

Nutritional Aspects and Challenges of Head and Neck Cancer

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Cover illustration: *Elin Wallmander*

The illustration is meant to capture some of the different aspects of this thesis: head and neck cancer, treatment, nutrition, muscle mass and quality of life, in a symbolic way.

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“Which is more important, the journey or the destination?”

“The company”

- James Norbury

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ABSTRACT

The aim of this thesis was to study the effects of disease and treatment on nutritional status, malnutrition, and health-related quality of life (HRQoL), as well as to evaluate the effects of an exercise program on muscle mass and fatigue in patients with head and neck cancer (HNC). Papers I and II included patients with advanced HNC, mainly oropharyngeal cancer, who received combination treatment. Paper III included patients with oral cancer who mainly received treatment with surgery with or without radiotherapy (RT), and in paper IV, survivors of HNC more than 5 years after diagnosis were studied. The Global Leadership Initiative on Malnutrition (GLIM) criteria was used to assess malnutrition, and HRQoL was measured with questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC). Body composition was measured with dual-energy X-ray absorptiometry (DXA) in papers I and II, and with bioelectrical impedance analysis (BIA) in papers III and IV.

Paper I was based on a randomized controlled trial (RCT) comparing the effects of treatment with cetuximab or cisplatin, in addition to RT. Patients treated with cisplatin needed tube feeding to a greater extent and lost more weight initially, but at the remaining follow-ups after 6 weeks no differences in weight loss were observed. No significant differences were observed between the treatment groups regarding the prevalence of malnutrition. **Paper II** included the same study cohort as in paper I, without the randomization allocation. Malnutrition was common, especially during treatment. The largest loss of muscle mass was observed at the end of treatment, thereafter the decline ceased, and a recovery was observed. Patients diagnosed with malnutrition reported poorer HRQoL at all follow-ups, except at the end of treatment, where all patients were negatively affected. **Paper III** was based on an RCT in which patients were randomized to a home-based exercise intervention or a control group. An increase in physical activity and a tendency towards reduced fatigue and better global QoL were observed among the patients in the exercise group. However, no effects on muscle mass were observed. In **paper IV**, many chronic nutrition impact symptoms were observed, and the majority of long-term survivors used dietary adjustments to facilitate food intake. Participants had worse HRQoL than age- and sex-

matched reference values from a Swedish normal population, and survivors with the most difficulties swallowing solid food had poorer HRQoL compared to the rest of the study group.

In conclusion, patients with HNC experienced many nutritional problems in both the short and long term. Treatment affected energy intake, body composition and HRQoL negatively, and malnutrition was common. Nutritional rehabilitation is important and might be needed for a long time after treatment. Early nutritional treatment together with muscle mass evaluation could help improve the nutritional status and recovery of patients with HNC.

Keywords: Head and Neck Cancer, Treatment, Nutrition impact symptoms, Malnutrition, Body composition, Health-related Quality of Life, Physical Activity, Long-term survivors

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SAMMANFATTNING PÅ SVENSKA

Vid huvud-halscancer (HH-cancer) är det vanligt att förmågan att äta och dricka påverkas negativt, vilket främst beror på tumörens lokalisering och biverkningar av behandling. Problem med smärta, muntorrhet, svälj-, tugg- och gapförmåga är vanliga biverkningar som ofta leder till ett för lågt energiintag, viktförlust och risk att utveckla undernäring. Sjukdom och behandling kan även leda till extrem trötthet (fatigue) och försämrad livskvalitet. I studierna som ligger till grund för denna avhandling bedömdes undernäring med de senaste kriterierna från *the Global Leadership Initiative on Malnutrition* (GLIM), kroppssammansättning mättes med dual-energy X-ray absorptiometry (DXA) eller med bioelektrisk impedansanalys (BIA). Hälsorelaterad livskvalitet utvärderades med väletablerade frågeformulär från *the European Organisation for Research and Treatment of Cancer* (EORTC). Syftet med denna avhandling var att studera hur sjukdom och behandling påverkar nutritionsstatus, undernäring, och livskvalitet på kort och lång sikt, samt att utvärdera effekten av ett träningsprogram på muskelmassa och fatigue.

Delarbete I baserades på en randomiserad kontrollerad behandlingsstudie där effekten av cetuximab eller cisplatin i tillägg till strålbehandling undersöktes hos patienter med avancerad HH-cancer. Patienter som behandlades med cisplatin hade en högre viktförlust initialt, men vid övriga uppföljningar, vid 3, 6 och 12 månader, observerades inga skillnader. Inga signifikanta skillnader sågs mellan behandlingsgrupperna gällande undernäring, men patienter behandlade med cisplatin behövde sondnutrition i större utsträckning. I **delarbete II** studerades samma studiekohort som i delarbete I, men utan randomiseringsgrupper. Flest patienter bedömdes med undernäring i slutet av behandlingen, då sågs också störst förlust av muskelmassa. Därefter började patienterna successivt återhämta muskelmassa trots fortsatt förlust av kroppsvikt och fettmassa. Vid jämförelse av livskvaliteten mellan patienter med och utan undernäring sågs ingen skillnad i slutet av behandlingen då livskvaliteten var kraftigt försämrad för samtliga patienter oberoende av nutritionsstatus. Vid övriga mättillfällen rapporterade patienter med undernäring signifikant sämre livskvalitet. I **delarbete III** randomiserades patienter med cancer i munhålan till en träningsintervention eller till en kontrollgrupp. Patienterna behandlades huvudsakligen med kirurgi med eller utan tillägg av postoperativ strålbehandling. De patienter som fick ett träningsprogram ökade sin fysiska aktivitet och hade även en tendens till minskad fatigue. Dock sågs ingen effekt på muskelmassan. **Delarbete IV**

baserades på en tvärsnittsstudie av HH-canceröverlevare diagnostiserade för mer än fem år sedan. Flera symtom som kan påverka nutritionen observerades, och majoriteten behövde anpassa maten för att underlätta ätandet. Långtidsöverlevarna hade sämre livskvalitet i jämförelse med referensvärden från en svensk normalpopulation. De överlevare som rapporterade mest problem med att svälja fast mat hade en sämre livskvalitet jämfört med övriga deltagare.

Sammanfattningsvis så besvärades patienter med HH-cancer av många nutritionsproblem, både på kort och lång sikt. Behandlingen påverkade energiintag, kroppssammansättning och livskvalitet negativt och undernäring var vanligt. Utvärdering av muskelmassa kan bidra till en förbättrad nutritionsbehandling och bedömning av undernäring. Tidig initiering av nutritionsbehandling, som fortsätter under och efter behandlingen, är betydelsefull, och rehabiliteringen kan behöva fortgå under lång tid.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their roman numerals.

- I. Berg, M*. Hansson, C*. Silander, E. Bove, M. Johansson, L. Haugen Cange, H. Bosaeus, I. Nyman, J. Hammerlid, E. *A randomized study comparing the nutritional effects of radiotherapy with cetuximab versus cisplatin in patients with advanced head and neck cancer.* *Head & Neck* 2024; 46:760–771. *Shared first authorship.
- II. Wallmander, C. Bosaeus, I. Silander, E. Berg, M. Haugen Cange, H. Nyman J, Hammerlid, E. *Malnutrition in patients with advanced head and neck cancer: Exploring the Global Leadership Initiative on Malnutrition (GLIM) criteria, energy balance and health-related quality of life.* *Clinical Nutrition ESPEN* 66 (2025) 332–342.
- III. Wallmander, C. Bosaeus, I. Silander, E. Haugen Cange, H. Nyman, J. Fagevik Olsén, M. Blomsterwall, E. Berg, M. Hammerlid, E. *Effect of a home-based exercise program on muscle mass, fatigue, and health-related quality of life among patients with oral cancer: A randomized trial.* *Head & Neck*, 2026; 48:680–695.
- IV. Wallmander, C. Haugen Cange, H. Silander, E. Larsson, H. Börjesson, M. Johansson, L. Bosaeus, I. Hammerlid, E. *Long-term follow-up study on nutritional problems and health-related quality of life among head and neck cancer survivors more than five years after diagnosis.* Manuscript submitted.

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ABBREVIATIONS

| | |
|-------|--|
| ALST | Appendicular Lean Soft Tissue |
| ALSTI | Appendicular Lean Soft Tissue Index |
| BIA | Bioelectrical Impedance Analysis |
| BMI | Body Mass Index |
| CRT | Chemoradiotherapy |
| DXA | Dual-energy X-ray Absorptiometry |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FFM | Fat-Free Mass |
| FFMI | Fat-Free Mass Index |
| FM | Fat Mass |
| FMI | Fat Mass Index |
| GLIM | Global Leadership Initiative on Malnutrition |
| Gy | Gray |
| HNC | Head and Neck Cancer |
| HPV | Human Papilloma Virus |
| HRQoL | Health-Related Quality of Life |
| IMRT | Intensity Modulated Radiotherapy |
| MDADI | M.D. Anderson Dysphagia Inventory |
| NIS | Nutrition Impact Symptom |

| | |
|-----------|---|
| PA | Physical Activity |
| PEG | Percutaneous Endoscopic Gastrostomy |
| PROM | Patient-Reported Outcome Measure |
| QLQ-C30 | Quality of Life Questionnaire, Core |
| QLQ- FA12 | Quality of Life Questionnaire, Fatigue |
| QLQ-H&N35 | Quality of Life Questionnaire, Head and Neck Module |
| QoL | Quality of Life |
| RCT | Randomized Controlled Trial |
| RT | Radiotherapy |
| WHO | World Health Organization |

1 INTRODUCTION

Eating and drinking are part of everyday life and take place in many different contexts. We need to eat and drink to live, but eating is much more than just getting the necessary nutrients. We eat when we are hungry, sad or happy. We eat and drink alone or together, we eat in a hurry or enjoy a meal for a long time. We eat when we celebrate or when we mourn. Most of the time we do not reflect on the fact that we have the ability to eat and drink, that we can open the mouth, chew, use the tongue to transport food and swallow.

Most of us take the ability to eat and drink for granted.

For those affected by head and neck cancer, eating difficulties are often experienced. Everything to do with eating and drinking suddenly becomes noticeable, and it is often difficult to understand how much eating problems will affect different aspects of one's life. Through my work as a clinical and research dietitian, I have had the opportunity to meet and learn from these patients, and I am grateful for all the insights it has given me. This thesis describes the nutritional challenges of head and neck cancer and the relation to physical, psychological and social aspects. With this thesis I wish to add new insights to the existing research in the field and hopefully these insights can be used to improve the care, especially the nutritional treatment, for patients with head and neck cancer.

1.1 HEAD AND NECK CANCER

Head and neck cancer (HNC) is a collective term and includes tumors of the lips, oral cavity, salivary glands, oropharynx, hypopharynx, larynx, nasopharynx, and nasal sinuses, as well as lymph node metastasis in the neck with an unknown primary tumor (Figure 1). Oral and oropharyngeal cancer are the two most common types of HNC, accounting for more than half of all HNC cases in Sweden.¹

Worldwide, HNC is the 6-7th most common cancer diagnosis, with a 5-year survival rate of approximately 50–60%, which varies greatly depending on the tumor site, and presents discrepancies across countries.^{2,3} In Sweden, HNC is a relatively rare diagnosis, with 1700 cases reported in 2024 and a relative

5-year survival rate of 68% for all patients during the period 2008-2024.⁴ For oral and oropharyngeal cancer, the 5-year survival rate is 62% and 72% respectively, while hypopharynx cancer has the lowest survival rate of 27%.¹

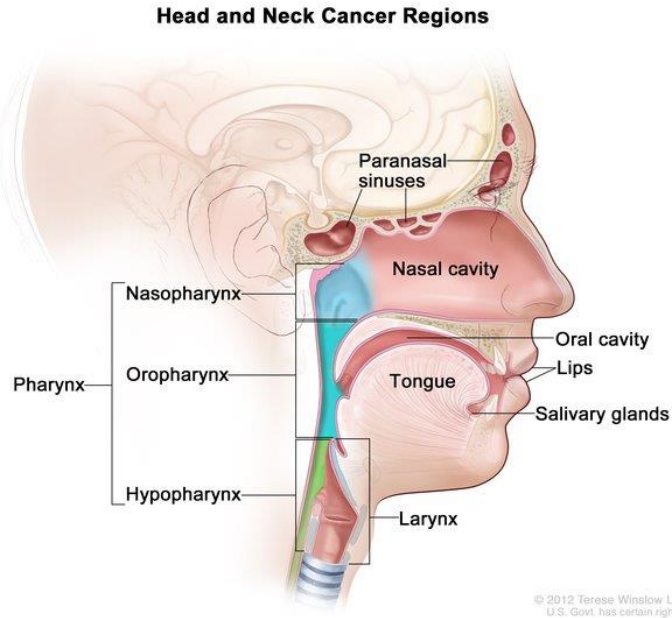


Figure 1. Regions affected by head and neck cancer. © (copyright 2012) Terese Winslow LLC, U.S. Govt. has certain rights.

Both globally and in Sweden, the incidence of HNC have increased, mainly due to human papilloma virus (HPV)-related carcinoma of the tonsils and base of the tongue. Other major risk factors are alcohol and tobacco use. Approximately 60% of patients with HNC are diagnosed at an advanced stage, more men than women are affected, and it is most common for people who develop HNC to be middle-aged or older.¹

In Sweden, patients with HNC are treated according to national guidelines.¹ The treatment recommendation is made by a multidisciplinary team and depends on the tumor location and the patient's performance status and medical conditions. For early-stage HNC, curative treatment often includes surgery or radiation as monotherapy, whereas patients with locally or locoregional advanced HNC receive combination treatment that includes concurrent chemoradiotherapy (CRT) or surgery with postoperative

radiotherapy (RT), where chemotherapy can also be added. After completion of treatment, patients are recommended clinical follow-ups for five years at the specialist clinic (e.g., at the Department of Otorhinolaryngology or Oncology).^{1,5}

Surgery for HNC includes resection of the primary tumor, often combined with selective or modified radical neck dissection, or sentinel node biopsy. For larger resectable tumors, microvascular reconstruction can be necessary. External RT is the first option for curative oncologic treatment and is administered for five days a week to a full dose of 68-70 Gray (Gy). Systemic therapy can be added to RT for advanced tumor stages if assessed as suitable for the patient.^{1,5} First line treatment with platinum-based cisplatin has been proven to increase survival rates when administered concomitantly with RT.⁶ When the first study in this thesis was conducted, the epidermal growth factor receptor (EGFR) antibody cetuximab had shown equal survival rates and was considered to induce less toxicity than concomitant cisplatin, which is why it was suggested as a potential alternative.^{7,8} Additionally, when the study was initiated, there was also no previous randomized controlled trial (RCT) that had directly compared cetuximab to cisplatin (combined with RT). Since then, studies have reported that cetuximab is inferior to cisplatin with worse survival and locoregional control.⁹⁻¹² Thus, cetuximab is still an option when there are contraindications for cisplatin.⁵ Treatment for HNC often affects many important functions, such as breathing and the ability to speak and eat.

