Impact of disease and treatment on body weight and eating in patients with head and neck cancer – experiences from a multicenter study

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"When we long for life without difficulty,
remind us that oaks grow strong under contrary winds
and diamonds are made under pressure."

Peter Marshall

Table of contents

Abstract

Background Nutritional deterioration in patients with head and neck cancer (HNC) has a multifactorial etiology mainly associated with tumor and treatment related factors. The objective of the present thesis was to investigate the impact of the disease and treatment on body weight and eating in patients with HNC treated with radiation therapy (RT) as the single modality treatment or as preoperative RT by analyzing body weight and body mass index (BMI) over time, predictive factors for weight loss and BMI, weight loss and BMI as prognostic factors for survival, and by studying the patients' own experience of food and eating.

Methods ARTSCAN is a randomized prospective multicenter trial conducted between the years of 1998 - 2006. Data were collected during and after RT with a total follow-up time of five years. Nutritional data from the whole study cohort (n = 712), from patients with oropharyngeal cancer (n = 232) and from two of the participating treatment centers (n = 101) were retrospectively analyzed in the present thesis. In addition, interviews (n = 13) were conducted nine months after the termination of RT as part of a care development project.

Results On a group level, the patients lost weight during and after RT with a nadir at five months after the termination of RT. Factors related to a higher weight loss were oropharyngeal cancer, a high BMI at the start of RT, post-treatment aspiration, no tube feeding at the start of RT, and larger treated volumes. Furthermore, a high BMI at the start of RT was shown to be significantly related to a better five-year overall survival in patients with oropharyngeal cancer, whereas weight loss was not. The patients' own narratives showed that all aspects of food, eating and meals were affected by the remaining sequelae, and that the patients found ways to accept and cope with the changes that had to be done to facilitate eating.

Conclusions and clinical implications The disease and treatment gave persistent effects on the HNC patients' weight and BMI which calls for a prolonged nutritional follow-up. The predictive factors found for weight loss can be used during patient history to find patients at risk for nutritional deterioration. In oropharyngeal cancer, patients with a high BMI at the start of RT had the best survival. This finding indicates that patients with a low BMI should be encouraged to gain weight before RT start. All aspects of food, eating and meals were affected during and after RT, and therefore the nutritional treatment should be given with a holistic approach to meet the multifaceted need patients with HNC experience.

Abbreviations

AF	Accelerated fractionation
ARTSCAN	Accelerated Radiotherapy of Squamous cell Carcinoma of the head and Neck
ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	Body mass index (weight in kilograms divided by height in meters squared)
CF	Conventional fractionation
CTV	Clinical target volume
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESPEN	European Society for Clinical Nutrition and Metabolism
FFM	Fat free mass
GTV	Gross tumor volume
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
HNC	Head and neck cancer
HPV	Human papilloma virus
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity-modulated radiation therapy
KPS	Karnofsky Performance Status (scale)
LENT-SOMA	Late Effects in Normal Tissues Subjective, Objective, Management and Analytic (scale)
MUST	Malnutrition Universal Screening Tool
PEG	Percutaneous endoscopic gastrostomy
PG-SGA	Patient-Generated Subjective Global Assessment
PTV	Planning target volume
QoL	Quality of life
RT	Radiation therapy
SALU	Swallowing dysfunction in ARTSCAN patients in Lund and Umeå
SCC	Squamous cells carcinomas
TF	Tube feeding
TNM	T: primary tumor size, N: regional nodal spread, M: distant metastases (M)
TV	Treated volume
UICC	Union for International Cancer Control
VF	Videofluoroscopy
3-DCRT	Three-dimensional conformal radiation therapy

Glossary

These terms have been defined in the present thesis as follows:

Nutritional status	Nutritional status reflects the extent to which the body's development, composition and function are affected by food intake (1), but also by other factors such as disease, changed metabolism or malabsorption (2).
Malnutrition	A state of nutrition in which a deficiency or excess of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function, and clinical outcome (3).
Nutritional deterioration	Worsening in a patients' nutritional status.
Patients at nutritional risk	Patients with or at risk of developing nutritional deterioration and consequently at risk of developing malnutrition.
Cancer cachexia	A multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment (4).

Svensk populärvetenskaplig sammanfattning

Nutritionsproblem vid huvud- och halscancer

Nutritionsproblem är mycket vanligt hos patienter med huvud- och halscancer och har en multifaktoriell förklaringsgrund. Förmågan till och vad som går att äta och dricka kan påverkas av själva tumören och dess anatomiska läge men även av den behandling som ges. Strålbehandling, som är den vanligaste behandlingsformen vid huvud- och halscancer, kan leda till olika behandlingsbiverkningar som direkt påverkar förmågan att äta och dricka. Det lägre matintaget kan ge negativa effekter på patientens nutritionsstatus vilket i sin tur kan leda till försämrad fysiskt funktion och lägre livskvalité.

ARTSCAN

ARTSCAN är en prospektiv, randomiserad multicenterstudie som genomfördes i Sverige mellan åren 1998 - 2006. Totalt inkluderades 750 patienter med huvud- och halscancer. Huvudsyftet med ARTSCAN var att studera effekten av två olika typer av strålbehandlingsprotokoll: den konventionella behandlingen med en behandling per dag under sju veckor och den accelererade behandlingen med två behandlingar per dag under fem veckor. Biverkningar och behandlingseffekt registrerades varje vecka under strålbehandlingen samt vid regelbundna uppföljningar efter behandlingens avslutning upp till fem år.

Data från 712 patienter i ARTSCAN studien användes till att studera faktorer som påverkar viktförlust och viktförändring över tid (Studie 1). Data från patienter med orofarynxcancer användes till att undersöka hur bestrålad volym korrelerar med viktutveckling samt om viktförändring och body mass index (BMI) har betydelse för överlevnaden (n = 232) (Studie 2). Data från två av de behandlande sjukhusen som ingick i ARTSCAN (Norrlands Universitetssjukhus och Lunds Universitetssjukhus) användes till att studera sväljningsfunktionens effekt på viktförändring och BMI på lång sikt efter avslutad behandling (n = 101) (Studie 3).

Vårdutvecklingsprojektet “Vägen tillbaka”

Under åren 2009 - 2011 genomfördes ett vårdutvecklingsprojekt (”Vägen tillbaka”) vid Norrlands universitetssjukhus med syftet att hjälpa patienter med huvud- och halscancer tillbaka till en normal vardag efter avslutad

behandling. Som en del av detta vårdutvecklingsprojekt genomfördes intervjuer med 13 patienter nio månader efter avslutad behandling för att undersöka upplevelsen av mat, måltider och ätande hos denna patientgrupp (Studie 4).

Viktförändring och faktorer för viktförlust

Resultatet från Studie 1 visade att studiegruppen som helhet förlorade i vikt under och efter behandling med lägsta nivå vid fem månader efter avslutad strålbehandling. Vidare visade Studie 3 att patienter med allvarliga sväljningssvårigheter minskade i vikt från 23 månader efter avslutad strålbehandling.

Patienter med tumör i orofarynx (Studie 1 och 3), patienter med högt BMI vid behandlingsstart (Studie 1 och 3), patienter utan nutritionsstöd vid behandlingsstart (Studie 1 och 2), patienter behandlade med större bestrålad volym (Studie 2) och patienter med allvarliga sväljningssvårigheter efter avslutad behandling (Studie 3) var de grupper som hade störst viktförlust. Ingen skillnad i viktförlust kunde påvisas mellan patienter som fått konventionell eller accelererad strålbehandling (Studie 1).

Förhållandet mellan viktförändring respektive body mass index och överlevnad

I Studie 2 undersöktes relationen mellan BMI vid behandlingsstart (undervikt, normalvikt, övervikt/fetma) respektive viktförändring upp till fem månader efter avslutad behandling (<10%, ≥10%) och femårsöverlevnad hos patienter med orofarynxcancer. BMI visade sig ha betydelse för femårsöverlevnaden medan ingen koppling kunde påvisas till viktförlust. Patienter med övervikt/fetma vid behandlingsstart hade bättre femårsöverlevnad än patienter med normalvikt eller undervikt.

Upplevelsen av mat, måltider och ätande efter behandling

Patienternas beskrivna upplevelser av tiden efter avslutad behandling visade att många aspekter av mat, måltider och ätande påverkades av de kvarvarande behandlingsbiverkningarna (Studie 4). Många patienter var tvungna att välja bort livsmedel och anpassa konsistensen på maten för att kunna äta tillräckligt. Detta påverkade både upplevelsen och njutningen av maten men skapade också svårigheter vid måltider tillsammans med andra individer.

