoradiotherapy, RT radiotherapy. Data expressed as median (IQ range) or number (%).

a. Did not participate in the study (7 refused, 2 participated in another clinical trial, and 14 for logistic reasons).
b. The Mann-Whitney’s U-test was used for comparison of medians between weight-losing and weight-stable patients at the end of treatment.
Appendix 4. The Finnish version of PG-SGA

Ravitsemustilan omakohtainen määrittäminen, PG-SGA

Potilas vastaa kysymyksiin 1-4 ja hoitohenkilökunta kysymyksiin 5-7

3. Oireet: Viimeisen kahden viikon aikana seuraavat seikat ovat estäneet minua syömästä tai annostelemasta

- ei syömisongelmia (0)
- ei ole ruokahalua, ei vain tee mieli syödä (3)
- pahoinvointi (1)
- oksentaminen (3)
- ummetus (1)
- ripuli (3)
- haavat suussa (2)
- kuiva suu (1)
- ruoka maistuu oudolta tai siinä ei ole makua (1)
- hajut häiritsevät minua (hajuherkkyys) (1)
- nieleminen on vaikeaa (2)
- vatsa täyttyy nopeasti (1)
- kivut, missä __________________________________ (3)
- muu: ________________________________________ (1)

Kohdan 3 pisteet

Kohdat 1-4 pisteet yhteensä

5. Sairaus ja sen vaikutus ravinnontarpeeseen (kts Työohje II)

Asiakkuut laaditsi diagnoosin (tarkenna):

- Ensisijainen levineisysylookusitus (ympyröi mikäli tiedossasi tai on tarkoituksenmukainen): I II III IV Muu, mikä

6. Metabolinen vaikutus (kts. Työohje III)

7. Kehonkoostumus (Kts. Työohje IV)

PG-SGA

- SGA-A Hyvää ravitsemustilaa, anabolinen tila
- SGA-B Keskivaikea tai epätäydellisiä vajaaravitsemustilaa
- SGA-C Vaikeaa vajaaravitsemusta

PG-SGA pisteet

Yhteensä A + B + C + D =

Suositus potilaaiden ravitsemushoidon kiireellisuokasta: Yhteenlaskettu pisteemäärä kuvaa ravitsemushoitoa, johon kuuluvat potilaan ja perheen ohjaus, oireiden hoito ja tarkoituksenmukainen ravitsemushoito (ruoka, täydennysravintovalmisteet, enteraalinen tai parenteraalinen ravitsemus). Ensimmäisen linjan ravitsemushoitoon kuuluu myös optimaalinen oireiden hoito.

0-1 Tällä hetkellä ei edellytä toimenpiteitä. Tilanno arvioidaan uudelleen rutinnominaisesti ja säännöllisesti hoidon aikana.

2-3 Potilaan ja perheen ohjaus, oireiden lääkkeiden hoito ja oireiden selvittelyn mukaisesti (Kohda 3) ja tarkoituksenmukaiset laboratoriotutkimukset. Enteralinen tai parenteraalinen ravitsemus. Ensimmäisen linjan ravitsemushoitoon kuuluu myös optimaalinen oireiden hoito.

4-8 Suosittelemme kiireellistä oireiden hoitoa ja / tai vaihtoehtoista ravitsemushoitotapaa (Kohda 3).

9 Suosittelemme kiireellistä oireiden hoitoa ja / tai vaihtoehtoista ravitsemushoitotapaa.
PG-SGA luokitteen ohjeet

I Työohje - Painonlaskun pisteytys

Käytä 1 kk painotetta, jos mahdollista. Käytä 6 kk tietoa vain, jos kuukauden painotetta ei ole käytettävissä. Käytä alla olevia arvio painonmuutoksen pisteyttäen ja lisää ylimääräinen piste, jos potilas on laittanut edeltävän kahden viikon aikana. Siirrä kokonaispistemäärä PG-SGA:n kohtaan 1:1

<table>
<thead>
<tr>
<th>Painonlasku</th>
<th>1 kk aikana</th>
<th>Pisteet</th>
<th>6 kk aikana</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 %</td>
<td>4</td>
<td>≥ 25 %</td>
<td></td>
</tr>
<tr>
<td>5 - 9,9 %</td>
<td>3</td>
<td>15 - 19,9</td>
<td></td>
</tr>
<tr>
<td>3 - 4,9 %</td>
<td>2</td>
<td>6 - 9,9</td>
<td></td>
</tr>
<tr>
<td>2 - 2,9 %</td>
<td>1</td>
<td>2 - 5,9</td>
<td></td>
</tr>
<tr>
<td>0 - 1,9 %</td>
<td>0</td>
<td>0 - 1,9</td>
<td></td>
</tr>
</tbody>
</table>

Työohjeen I pisteet, siirrä kohtaan 1.

II Työohje - Sairauksen pisteytys

Kokonaispistemäärä saadaan laskemalla yhteen pisteet jotkaisesta potilaalla olevasta tilasta.