1.2 NUTRITIONAL PROBLEMS

There are several factors that affect the ability to eat and drink for patients with HNC: the location of the tumor, often in the pharynx and oral cavity, which can lead to obstruction and pain; the cancer itself, which can cause inflammation that affects appetite; and side effects from treatment that often lead to the development of nutrition impact symptoms (NISs). Common NISs are pain, mucositis, dysphagia, taste alterations, dry mouth, sticky saliva, problems with chewing and trismus.^{13,14} Eating difficulties can occur before treatment and often intensify during and shortly after treatment, when the most deterioration has been observed.^{14,15} After treatment, nutritional problems gradually improve, but recovery often takes long time, and some problems may persist long after treatment ends, potentially becoming chronic.^{13,16,17}

Nutritional problems can lead to increased time to consume meals, food sticking, food and drink leakage, coughing and aspiration. Patients often need to adjust their food intake, for example by excluding certain types of food, adjusting the texture of the food, and eating smaller portions and/or fewer meals per day. These problems may contribute to an insufficient intake of energy and nutrients, leading patients to lose body weight and muscle mass and being at risk of developing malnutrition.¹⁸ The ability to eat in a social context can also be inhibited by nutritional problems, and health-related quality of life (HRQoL) can be negatively affected.¹⁹⁻²¹

1.3 MALNUTRITION

Malnutrition is defined by an imbalance in energy and nutrient intake, either as a deficiency or excess. For patients with HNC, undernutrition is the main problem, and in this thesis the term malnutrition is used to describe undernutrition. Disease-related malnutrition is a complex and multifactorial condition that occur through two major pathways: inadequate energy and nutrient intake with or without the presence of inflammation (Figure 2).²²

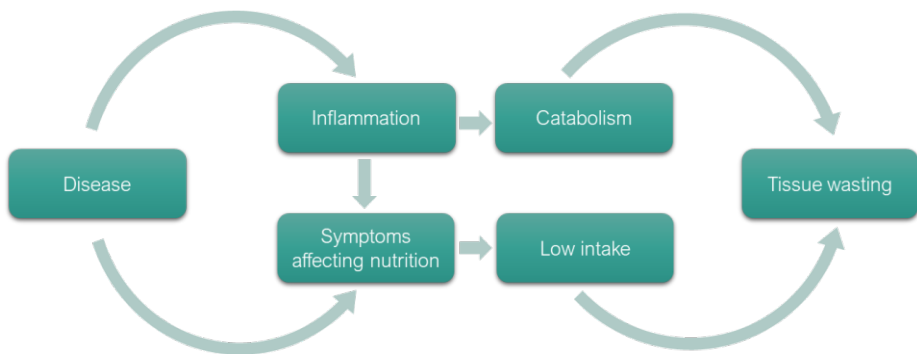


Figure 2. The two pathways of development of disease-related malnutrition. Head and neck cancer and its treatment result in symptoms, such as dysphagia, chewing problems, pain, appetite loss and fatigue, which negatively affect food intake and result in weight and muscle mass loss. The disease and treatment can also cause inflammation that drives catabolism and increases tissue breakdown. Inflammation can also cause symptoms such as appetite loss and fatigue. The figure is illustrated by the author.

HNC and its treatment often causes side effects that result in a low energy intake. When energy intake is compromised without additional inflammation the metabolism adapts, for example by decreasing resting energy expenditure and physical activity. Glucose and body fat will be used as the main energy source; therefore, muscle mass is partially preserved. However, some muscle breakdown will still occur for protein synthesis along with oxidation for energy. HNC and its treatment can also cause inflammation, and when inflammation is present, the metabolism no longer adapts to the insufficient energy intake. The inflammation drives the catabolic state with an increased resting energy expenditure and greater loss of skeletal muscle mass. Symptoms such as appetite loss and fatigue can also be induced by inflammation, which can reduce energy intake. Inflammation reduces the effects of nutritional treatment, meaning that muscle wasting can still occur despite an adequate intake of energy and nutrients.

There are many established assessment tools that have been developed to identify malnutrition, for example, the Subjective Global Assessment (SGA),^{23,24} the Patient-Generated SGA (PG-SGA)^{25,26} that were recently translated and validated into a new Swedish version,²⁷ the Academy of Nutrition and Dietetics (Academy)-American Society for Parenteral and Enteral Nutrition (ASPEN) recommended characteristics for the identification of malnutrition²⁸ and the European Society of Clinical Nutrition and Metabolism (ESPEN) diagnostic criteria.²⁹ Common to all methods is the use of similar phenotypic and etiologic criteria, but different criterion combinations and cutoffs are applied, which generates differences in prevalence.

In 2019, the most recent criteria for assessing malnutrition were published by the Global Leadership Initiative on Malnutrition (GLIM) working group.³⁰ The working group includes professionals from major global nutrition societies, and the aim was to establish a global consensus on malnutrition and how malnutrition is assessed worldwide. Since its introduction, the GLIM criteria have been validated, with good results for the criteria included as well as for predicting outcome, with overall survival as the main outcome measure.³¹ Assessment with the GLIM criteria is a two-step process (Figure 3). In step one, the risk of malnutrition is evaluated, and if the assessment shows risk, step two, where malnutrition is evaluated, is initiated. The assessment of malnutrition includes three phenotypic criteria, i.e., weight loss, low body mass index (BMI) and reduced muscle mass, and two etiological criteria, i.e., reduced food intake or food assimilation and inflammation, acute or chronic

disease related. At least one phenotypic and one etiologic criterion are required for diagnosis, and the severity grading is determined by the phenotypic criteria.³⁰ To date, cutoffs for identifying moderate and severe reductions of muscle mass are lacking; therefore, this phenotypic criterion was not used for severity grading in this thesis.^{31,32}

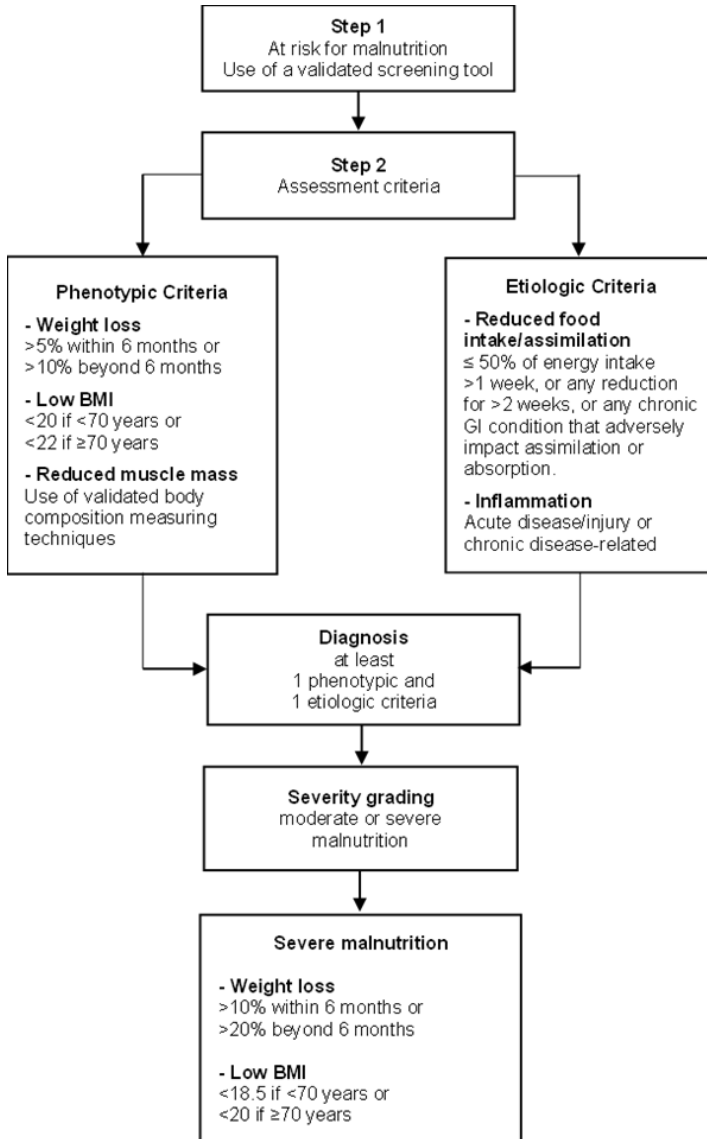


Figure 3. The GLIM criteria for assessment of malnutrition in adults (Wallmänder, *Clinical Nutrition ESPEN*, 2025).

Assessment of weight loss is probably the most commonly used criteria to assess malnutrition, both in research and in clinical practice. Assessing weight loss is simple and does not require specific knowledge and is therefore easy for different health care professionals to perform. Weight loss of more than 5-10% during the recent 1-6 months have been used extensively as cutoffs.³⁰ The use of BMI to identify malnutrition is also common worldwide. However, in the western world, underweight is generally not a problem, and BMI in the Swedish HNC population often reflects the BMI of the normal population, with approximately 50% being overweight or obese. In contrast, measurement of muscle mass is probably the least implemented criterion in clinical practice, and the assessment methods require special knowledge for practice and evaluation. Studies on patients with HNC have reported that muscle mass accounts for approximately 60-70% of weight loss during treatment and that overweight and obesity is a risk factor for increased weight loss.³³⁻³⁵ Therefore, weight loss regardless of BMI needs to be taken seriously.

Muscle strength is not included in the diagnostic criteria for malnutrition but can be used as a supportive measure and is required in the assessment of sarcopenia and frailty, conditions associated with malnutrition.³⁰ Sarcopenia is a disease characterized by loss of muscle mass and muscle strength that is associated with falls, fractures, physical disability, poor HRQoL and mortality. Sarcopenia can be age-related (primary) or disease-related (secondary) but can also develop due to physical inactivity or inadequate energy and protein intake.^{36,37} The European Working Group on Sarcopenia in Older People (EWGSOP) has published criteria for assessing sarcopenia, where low muscle strength and reduced muscle mass are required for diagnosis, and severity is determined based on physical performance.³⁷

The prevalence of malnutrition varies in older adults, and in the community-dwelling setting, approximately 5-10% of older adults are considered malnourished, in contrast this number is approximately 20-30% for persons in hospitals and nursing homes.³⁸ A slightly higher prevalence has been seen when the GLIM criteria have been used, with a prevalence rate of 7-13% for independent individuals in the community and approximately 50% for individuals in hospitals and nursing homes.³⁹ Malnutrition is associated with an impaired immune system, decreased muscle strength, physical weakness, and an increased risk of fall, fractures, and the development of frailty and sarcopenia. Malnutrition also increases the risk of hospitalization with a longer length of stay and extra costs, prolonged rehabilitation, and reduced quality of life (QoL).^{22,40}

The prevalence of malnutrition in HNC varies in studies between 20% and 80%, and the large variation can be explained by the use of different diagnostic criteria and the heterogeneity of HNC as a disease, where advanced stage and combination treatment are associated with more nutritional problems and a higher prevalence of malnutrition.⁴¹⁻⁴⁴ Prevalence rates during treatment of 52% and 66% have been reported when weight loss >10% was used,^{33,43} a prevalence of 74% was reported using the PG-SGA,⁴¹ and lower frequencies of 14% and 26% have been reported when a low BMI was used.^{33,45} Few studies have used the GLIM criteria to diagnose malnutrition in patients with HNC,^{42,46-48} with reported prevalence rates of 22% and 32% during treatment.^{42,46} For patients with HNC, malnutrition has been associated with reduced muscle mass and function, poorer HRQoL, more treatment-related complications, discontinued treatment, worsened prognosis and poorer survival.^{41,47,49-52}

1.4 BODY COMPOSITION

Body composition can be assessed in a variety of ways, using simpler or more advanced methods. Technical methods for measurements of body composition include dual-energy X-ray absorptiometry (DXA), computerized tomography (CT) and bioelectrical impedance analysis (BIA). If technical methods are not available, anthropometric methods, such as calf circumference, mid-upper arm circumference, or physical examination can be used instead.^{30,32}

In addition to measuring bone density, DXA can provide information about body fat and lean soft tissue from whole-body scans using low radiation emission. X-rays are absorbed differently by various body components (fat, lean tissue and bone), and the attenuation of the X-rays can be measured. DXA can be used to measure lean soft tissue in the arms and legs, called appendicular lean soft tissue (ALST), which was used to estimate muscle mass in papers I and II. DXA scans generally provide more accurate and direct measurements, with fewer assumptions than for example BIA. Disadvantages of DXA include the limited availability in clinical practice, and the width and length limitations of the scanner that may compromise accuracy for adults with obesity.⁵³

In papers III and IV, body composition was measured via BIA, using a portable device, which was an advantage since measurement of body composition in paper IV was carried out in four different hospitals. When assessing body

composition with BIA, a low current passes through the body. Muscle mass will conduct electricity well (low impedance) due to high water content, while fat mass (FM) will act as a poor conductor. The fat-free mass (FFM) is calculated using equations based on total body water, which is estimated from the electrical properties (resistance and reactance) of the current.⁵⁴ BIA results are therefore influenced by hydration status, and overhydration and edema can result in overestimation of FFM while dehydration can result in underestimation of FFM. The equations used to estimate FM and FFM are device and population specific, and this needs to be considered when using this method and evaluating the results. BIA accuracy can also be reduced in adults with obesity due to excess adipose tissue that causes a disproportion between body mass and electrical conductivity.⁵⁵

Both DXA and BIA measurements can provide good results for estimating muscle mass and changes over time. These methods are also recommended for use in assessing malnutrition by the GLIM working group.³²

1.5 PHYSICAL ACTIVITY

Physical activity (PA) has been defined by the World Health Organization (WHO) as “*any bodily movement produced by skeletal muscles that requires energy expenditure*”.⁵⁶ PA can be performed at a variety of intensities and refers to all movement, including during leisure time, for transport, as part of work, domestic activities or when engaging in exercise or sport. Regular PA can contribute to several health benefits such as reducing symptoms of depression and anxiety, preventing and managing diseases such as cancer, diabetes, and cardiovascular diseases, as well as helping to maintain a healthy weight and improve overall QoL.⁵⁶

Adults are recommended to do at least 150-300 minutes of moderate-intensity or at least 75-150 minutes of vigorous-intensity aerobic PA (or a combination) per week. In addition, muscle strengthening activities that involve the major muscle groups on two or more days a week are recommended. For older adults (defined as >65 years by the WHO), PA that emphasizes functional balance and strength training are recommended on at least three or more days a week.^{56,57} These recommendations also apply to patients undergoing cancer treatment, based on the ability and status of the patient, as well as for cancer survivors.⁵⁸ PA can be assessed by self-reported methods such as

questionnaires, interviews or diaries, or with help of more objective methods, such as pedometers, accelerometers or heart rate monitors.⁵⁹

PA has been widely studied in patients with cancer, particularly among patients with breast, colon, and prostate cancer, where PA during and after cancer treatment has been reported to reduce fatigue and improve QoL, physical function, and survival.⁶⁰⁻⁶⁴ In patients with HNC, PA interventions have shown positive results, but evidence remains limited, and few studies have examined the effects on muscle mass.⁶⁵⁻⁶⁷ These studies have also reported limitations in the existing research, such as small sample sizes, risk of bias, and a variety of outcome measures.