Slutsats och kliniska implikationer

Viktförlust hos patienter med huvud- och halscancer påverkas av olika faktorer. I studie 1 - 3 fann vi specifika faktorer av direkt betydelse för viktutvecklingen hos denna patientgrupp vilket är information som kan bidra till att hitta patienter med speciella behov av nutritionsstöd. Vi visade även att ett högre BMI vid behandlingsstart har betydelse för överlevnaden hos patienter med orofarynxcancer vilket kan tala för att överlevnaden hos patienter med ett lågt BMI kan främjas genom att uppmuntra patienter till att öka i vikt inför behandlingsstart.

Många patienter som behandlas för huvud- och halscancer upplever omfattande påverkan på olika aspekter av mat, måltider och ätande – även efter avslutad behandling. Vi fann att patienterna når sin lägsta vikt vid fem månader efter avslutad strålbehandling och därefter i regel har svårt att återfå sin ursprungsvikt. Patienterna bör därför följas upp regelbundet efter avslutad behandling för att hitta patienter i behov av nutritionsstöd. Vidare bör nutritionsbehandlingen som ges till denna patientgrupp inkludera alla aspekter av mat, måltider och ätande dvs. ges med ett helhetsperspektiv för att tillgodose alla behov hos patienten.

Prologue

During the last semester at the Dietetics program I was given the opportunity to do my clinical practice at the Department of Oncology at the University Hospital of Umeå. This was where it all started – my special interest in patients with head and neck cancer. When meeting these patients I understood that the dietitian had an important role to play in the treatment of this group of patients, and this was something that I became intrigued about.

After some years of working both as a clinical dietitian and as a teacher at the Dietetics program at the Umeå University, I was lucky to meet a physician (my main supervisor to be) with a great passion for nutrition in head and neck cancer and research. This was where my journey as a PhD student began.

During my years as a PhD student, I have met a lot of interesting people (patients, researchers, dietitians and other health-care professionals) all with the common ground in head and neck cancer. This has enhanced and deepened my interest further and acknowledged the fact that we need to learn more about nutrition for this group of patients.

Before reading this thesis, take a moment and reflect on the deeper meaning that food and eating has to each of us. For me, food comprises pleasure and socialization, and I enjoy working with food and nutrition as part of my daily work. However, I have been told by the patients I have met that their meaning of food has changed - that some types of food are impossible to eat because of their composition and texture, the former making it hard to swallow and the latter making the sensitive mucosa in the mouth sore; in total this leaves the patient with an unclean and painful mouth making dining with others difficult. Therefore, I hope this thesis both broadens and deepens the understanding of the different challenges related to food and eating that patients with head and neck cancer face, and highlights the importance of nutrition and care to this group of patients. So, enjoy!

Sincerely,

Sandra Ottosson

Original papers

This thesis is based on the following papers:

I. Ottosson S, Zackrisson B, Kjellén E, Nilsson P, Laurell G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. Acta Oncol. 2013;52:711–8.

II. Ottosson S, Söderström K, Kjellén E, Nilsson P, Zackrisson B, Laurell G. Weight and body mass index in relation to irradiated volume and to overall survival in patients with oropharyngeal cancer: a retrospective cohort study (submitted).

III. Ottosson S, Lindblom U, Wahlberg P, Nilsson P, Kjellén E, Zackrisson B, Levring Jäghagen E, Laurell G. Weight loss and Body Mass Index in relation to aspiration in patients treated for head and neck cancer: a long-term follow-up (submitted).

IV. Ottosson S, Laurell G, Olsson C. The experience of food, eating and meals following radiotherapy for head and neck cancer: a qualitative study. J Clin Nurs. 2013;22:1034-43.

Introduction

Food and eating are for most of us elements in everyday life that are taken for granted. Given its multidimensional nature, food and eating include important aspects correlated with physiological, psychological, social and cultural elements (5). Inevitably, when not being able to eat and enjoy food together with others, fundamental aspects of life may change. Having head and neck cancer (HNC) often means that different aspects of food and eating become affected by the disease and related treatment.

Head and neck cancer

HNC is a collective name for malignant tumors in the upper aero-digestive tract, i.e. tumors of the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, and salivary glands (6-8) (**Figure 1**). The tumors are primarily squamous cells carcinomas (SCC), which account for more than 90% of all cases (8).

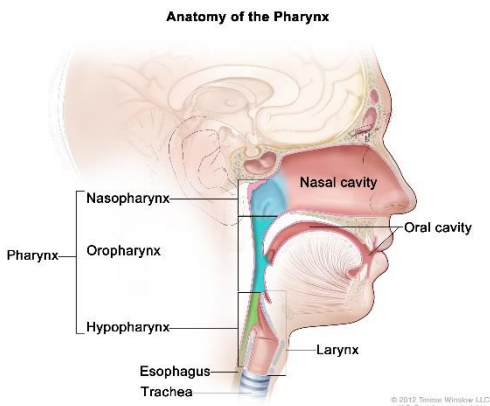

Figure 1. Anatomy of the pharynx. ©2012 Terese Winslow LLC.

HNC represents 6% of all cases of cancer in the world (6), and in Sweden, HNC accounts for approximately 2.3% of all cases with an incidence of 1300 new cases per year (9). Common symptoms on disease presentation are sore throat, hoarseness, swallowing difficulties, and oral ulceration (7). Patients who get diagnosed with HNC are most commonly in their early 60s and men are overrepresented (6, 7, 10). Main risk factors are alcohol and tobacco smoking, which have been estimated to account for 75% of all cases with a joint effect if the two are combined (6, 7). Convincing evidence also exists for the connection between the human papilloma virus (HPV) and a specific subset of HNC, which gives an explanation to why oropharyngeal cancer now becomes more common in the younger population (6-8, 11). HNC is often

regarded a loco-regional disease with a low incidence of distant metastases at diagnosis (6) and the majority of treatment failures occur at the tumor site and/or in regional lymph nodes. Due to the vague symptoms at disease presentation, HNC is commonly diagnosed at a late stage (6), which gives a poor prognosis (12). Half of the patients with advanced disease will develop relapses, usually within the first two years following treatment (6). This gives an approximately 60% survival rate at five years (6, 8).

The tumors in the head and neck are anatomically classified according to primary tumor size (T), regional nodal spread (N) and distant metastases (M) with different criteria for different primary sites. The Union for International Cancer Control (UICC) TNM staging system has been used for decades worldwide for the staging of tumors (13, 14). The tumors are staged I-IV with stages III-IV defining a more advanced disease. The staging of tumors is an important tool in clinical practice for guidance in therapeutic decision making and for reporting and comparing outcomes of therapy.

Medical treatment and related morbidity

The treatment of HNC requires a multidisciplinary approach, and the treatment regimens applied are radiation therapy (RT) or surgery used alone, in combination and/or with chemotherapy (6, 8). Reasons for choosing the one treatment approach over the other are primarily based on tumor related factors such as tumor site and stage and if the treatment is given with a curative or palliative intent (6).

RT is commonly delivered using three-dimensional conformal radiation therapy (3-DCRT) or intensity-modulated radiation therapy (IMRT) techniques during weekdays to a total dose of 50 - 70 Gray (Gy) (6, 8, 15). The total radiation dose is split into fractions to get a sparing effect on irradiated late-responding healthy tissue (15). Different approaches in the delivery of fractionations and thus overall treatment time have been developed due to the fear of repopulation of cancer cells during RT (16). The standard treatment is conventional fractionation (CF) but other fractionation alternatives like accelerated fractionation (AF) and hyper-fractionation are also used. CF is mainly given on consecutive weekdays with one fraction daily (usually 2 Gy per day), e.g. during seven weeks for a total dose of 70 Gy (6). In comparison, hyper-fractionated RT is given with more fractions per day with a reduced dose per fraction. For AF, the total treatment time is shortened as the daily dose is larger and given with two or more fractions. Several randomized controlled trials have been conducted to evaluate the treatment effect between CF and the other fractionation alternatives (17, 18). These studies have been the subject of a meta-analysis with findings showing beneficial outcomes in

tumor control and survival with these schedules compared to CF (19). Contrary to the better treatment outcome, the multiple fractionation alternatives have been shown to result in a higher frequency of both acute and late toxicities (17, 18, 20).

The aim in the RT planning is to deliver the prescribed dose to the tumor volume while keeping the irradiated dose to normal tissue at a minimum. The International Commission on Radiation Units and Measurements (ICRU) has developed guidelines for volume definitions for RT (**Figure 2**) (21-23). The gross tumor volume (GTV) is defined as the volume containing the malignant tumor mass. The clinical target volume (CTV) includes GTV with a safety margin for subclinical malignant spread, i.e. microscopic tumor undetectable by clinical examination. The planning target volume (PTV) includes CTV with a margin for geometric uncertainties including setup variations. The volume delineations are tailored for each patient and diverse routines gives heterogeneity in the target definitions between different treatment centers (24).