Tila:
- Syöpä                                 1
- AIDS                                 1
- Keuhkojen tai sydämen kakeksia       1
- Painehaava, avoahaava tai fisteli     1
- Trauma                               1
- Yli 65-vuotias                        1

Työohjeen II pisteet, siirrä kohtaan B

III Työohje - Metabolista aiheutuvan stressin pisteytys

Metabolistista aiheutuvat pisteet määritellään näiden muuttujien summana, joiden tiedetään lisäävän proteiinin ja energiaa tarvittaessa. Esimerkiksi potilas, jolla on kuorma >38,9 astetta (3 pistettä) ja Prednison 10 mg/dk jatkuvana lääkityksensä (2 pistettä), saa yhteensä 5 pistettä.

<table>
<thead>
<tr>
<th>Aineenvaihdunta</th>
<th>0</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuume</td>
<td>ei kuormaa</td>
<td>&lt;72 tuntia (&lt;3 yrk)</td>
<td>72 tuntia (3 yrk)</td>
<td>&gt;72 tuntia (&gt;3yrk)</td>
</tr>
<tr>
<td>Steroidiohdo:</td>
<td>ei steroideja</td>
<td>pieni annos:</td>
<td>keskisuurin annos:</td>
<td>iso annos:</td>
</tr>
<tr>
<td>Prednison</td>
<td>&lt;10 mg/dk</td>
<td>&gt;10 ja &lt;30 mg</td>
<td>&gt;30 mg</td>
<td>&gt;30 mg</td>
</tr>
<tr>
<td>Hydrokortison</td>
<td>&gt;2,5 ja &lt;7,5 mg</td>
<td>&gt;7,5 mg</td>
<td>&gt;7,5 mg</td>
<td>&gt;7,5 mg</td>
</tr>
<tr>
<td>Dietsamedesin</td>
<td>&gt;70 mg/dk</td>
<td>&gt;70 ja &lt;210 mg</td>
<td>&gt;210 mg</td>
<td>&gt;210 mg</td>
</tr>
</tbody>
</table>

Työohjeen III pisteet, siirrä kohtaan C

IV Työohje - Kehonkoostuminen

Kliiniseen tutkimukseen sisältyy kehonkoostumukset arviointi: rasva- ja lihasstatus sekä nestetasapaino. Koska tämä on omakohtainen (subjektiivinen) arvio, jokainen kohta on arvioinudennolla omakohtaisella (subjektiivisella) luokituksella.

Kehonkoostumus
- Ei rajoitteita tai
- Toimintakyky lasken huomattavasti
- Toimintakyky lasken suorittimata
- Toimintakyky lasken kohtalaisesti

Vaikeusasteet
- Ei menetyksiä
- Vähäinen
- Vaikein
- Epäillny

Rasvavarastot
- Nestetasapaino:
- Nestetasapainon kokonaisluokitus

Työohjeen IV pisteet, siirrä kohtaan D

5. Työohje – PG-SGA kokonaisarvioinnin luokat

<table>
<thead>
<tr>
<th>Luokka</th>
<th>Hyvä ravitsemusluista</th>
<th>Stage B - Keskivaitea tai epäilly vajaaravitsemusluista</th>
<th>Stage C - Vaikea vajaaravitsemusluista</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paino</td>
<td>Paino ei ole laskenut TAI paino on erittäin riittävän ravitsemusluista</td>
<td>Paino ei ole laskenut TAI paino on riittävän ravitsemusluista</td>
<td>Paino on laskenut TAI paino on epäilla vajaaravitsemusluista</td>
</tr>
<tr>
<td>Ravinnonsaanti</td>
<td>Ei vajeta tai</td>
<td>Vahentynyt</td>
<td>Vahentynyt huomattavasti</td>
</tr>
<tr>
<td>Ravitsemukseen vaikuttavat oireet</td>
<td>Ei lainakaan TAI</td>
<td>Vahentynyt</td>
<td>Vahentynyt huomattavasti</td>
</tr>
<tr>
<td>Toimintakyky</td>
<td>Ei menetyksiä TAI</td>
<td>Toimintaan riittävän ravitsemusluista</td>
<td>Toimintaan riittävän ravitsemusluista</td>
</tr>
<tr>
<td>Fysiinen tutkimus</td>
<td>Ei menetyksiä TAI</td>
<td>Vahentynyt</td>
<td>Vahentynyt huomattavasti</td>
</tr>
</tbody>
</table>

Kokonais PG-SGA:n luokitus (A, B tai C)
Malnutrition has detrimental effect on patient's quality of life and survival. In patients with head and neck cancer (HNC) the tumor itself, its location, surgical procedures, and oncological therapies cause significant symptoms and side effects, which interfere with eating and expose to malnutrition. This thesis focuses on different nutritional status assessment methods and nutrition intervention strategies, which may be applied in the development of novel nutrition support strategies among HNC patients.