1.6 NUTRITIONAL TREATMENT

Nutritional treatment is individualized based on the patient's nutritional status, condition and abilities. The dietitian is responsible for the nutritional treatment, which includes nutrition assessment, identification of nutrition problems, nutrition intervention, and follow-up and evaluation of the intervention.

For patients with HNC, the oral nutritional treatment is individually modified and often includes advice regarding texture-adapted food, food fortified using extra fat and protein, advice about meal order and oral nutritional supplements (ONSs), typically energy and protein-enriched nutritional drinks (Figure 4). Studies have reported that the use of ONSs are associated with an increased energy and protein intake, improved functional capacity, and reduced readmission and mortality rates.^{68,69} Positive effects on weight, energy and protein intake, treatment tolerance and QoL have also been reported in patients with HNC.⁷⁰ When it is not possible to meet energy and nutrient requirements orally, enteral or parenteral nutrition is initiated. Patients with HNC most often have a functioning gastrointestinal tract, which is why the first option is an enteral feeding tube. A nasal feeding tube is often used when eating difficulties are expected for a shorter amount of time, approximately 4-6 weeks; for longer periods, a gastric feeding tube, usually a percutaneous endoscopic gastrostomy (PEG), is indicated instead. Feeding tubes can be placed reactively or prophylactically. If enteral nutrition via a feeding tube is not possible or not sufficient, parenteral nutrition (PN) is initiated, as a complement or as total PN (Figure 4). Patients are often treated with a combination of these nutritional

interventions, for example, a limited oral intake, together with enteral and/or parenteral nutrition.

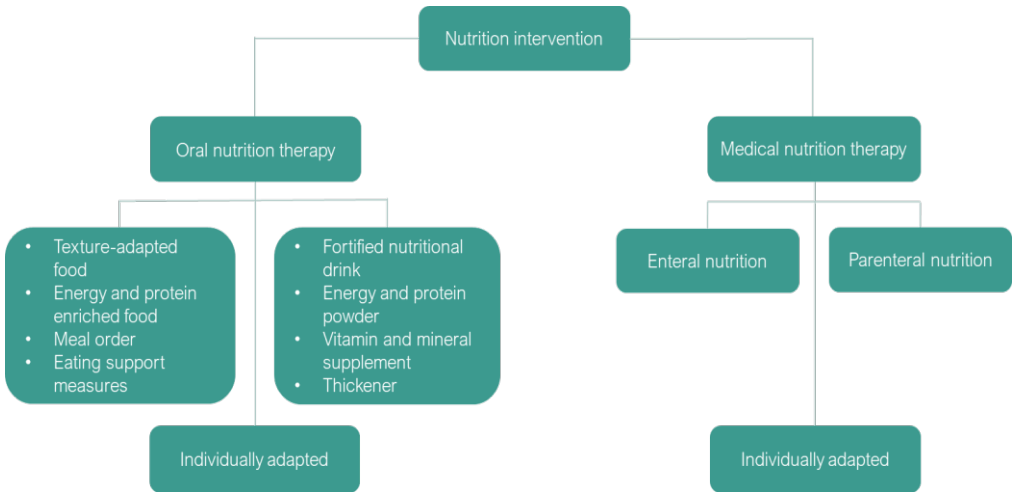


Figure 4. Nutrition interventions. Oral nutrition therapy often includes texture-adapted food, enriched food and fortified nutritional drinks. When it is not possible to meet energy and nutrient needs orally, enteral and/or parenteral nutrition is initiated. Nutritional treatment is always individualized, considering the patient's conditions and needs. The figure is illustrated by the author.

At the Department of Otorhinolaryngology, Sahlgrenska University Hospital, the dietitian conducts a nutrition assessment for all patients with oral cancer 1-2 weeks before surgery. The routine makes it possible to optimize the condition of patients for the upcoming surgery, and the intervention for patients with nutrition problems includes ONSs. For patients with no eating difficulties and no risk of malnutrition, the dietitian still provides information to the patient regarding postoperative nutritional treatment and the benefits of adequate energy and protein intake and stable body weight before treatment. These patients also receive ONSs for tasting and are encouraged to use them before the surgical treatment.

In the included papers of this thesis, patients underwent treatment with curative intent, where the goal of the nutritional treatment was to meet energy and nutrient requirements and prevent weight loss. Patients received nutritional treatment at the Department of Otorhinolaryngology and/or at the Department

of Oncology. In these departments, the dietitians work in the clinic via close teamwork with the other professionals around the patient. This enables early nutrition intervention and continuous follow-up based on the patient's needs, which are important since nutritional difficulties can deteriorate quickly.

1.7 HEALTH-RELATED QUALITY OF LIFE

HRQoL can be described as the patient's subjective perception of their well-being in relation to their health and includes aspects of physical, emotional and social functioning, disease symptoms and side effects of treatment. Measurement of HRQoL has become increasingly important, and patient-reported outcome measures (PROM) can complement objective outcomes when evaluating positive and negative effects of disease and treatment. These insights may be valuable in clinical decision making and help healthcare professionals to fully understand the impact of the condition on patients.

Questionnaires that measure HRQoL can be generic or specific. A generic questionnaire focuses on overall health and can be used in various diseases or in the general population. The 36-item short-form health survey is an example of a commonly used generic questionnaire.^{71,72} Specific questionnaires better address problems and symptoms related to, for example, cancer or a specific type of cancer diagnosis such as HNC. The European Organisation for Research and Treatment of Cancer (EORTC) has developed a cancer-specific questionnaire, the EORTC Core 30 (QLQ-C30) (Appendix 1),⁷³ and specific modules for different cancer diagnoses, one of which is the EORTC Head and Neck 35 (QLQ-H&N35) (Appendix 2).⁷⁴ Both questionnaires are validated and extensively used in research. Other examples of well-established disease- and diagnosis-specific questionnaires are the Functional Assessment of Cancer Therapy Scale (FACT-G), the HNC-specific FACT-H&N and the University of Washington Quality of life Questionnaire (UW-QoL).⁷⁵⁻⁷⁸ Additionally, there are also symptom-specific questionnaires, for example, the EORTC QLQ fatigue 12 (QLQ-FA12) (Appendix 3)^{79,80} that evaluates cancer-related fatigue and the M.D. Anderson Dysphagia Inventory (MDADI) (Appendix 4)^{81,82} that evaluates HRQoL in relation to swallowing ability in patients with HNC.

PROMs must be carefully designed and psychometrically evaluated to confirm *validity*, which indicates that the questionnaire measures the intended outcome, *reliability*, which states that the questionnaire can detect the same results on repeated measurements if conditions remain unchanged, *responsiveness*, which means that meaningful changes can be detected over time, and *sensitivity*, which indicates the possibility of distinguishing between groups.⁸³

The results from the HRQoL questionnaires need to be interpreted to evaluate absolute scores and clinically meaningful changes within groups or differences between groups. One way to interpret results is to compare the obtained scores with reference values from a normal population that is matched for age, sex and country. For the EORTC QLQ-C30 and QLQ-H&N35, there are Swedish population-based reference values established.⁸⁴⁻⁸⁶ Interpretation can also be done using the minimal clinically important difference (MCID), which is the smallest change for a scale that a patient identifies as important.⁸⁷ The MCID can help identify clinically meaningful differences beyond those identified by statistical analysis. For the EORTC questionnaire, a difference of 10 points is typically used and indicates a clinical impact on the patient.⁸⁷ However, different MCID scores could be applied to different scales, and can also vary depending on whether the change of a scale is an increase or a decrease.^{88,89}

For patients with HNC, most studies have evaluated HRQoL before and during treatment with follow-up periods of up to 1-2 years, and some of up to 5 years. Patients often experience a deterioration during treatment, with a gradual improvement during the first year.^{15,20,90,91} Specific problems common for HNC have been reported to persist at 12 months when compared with those at diagnosis.^{15,92-94} There are only a few studies that have evaluated HRQoL in HNC beyond five years, and some of the long-term studies report a wide variation in follow-up time within the same study.⁹⁵⁻⁹⁸ Currently, there is a knowledge gap about how the course of HRQoL, including symptoms that may affect nutrition, develops after five years.

1.7.1 CANCER-RELATED FATIGUE

Fatigue is one of the most frequently reported side-effects of cancer treatment and affects approximately 50% of cancer patients, with variations by tumor site, stage and treatment.⁹⁹ Cancer-related fatigue can be described as “*a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning*”.¹⁰⁰ The condition is more persistent and severe than normal tiredness and cannot be relieved by sleep or rest. Physical exercise has proven to be an effective treatment for cancer-related fatigue,^{101,102} and promising results have also been reported in patients with HNC, but more research is warranted.¹⁰³

Fatigue can be assessed through PROMs and can be incorporated as one scale in QoL questionnaires that measure multiple symptoms or through questionnaires focusing on fatigue. Most questionnaires measure general and physical fatigue, as is the case for the fatigue scale in the EORTC QLQ-C30, while cognitive and emotional fatigue are less frequently measured.¹⁰⁴ To enable measurement of more aspects of fatigue, the EORTC developed a symptom-specific questionnaire, EORTC QLQ-FA12, which is a multidimension instrument that assess physical, cognitive and emotional fatigue.^{79,80}

2 AIM

2.1 OVERALL AIM

Overall aim was to study the nutritional aspects and HRQoL of HNC, in terms of impact from disease and treatment in both the short and long term, to improve nutritional rehabilitation.

2.2 SPECIFIC AIMS

Paper I: To compare the effects of treatment with cetuximab or cisplatin, in combination with RT, on weight loss, prevalence of malnutrition, feeding tube dependence and HRQoL in patients with advanced HNC.

Paper II: To evaluate the prevalence of malnutrition according to the GLIM criteria, explore the combinations of the GLIM criteria, study changes in body composition and energy balance, and investigate the associations between malnutrition and HRQoL in patients with advanced HNC.

Paper III: To study the effects of a home-based exercise program, primary on muscle mass and fatigue and secondarily on self-reported physical activity level, body weight, prevalence of malnutrition and HRQoL in patients with oral cancer.

Paper IV: To evaluate the nutritional rehabilitation need for HNC survivors by assessing nutritional problems, dietary adjustments, muscle mass, muscle strength, sarcopenia and HRQoL. Furthermore, to describe a subgroup with the most difficulties swallowing solid food, and to compare HRQoL with reference values from a Swedish normal population.

3 PATIENTS AND METHODS

3.1 STUDY POPULATIONS

Papers I and II: Patients had newly diagnosed advanced HNC, were included in the randomized ARTSCAN III study⁹ from Sahlgrenska University Hospital and received curative treatment with RT and concomitant cisplatin or cetuximab.

Paper III: Patients with newly diagnosed carcinoma of the oral cavity who received curative-intent treatment were consecutively invited after the multidisciplinary tumor board meeting held weekly at Sahlgrenska University Hospital.

Paper IV: Long-term survivors of HNC more than five years after diagnosis were invited. The participants were identified via the register available from the multidisciplinary tumor board at Sahlgrenska University Hospital.

3.2 STUDY DESIGN

Paper I: Randomized controlled trial where the effect on nutritional status and HRQoL from two different treatment regimens — RT with concomitant cisplatin or cetuximab — were studied.

Paper II: Prospective longitudinal study with the same cohort as in paper I, but without the randomized allocation. In both papers I and II, patients were followed prospectively for one year after treatment had started.

Paper III: Randomized controlled trial where the effects from an individualized home-based exercise program on muscle mass, fatigue and HRQoL were studied. Patients were followed for one year after diagnosis.

Paper IV: Cross-sectional long-term follow-up study of HNC survivors more than five years after diagnosis, conducted in four hospitals in western Sweden. The study was part of the multinational study by the QoL Group and the HNC

Group of the EORTC,¹⁰⁵ which aimed to describe late toxicity and HRQoL in HNC survivors. Our study included an additional nutritional and body composition assessment as well as a comparison of HRQoL with reference values from a Swedish normal population.

Table 1. Overview of the four included papers

| | Paper I | | Paper II | Paper III | Paper IV |
|-------------------------------|---|---|---------------------------|--|---|
| Number of participants | 80 | | | 108 | 114 |
| Study design | RCT | | Longitudinal, prospective | RCT | Cross-sectional |
| Study period | April 2014-May 2019 | | | Aug 2018-Jan 2024 | April 2021-Dec 2021 |
| Inclusion criteria | Cancer of the oropharynx, hypopharynx, larynx and oral cavity, stage III-IV, age >18 years, WHO 0-1 | | | Oral cancer, age >18 years, WHO 0-1, all stages | Cancer of the lips, oral cavity, oro-, naso-, hypopharynx, larynx, salivary glands and HNCUP, >5 years after diagnosis, age >18 years, all stages |
| Treatment | Curative-intent treatment with RT + cisplatin or cetuximab | | | Curative-intent treatment with surgery, surgery + RT ± systemic therapy or RT + systemic therapy | Curative-intent treatment with surgery, surgery + RT ± systemic therapy or RT ± systemic therapy |
| Outcome measures | Weight loss, malnutrition, tube dependency, EORTC QLQ-C30, QLQ-H&N35 | Malnutrition, body composition (DXA), EORTC QLQ-C30, QLQ-H&N35, MDADI | | FFM (BIA), fatigue, malnutrition, physical activity level, EORTC QLQ-C30, QLQ-H&N35, QLQ-FA12 | Dietary adjustments, muscle mass, muscle strength, physical performance, sarcopenia, EORTC QLQ-C30, QLQ-H&N35 |
| Study follow-ups | Baseline (at diagnosis), 6 weeks, and 3, 6 and 12 months after treatment started | | | Baseline (at diagnosis) and 2, 4, 6 and 12 months after diagnosis | One visit >5 years after diagnosis |

RCT: Randomized Controlled Trial, WHO: World Health Organization, HNCUP: Head and Neck Cancer of Unknown Primary, RT: Radiotherapy, DXA: Dual-energy X-ray Absorptiometry, BIA: Bioelectrical Impedance Analysis, FFM: Fat-Free Mass, EORTC QLQ C30: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, H&N35: Head and Neck 35, FA12: Fatigue 12, MDADI: M.D. Anderson Dysphagia Inventory.