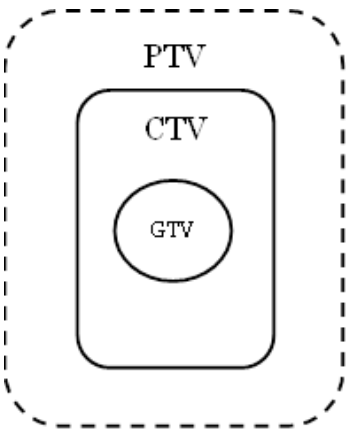

Figure 2. Volume definitions in radiation therapy. Abbreviations: gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV).

Radiation damage to healthy cells within the treatment area leads to RT toxicities. Skin, mucosa, subcutaneous tissues, bone, and salivary glands are tissues in the head and neck area that are frequently exposed to RT, and from where treatment toxicities may develop (25). The frequency and severity of these toxicities are dependent on factors such as total dose, dose per fraction, fractionation schedule, and overall treatment time, but also on a number of patient-related factors such as age and smoking (25, 26). There is also an individual susceptibility and reaction to RT.

The RT toxicities are defined as acute or late. Acute toxicities are due to damage on cells with rapid turnover (15, 25) and have been suggested to be defined as acute from day one of RT through day 90 commencing RT (27). However, the development and use of alternative fractionation schedules have led to the questioning of the previously set cut-off point for acute toxicities, i.e. prolonged acute toxicities have been noticed beyond the 90-day mark (28). Pain, mucositis, taste alterations, changes in quantity and composition of saliva, and swallowing dysfunction are all examples of acute RT toxicities (15, 25, 29). Late toxicities may primarily develop due to damage to cells with slow

turnover (15, 25). Most of the late effects develop during the first three years after the termination of treatment, but a few may appear or progress after that time point (28) and some patients may experience permanent unwanted changes (30). Patients with severe acute treatment toxicities do not necessary develop late toxicities (25). Swallowing dysfunction, loss of taste, trismus (restricted mouth opening), and xerostomia (dry mouth) are all examples of late treatment toxicities due to RT (15, 29, 30) with xerostomia being the most frequently reported (31).

Surgery is most commonly given in conjunction to RT, either before or after (6). The treatment approach is to remove the tumor (resection of primary tumor), remove metastases and/or microscopic spread to lymph nodes of the neck (neck dissection) or a combination of both. The functional outcome is dependent on tumor related factors and type of reconstruction with the most frequently reported side-effects of surgery being disfigurement, voice loss and difficulties with eating (31).

Chemotherapy has primarily been used for treatment of HNC with a palliative intent, but during recent years has been argued to be an important part of combined-modality curative treatment of locally advanced HNC (6, 32). The aim for this multimodal treatment approach is to reduce distant disease and to enhance loco-regional control by an increased sensitization effect on RT. Although this type of combined treatment approach might give a better treatment outcome in advanced disease, it also gives an increased toxicity (6, 28). Almost half of the patients experience symptoms one year after the commencement of chemotherapy (33). Frequently reported morbidity of chemotherapy when used in combination with RT has been correlated with reduced or changed saliva, swallowing dysfunction, and taste alterations (31).

Treatment of head and neck cancer in Sweden

Today there are eleven treatment centers responsible for the medical treatment of patients with HNC in Sweden. In northern Sweden, the treatment is centralized to one University hospital (the University Hospital of Umeå) that treats approximately 110 new patients per year from almost half the area of Sweden. Therefore, many patients stay at a patient hotel during treatment due to the long distance to travel. The treatment is given with a multidisciplinary approach and is handled by the health-care system close to the patients' home after treatment.

Factors related to nutritional deterioration in head and neck cancer

Patients with HNC are a nutritionally vulnerable group due to the large number of factors that may impact on their ability to eat, and thus lead to nutritional deterioration. In simple terms, these factors can be summarized into three groups: tumor-related factors, treatment-related factors, and psychological and social elements (**Figure 3**).

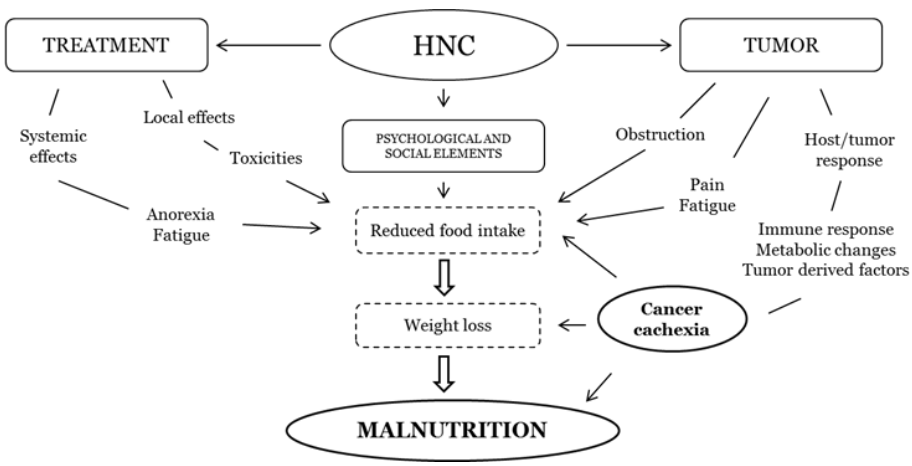

Figure 3. Simplified picture of the multifactorial nature of nutritional deterioration in head and neck cancer (HNC) (2, 31, 34-41).

Tumor impact

The tumor itself may directly impact food intake negatively by obstruction of the bolus passage (31, 37). Hence, a high prevalence of weight loss and dysphagia have been reported before treatment in patients with HNC (42-44) with the highest frequency of dysphagia seen in patients with locally advanced tumors (44). Besides the direct obstructional effect, the tumor may also cause pain, enhanced inflammatory activity and altered metabolic function, and together with host-induced responses and anticancer treatment result in a syndrome called cancer cachexia (34-36, 40). Cancer cachexia is defined as *"a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment"* (4). Common symptoms in patients with cancer cachexia are anorexia, weight loss, muscle wasting, and metabolic disturbances (4, 34-36, 40) that all may exert profound effects on the patients' nutritional status.

Treatment impact

The treatment related toxicities in HNC have been established in earlier studies as a strong denominator for reduced food intake (45-48) and weight loss (42, 45, 46, 48-50). Clinically examined predictive factors for nutritional deterioration based on weight loss found in earlier studies are summarized in **Table 1** (42, 45, 46, 48-57). Besides the local effects on healthy tissues, it is also important to recognize the RT systemic effects (38) that might lead to anorexia and fatigue (34, 41) and consequently reduced food intake.

Psychological and social elements

The patients' own experiences of how the disease and treatment may affect food and eating have been described in previous research using a qualitative approach (39, 58-62). During and after treatment, many patients highlight food and eating as being significantly affected by the treatment toxicities (39, 58-62). Thus, eating problems are a frequently described symptom during the trajectory of care (39, 60, 62) that have a huge impact on the patients' daily life (60, 61). Besides affecting food intake, the eating problems also impact the psychosocial aspects of eating both during and after treatment (39, 59, 61). Hence, the changes in eating and food choices that needs to be done to facilitate eating give problems when eating together with others and in public environments (39, 61).

Nutritional deterioration in patients with head and neck cancer

It is evident that there are a diverse number of factors related to tumor, treatment and life-aspects that may impact negatively on the HNC patients' ability to eat and hence lead to nutritional deterioration. The fundamental base for nutritional deterioration is an energy imbalance where the total energy expenditure exceeds the energy intake (63). The resting energy expenditure in patients with cancer can be elevated, normal or reduced (64), and this response varies between different cancer types (65) as well as between patients with the same tumor site (66). In patients with HNC, resting energy expenditure has been shown to remain stable between the pre-treatment and post-treatment period (67). Hence, an energy imbalance in this patient group is most probably due to reduced energy intake related to tumor obstruction and/or treatment toxicities.

Table 1. Predictive factors for nutritional deterioration in head and neck cancer (HNC) based on weight loss. Abbreviations: radiation therapy (RT), Karnofsky Performance Status (KPS) scale, body mass index (BMI).

First author	n	Study population	Results
Beaver et al.	249	HNC Diverse stages and tumor sites	Tumor site, use of chemo-RT, and severe pre-treatment weight loss were significantly associated to weight loss during RT using univariate analyses.
Jager-Wittenaar et al.	407	HNC Diverse stages and tumor sites	Tumor site, loss of appetite, dysphagia/passage difficulties, and loss of taste/aversion were significantly associated to weight loss (>5% in 1 months or >10% in 6 months) preceding RT using multivariate analysis.
Kubrak et al.	341	HNC Diverse stages and tumor sites	Anorexia, dysphagia, mouth sores, and other (depression, no money, disfigurement, difficulty chewing) were significantly associated to weight loss ≥2% during six months preceding RT in multivariate analysis.
Kubrak et al.	38	HNC Diverse stages and tumor sites	Pain and mucositis were significantly associated to weight loss in patients treated with RT, and CRP, loss of appetite, pain, mucositis, and xerostomia were significantly associated to weight loss in patients treated with chemo-RT using multivariate analyses.
Kubrak et al.	52	HNC Diverse stages and tumor sites	Dysphagia and sore mouth were significantly associated to weight loss during and after treatment using multivariate analysis.
Mallick et al.	103	HNC Diverse stages and tumor sites	Planning target volumes and chemo-RT were significantly associated to >5% weight loss during RT using multivariate analysis.
Munshi et al.	140	HNC Diverse stages and tumor sites	A low initial KPS and use of chemo-RT were significantly associated to weight loss >10% during RT using univariate analyses.
Nourissat et al.	540	HNC Stage I+II and diverse tumor sites	Tumor site, pre-RT body weight, stage II disease, dysphagia and/or odynophagia, and a low KPS (all characters at the start of RT) were significantly associated to weight loss during RT using multivariate analysis.
Nourissat et al.	540	HNC Stage I+II and diverse tumor sites	Tumor site, stage II disease, pre-RT body weight, pre-RT dysphagia and/or odynophagia, dietary energy intake during RT, mucosa adverse effect of RT, constipation, and other digestive symptoms were significantly associated to weight loss during RT using multivariate analysis.
Ravasco et al.	205	HNC, gastro-oesophageal, colon and rectum cancer Diverse stages and tumor sites	Clinical stage was significantly associated to weight loss (>10% in 6 months) preceding RT using multivariate analysis.
Schmidt et al.	368	HNC Diverse stages and tumor sites	Advanced clinical stage, loss of appetite, and difficulty swallowing were significantly associated to ≥5% weight loss over 6 months using multivariate analysis.
Silander et al.	134	Oral and pharyngeal cancer	Use of chemotherapy and a high BMI at the start of RT were significantly associated to >10% weight loss up to 6 months after diagnosis using multivariate analysis.
Tiblom Ehrsson et al.	232	HNC Diverse stages and tumor sites	Clinical stage was significantly associated to maximum body weight loss during and after RT using multivariate analysis.

The nutritional deterioration in patients with HNC displays a wide range. Some patients may suffer light changes whereas others may develop more severe changes in their nutritional status. Eventually, if not properly managed, the nutritional deterioration may lead to malnutrition. Malnutrition is defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as *"a state of nutrition in which a deficiency or excess of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function, and clinical outcome"* (3). Although the definition includes both over and under-nutrition, the focus in patients with HNC is on under-nutrition. Diversity exists in how to accurately diagnose malnutrition and therefore, the prevalence of malnutrition in patients with HNC may vary between 20 - 67% (68).

Severe weight loss may be used as an indicator for finding patients at nutritional risk (54, 68), i.e. patients with or at risk of developing nutritional deterioration and consequently at risk of developing malnutrition. A weight loss of 5 - 10% over the previous 3 - 6 months can be summarized as cut-off points commonly found in the literature to identify patients at nutritional risk (2). Weight loss in HNC is a common feature through the trajectory of care and may be present before (42, 43, 54, 69), during (47, 55, 67, 70-74) and after treatment (47, 55, 67, 71, 74, 75). It has been shown that more than half of the patients lose weight before treatment (43), and that a weight loss of ≥5% in 1 month or ≥10% in 6 months can occur in every fifth patient preceding treatment (42). After treatment, patients are reported to continue to lose weight with a nadir of weight loss at approximately six months after the termination of RT (55, 70, 74). After the nadir point of weight loss, few patients are able to regain their previous weight. During the first year, more than half of the patients are reported to have had a weight loss of >10% from pre-treatment weight (75) with a mean weight loss ranging between 7.5 – 17.4% (47, 55, 74). Up to two years, the weight has been shown to stabilize (70) or increase (74), but the patients may still display a weight loss of 12% compared to pre-treatment weight (74). Little is known about the long-time weight change beyond two years in HNC, i.e. if the patients are able to reach weight stability or gain, and if so, how long it will take to return to pre-treatment weight after the termination of treatment.

Body mass index (BMI, weight in kg divided by height in meter squared) is a measure used to assess the patients' current nutritional situation (76). The ESPEN guidelines defines borderline underweight as BMI <20 kg/m^2 (76) and the World Health Organization uses BMI <18.5 kg/m^2 as the cut-off point for underweight (77). Higher cut-off points for BMI in aging have been proposed (78) since the amount of fat free mass (FFM, body mass minus fat mass) decreases with age (2). The average BMI at the start of treatment in patients

with HNC has been shown to be within or above normal range on a group level, both in Sweden as well as in other countries (43, 45, 46, 54, 55, 67, 75). Older patients, patients with tumors of the pharynx or oral cavity and patients with stage III-IV disease are usually those presented with the lowest BMI (46, 54). Following treatment, the BMI decreases (45, 67) resulting in a higher number of patients with underweight (75).

Consequences of nutritional deterioration head and neck cancer

Physical consequences

The definition for malnutrition (see Glossary) implies that the changes in body composition should be of such a degree that it impairs normal function, i.e. leads to loss of FFM, diminished immune function and reduced muscle strength (2, 79). A number of previous studies in HNC have displayed a relation between significant weight loss and reduced physical function (67-69, 80-82). More specifically, critical weight loss in this group of patients has been correlated to reduced immune function, impaired performance status and a decline in hand grip strength (67, 80, 81) and thus increased risk of infections, postoperative complications and higher hospital readmission rates (68, 69).

Psychological consequences

Quality of life (QoL) is a multidimensional concept that includes social, personal, cultural, demographical, and environmental elements (83). The concept of health-related QoL is narrower and is related to factors associated with the disease and treatment, i.e. impairments and disability, and is therefore a common term used in clinical practice and research. It has previously been shown that a poor nutritional status may reduce QoL in patient with cancer (84). Patients with HNC having weight loss either before, during or after treatment score worse in health-related QoL (73, 85, 86) and generally have impaired outcome on QoL items (85, 86) especially on items related to physical function (87) and social eating (73, 86).

Nutritional screening and assessment

Nutritional screening aims to find patients at risk of nutritional deterioration before it progresses to malnutrition. There are a number of different screening tools available for clinical use and many incorporate information on the patients' BMI and previous weight loss (2). Both the ESPEN guidelines for nutritional screening and The National Board of Health and Welfare in Sweden states that involuntary weight loss in combination with information

about BMI and eating difficulties are fundamental to find patients at risk of a poor nutritional status (76, 88). Similarly, the Malnutrition Universal Screening Tool (MUST) is a screening tool that uses weight loss, BMI and disease effect to find patients at nutritional risk and in need of further actions (89) and is stated to be a reliable tool to use in patients with HNC (90).

If patients during the screening process have been found to be at nutritional risk, further investigation and assessment of the patients' nutritional status are warranted. Several assessment tools have been developed to assess the patients' nutritional status in clinical practice (40, 76). For patients in general, presence of two or more of the following characteristics is recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) for the diagnosis of malnutrition: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, and diminished functional status (91). The Patient-Generated Subjective Global Assessment (PG-SGA) is an assessment tool specially developed for cancer patients (92) that has been translated into Swedish (93) and is recommended to be used for the assessment of nutritional status in patients with HNC (90). PG-SGA incorporates both objective and subjective measurements and as a result of the PG-SGA the patients can be classified into three groups according to their nutritional status: well-nourished, moderately malnourished/suspected malnutrition or severely malnourished.

Nutritional support in head and neck cancer

The initial screening and assessment process makes it possible to find patients at nutritional risk that may need proactive or reactive nutritional interventions to reduce the risk of malnutrition. The goals for nutritional treatment in patients with cancer are primarily to prevent and treat malnutrition and improve QoL (94). Similarly, for patients receiving RT the aims are to minimize weight loss, maintain QoL and manage symptoms (95). No "gold standard" for nutritional support exists, but different guidelines have been developed for cancer patients in general (94, 96), for patients receiving RT (95), and for patients with HNC (90).

During and after treatment many patients are in need of nutritional support, either as oral nutritional supplements, tube feeding (TF), and/or parenteral nutrition (94). Dependent on the extent of the eating difficulties, the nutritional support may either be used as a supplement to regular food intake or include the entire need of energy and nutrients. TF is given using nasogastric, nasoenteral or percutaneous tubes (3). When TF should be administered in patients with HNC has caused controversy within clinical practice and research, and thus no guidelines exist on when in the treatment

process TF should be initiated. Some treatment centers give TF with a prophylactic intent, that is, all patients are provided with a percutaneous endogastric gastrostomy (PEG) to counteract the anticipated reduction in nutritional status during treatment. Other treatment centers only install a feeding tube when there is a specific indication.