3.3 TREATMENT

In papers I and II, the patients were treated according to the ARTSCAN III study protocol and received RT at doses of 68.0 or 73.1 Gy to the primary tumor, given as daily fractions of 2.0 or 2.15 Gy, 5 days per week. Lymph node metastases were treated with 68.0 Gy, and adjuvant neck nodes were treated with 54.4 Gy. Cetuximab was given intravenously 1 week before the start of RT as a loading dose of 400 ml/m² followed by seven weekly doses of 250 ml/m². Cisplatin was administered at an intravenous weekly dose of 40 mg/m², with a maximum dose of 70 mg, during the 7 weeks of RT.⁹

In papers III and IV, all patients were treated according to national guidelines.¹ The first treatment option for all patients in paper III was surgery alone or surgery with postoperative RT. Larger tumors were treated with extensive surgery with or without reconstruction followed by RT, and nonresectable tumors were treated with RT or CRT if possible. RT was given with intensity-modulated radiation therapy (IMRT) to a total tumor dose of 68 Gy in 6 fractions/week. Additional treatment when needed was concomitant chemotherapy with weekly cisplatin, or antibody treatment with cetuximab if cisplatin was contraindicated.

In paper IV, participants had been diagnosed and treated more than five years before inclusion in the study. RT together with systemic therapy was the most common treatment (46%). In total, 80% received RT and of those, 95% received IMRT. Systemic therapy had been given to almost 55% of the participants, nearly 90% of whom had received cisplatin. The majority of participants treated with surgery had undergone resection of the primary tumor together with neck dissection.

All patients were under nutritional surveillance in the Departments of Otorhinolaryngology or Oncology according to the clinics' routine. Follow-ups were performed by a dietitian according to the patients' nutritional needs. Nutritional treatment included individualized counseling, protein-enriched oral nutritional supplements (ONSs), and enteral (EN) and/or parenteral nutrition (PN), which were primarily introduced reactively when needed, e.g., when oral food intake was insufficient.

3.4 NUTRITIONAL ASSESSMENT

In all papers, body weight was measured to the nearest 0.1 kg, height was measured to the nearest 0.5 cm, and body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m²). Blood samples were collected for analysis of C-reactive protein (CRP) levels. Whether food intake was oral, by enteral feeding tube and/or by PN was recorded in all papers. The use of ONSs was assessed in papers III and IV. In papers I-III, the research dietitian estimated the energy requirement at 30 kcal/kg and assessed the patients' energy intake via a dietary recall. The energy intake was categorized as <25%, 25-50%, 51-75% and >75% of the estimated energy requirement.

3.4.1 BODY COMPOSITION

In papers I and II, body composition was measured with dual-energy X-ray absorptiometry (DXA) via a Lunar prodigy scanner (Scanex, Helsingborg, Sweden) (Figure 5). Whole-body scans were performed, and body fat, lean soft tissue and bone mineral content were analyzed via EnCore version 14.1 software. Fat-free mass (FFM) was defined as the sum of lean soft tissue (LST) and body mineral content (BMC). Appendicular lean soft tissue (ALST) was defined as the sum of LST in the arms and legs. The appendicular lean soft tissue index (ALSTI) was calculated by dividing ALST (kg) by height squared (m²). Cutoffs for reduced muscle mass were ALSTI <7 kg/m² for men and <5.5 kg/m² for women.³² Changes in body composition were translated into changes in energy content (EC) of the body based on energy values established for fat mass (FM) and FFM according to the following equation:¹⁰⁶

$$\Delta EC = (\Delta FM \text{ (kg)} \times 39.4 \text{ MJ}) + (\Delta FFM \text{ (kg)} \times 3.7 \text{ MJ})$$

In papers III and IV, bioelectrical impedance analysis (BIA) was used to estimate FFM. A 50-kHz single-frequency device called Nutribox (Data input, Lindenberg 7 82343 Pöcking, Germany) was used. BIA evaluations were conducted with patients in the supine position on the patient's right side, using two surface electrodes on the hand and two on the foot (Figure 5). Before measurement was conducted, participants were required to lie supine for 5–10 minutes.

The equation by Dey et al.¹⁰⁷ was used to calculate FFM:

$$FFM (kg) = 11.78 + (0.499 \times H^2 (cm)/R (\Omega)) + (0.134 \times Weight (kg)) + (3.449 \times sex)$$

where H=height, R=resistance and sex=0 for females and 1 for males. The equation by Dey et al.¹⁰⁷ was selected because it was developed from population-based representative samples in the same region of Sweden as the study participants in this thesis. The population in which the equation was developed were healthy 75 year olds, and the equation was also applied to 70 year olds. The calculated FFM was used as a surrogate measure of skeletal muscle mass, and the fat-free mass index (FFMI) was calculated by dividing the FFM (kg) by height squared (m²). Cutoffs for reduced muscle mass were FFMI <17 kg/m² for men and <15 kg/m² for women.³⁰



Figure 5 Left: Electrodes on the right hand and foot, for measurement by bioelectrical impedance analysis. Right: Dual-energy X-ray absorptiometry. Photos by the author.

3.4.2 MALNUTRITION

The GLIM criteria were used to diagnose malnutrition in papers I-III.³⁰ Screening for the risk of malnutrition was not performed since all patients were considered to be at risk due to cancer treatment and expected eating difficulties. The thresholds for the phenotypic criteria were weight loss >5% within 6 months or >10% beyond 6 months; low BMI, defined as <20 kg/m² in patients aged <70 years or <22 kg/m² in patients aged ≥70 years; and reduced muscle mass, defined as ALSTI <7 kg/m² for men and <5.5 kg/m² for women, or FFMI <17 kg/m² for men and <15 kg/m² for women. At baseline, weight loss >5% within the last 6 months was calculated based on patient self-reports. At all follow-ups before the 12-month follow-up, weight loss >5% within 6 months was calculated from baseline values. At 12 months, weight loss >5% within 6 months was calculated from weight at the 6-month follow-up, and weight loss >10% beyond 6 months was calculated from baseline values. For the etiologic criteria, an intake ≤50% of the estimated energy requirement for >1 week was considered to indicate reduced food intake. Additionally, we decided that the use of an enteral feeding tube and the use of parenteral nutrition also indirectly indicated a reduced food intake, since enteral and parenteral nutrition were introduced when oral food intake became insufficient. A CRP level >5 mg/L was used as cutoff for inflammation. Severe malnutrition was assessed through the phenotypic criteria BMI <18.5 kg/m² for patients aged <70 years or <20 kg/m² for patients aged ≥70 years or weight loss >10% within 6 months or >20% beyond 6 months.

3.5 PERFORMANCE STATUS

Two different performance status scores were used to assess how the disease affected patients' daily life. The *WHO performance status scale*, a 5-point scale where a lower score indicates a better performance status, was assessed in papers I-III.¹⁰⁸ The *Karnofsky performance status scale*, an 11-point scale ranging from 0-100%, where a higher percent indicates a better performance status, was used in paper IV.¹⁰⁹

3.6 MUSCLE STRENGTH AND PHYSICAL PERFORMANCE

In paper IV, muscle strength and physical performance were evaluated by assessing hand grip strength and maximum walking speed. Both methods are validated and well used in the literature.^{37,110} Hand grip strength was measured with a digital hand dynamometer JAMAR® Plus+. The participants sat upright in a chair with both feet firmly placed on the floor and with the forearms in a neutral position on the armrests (wrist and hand was placed outside the armrest). The participants held the hand dynamometer themselves, and the first attempt was done with the left hand, and the next attempt was made with the right hand. In total, three attempts with each hand were performed, and the best result was recorded. The examiner encouraged the participant during the attempt by saying “squeeze the handle tighter, tighter and tighter”.¹¹¹

The 10-meter walk test was done in maximum pace, with an acceleration and deceleration phase of 2 meters each.¹¹² Participants were instructed to walk as fast as possible, safely without running, from the starting point to a visual cone placed at 14 meters. The participants started on “go” when the examiner said “ready-steady-go”. The time started when the participants first foot crossed the line at 2 meters and stopped when the first foot crossed the line at 12 meters. An electronic stopwatch was used for timing of the 10-m walk. Two attempts with a small break in between were performed, and the best result recorded.

3.6.1 SARCOPENIA

In paper IV, sarcopenia was assessed by using the most recent diagnostic criteria of the European Working Group on Sarcopenia in Older People (EWGSOP2).³⁷ Low muscle strength together with low muscle mass is required for diagnosis. Muscle strength was measured through hand grip strength and muscle quantity with BIA. The cutoffs for reduced muscle strength were <27 kg for men and <16 kg for women,³⁷ and an FFMI <17 kg/m² for men and <15 kg/m² for women indicated reduced muscle mass.³⁰

3.7 PHYSICAL ACTIVITY

3.7.1 EXERCISE PROGRAM

Patients randomized to the exercise group in paper III, received an exercise program that included resistance training and aerobic activity and was to be carried out for 6 months. A physiotherapist had one clinic visit with each patient in the intervention group where information about the aim of the intervention and instructions were given on how to perform four muscle strengthening exercises: squats, heel raises, hip thrusts, and push-ups (Figure 6). Each exercise had four levels of difficulty, which were individualized; for example, the easiest level of push-ups was performed while standing against a wall, and the hardest level was performed on the floor on the toes. The resistance training included 3 sets of 10–15 repetitions of the four strengthening exercises per day, and in addition, the patients chose an aerobic activity of at least moderate intensity to do for at least 30 minutes per day, 5 to 7 days a week. The exercise program corresponded to the recommendations of at least 150 minutes of moderate intensity PA per week with both aerobic and muscle strengthening activity.^{56,57} Moderate intensity was explained as working hard enough to breathe faster and feel warmer but still be able to talk. Patients who were already active were encouraged to increase the intensity and/or duration. The resistance training was not recommended to be performed during the first 2 weeks after surgery, but the patients were encouraged to take shorter walks at a leisurely pace. To increase motivation, patients received a diary in which they were instructed to mark each day they performed the resistance training and aerobic activity. Five follow-up calls by telephone were held for the physiotherapist to answer questions, motivate the patients to continue being physically active, and instruct the patients on how to intensify aerobic activity and/or increase the difficulty level of the resistance training, if possible. Patients in the control group received general information about the study and information about the potential health benefits of being physically active during and after cancer treatment. In accordance with clinical practice, patients who underwent neck dissection were instructed about a specific postoperative exercise program for shoulder mobility by a physiotherapist.

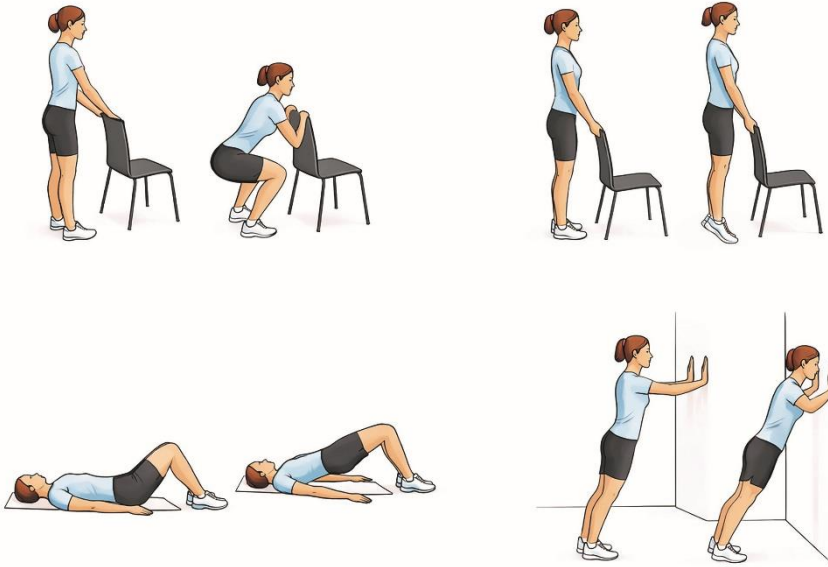


Figure 6. Illustrations of the four strengthening exercises, level 1 of 4, in paper III: squats, heel raises, hip thrusts and push-ups. Illustrations by Elin Wallmänder.

3.7.2 PHYSICAL ACTIVITY ASSESSMENT

In paper III, PA was assessed via the Frändin/Grimby 6-level activity scale (Appendix 5).¹¹³ The original 4-level scale by Saltin and Grimby is one of the oldest questionnaires for PA assessments and has been used in large-scale population and epidemiological studies.^{114,115} The extended 6-level version also includes two more PA levels and household activities. Patients graded their activity from hardly any PA (level 1) to hard or very hard exercise regularly (level 6).¹¹³

Patients also answered a questionnaire from the National Board of Health and Welfare (Socialstyrelsen) that included three questions about the amount of time (minutes) spent per week on PA (at least 10 minutes at a time of moderate intensity, e.g., walks, bicycling or gardening), the amount of time (minutes) spent per week on physical exercise (at least 10 minutes at a time of high intensity, which makes you short of breath, e.g., running, gymnastics or ball

sports) and the amount of time (hours) spent per day on sedentary behaviours (excluding the number of hours of sleep) (Appendix 6).^{116,117} The results from the questions are presented separately, but questions 1 and 2 were also weighed together into a common measure: activity minutes per week. The median value of the categories was used for summing. When the results were weighed together, the time spent on physical exercise was counted twice. Patients were then categorized into two groups depending on whether they reached the recommendation of at least 150 activity minutes per week. The questionnaire about PA level from the National Board of Health and Welfare is included in the national guidelines on prevention and treatment of unhealthy lifestyle habits, which are recommended for use in clinical practice.

3.8 PATIENT-REPORTED OUTCOME MEASURES

To better understand the patient's own experience of HNC and treatment, HRQoL was evaluated through questionnaires in all studies of this thesis. Two questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC) were used in all papers: EORTC QLQ-C30 (Appendix 1)⁷³ and the EORTC QLQ-H&N35 (Appendix 2).⁷⁴ In addition, the EORTC QLQ-FA12 (Appendix 3)^{79,80} was used in paper III, and the MDADI (Appendix 4)^{81,82} was applied in paper II. Differences of ≥ 10 points between groups or in changes over time indicated a clinically significant difference in HRQoL.⁸⁷

3.8.1 EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)

The EORTC QLQ-C30 is a well-established questionnaire developed for all cancers and includes 30 questions transformed into 5 functional scales (Physical, Role, Emotional, Cognitive and Social functioning), 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), 6 single questions (Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea and Financial difficulties) and one global QoL scale.⁷³

The EORTC QLQ-H&N35 incorporates problems and symptoms common to HNC patients and is used together with the EORTC QLQ-C30. It consists of 35 questions transformed into 7 scales (Pain, Swallowing, Senses, Speech, Social eating, Social contact, Less sexuality), 6 single questions (Teeth, Opening mouth, Dry mouth, Sticky saliva, Coughing and Felt ill) and 5 dichotomous (yes or no) questions about pain killers, nutritional supplements, feeding tube use and weight change.⁷⁴

The EORTC QLQ-FA12 measures cancer-related fatigue and consists of 3 symptom scales for physical, emotional and cognitive fatigue, as well as 2 single-items regarding interference of tiredness with daily activities and understanding of the tiredness from close relatives.^{79,80}

Most of the questions are answered on a four-point Likert scale with the answers: “Not at all”, “A little”, “Quite a bit” and “Very much”. The answers are converted with linear transformation to a final score ranging from 0–100. A higher score on a functional scale and the global QoL scale represents a high level of function, but a higher score on a symptom scale represents a high level of symptoms or problems.¹¹⁸

Selected scales from the questionnaires mentioned above were used in the included papers of this thesis. Additionally in paper IV, participants with most difficulties swallowing solid food were identified by answering, “*quite a bit*” or “*very much*” to the question “*Have you had problems swallowing solid food?*” from the EORTC QLQ-H&N35.

3.8.2 M.D. ANDERSON DYSPHAGIA INVENTORY

The MDADI questionnaire was designed to measure HRQoL in relation to swallowing ability in patients with HNC. The questionnaire includes four subdomains: global, emotional, functional and physical. Each question is rated on a five-point Likert scale, and the total score ranges from 20 to 100. Higher scores indicate a better QoL.^{81,82}

3.9 STATISTICAL ANALYSIS

The results in all papers are presented as means and standard deviations for continuous variables and as numbers and percentages for categorical variables. In papers I, III and IV, mean differences between groups are presented together with a 95% confidence interval (CI).

For comparisons between two groups, Fisher's exact test was used for dichotomous variables, the Mantel-Haenszel chi-square test for ordered categorical variables, and the chi-square test for nonordered categorical variables. For comparison of continuous variables between groups, Fisher's nonparametric permutation test (paper I, IV), t test (paper III) or Mann-Whitney U test (paper II and III) was used. For comparisons within the group in paper II, paired t tests were used. Kaplan-Meier analysis was used to estimate overall survival in papers I and III, reporting the log-rank p value for differences between groups.

The prevalence of malnutrition was determined according to the GLIM criteria, which are based on dichotomous variables. Patients were categorized as either malnourished or nonmalnourished and assigned numerical values and percentages.

In paper IV, patients' HRQoL, measured by the EORTC QLQ-C30 and QLQ-H&N35, was compared to reference values from a Swedish normal population. The EORTC QLQ-C30 and QLQ-H&N35 reference values from the normal population were age- and sex-matched with those of the study group by using a greedy group matching approach. Matching was performed by iteratively selecting the closest individuals from the normal population with the minimum t statistic tested against the study population. The matching ratio was determined by identifying the point where the t-statistic began to increase markedly while maintaining good matching quality (t-statistic ≈ 0.02 , $p \approx 0.98$), resulting in a 4:1 matching ratio.

In paper I, the primary outcome was a 3 kg difference in weight loss between the study groups at 3 months. For a power of 80% to detect this difference, a total of 116 patients were required to be included. The differences in weight loss between the two treatment groups were calculated only for patients with weight loss.

In paper III, one power analyse was performed for the primary outcome of FFM and one for the primary HRQoL outcome of fatigue. To detect a difference of 2.8% (SD 3.0%) in change in FFM between the groups, with a power of 90%, a total of 54 patients were required to complete the 4-month follow-up. For a power of 90% to detect a difference of 20 points (SD 24.6) between the groups for the EORTC QLQ-C30 fatigue scale, 70 patients were required at the 4-month follow-up.

The statistical analyses included only patients who were assessed at the different follow-ups. For the HRQoL questionnaires, at least 50% of the questions on a scale needed to be answered to qualify for analysis. The threshold for statistical significance was a two-sided p value of 0.05, and analyses were performed via SAS version 9.4 statistical software.

3.10 ETHICAL CONSIDERATIONS

All participants received oral and written information about the studies and provided written informed consent to take part in the studies. All procedures in the studies were conducted in accordance with the Declaration of Helsinki, and the studies was approved by the Regional Ethical Committee in Gothenburg, Sweden, with the following approval numbers: papers I and II (117–14), paper III (103–18), and paper IV (2021–00664).

4 RESULTS

4.1 PAPER I

The study compared nutritional status and HRQoL in 80 patients enrolled in the ARTSCAN III study and treated with either RT together with cisplatin or cetuximab. Of the included patients, 38 were randomized to receive cetuximab and 42 to receive cisplatin. A majority of the study group were male, and over 90% had advanced oropharyngeal cancer.

At the end of treatment, at 6 weeks, patients treated with cisplatin had a higher prevalence of enteral feeding tubes and lost more body weight than patients treated with cetuximab, -6.2 kg vs. -4.5 kg (Figure 7). In contrast, patients in the cetuximab group lost more weight after the 6-week follow-up, resulting in similar weight loss in both treatment groups at 3 months. There were also no significant differences in body weight at 6 or 12 months. No differences in the prevalence of malnutrition were observed between the treatment groups.

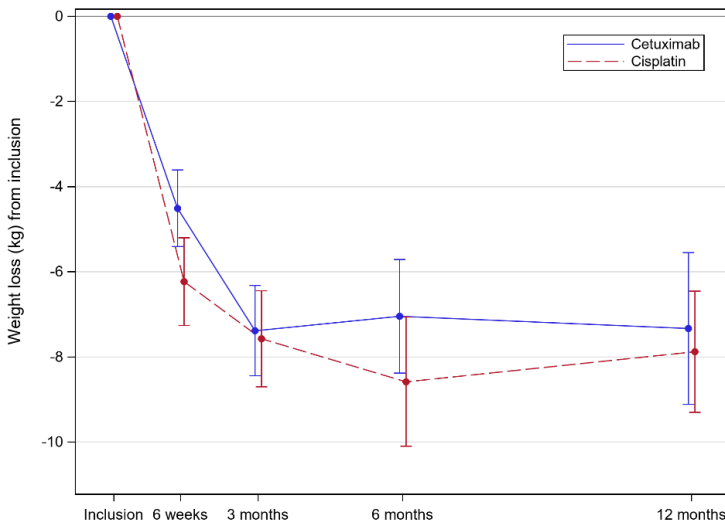


Figure 7. Weight loss at each follow-up compared with body weight at inclusion for the two treatment groups (cetuximab and cisplatin). The mean weight loss (kg) was calculated only for patients who lost weight, cetuximab: 6w: n=34, 3m: n=34, 6m: n=32, 12m: n=26, cisplatin: 6w: n=39, 3m: n=39, 6m: n=39, 12m: n=39 (Berg & Hansson, Head & Neck, 2024).

HRQoL deteriorated for both groups at the end of treatment, with cisplatin-treated patients reporting worse physical functioning, and more problems with appetite loss and diarrhea. At 3 months, a recovery in HRQoL was observed, especially among the cisplatin-treated patients, and patients in the cetuximab group reported more problems with pain, appetite loss and social eating. No significant differences were found at 6 or 12 months.

4.2 PAPER II

Patients with almost exclusively advanced oropharyngeal cancer and treated with RT combined with systemic treatment were followed for one year. Prevalence rates of malnutrition varied during the study period with a peak at the 6-week follow-up (71%), where a majority were diagnosed with moderate malnutrition (Figure 8). At the end of treatment, the most common combination of the GLIM criteria included weight loss, reduced food intake and inflammation (31%), and weight loss was the most frequent phenotypic criterion at all follow-ups.

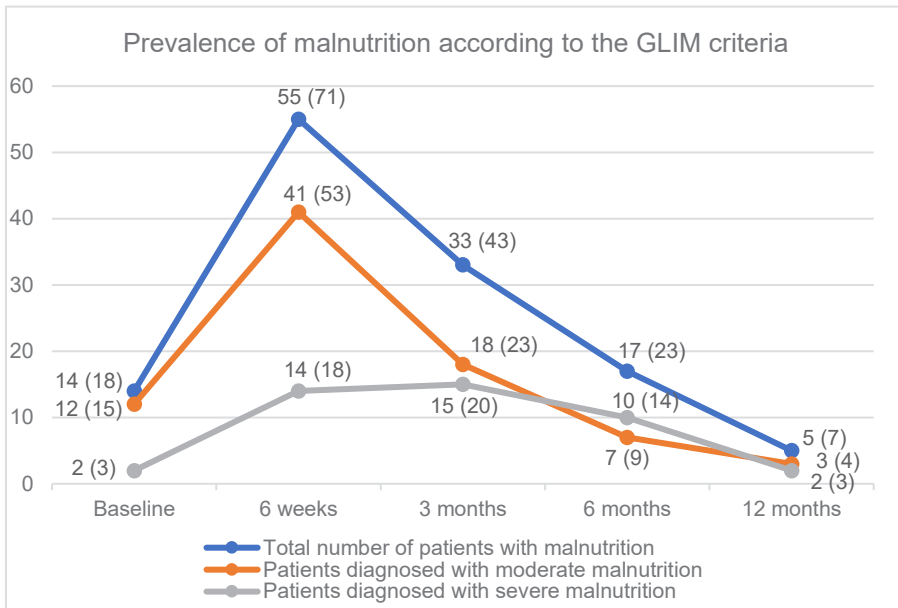


Figure 8. Total number of patients with malnutrition according to the GLIM criteria at all study follow-ups. Numbers (%) are presented. Patients not able to be diagnosed because of missing values: 6 weeks: $n=3$, 3 months: $n=1$, 6 months: $n=3$. (Wallmander, *Clinical Nutrition ESPEN*, 2025).

Between baseline and the 6-week follow-up, body weight decreased with 5.6%, muscle mass with 8.0% and body fat with 5.9% (Figure 9). At the 3-month follow-up, the decline in muscle mass had ceased and patients started to recover muscle mass, despite a negative energy balance. After one year, the mean reductions in body weight, muscle mass and body fat were 7.4%, 2.4% and 18.9% respectively (Figure 9).

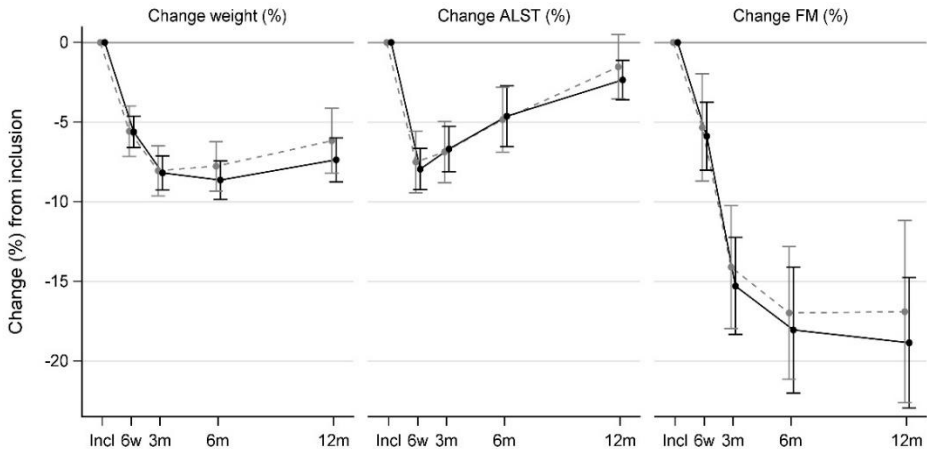


Figure 9. Percentage weight change, change in appendicular lean soft tissue (ALST), and change in fat mass (FM) at 6 weeks, 3, 6 and 12 months after the start of treatment compared with baseline values. The solid line includes all patients whose measurements were taken at the different time points, $n=80$. Missing values: 6 w: ALST: $n=3$, FM: $n=3$, 6 m: ALST: $n=36$, FM: $n=36$. The dashed line includes only patients with DXA measurements at all time points, $n=36$. The numbers are presented as the change in the mean, in percent, with a 95 % confidence interval (Wallmänder, *Clinical Nutrition ESPEN*, 2025).

Malnourished patients reported significantly poorer HRQoL than nonmalnourished patients, at diagnosis, 3 months, and 6 months. However, at the end of treatment, HRQoL was severely affected in all patients, and no differences were observed between patients with or without malnutrition.

4.3 PAPER III

In this RCT, patients with oral cancer were randomized to an individualized home-based exercise intervention or a control group. In total, 108 patients participated in the study (intervention group, n=50; control group, n=58). The exercise program was performed for six months, and muscle mass, fatigue, PA level and HRQoL were assessed over a one-year period.

Significantly more patients in the intervention group reported engaging in PA for 150 minutes or more per week at the 2-month follow-up (Figure 10). Patients in the intervention group also reported a significantly larger increase in PA level during the entire study period compared with those in the control group.

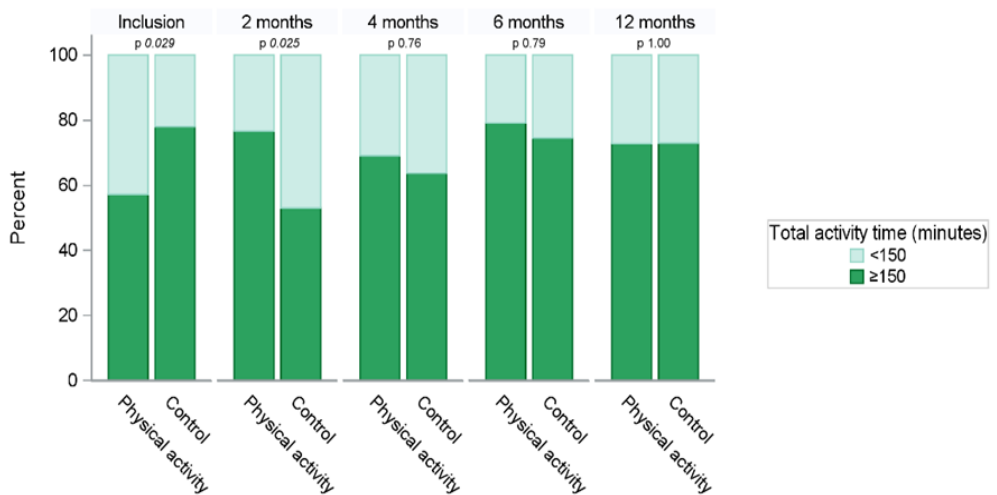


Figure 10. Comparison of the proportion of patients with <150 min of activity and ≥ 150 min of activity per week between the exercise group and the control group at inclusion and at 2, 4, 6, and 12 months after enrollment (Wallmander, Head & Neck, 2025).