Nutritional treatment in patients with head and neck cancer in Sweden

Most treatment centers for HNC in Sweden have a dietitian responsible for the nutritional treatment (*survey from ten treatment centers in Sweden, unpublished data, 2012*). The majority of treatment centers in Sweden wait to install the feeding tube until indicated, that is, few centers practice prophylactic PEG use.

Aims and objectives

The main aim of this thesis was to describe the impact of the disease and treatment on body weight and eating in patients with HNC treated with RT as the single modality treatment or as preoperative RT.

Specific objectives:

- *To analyze weight change over time in patients with HNC with focus on two fractionation schedules, and to explore other predictive factors for weight change during and after RT (Paper I).*

- *To analyze if the treated volume (TV) can predict weight loss in patients with oropharyngeal cancer and thereby provide information on patients at risk of malnutrition and in need of special nutritional surveillance, and to analyze weight loss and BMI in patients with oropharyngeal cancer in relation to five-year overall survival. (Paper II).*

- *To investigate the long-term impact of pharyngeal swallowing function with focus on aspiration on weight development and BMI in patients with HNC treated with RT (Paper III).*

- *To describe the experience of food, eating and meals in patients with HNC in a long-term perspective after the termination of RT (Paper IV).*

Materials and methods

The papers in this thesis are based on data from the ARTSCAN (Accelerated Radiotherapy of Squamous cell Carcinoma of the head and Neck) trial and a care development project, both of which are described in more details below. For a summary on the study participants from the ARTSCAN trial (Papers I - III) see **Figure 4**.

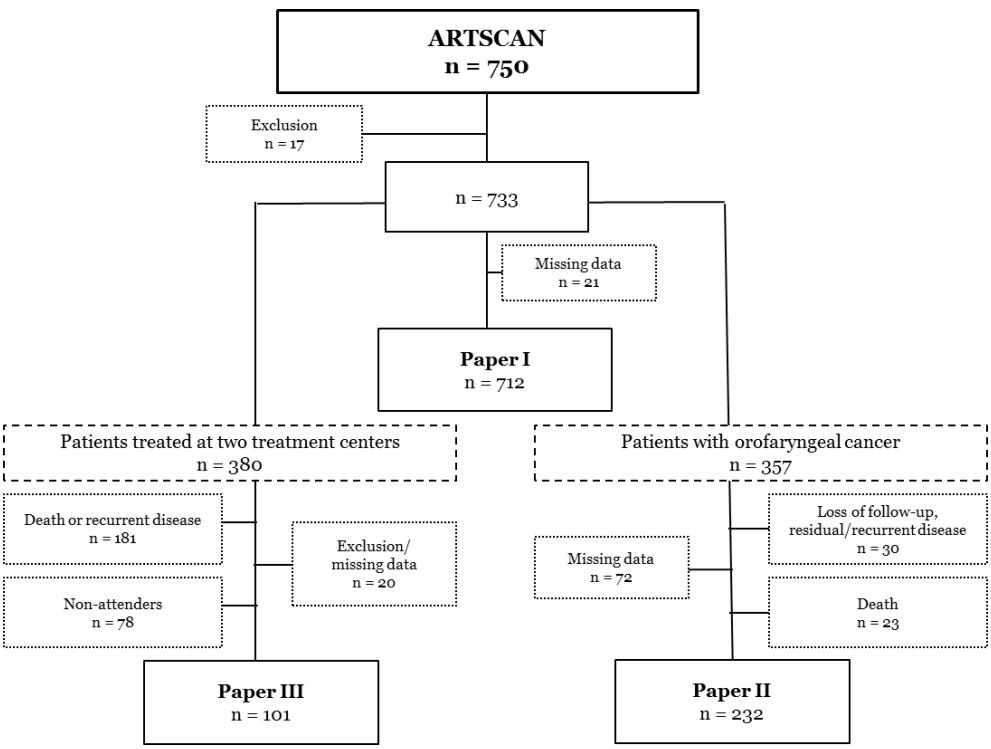

Figure 4. Study participants in Papers I – III.

ARTSCAN

ARTSCAN is a randomized prospective Swedish phase III multicenter trial conducted between the years of 1998 - 2006 (20, 97). Twelve treatment centers for HNC in Sweden participated in the study, thus making it national. The main aim of the ARTSCAN trial was to evaluate the effect of two different fractionation schedules on local tumor control, survival, treatment related morbidity, and QoL. The RT process in the ARTSCAN trial was evaluated using a quality assurance program with the aim to ensure uniformity of all RT data for each patient in the trial (97).

The tumors were classified using the UICC TNM staging system (13, 14). In total, 750 patients with non-distant metastatic SCC of the oral cavity, oropharynx, hypopharynx, and larynx (except glottic T1-2, N0) were randomized to receive either CF or AF (**Table 2**). In addition, 40.8% of the patients received surgery post RT. No chemotherapy was given within three months prior to RT. Exclusion criteria were previous malignant disease of the head and neck, age under 18 years, inability to understand the information about treatment, and expected non-compliance. Seven-hundred and thirty-three patients were available for evaluation after exclusion.

Table 2. Fractionation schedules in the ARTSCAN trial. Abbreviations: conventional fractionation (CF), accelerated fractionation (AF), planning target volume (PTV), Gray (Gy).

		CF		**AF**	
Week		*PTV- B*	*PTV -A*	*PTV- B*	*PTV- A*
1	*Day 1-5*	2.0Gy		2.0Gy 1.1Gy	
2	*Day 1-5*	2.0Gy		2.0Gy 1.1Gy	
3	*Day 1-5*	2.0Gy		2.0Gy 1.1Gy	
4	*Day 1-5*	2.0Gy		2.0Gy 1.1Gy	
5	*Day 1*	2.0Gy		2.0Gy	
	Day 2	2.0Gy		2.0Gy	
	Day 3	2.0Gy		2.0Gy	
	Day 4	2.0Gy			
	Day 5	2.0Gy			
6	*Day 1-5*	2.0Gy			
7	*Day 1*	2.0Gy			
	Day 2	2.0Gy			
	Day 3	2.0Gy			
	Day 4	2.0Gy			
Total		68Gy	46Gy	68Gy	46Gy

For the target volumes used in the ARTSCAN trial see **Figure 5**. The target volume treated prophylactic, i.e. PTV-A, was irradiated with 2 Gy on every weekday to a total dose of 46 Gy in both treatment arms (**Table 2**). The target

volume encompassing GTV and positive lymph node/nodes, i.e. PTV-B, was given a total dose of 68 Gy. Patients received either a concomitant boost to PTV-B with 1.1 Gy per fraction with a planned total treatment time of 4.5 - 5 weeks (AF) or with 2 Gy on weekdays with a planned total treatment time of seven weeks (CF). The corresponding TV, as a measure of the radiation dose burden, was defined as the volume of the patient receiving at least 95% of the prescribed doses to PTV-B and PTV-A (21, 22), i.e. $TV_{64.6\ Gy}$ and $TV_{43.7\ Gy}$, respectively. The dose variation of ± 5% is regarded an acceptable deviation from the prescribed dose.

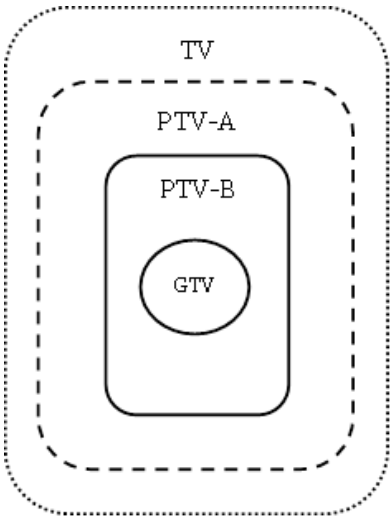

Figure 5. Target volumes used in the ARTSCAN trial. Abbreviations: gross tumor volume (GTV), planning target volume (PTV), treated volume (TV).
PTV-B: Planning target volume encompassing GTV and positive lymph node/nodes.
PTV-A: Planning target volume encompassing PTV-B and elective lymph nodes of the neck.

Treatment delivery techniques were either 3-DCRT and/or IMRT with dose prescriptions according to the recommendations by ICRU (21, 22).

The study protocols including medical and treatment data were completed by a physician during treatment and at the planned follow-up visits after treatment. The data collection continued up to five years after the termination of RT in surviving patients (**Figure 6**), i.e. every week of RT, at 4 - 6 weeks after RT, every three month after RT during the first two years, and thereafter every six month up to five years. After that time point, survival data were gathered through the Swedish population registry.

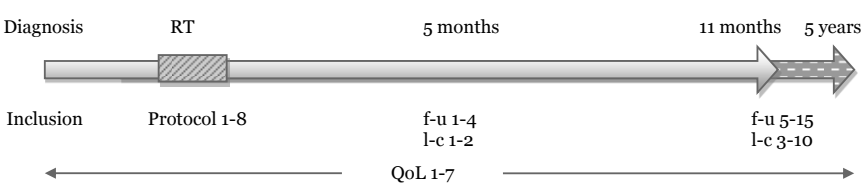

Figure 6. Data collection in the ARTSCAN trial. Abbreviations: radiation therapy (RT), follow-up (f-u), late complications (l-c), quality of life (QoL).

The Late Effects in Normal Tissues Subjective, Objective, Management and Analytic (LENT-SOMA) scale was used in the ARTSCAN trial to define treatment toxicities (98, 99). The LENT-SOMA scale uses a scale 1 - 4 with 1 being minor adverse events and 4 corresponding to irreversible function damage. Treatment toxicities present up to six months after RT were defined as acute treatment toxicities. Health-related QoL, patient reported function, and symptoms were assessed using The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) combined with the disease specific protocol for patients with HNC (EORTC QLQ-H&N35) (100, 101). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (102). These questionnaires were completed by the patients at the start and end of RT, and at three, six, twelve months and two and five years after the termination of RT. Function ability was assessed using the Karnofsky Performance Status (KPS) scale (103). This scale rates from 0 – 100 and higher scores correlates with better function.

In the ARTSCAN trial, it was stated that nutritional support should be given during and after treatment when needed, i.e. no collective guidelines for nutritional surveillance and treatment were used at the participating treatment centers. Therefore, nutritional counseling and nutritional support were administrated based on clinical evaluation and patient approval. The patients in the ARTSCAN trial had oral intake (with or without nutritional counseling and/or oral nutritional supplements), TF (nasogastric feeding tube or PEG) and/or parenteral nutrition. Presence of TF and parenteral nutrition was registered in the ARTSCAN protocol.

Weight was measured at each follow-up and height was collected in addition to the ARTSCAN protocol through the medical records. Weight change percent at follow-up was calculated with weight at the start of RT as the reference. When applicable, weight loss was dichotomized and patients with ≥10% weight loss were defined as patients at nutritional risk (76). BMI was either used as a continuous variable or classified into three groups: underweight <20 kg/m^2 (<22 kg/m^2 if ≥70 years of age), normal weight 20 - 25 kg/m^2 (22 - 27 kg/m^2 if ≥70 years of age), and overweight/obesity >25 kg/m^2 (>27 kg/m^2 if ≥70 years of age) (76, 78).

Paper I

In Paper I, data from patients with weight data at the start of RT were used (n = 712) (**Figure 4**). At follow-up (five months) the number of patients with weight data registrations were reduced to 432 of 712 patients (60.7%) due to death (n = 85), residual/recurrent disease or loss of follow-up (n = 57), or

missing weight data registrations (n = 138). For 175 patients, weight was available at five time points from the start of RT up to 11 months after the termination of RT and was used to study weight change over time in patients treated with AF and CF, respectively. Information on both BMI at the start of RT and weight change from the start of RT up to five months after the termination of RT was available for 254 patients.

Weight change up to five months after the termination of RT was analyzed retrospectively in relation to patient (age, sex and KPS), tumor (site and clinical stage), treatment (RT schedule and surgery), nutritional (BMI and use of TF at the start or end of RT), medical (use of morphine) and clinical parameters (**Table 3**). For the clinical parameters, grade three and four (i.e. moderately severe and severe reactions) from the LENT-SOMA scale (98) were used to define presence of the toxicity. The KPS was also dichotomized and patients with ≥80 were defined as patients able to carry out normal activity (103).

TF use at the start and end of RT was analyzed together with patient (age, sex and KPS), tumor (site and clinical stage), treatment (RT schedule), nutritional (BMI), medical (use of morphine) and clinical parameters (**Table 3**).

Table 3. Classification of treatment toxicities using the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic (LENT-SOMA) scale (98) where grades three and four were used to define presence of the toxicity.

Treatment toxicities	*Classification*
Dysphagia	*Yes (Grade 3+4):* Patients were only able to swallow mashed food or liquids or not able to swallow at all *No (Grade 1+2):* No dysphagia or problems swallowing solid food
Mucositis	*Yes (Grade 3+4):* Spotted or confluent mucositis *No (Grade 1+2):* No mucositis or redness

Paper II

In Paper II, data from patients with oropharyngeal cancer were used (n = 357) (**Figure 4**). Weight change between the start of RT up to five months after the termination of RT was available for 232 of 357 patients (65.0%). The number of cases at follow-up were reduced due to death (n = 23), residual/recurrent disease or loss of follow-up (n = 30), or missing weight data registrations (n = 72). BMI at the start of RT was available for 203 patients.

Weight change up to five months after the termination of RT was analyzed retrospectively in relation to tumor (clinical stage) and treatment parameters (RT schedule, surgery, TV, and use of TF at the start and end of RT). Also, weight change up to five months after the termination of RT (dichotomized into <10% and ≥10%) and BMI at the start of RT were analyzed together with five-year overall survival.

SALU

After the closure of the ARSCAN trial, the long-term swallowing function from two of the participating treatment centers (the University Hospital of Umeå and Lund University Hospital) were investigated in the SALU study (Swallowing dysfunction in ARTSCAN patients in Lund and Umeå). Fifteen months after the ARTSCAN trial was closed, surviving patients (n = 202) were asked to participate and 124 patients accepted participation.

Patients were examined with a clinical examination including an ear-, nose- and throat evaluation and a fiber endoscopy examination of the swallowing function at a mean of 69.3 months (± 29.6) from the start of RT. These were performed by an otolaryngologist at each of the treatment centers. In addition, the swallowing function was examined with videofluoroscopy (VF) (104) at a mean of 71.6 months (± 28.3) from the start of RT by an oral and maxillofacial radiologist. VF is regarded the "gold standard" of examinations used in clinical practice and in research to examine swallowing function (105). Before the examination, the patients answered routine clinical questions about symptoms of dysphagia. The VF examination included the oral and pharyngeal swallowing function and was performed in lateral and frontal projections, viewing structures of the oral cavity, the pharynx and the upper esophageal sphincter. The patients swallowed a liquid bolus and a modified bolus (if the liquid swallow was without severe aspiration). Information on aspiration was used in Paper III as aspiration diagnosed with VF is a reliable and severe sign of swallowing dysfunction (106). Aspiration was defined as present when bolus passed into the larynx and continued down below the vocal cords into the trachea.

Paper III

Weight and BMI at the Final follow-up (collected at the time of the clinical examination, mean 69.3 ±29.6 months, i.e. >5 years) were available for 101 of 124 patients (81.5%) (**Figure 4**). Patients were excluded due to: ischemic stroke (n = 2), additional tumor disease (n = 2), TF dependence (n = 3), laryngectomy (n = 2), or had missing data (n = 11). For 49 patients, weight was available at four time points from the start of RT up to the Final follow-up and

was used to study weight change over time in patients with and without aspiration.

Weight change from the start of RT to the Final follow-up and BMI at the Final follow-up were analyzed retrospectively in relation to patient (age and sex), tumor (site and clinical stage), treatment (RT schedule and surgery), nutritional (BMI and previous TF use), and clinical parameters (post-treatment aspiration).

The care development project

During the years of 2009 - 2011, a care development project was implemented at the University Hospital of Umeå with the aim of improving the aftercare for patients with HNC as well as working for an enhanced collaboration between the hospitals in the northern region of Sweden. As part of a research project, both quantitative and qualitative nutritional data were gathered within the care development project.

Quantitative data collection

Patients (aged > 18 years) with a newly diagnosed tumor in the oral cavity or oropharynx that were planned for RT with a curative intent were eligible for the quantitative data collection. Information about energy expenditure and energy intake was collected at the start of RT and at a 6 - 9 month follow-up after the termination of treatment in 19 patients. Data for assessment of energy intake were collected during three days (two weekdays and one weekend) using 24-h recalls. Data for energy expenditure were collected using a multisensory device called the Sense Wear Armband Pro3 (Body Media, Inc., Pittsburgh, PA, USA) (107, 108) and were collected during the same three days as the 24-h recalls. Resting energy expenditure was measured with indirect calorimetry (DeltratracTM II MBM 200) (109) (**Figure 7**). At each time of data collection, blood samples were gathered for analyses of high sensitive C-reactive protein, interleukin-6, hemoglobin, and albumin (110).

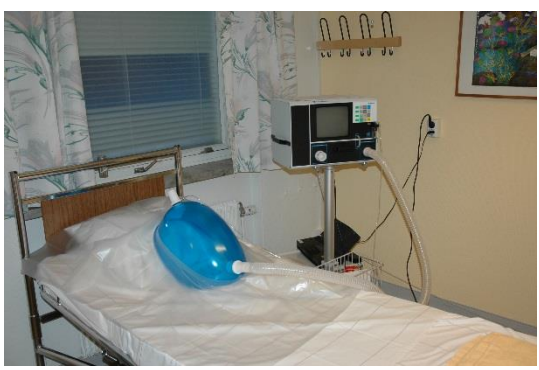

Figure 7. The indirect calorimetry equipment. © Inger Arnesjö.