The decrease in muscle mass and body weight was small in both groups and did not exceed 3% on average. No effect on muscle mass was established when the exercise group was compared with the control group. The exercise group tended to have fewer problems with fatigue at 2 months (EORTC QLQ-C30 fatigue scale, -11 vs. -17; QLQ-FA12 physical fatigue scale -6 vs. -16) and better global QoL at 2 months (-3 vs. -10) and 4 months (2 vs. -8), as well as significantly better role functioning at 4 months (-1 vs. -16).

4.4 PAPER IV

In this long-term follow-up study, 114 participants were assessed an average of 7.5 years after diagnosis. Almost 80% of participants reported a need to adjust their diet to facilitate food intake. The most common adjustments were the need for extra liquid with meals and/or the need for moist food and more time to consume meals (Figure 11). Low BMI and reduced muscle mass were assessed in 16 respectively 14 participants, and 2 participants had a reduced muscle strength. No participant was diagnosed with sarcopenia.

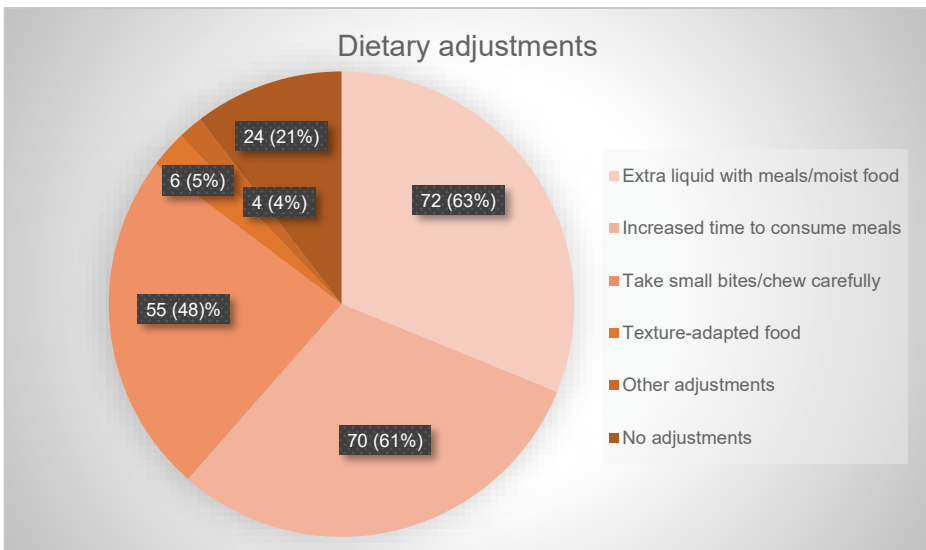


Figure 11. Among the 111 participants that answered the questions about dietary adjustments, 87 reported a need to adjust their food to facilitate intake. These 87 survivors reported a total of 207 adjustments. The use of three dietary adjustments was most common, followed by two adjustments. “Other adjustments” included the use of saliva gel and not eating warm food. The three participants that did not answer the questions had a PEG and their oral intake was nonexistent or sparse (taste portions).

HRQoL was compared with age- and sex-matched reference values from a Swedish normal population, and the survivors reported both clinically and significantly greater symptom burden on all scales from the QLQ-H&N35 module. The most prominent problems were dry mouth (49 vs. 14), followed by sticky saliva (38 vs. 8).

The survivors with most problems swallowing solid food, defined by answering “*quite a bit*” or “*very much*” on the question “*Have you had problems swallowing solid food?*”, reported a greater symptom burden on all scales from the EORTC QLQ-H&N35, and significantly worse role and social functioning on the EORTC QLQ-C30, compared with the group with no or small problems swallowing solid food.

5 DISCUSSION

This thesis consists of three studies of different HNC populations; a strength of these studies is the inclusion of homogeneous patient cohorts with respect to tumor site and treatment in papers I-III. In papers I and II, patients had advanced cancer, mainly oropharyngeal, and received combination treatment with either RT and cisplatin or RT with cetuximab. Paper III included patients with oral cancer, the majority of whom had stage I-II cancer (70%) and were treated with surgery as monotherapy (60%). In paper IV, patients had been diagnosed with HNC more than five years before inclusion. Approximately 60% had been diagnosed with an advanced stage, and almost half of the participants included had received combination therapy with radiation and systemic therapy.

Different study designs can provide different information and evidence. Well conducted RCTs can provide strong evidence for causality, and this design was used in the studies for papers I and III. Longitudinal prospective studies can also provide good evidence and give information about changes over time, which was the case in paper II. In contrast, a cross-sectional design, as used in paper IV, provides a snapshot of the current situation and can provide information about prevalence, but not causality and changes over time. When patients are followed over time, dropouts and missed measurements are factors that can negatively affect the analysis and results. For the studies in this thesis, the compliance was good overall, with few dropouts. In the study on which papers I and II are based on, no patients discontinued the study, and only two patients had missed follow-ups (one and two missed follow-ups respectively). The response rate for the HRQoL questionnaires in paper I was good and varied between 90% and 100% at follow-ups (cetuximab: 92%-100%, cisplatin: 88%-98%). In paper III, 7 patients discontinued the study, follow-ups were affected by the Covid-19 pandemic, but the response rates for the HRQoL questionnaires were still good and varied approximately between 80% and 90% at follow-ups (exercise group: 82%-94%, control group: 76%-88%).

5.1 NUTRITIONAL PROBLEMS

Nutritional problems, such as dysphagia, pain, sticky saliva, dry mouth and problems with oral function and chewing are well-known to affect patients with HNC. In papers I and II, the use of enteral nutrition via a feeding tube was common at the end of treatment, especially due to side effects during treatment (60%). When comparing treatment groups, we found that more patients in the cisplatin group than the cetuximab group used an enteral feeding tube at 6 weeks, and in total throughout the study. This result is consistent with a previous study by Ishimaru et al.¹¹⁹, but in contrast with two other studies that reported an equal or even higher need for enteral feeding tubes in cetuximab-treated patients.^{120,121} A consideration regarding that more cisplatin-treated patients received an enteral feeding tube during treatment, could be that they lost weight rapidly when they also were monitored frequently in the hospital. In comparison, cetuximab-treated patients lost more weight after completing treatment, without any increase in the use of enteral nutrition. Although enteral nutrition was common during treatment, the number of patients needing an enteral feeding tube declined after 6 weeks, and at the one-year follow-up, only one patient used an enteral feeding tube. This reflects the course of nutritional problems, with the greatest deterioration during and shortly after treatment, followed by improvements up to one year.

In paper III, fewer patients needed an enteral feeding tube in total during the study period (25%), compared with the study population in papers I and II (70%). Tumor location, tumor stage and treatment regimen are most likely the explanations for this difference, as advanced cancer and combination treatment are associated with severe nutritional problems. However, the use of oral nutritional supplements (ONSs) in paper III was pronounced, with 80% of patients using ONSs at some point during the study period; this result indicates that nutritional problems and the need for nutritional treatment is prevalent also among patients with smaller tumors of the oral cavity. The use of ONSs was not registered in the study on which papers I and II are based on, but clinical experience tells us that probably close to everyone that receives combination treatment will need ONSs. Furthermore, we speculate that ONSs probably constituted a larger portion of total energy intake for the patients in papers I and II.

More than five years after diagnosis in paper IV, the use of an enteral feeding tube and ONSs was low; 10% used ONSs, and 3% received enteral nutrition via PEG. However, almost 80% of long-term survivors reported a need for

dietary adjustments and approximately 25% of the participants reported “*quite a bit*” or “*very much*” problems swallowing solid food. Common adjustments were the need for extra liquid with meals and/or the need for moist food, as well as increased time to consume meals, which is consistent with findings from previous qualitative studies.^{19,122,123} This suggests that eating difficulties may persist long after treatment and that many survivors adjust their food to facilitate oral intake. An interesting result was that only six participants reported the need for texture-adapted food, which may indicate that the other adjustments were sufficient to facilitate eating. When survivors adapt to their eating difficulties, this results in a “new normal” where survivors do not always perceive their nutritional difficulties as problems.^{19,124} Adaptation to nutritional problems and the use of dietary adjustments need to be considered by healthcare professionals who meet survivors of HNC, to identify patients in need of nutritional treatment.

Although many survivors in the long-term follow-up study reported nutritional problems and dietary adjustments, we do not know the quality of their food intake. A hypothesis for future research could be to investigate whether long-term nutritional problems can lead to negative effects on nutritional intake, for example, a high intake of saturated fat and low intake of vegetables, fruit and fiber. Other studies have reported that HNC survivors have lower diet quality scores compared with reference values and that better diet quality is associated with a lower NIS burden and better survival.^{98,125,126}

5.2 MALNUTRITION

Malnutrition according to the GLIM criteria was assessed in papers I-III. As patients with HNC have a high risk of developing malnutrition, we did not assess the risk of malnutrition via a screening tool (step 1 of the GLIM criteria). To date, there is also no global consensus on how to define “risk of malnutrition”, and after the introduction of the GLIM criteria, studies have reported that the screening tool selected affects the prevalence of malnutrition assessed via the GLIM criteria.^{127,128} Currently, there is a new GLIM working group initiative with the aim of providing guidelines on how and when the risk of malnutrition can be evaluated.^{129,130}

The highest prevalence of malnutrition was reported in papers I and II, where many patients developed malnutrition, especially at the end of treatment

(71%). There were no significant differences in malnutrition between treatment modalities in paper I, but a higher prevalence rate in patients receiving cisplatin was observed, especially at 6 weeks (78% vs. 65%). In paper III, the highest prevalence rates of malnutrition were observed at 4 months (exercise 14% vs. control 18%) and 6 months (exercise 14% vs. control 17%). Patients in papers I and II also lost more weight and muscle mass than patients in paper III. The large difference between the studies, despite the GLIM criteria being interpreted in the same way, is explained by patients having an advanced cancer and combination treatment in papers I and II, which resulted in severe nutritional problems and larger loss of weight and muscle mass. The GLIM criteria have so far only been used in few studies on patients with HNC.^{42,46-48} Einarsson et al.⁴² and Steer et al.⁴⁶ reported a prevalence of malnutrition of 32% and 23% respectively, during treatment. These studies evaluated different study populations of HNC, and differences in how the criteria were interpreted may also have an impact on the outcome. For example, Steer et al.⁴⁶ used subjective methods to assess muscle mass, inflammation was determined by the presence of metastatic disease, and the criteria for reduced food intake did not include the use of EN or PN. The prevalence rates found in our studies varied depending on when malnutrition was assessed (paper II: 7-71%, paper III 0-18%), which may also contribute to differences when comparing results between studies. The high prevalence of malnutrition among patients with advanced stage and combination treatment found in this thesis stresses the importance of nutritional treatment that is early initiated with frequent follow-ups during and after treatment.

Patients treated with a combination regimen showed the most rapid weight loss between baseline and the first follow-up at 6 weeks. Body weight continued to decrease until 3 months, but then it started to level off. Patients treated with cisplatin lost more weight during treatment, while cetuximab-treated patients lost more weight after treatment during the early recovery phase, resulting in similar weight loss in both treatment groups at 3 months; no differences were observed at the remaining follow-ups. Thus, it may be that the two systemic treatments have a similar negative effect on nutritional status, or that the negative effect of RT outweighs the effect of systemic therapy. The fact that more cisplatin-treated patients received an enteral feeding tube during treatment may also have contributed to slowing further reductions. Similar weight loss was reported in a previous Swedish study where different RT fractionation schedules without systemic therapy were evaluated; 9.4 kg at 5 months compared with 7.1 and 8.6 kg at 6 months in our study.¹³¹ In paper II, we explored the different GLIM criteria and combinations. Weight loss was

the most frequent criterion fulfilled by a majority of patients at all follow-ups. Three other studies have also found the weight loss criterion to be the most commonly met among patients with HNC.^{42,46,48} This highlights the need for frequent measurements of body weight for evaluation of nutritional status, which should be done routinely in clinical practice.

At the end of treatment, patients in paper II experienced the largest loss of muscle mass (8.0 %), and a majority had an elevated CRP level. In paper III, the loss of muscle mass was lower and similar at the different follow-ups, probably due to the smaller and slower loss of body weight; additionally fewer patients had an elevated CRP level. Reductions in muscle mass during treatment for HNC have been reported in several studies.^{35,132,133} The inflammatory process that leads to muscle depletion is challenging during treatment, and prevention with nutritional treatment alone is difficult. Interestingly, in paper II, the loss of muscle mass had ceased at 3 months and started to recover, despite a negative energy balance. Studies that have evaluated body composition in HNC patients often report few measurement time points, assess inconsistent time points, and use various methods for measurement; additionally, the studies are often heterogenous regarding tumor site and treatment.¹³² Furthermore, few studies have measured body composition with DXA in HNC patients.^{34,35,43,134} Two of these studies found no recovery of muscle mass, whereas body fat decreased¹³⁴ or remained stable after treatment.⁴³ The two other studies using DXA reported a reduction in muscle mass of 4.7 kg at 8 weeks, and 6.8 kg at 11 weeks after treatment start, compared to a reduction of 3.4 kg at 6 weeks and 3.0 kg at 3 months in our study.^{34,35} In addition, Lønbro et al.³⁵ found a 3.1 kg greater loss of muscle mass in patients receiving CRT compared to patients receiving radiotherapy alone. Explanations for the observed muscle mass recovery after treatment in paper II, could be that fewer patients had an elevated CRP level and that patients received active nutritional care. Nutritional interventions and increased protein intake (>1.4 g/kg) have been associated with reduced loss of body weight and muscle mass.^{135,136} In summary, reduced muscle mass occurred in many patients' receiving combination treatment, and it was the second most common phenotypic criterion in paper II. Monitoring changes in body composition during and after treatment could be valuable in improving malnutrition assessment and nutritional treatment for patients with low muscle mass or nonrecovery.

Consistent with previous studies, only few patients had a low BMI, why underweight is less useful as a phenotypic criterion in patients with HNC.^{42,46,48}

However, BMI remains a useful measure for assessing nutritional status and planning nutritional treatment. CRP was used to assess the etiological criterion inflammation and has been used in previous studies when malnutrition has been evaluated in patients with HNC.^{42,47,48} Guidance for assessing inflammation has been published by the GLIM working group, concluding that diseases associated with inflammation, such as malignancies, clinical signs and CRP may confirm the inflammation criterion.¹³⁷ One could argue that the malignancy itself could be sufficient to confirm inflammation in our studies. However, support by objective measures such as CRP may be preferable in research. According to clinical practice, EN was introduced reactively when energy intake became inadequate. Therefore, the use of enteral feeding tubes may work well as a supportive measure for the GLIM etiologic criterion for reduced food intake in this population. A limitation of including EN and PN as part of the criteria for reduced food intake may be the long-term use of medical nutrition. For example, patients that received an enteral feeding tube during treatment and continued to use EN after treatment in paper II were assessed with a reduced food intake at both 6 weeks and 3 months. This might have resulted in patients being diagnosed as malnourished at 3 months despite an adequate energy intake via EN for several weeks. It is likely that this problem was most prominent at 3 months, since the number of patients with EN or PN decreased significantly at 6 and 12 months.