Paper IV

Qualitative data collection

For qualitative data collection, in-depth semi-structured interviews were used. Patients with HNC that were previously treated with a single or combined modality treatment were recruited by a nurse at the clinic of Otorhinolaryngology, University Hospital of Umeå. Predefined exclusion criterion were age < 18 years, dementia and difficulty to understand the Swedish language. Nineteen patients were asked to participate in the interviews and six declined due to practical reasons.

The interviews were conducted by a registered dietitian (SO) at the approximately nine month (minimum 8, maximum 11) revisit to the physician after the termination of RT. The interviews took place in a room adjacent to the outpatient clinic. A topic guide was used during the interviews which consisted of four themes: "Not being able to eat", "Food as a physiological need", Food as a psychological need", and "Before and after". Each theme had open-ended questions reflecting the essence of the theme. The topic guide was constructed from both a review of previous research and from the researchers pre-understanding based on clinical experience. Two pilot interviews were conducted to investigate how the topic guide reflected the aim of the study. No larger adjustments were done after this, and therefore these two interviews were included in the final data analysis. The median length of the interviews was 39 minutes (minimum 18, maximum 67). All interviews were audio taped and transcribed verbatim.

Ethical considerations

Ethical approval was received for the ARTSCAN trial and SALU study from the local Ethics Committee of each participating treatment center (Dnr 07-023M/FEK98-139 and Dnr 07-023M) and for the care development project from the regional board in Umeå (Dnr 2010-24-31). All patients were informed about the study and gave written consent before participation. All data were depersonalized before analysis and data presentation. Alias names were used in the data presentation for citations.

Statistical methods

The statistical analyses used in Papers I – III are summarized in **Table 4**. Parametric tests were used for normally distributed data. Univariate analyses were used to analyze the difference in treatment toxicities between AF and CF (Paper I), factors for TF use (Paper I), and impact factors for weight loss

(Papers I – III) and BMI (Paper III). These analyses were performed using the Independent Samples T-test, One-way between-groups ANOVA or the Fisher's Exact test. The paired samples T-test (Paper I) and One-way repeated measures ANOVA (Papers I and III) were used to analyze change of mean weight over time. A regression model based on cubic splines (111) was used to analyze the non-linear correlation between TV and weight change, simultaneously controlling for confounding factors (Paper II). All tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

Table 4. Statistical analyses used in Paper I – III.

Method	Paper I	Paper II	Paper III
Independent Samples T-test	X	X	X
One-way between-groups ANOVA	X	X	X
Fisher's Exact test	X	X	X
Paired samples T-test	X		
One-way repeated measures ANOVA	X		X
Regression model based on cubic splines		X	
Multiple linear regression	X	X	X
Log rank test		X	
Cox regression		X	

Multiple linear regression

A multiple linear regression analysis was used in Paper I – III to analyze how much of the variation in the dependent variable that could be explained by the independent variables included in the model as well as the relation between the dependent variable and each of the independent variables. The dependent variable was either weight loss (Papers I – III) or BMI (Paper III). The independent variables were chosen from the univariate analyses. The dependent variables were continuous (weight change % and BMI), and the independent variables were either continuous or dichotomized (or included in the model as dummy variables if they consisted of more than two categories). The regression coefficients (B) represent the increase (positive values) or a decrease (negative values) in weight (percentage points) or BMI.

The decision to give a patient TF may be based on many factors and may influence the effect of other variables. Therefore, interaction effects between TF and the other variables in the multivariate model were analyzed and included if significant (Paper I).

Survival analysis

The impact of weight loss and BMI, respectively, on overall survival based on a follow-up time of five years was analyzed in Paper II. Time to death was calculated from the start of RT up to five years in surviving patients. The Kaplan-Meier estimators were compared using the log rank test. Cox regression was used to calculate the Hazard Ratios and their confidence intervals. Besides the variable of interest (BMI), the other variables in the model were related to patient characteristics (age, sex), tumor characteristics (clinical stage) or treatment parameters (RT schedule, surgery). The independent variables were continuous or dichotomized. Variables that violated the proportional hazards assumption were stratified in the Cox model.

The data software Statistical Package for the Social Sciences (SPSS, IL, Chicago, USA) version 19.0 or 21.0 and R version 2.15.2 was used for the statistical analyses.

Qualitative content analysis

Content analysis as described by Graneheim and Lundman (112) was used for the analysis of the interviews, and Microsoft Office Excel 2007 was used as the analysis data package. The interviews were read through repeatedly and separated into meaning units. These were condensed and coded with a word or sentence which described the core essence of the condensed meaning units. The codes were further clustered into sub-categories and categories that described the essence of the codes and subcategories, respectively. All categories were mutually exclusive.

Results

Patient characteristics

In **Table 5**, patient characteristics from Papers I – IV are given with data from The Swedish Head and Neck Cancer Register (113) for tumors of the oropharynx, hypopharynx, larynx, and oral cavity.

Table 5. Patient characteristics for Papers I – IV compared with data from The Swedish Head and Neck Cancer Register for tumors of the oropharynx, hypopharynx, larynx, and oral cavity.

Characteristics		**Sweden 2008-2012**	**Paper I**	**Paper II**	**Paper III**	**Paper IV**
Age, median (range)		-	62 (26 – 91)	57 (32 – 86)	62 (34 – 84)	60 (47 – 70)
Age,	*<65*	2456 (64.4)	441 (61.9)	184 (79.3)	60 (59.4)	11 (84.6)
*n (%)**	≥65	1355 (35.6)	271 (38.1)	48 (20.7)	41 (40.6)	2 (15.4)
Sex,	*Male*	2526 (66.3)	530 (74.4)	173 (74.6)	76 (75.2)	11 (84.6)
n (%)	*Female*	1285 (33.7)	182 (25.6)	59 (25.4)	25 (24.8)	2 (15.4)
Tumor site,	*Oropharynx*	1322 (34.7)	347 (48.7)	232 (100)	62 (61.4)	6 (46.2)
n (%)	*Hypopharynx*	270 (7.1)	120 (16.9)	-	8 (7.9)	
	Larynx	758 (19.9)	149 (20.9)	-	11 (10.9)	1 (7.6)
	Oral cavity	1461 (38.3)	96 (13.5)	-	20 (19.8)	6 (46.2)
Clinical	*I*	861 (23.1)	30 (4.2)	8 (3.4)	11 (10.9)	-
stage,	*II*	676 (18.2)	93 (13.1)	16 (6.9)	16 (15.8)	-
*n (%)***	*III*	557 (15.0)	195 (27.4)	54 (23.3)	28 (27.7)	-
	IV	1628 (43.7)	394 (55.3)	154 (66.4)	46 (45.5)	-
Number of patients		n = 3811	n = 712	n = 232	n = 101	n = 13

*The Swedish Head and Neck Cancer Register dichotomized age into <70 and ≥70 years.
**Missing n = 89 for the stage data from The Swedish Head and Neck Cancer Register.

Acute toxicity and long-term sequelae

At the start of RT (n = 712), 13.9% of the patients reported dysphagia and 10.6% used opioid analgesics. The corresponding numbers at the end of RT were 76.9% for dysphagia and 48.4% for use of opioid analgesics. Also, 87.1% of the patients had mucositis at the end of RT. Significantly more patients treated with AF were reported to have dysphagia ($p < 0.001$), mucositis ($p < 0.001$) and used opioid analgesics ($p < 0.001$) more frequently at the end of RT compared to patients treated with CF (**Figure 8**) (Paper I).

Aspiration was diagnosed using VF in 47.5% of the patients at the Final follow-up (mean 69.3 ±29.6 months, i.e. >5 years), and 68.8% had silent aspiration (Paper III).