In paper IV, we aimed to study whether survivors experienced long-term side effects from treatment affecting nutrition and whether negative effects on body composition, muscle strength and physical performance could be observed. Malnutrition was not evaluated according to the GLIM criteria in paper IV, as the criteria for weight loss, inflammation and reduced food intake are unlikely to reflect long-term side effects. Considering that many survivors reported a high NIS burden and need for dietary adjustments, relatively few survivors had a low BMI, reduced muscle mass, muscle strength and physical performance, and none were diagnosed with sarcopenia. Additionally, the average values for muscle strength and maximum walking speed were comparable to reference values.^{112,138} This may imply that many survivors with nutritional problems adapted and compensated for their NISs; we speculate that this adaptation allowed the majority to meet energy and nutritional needs and thereby maintaining body mass and function. However, for some survivors, nutritional rehabilitation may be needed long after treatment has ended, focusing on nutrition impact symptoms related to HRQoL and the management of eating difficulties.

5.3 PHYSICAL ACTIVITY

In paper III, PA was assessed via the Frändin/Grimby activity scale and via a questionnaire from the National Board of Health and Welfare. Patients that participated in an exercise program for 6 months increased their self-reported PA during the intervention period, and the increase was also maintained at the 12-month follow-up. This is an important finding since studies in patients with HNC have shown a reduction in PA and low PA levels after treatment.^{139,140} Unfortunately, the adherence to the exercise program could not be assessed because few exercise diaries were submitted or were not used properly. Therefore, we do not know whether the increase in PA involved resistance training, aerobic activity or both. No difference in muscle mass loss was observed between the two groups, and the loss of weight and muscle mass did not exceed 3% at any follow-up. The lower loss of body weight and muscle mass could be explained by most patients having a nonadvanced diagnosis and undergone surgery as a single-modality treatment, allowing for faster recovery. Another explanation may be that all patients received active nutritional treatment with frequent follow-ups, which included contact with a dietitian at the time of diagnosis. Other studies have shown that nutritional counseling, protein-enriched ONSs and increased protein intake reduce loss of body weight and muscle mass.^{135,141,142}

Few studies, especially RCTs, have examined the effects of PA on muscle mass, and these studies have shown varying results.^{143,144} In a study by Lønbro and colleagues, the resistance training was initiated at different time-points after treatment had ended and showed positive effects on muscle mass and muscle strength.¹⁴³ Thus, we do not know how much muscle mass was lost during treatment, and if the recovery observed with the exercise intervention resulted in similar, less or more muscle mass compared with baseline values. Nevertheless, increasing nutritional difficulties and inflammation-driven muscle depletion during treatment is common; therefore, exercise might be less effective in terms of reducing muscle mass loss. The treatment burden may also affect adherence, and posttreatment exercise may therefore be more beneficial for muscle mass recovery.

Patients in the exercise group had better global QoL at 2 and 4 months and better role functioning at 4 months. Patients in the exercise group also reported a tendency towards less problems with fatigue on the QLQ-C30 fatigue scale and the QLQ-FA12 physical fatigue scale at 2 months. The QLQ-C30 fatigue scale largely includes aspects of physical fatigue, which explains the similarity

with the results from the QLQ-FA12 physical fatigue scale.¹⁰⁴ Other studies have also confirmed the benefits from exercise on fatigue and QoL both during and after treatment.^{143,145,146} This suggests that regardless of when exercise is introduced, it is possible to reduce fatigue and improve HRQoL. Early initiation of exercise before treatment may be preferable to prevent severe deterioration, maintain well-being, and promote recovery.

The individualized home-based exercise program was designed to meet the current recommendations for PA.^{56,57} Apart from one face-to-face meeting, where information about the exercise program was provided, the exercise was unsupervised, home-based, and performed using body weight as resistance. The intention of a home-based program with higher-frequency and shorter duration training sessions was to ease participation, facilitate regular training, minimize workload (e.g., extra visits, travel), and provide flexibility for patients. If the program had shown significant effects on muscle mass, fatigue and HRQoL it would also have been easier to implement a home-based training program into clinical practice. Studies in patients with HNC have shown that face-to-face instructions, unsupervised exercise, and exercising at home or outdoors are common exercise preferences, and that fatigue is a frequently reported barrier to exercise.^{147,148} Gender-specific patterns regarding exercise preferences have also been reported among HNC patients.¹⁴⁹ Understanding preferences and barriers to exercise is important, as these factors may also affect participation and adherence. In the clinic, routines for specific HNC problems, such as training programs for shoulder mobility, are often implemented, while routines for general exercise during and after treatment are often lacking, despite proven beneficial effects, and there is a great potential for improvement in this area.

5.4 HEALTH-RELATED QUALITY OF LIFE

HRQoL was evaluated in both the short and long term. In paper I, we found that HRQoL was severely affected by the treatments in both study groups, which is typically for patients treated with RT, where additional chemotherapy worsens treatment-induced symptoms.^{150,151} Although, we did not find many significant differences in HRQoL between treatment groups, it appeared that patients receiving cisplatin deteriorated more rapidly and had an overall poorer HRQoL at the end of treatment, and at the same follow-up cisplatin-treated patients also had lost more weight. At 3 months, the reverse was observed with

a trend towards worse HRQoL for cetuximab-treated patients, consistent with a larger weight loss in this group between 6 weeks and 3 months.

An impaired nutritional status is associated with poorer HRQoL^{152,153}, and in a previous study where the GLIM criteria were used, HNC patients with malnutrition reported poorer HRQoL than nonmalnourished patients before treatment, at the end of treatment and one year after treatment.⁵¹ Similarly, in paper II, we found that patients with malnutrition had worse HRQoL at diagnosis and at follow-ups after treatment, but unexpectedly, we found no differences at the end of treatment, as all patients reported a significantly worse HRQoL. This might be explained by the study group being homogenous, mainly suffering from advanced oropharyngeal cancer and subjected to combination therapy, resulting in acute toxicity symptoms with a high negative impact on all patients during treatment regardless of nutritional status.

When long-term survivors of HNC, with an average follow-up of 7.5 years after diagnosis, were compared with an age- and sex-matched normal population, they reported poorer HRQoL on all scales on the EORTC QLQ-H&N35. The high symptom burden may explain why a large proportion of survivors needed to adjust their food to facilitate intake. Survivors reported similar results compared with the normal population on the EORTC QLQ-C30, and no differences were observed. These findings were also consistent with a previous study that compared HRQoL with reference values 5 years after treatment with RT.¹⁵⁴ It is common for patients to experience a “response shift” through the years after disease and treatment, where their thoughts on “good” QoL change as they adapt to their side effects from treatment.¹⁵⁵ However, specific HNC symptoms might be easier to recognize, which can be reflected in the results from the EORTC QLQ-H&N35 in paper IV. Long-term survivors of oral cancer reported either equivalent or better scores on the EORTC QLQ-H&N35 scales, except for problems with teeth, when compared to survivors of oropharyngeal cancer. This difference may be explained by the different treatment regimen; most of the participants diagnosed with oropharyngeal cancer had advanced-stage disease and received combination therapy, whereas the majority in the oral cancer group had stage I-II cancer and received treatment with a single modality. Likewise, the EORTC 1629 study, which compared HRQoL between single and multimodal treatment for long-term HNC survivors, reported a similar or reduced symptom burden for survivors treated with a single modality.¹⁰⁵

Almost 25% of the survivors reported “*quite a bit*” or “*very much*” to the question “*Have you had problems swallowing solid food?*”. In a previous long-term follow-up study on patients with advanced HNC, these numbers were similar for patients at both 2 and 8 years (27% and 25% respectively).¹⁵⁶ The scores for social eating were also similar to those found in our study, but problems with dry mouth and mouth opening were worse in the study by Axelsson et al.¹⁵⁶ Another study in long-term HNC survivors reported that difficulty swallowing was the second most common self-reported problem.¹⁵⁷ In our long-term follow-up, survivors with problems swallowing solid food reported poorer role and social functioning, and significantly worse on all scales from the EORTC QLQ-H&N35. Impaired role and social functioning, as well as problems with social eating, may lead survivors to withdraw from social situations involving food and eating, such as family dinners, restaurant visits and travel, which may increase the risk of loneliness. Difficulty swallowing solid food may indicate poorer HRQoL with significant symptom burden and need for nutritional support more than five years after diagnosis.

5.5 LIMITATIONS

There are some limitations to the studies in this thesis, some of which have already been addressed in the different sections above.

The study on which papers I and II are based, the ARTSCAN III study, was closed prematurely; therefore, the calculated sample size to be included could not be reached, and the results need to be interpreted with caution. The randomization was performed for the ARTSCAN III study, and only 6 participants of the 86 included at Sahlgrenska University hospital were not included in our sub-study. The availability of DXA measurements was limited during the first part of the study. This resulted in approximately half of the study group being measured at the 6-month follow-up, and there were probably more patients with a reduced muscle mass at this time point. However, when the patients who had DXA measurements at all follow-ups were analyzed separately, the changes in body weight, muscle mass and body fat were similar to those in the entire study group at all follow-ups, and more measurements at 6 months would probably not have changed the results. In paper II, patients were analyzed as one study group without the randomization allocation, and the statistical analyses became explorative.

The patients included in paper III were not stratified according to PA level, and unfortunately PA level in the study groups differed at diagnosis. Taking this into account, changes in PA levels at the follow-ups were presented. The study participants and outcome assessors were not blinded, which may have caused performance bias. Finally, the number of missed follow-ups during the study period was high due to the COVID-19 pandemic, and more patients than expected needed to be included.

Paper IV was a cross-sectional study, where information about causality or changes over time could not be obtained. No information was collected on survivors who declined participation, and we do not know whether these differed from the study group, which poses a risk of selection bias. Participants answered questions about dietary adjustments that were based on extensive clinical experience and existing research but not validated. The subgroups created based on swallowing difficulties and tumor locations became relatively small, and the analyses were explorative, which may have affected the generalizability of the study findings.

6 CONCLUSIONS

- Patients treated with cisplatin or cetuximab together with RT experienced severe nutritional problems, and malnutrition was prevalent, especially at the end of treatment. At 6 weeks, more cisplatin-treated patients used an enteral feeding tube and had lost more weight, compared to cetuximab-treated patients who lost more weight after treatment, resulting in similar weight loss at 3 months.
- Completely avoiding weight loss during RT together with systemic therapy is difficult, and treatment-induced muscle wasting due to inflammation is challenging. However, regaining muscle mass after therapy seems possible.
- Patients with advanced HNC who were diagnosed with malnutrition reported poorer HRQoL at baseline and at follow-ups, but no differences were observed at the end of treatment, as patients with and without malnutrition reported a significantly worse HRQoL.
- The individualized home-based exercise program resulted in increased physical activity among patients with oral cancer. Physical activity may also be able to help reduce fatigue and improve global QoL.
- The loss of body weight and muscle mass was low among patients with oral cancer, and no advantage from an exercise program was observed in terms of muscle mass or the prevalence of malnutrition.
- Long-term survivors of HNC, assessed more than five years after diagnosis, experienced many chronic nutrition impact symptoms and had poorer HRQoL compared with age- and sex-matched reference values from a Swedish normal population.
- A majority of long-term survivors of HNC needed to adjust their food intake to compensate for their nutritional problems, and for some survivors nutritional rehabilitation may be required long after treatment has ended.

7 CLINICAL IMPLICATIONS

- Measurement of muscle mass in clinical practice is valuable for optimizing nutritional treatment and assessing the GLIM criteria, which should be used to assess malnutrition in clinical practice.
- Physical activity might have beneficial effects on reducing fatigue and improving overall QoL in HNC patients, which should be taken into consideration in clinical practice. The questions about PA level in the national guidelines from the National Board of Health and Welfare are recommended for use in clinical practice and can be used to identify patients with low physical activity.
- QoL questionnaires, such as the EORTC QLQ-C30 and QLQ-H&N35, could be valuable to use in clinical practice, enabling information about symptoms and problems experienced by the patient, in both the short and long term, to improve rehabilitation and nutritional treatment.

8 FUTURE PERSPECTIVES

Nutritional treatment and rehabilitation before, during and after treatment are important, as this thesis emphasizes. The results from papers I and II showed not only a high prevalence of malnutrition during treatment but also that recovery of muscle mass after treatment is possible. This shows that measurement of body composition is valuable and could be used in the clinical setting to optimize individualized nutritional treatment. Future research in this field might involve measurement of body composition with more frequent time points to further explore where patients with HNC start to lose and regain muscle mass, which could reveal trends and optimize nutritional treatment even further.

The GLIM criteria are now established and accepted as a diagnostic tool for assessing malnutrition and should be implemented in the clinics. Guidelines on how to apply the muscle mass criteria and inflammation criteria are available, and the risk screening is under revision. However, the criteria for reduced energy intake still raise some questions, especially regarding how to assess this criterion in research and whether and how enteral and parenteral nutrition can be used to fulfill the criteria. Few studies have assessed malnutrition via the GLIM criteria in patients with HNC. Hence, it is important to continue to assess malnutrition according to the GLIM definition, and to study the different criteria included.

PA has shown benefits for patients with cancer, and our results add to these benefits by an increased PA level and a tendency toward reduced fatigue and better global QoL and role functioning in patients with oral cancer who participated in an exercise program. Future research on the effects of exercise on muscle mass, different aspects of fatigue and HRQoL is warranted, preferably via RCTs including larger sample sizes and different HNC populations. Assessment of PA levels may be valuable for identifying patients in need of exercise interventions, and both objective and subjective methods of assessing PA could be evaluated. The timing of when it is most beneficial to introduce an exercise intervention also needs to be explored further, and PA interventions in the HNC population can be designed to offer more individualized options to meet different preferences and increase adherence.

Long-term follow-up studies in HNC often follows a cross-sectional design. A longitudinal study design is desirable but require the inclusion of larger study groups to have enough participants for evaluation at the long-term follow-up.

A project that is now under consideration in our research group is to invite patients from the first study (papers I and II) for evaluation at a follow-up approximately 10 years after diagnosis. In addition to providing information about body composition and HRQoL, this follow-up could also be used to study survival in relation to HRQoL, phase angle and malnutrition according to the GLIM criteria. In Paper IV we did not include information on the survivors' food intake; this will be further explored in order to evaluate the diet quality. Additionally, our research group is currently planning a study where rehabilitation needs in patients with oral cancer will be evaluated one year after treatment.

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11 APPENDIX



EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med dig och din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på dig. Det finns inga svar som är "rätt" eller "fel". Den information du lämnar kommer att hållas strikt konfidentiell.

Dagens datum (Dag, Månad, År):

| | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|
| | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|

| | | Inte alls | Lite | En hel del | Mycket |
|-------------------------------|--|----------------------|-------------|-----------------------|---------------|
| 1. | Har du svårt att göra ansträngande saker, som att bära en tung kasse eller väska? | 1 | 2 | 3 | 4 |
| 2. | Har du svårt att ta en <u>lång</u> promenad? | 1 | 2 | 3 | 4 |
| 3. | Har du svårt att ta en <u>kort</u> promenad utomhus? | 1 | 2 | 3 | 4 |
| 4. | Måste du sitta eller ligga på dagarna? | 1 | 2 | 3 | 4 |
| 5. | Behöver du hjälp med att äta, klä dig, tvätta dig eller gå på toaletten? | 1 | 2 | 3 | 4 |
| Under veckan som gått: | | Inte alls | Lite | En hel del | Mycket |
| 6. | Har du varit begränsad i dina möjligheter att utföra antingen ditt förvärvsarbete eller andra dagliga aktiviteter? | 1 | 2 | 3 | 4 |
| 7. | Har du varit begränsad i dina möjligheter att utöva dina hobbyer eller andra fritidssysselsättningar? | 1 | 2 | 3 | 4 |
| 8. | Har du blivit andfädd? | 1 | 2 | 3 | 4 |
| 9. | Har du haft ont? | 1 | 2 | 3 | 4 |
| 10. | Har du behövt vila? | 1 | 2 | 3 | 4 |
| 11. | Har du haft svårt att sova? | 1 | 2 | 3 | 4 |
| 12. | Har du känt dig svag? | 1 | 2 | 3 | 4 |
| 13. | Har du haft dålig aptit? | 1 | 2 | 3 | 4 |
| 14. | Har du känt dig illamående? | 1 | 2 | 3 | 4 |
| 15. | Har du kräkts? | 1 | 2 | 3 | 4 |
| 16. | Har du varit förstoppad? | 1 | 2 | 3 | 4 |

Fortsätt på nästa sida

Under veckan som gått:

| | Inte alls | Lite | En hel del | Mycket |
|--|----------------------|-------------|-----------------------|---------------|
| 17. Har du haft diarré? | 1 | 2 | 3 | 4 |
| 18. Har du varit trött? | 1 | 2 | 3 | 4 |
| 19. Har dina dagliga aktiviteter påverkats av smärta? | 1 | 2 | 3 | 4 |
| 20. Har du haft svårt att koncentrera dig på saker som att läsa en tidning eller titta på TV? | 1 | 2 | 3 | 4 |
| 21. Har du känt dig spänd? | 1 | 2 | 3 | 4 |
| 22. Har du oroat dig? | 1 | 2 | 3 | 4 |
| 23. Har du känt dig irriterad? | 1 | 2 | 3 | 4 |
| 24. Har du känt dig nedstämd? | 1 | 2 | 3 | 4 |
| 25. Har du haft svårt att komma ihåg saker? | 1 | 2 | 3 | 4 |
| 26. Har ditt fysiska tillstånd eller den medicinska behandlingen stört ditt <u>familjeliv</u> ? | 1 | 2 | 3 | 4 |
| 27. Har ditt fysiska tillstånd eller den medicinska behandlingen stört dina <u>sociala</u> aktiviteter? | 1 | 2 | 3 | 4 |
| 28. Har ditt fysiska tillstånd eller den medicinska behandlingen gjort att du fått ekonomiska svårigheter? | 1 | 2 | 3 | 4 |

Sätt en ring runt den siffran mellan 1 och 7 som stämmer bäst in på dig för följande frågor:

29. Hur skulle du vilja beskriva din hälsa totalt sett under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig

Utmärkt

30. Hur skulle du vilja beskriva din totala livskvalitet under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig

Utmärkt



EORTC QLQ - H&N35

Patienter uppger ibland att de har följande symptom eller problem. Var vänlig och ange i vilken grad du har haft dessa besvär under veckan som gått. Sätt en ring runt den siffra som stämmer för dig.

| Under veckan som gått : | Inte alls | Lite | En hel del | Mycket |
|---|----------------------|-------------|-----------------------|---------------|
| 31. Har du haft smärtor i munnen? | 1 | 2 | 3 | 4 |
| 32. Har du haft smärtor i käken? | 1 | 2 | 3 | 4 |
| 33. Har du haft sveda i munnen? | 1 | 2 | 3 | 4 |
| 34. Har du haft smärtor i svalget? | 1 | 2 | 3 | 4 |
| 35. Har du haft problem med att svälja flytande? | 1 | 2 | 3 | 4 |
| 36. Har du haft problem med att svälja mosad mat? | 1 | 2 | 3 | 4 |
| 37. Har du haft problem med att svälja fast föda? | 1 | 2 | 3 | 4 |
| 38. Har du "satt i halsen" när du svält? | 1 | 2 | 3 | 4 |
| 39. Har du haft problem med tänderna? | 1 | 2 | 3 | 4 |
| 40. Har du haft problem med att gäpa? | 1 | 2 | 3 | 4 |
| 41. Har du varit torr i munnen? | 1 | 2 | 3 | 4 |
| 42. Har saliven varit seg? | 1 | 2 | 3 | 4 |
| 43. Har du haft problem med luktsinnet? | 1 | 2 | 3 | 4 |
| 44. Har du haft problem med smaksinnet? | 1 | 2 | 3 | 4 |
| 45. Har du hostat? | 1 | 2 | 3 | 4 |
| 46. Har du varit hes? | 1 | 2 | 3 | 4 |
| 47. Har du känt dig sjuk? | 1 | 2 | 3 | 4 |
| 48. Har ditt utseende besvärat dig? | 1 | 2 | 3 | 4 |

Fortsätt på nästa sida

Under veckan som gått :

| | Inte alls | Lite | En hel del | Mycket |
|--|----------------------|-------------|-----------------------|---------------|
| 49. Har du haft problem med att äta? | 1 | 2 | 3 | 4 |
| 50. Har du haft svårt att äta inför familjen? | 1 | 2 | 3 | 4 |
| 51. Har du haft svårt att äta inför andra människor? | 1 | 2 | 3 | 4 |
| 52. Har du haft svårt att njuta av måltiderna? | 1 | 2 | 3 | 4 |
| 53. Har du haft svårt att prata med andra människor? | 1 | 2 | 3 | 4 |
| 54. Har du haft problem med att prata i telefon? | 1 | 2 | 3 | 4 |
| 55. Har du haft svårt att umgås med din familj? | 1 | 2 | 3 | 4 |
| 56. Har du haft svårt att umgås med dina vänner? | 1 | 2 | 3 | 4 |
| 57. Har du haft svårt för att gå ut offentligt bland andra människor? | 1 | 2 | 3 | 4 |
| 58. Har du haft svårt för fysisk kontakt med din familj eller dina vänner? | 1 | 2 | 3 | 4 |
| 59. Har du känt dig mindre intresserad av sex? | 1 | 2 | 3 | 4 |
| 60. Har du känt mindre sexuell njutning? | 1 | 2 | 3 | 4 |

Under veckan som gått:

| | Nej | Ja |
|--|------------|-----------|
| 61. Har du använt smärtstillande mediciner? | 1 | 2 |
| 62. Har du tagit något näringstillskott? (förutom vitaminer) | 1 | 2 |
| 63. Har du haft matsond? | 1 | 2 |
| 64. Har du gått ner i vikt? | 1 | 2 |
| 65. Har du gått upp i vikt? | 1 | 2 |



EORTC QOL - FA12

Patienter berättar ibland att de har följande symptom. Markera i vilken utsträckning som du har haft dessa symptom under den senaste veckan. Svara genom att ringa in den siffra som bäst passar in på dig.

| Under veckan som gått: | Inte alls | Lite | En hel del | Mycket |
|---|----------------------|-------------|-----------------------|---------------|
| 1. Har du saknat energi? | 1 | 2 | 3 | 4 |
| 2. Har du känt dig utmattad? | 1 | 2 | 3 | 4 |
| 3. Har du upplevt att du varit tvungen att dra ner på tempot? | 1 | 2 | 3 | 4 |
| 4. Kände du dig sömnig under dagen? | 1 | 2 | 3 | 4 |
| 5. Hade du svårt för att sätta igång med saker och ting? | 1 | 2 | 3 | 4 |
| 6. Kände du dig nedstämd? | 1 | 2 | 3 | 4 |
| 7. Kände du dig hjälplös? | 1 | 2 | 3 | 4 |
| 8. Kände du dig frustrerad? | 1 | 2 | 3 | 4 |
| 9. Hade du svårt för att tänka klart? | 1 | 2 | 3 | 4 |
| 10. Kände du dig förvirrad? | 1 | 2 | 3 | 4 |
| 11. Stördes du av trötthet i dina dagliga aktiviteter? | 1 | 2 | 3 | 4 |
| 12. Kände du att dina närstående inte hade förståelse för din trötthet? | 1 | 2 | 3 | 4 |

INSTRUKTION: Detta formulär handlar om hur Du uppfattar Dina problem med att äta, dricka och svälja och hur Du tycker att det påverkar Dig. Besvara frågorna genom att ringa in det svarsalternativ Du tycker stämmer bäst in på Din situation de senaste 7 dagarna. Om Du är osäker, markera det alternativ som känns mest riktigt.

| | | Stämmer precis | Stämmer ganska bra | Osäker/ har ingen åsikt | Stämmer inte särskilt bra | Stämmer inte alls |
|-----|---|-------------------|--------------------------|-------------------------------|------------------------------------|-------------------------|
| 1. | Mina vardagsaktiviteter begränsas av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| E2. | Jag är genererad över mitt ätande | 1 | 2 | 3 | 4 | 5 |
| E4. | Jag blir upprörd, illa berörd av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| F1. | Det är svårt för andra att laga mat åt mig | 1 | 2 | 3 | 4 | 5 |
| P2. | Det är svårare att äta, dricka, svälja mot slutet av dagen | 1 | 2 | 3 | 4 | 5 |
| E7. | Jag känner mig besvärad när jag äter, dricker, sväljer | 1 | 2 | 3 | 4 | 5 |
| F5. | Jag har fått lägre inkomster på grund av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| P3. | Andra frågar "Varför kan du inte äta det?" | 1 | 2 | 3 | 4 | 5 |
| P7. | Det tar längre tid för mig att äta på grund av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| E3. | Andra blir irriterade på mina ätproblem | 1 | 2 | 3 | 4 | 5 |
| E6. | Jag har dålig självkänsla på grund av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |

| | Stämmer precis | Stämmer ganska bra | Osäker/ har ingen åsikt | Stämmer inte särskilt bra | Stämmer inte alls |
|--|-------------------|--------------------------|-------------------------------|------------------------------------|-------------------------|
| P8. Jag hostar när jag försöker dricka | 1 | 2 | 3 | 4 | 5 |
| F3. Mitt privata och sociala liv begränsas av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| F2. Jag har problem med att gå ut och äta med vänner, grannar eller släktingar | 1 | 2 | 3 | 4 | 5 |
| P6. Det är ansträngande att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| E5. Jag går inte ut på grund av mina sväljningsproblem | 1 | 2 | 3 | 4 | 5 |
| P5. Jag begränsar mitt födointag på grund av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| F4. Jag känner mig utanför på grund av mina ätproblem | 1 | 2 | 3 | 4 | 5 |
| P1. Jag kan inte behålla min vikt på grund av mina problem med att äta, dricka, svälja | 1 | 2 | 3 | 4 | 5 |
| P4. Det känns som om jag sväljer för mycket mat åt gången | 1 | 2 | 3 | 4 | 5 |
| X1. Det gör ont när jag äter, dricker, sväljer | 1 | 2 | 3 | 4 | 5 |
| X2. Maten fastnar när jag sväljer | 1 | 2 | 3 | 4 | 5 |
| X3. Jag har svårt att svälja för att jag är torr i munnen och halsen | 1 | 2 | 3 | 4 | 5 |
| X4. Jag måste skölja ned det jag äter för att kunna svälja | 1 | 2 | 3 | 4 | 5 |

TACK FÖR DIN MEDVERKAN !

Frändin/Grimby aktivitetsskala

Varje siffra framför nedanstående påståenden representerar en specifik nivå av fysisk aktivitet. Markera, med en ring runt den av siffrorna 1–6 som bäst motsvarar din nivå av fysisk aktivitet under den senaste veckan. Det räcker att uppfylla ett av påståendena för att denna skall kunna ringas in som din fysiska aktivitetsnivå.

1. Knappast någon fysisk aktivitet.
2. Mestadels sittande, ibland promenad, lätt trädgårdsarbete, ibland lätt hushållsarbete såsom att värma upp mat, damma eller "plocka undan".
3. Lätt fysisk aktivitet cirka 2–4 h per vecka såsom promenader, fiske, dans, trädgårdsarbete etc. inklusive promenad till och från affären. Huvudansvaret för lättare hemarbete såsom matlagning, damning, "plocka undan" och bädda sängarna. Utför eller tar del av veckostädning.
4. Medelmåttig fysisk aktivitet 1–2 h i veckan såsom jogging, simning, gymnastik, hårdare trädgårdsarbete, laga saker hemma eller lätt fysisk aktivitet mer än 4 h per vecka. Huvudansvaret för allt hemarbete, lätt såväl som tungt. Veckostädning med dammsugning, golvtvätt och fönsterputs.
5. Medelmåttig fysisk aktivitet 3 h per vecka såsom tennis, simning, jogging etc.
6. Hård eller mycket hård fysisk aktivitet regelbundet och flera gånger per vecka, där den fysiska ansträngningen är stor såsom vid jogging och skidåkning.

Tre frågor om vardagsmotion

Räkna samman all tid som är minst 10 minuter åt gången för varje fråga.

1. Hur mycket tid ägnar du en vanlig vecka åt vardagsmotion, till exempel promenader, cykling eller trädgårdsarbete?

0 minuter/Ingen tid

Mindre än 30 minuter

30-60 minuter (0,5-1 timmar)

60-90 minuter (1-1,5 timmar)

90-150 minuter (1,5-2,5 timmar)

150-300 minuter (2,5-5 timmar)

Mer än 300 minuter (5 timmar)

2. Hur mycket tid ägnar du en vanlig vecka åt fysisk träning som får dig att bli andfådd, exempelvis löpning, motionsgymnastik eller bollsport?

0 minuter/Ingen tid

Mindre än 30 minuter

30-60 minuter (0,5-1 timmar)

60-90 minuter (1-1,5 timmar)

90-120 minuter (1,5-2 timmar)

Mer än 120 minuter (2 timmar)

3. Hur mycket sitter du under ett normalt dygn om man räknar bort sömn?

Så gott som hela dagen

13-15 timmar

10-12 timmar

7-9 timmar

4-6 timmar

1-3 timmar

Aldrig