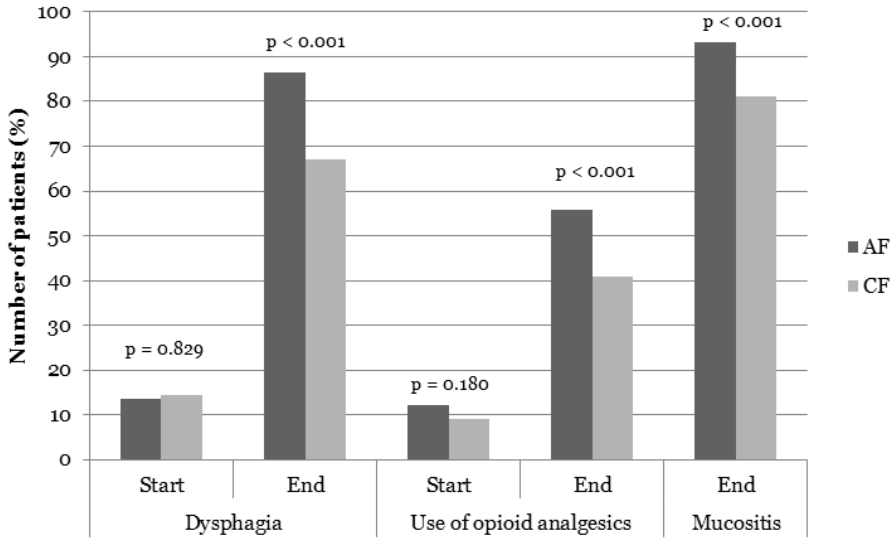

Figure 8. Prevalence of acute toxicities and use of opioid analgesics at the start and end of conventional fractionation (CF, n = 357) and accelerated fractionation (AF, n = 355).

Tube feeding

At the start of RT, 10.7% of the patients had TF (Paper I) and the corresponding number for patients with oropharyngeal cancer was 5.2% (Paper II). The following factors were significantly related to TF use at the start of RT (Paper I): age ≥65 years ($p = 0.006$), tumor site ($p < 0.001$), clinical stage ($p = 0.041$), BMI at the start of RT ($p = 0.001$), KPS < 80 at the start of RT ($p < 0.001$), presence of dysphagia at the start of RT ($p < 0.001$), and use of opioid analgesics at the start of RT ($p < 0.001$).

At the end of RT, 47.1% of the patients had TF (Paper I) and the corresponding number for patients with oropharyngeal cancer was 46.0%. The following factors were significantly related to TF use at the end of RT (Paper I): tumor site ($p < 0.001$), AF ($p < 0.001$), BMI at the start of RT ($p = 0.041$), presence of dysphagia at the end of RT ($p < 0.001$), presence of mucositis at the end of RT ($p = 0.007$), and use of opioid analgesics at the end of RT ($p < 0.001$).

In Paper III, it was shown that 58.4% of the patients had previously received TF sometime during the period from the start of RT to the Final follow-up. TF use during this time-period had no significant impact on long-term weight loss ($p = 0.895$), BMI at the Final follow-up ($p = 0.312$) or post-treatment aspiration ($p = 0.545$).

Weight and body mass index during and after radiation therapy

During the period from the start of RT up to five months after the termination of RT (n = 254), 59.8% of the patients had a weight loss of ≥10% and 13.8% a weight loss of ≥20%. Twenty-one patients (8.3%) remained weight stable or gained weight during that time period. On a group level, mean BMI at the start of RT was 26.0 kg/m². According to the three BMI groups, 9.1% of the patients were underweight, 37.4% were normal weight, and 53.5% were overweight/obese. In **Figure 9,** the weight change from the start of RT up to five months after the termination of RT was stratified into four weight groups and combined with information on BMI at the start of RT. The patients with ≥10% weight loss up to five months after the termination of RT had the following BMI grouping at the start of RT: underweight n = 4 (2.6%), normal weight n = 44 (29.0%), and overweight/obese n = 104 (68.4%).

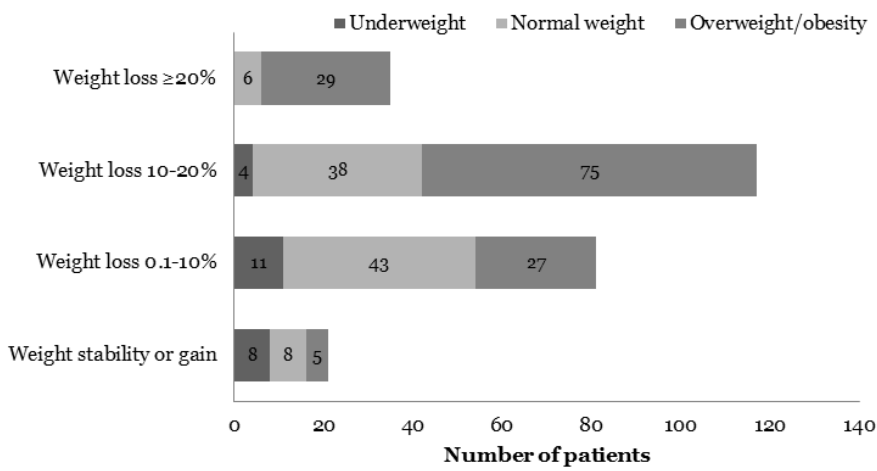

Figure 9. Weight change from the start of radiation therapy (RT) up to five months after the termination of RT stratified into four weight groups and combined with information on body mass index (BMI) at the start of RT (n = 254). BMI was defined as: underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 - 25 kg/m² (BMI 22 - 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).

During the period from the start of RT up to the Final follow-up (n = 101), 34.7% of the patients had a weight loss of ≥10%, and 7.9% had a weight loss of ≥20%. Twenty-three patients (22.8%) had returned to pre-treatment values or had gained weight at the Final follow-up. On a group level, mean BMI at the Final follow-up was 24.6 kg/m² (Paper III). According to the three BMI groups, 9.9% were underweight, 53.5% were normal weight, and 36.6% were overweight/obese. In **Figure 10,** the weight change from the start of RT up to the Final follow-up was stratified into four weight groups and combined with information on BMI at the Final follow-up. Ten patients were underweight at the Final follow-up and four of these displayed a previous weight loss of ≥10% (Paper III).

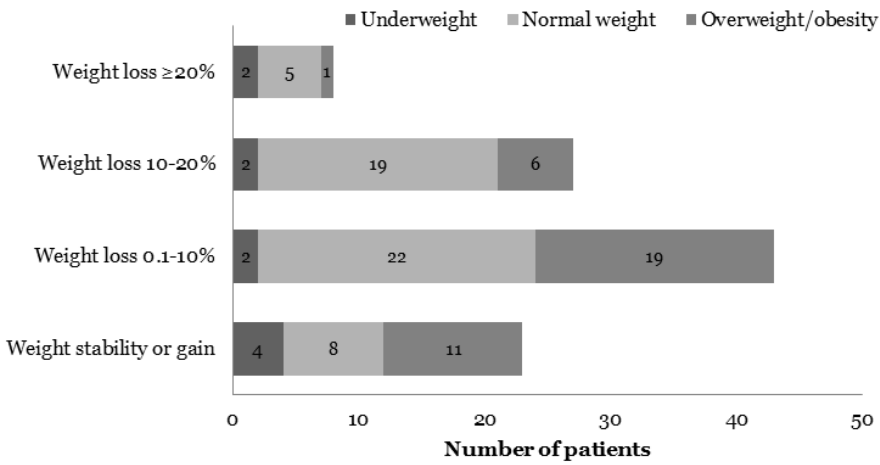

Figure 10. Weight change from the start of radiation therapy (RT) up to the Final follow-up (mean 69.3 ±29.6 months, i.e. >5 years) stratified into four weight groups and combined with information on body mass index (BMI) at the start of RT (n = 101). BMI was defined as: underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 - 25 kg/m² (BMI 22 - 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).

The patients with underweight at the Final follow-up (n = 10) were distributed in the following BMI groups at the start of RT: underweight (n = 6), normal weight (n = 2) or overweight/obese (n = 2). The distribution of patients according to BMI groups and changes between the start of RT and the Final follow-up are shown in **Table 6** (n = 101).

Table 6. The distribution of patients according to body mass index (BMI) groups (underweight, normal weight and overweight/obese) and changes between the start of radiation therapy (RT) and the Final follow-up (mean 69.3 ±29.6 months, i.e. >5 years) (n = 101). BMI was defined as: underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 - 25 kg/m² (BMI 22 - 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).

		Final follow-up		
		Underweight *n = 10*	*Normal weight* *n = 54*	*Overweight/obese* *n = 37*
Start RT	*Underweight* n = 7	6	1	0
	Normal weight *n = 33*	2	29	2
	Overweight/obese *n = 61*	2	24	35

Weight change over time

In **Figure 11,** weight change percent (mean, 95% CI) over time in patients with HNC is shown using data from Papers I and III. In Paper I, weight change was studied in a cohort of patients (n = 175) with weight data registrations at different time points during and after RT up to 11 months with focus on the two fractionation schedules. Looking at the total cohort, patients lost weight during and after RT with a nadir at five months after the termination of RT (Paper I).

In Paper III weight change was studied in a cohort of patients (n = 49) with weight data registrations at different time points after RT up to the Final follow-up with focus on patients with and without aspiration. Looking at the total cohort, patients reached weight stability between 23 months and the Final follow-up (**Figure 11**). Patients with post-treatment aspiration lost weight between 23 months after the termination of RT and the Final follow-up (p = 0.006) (Paper III).

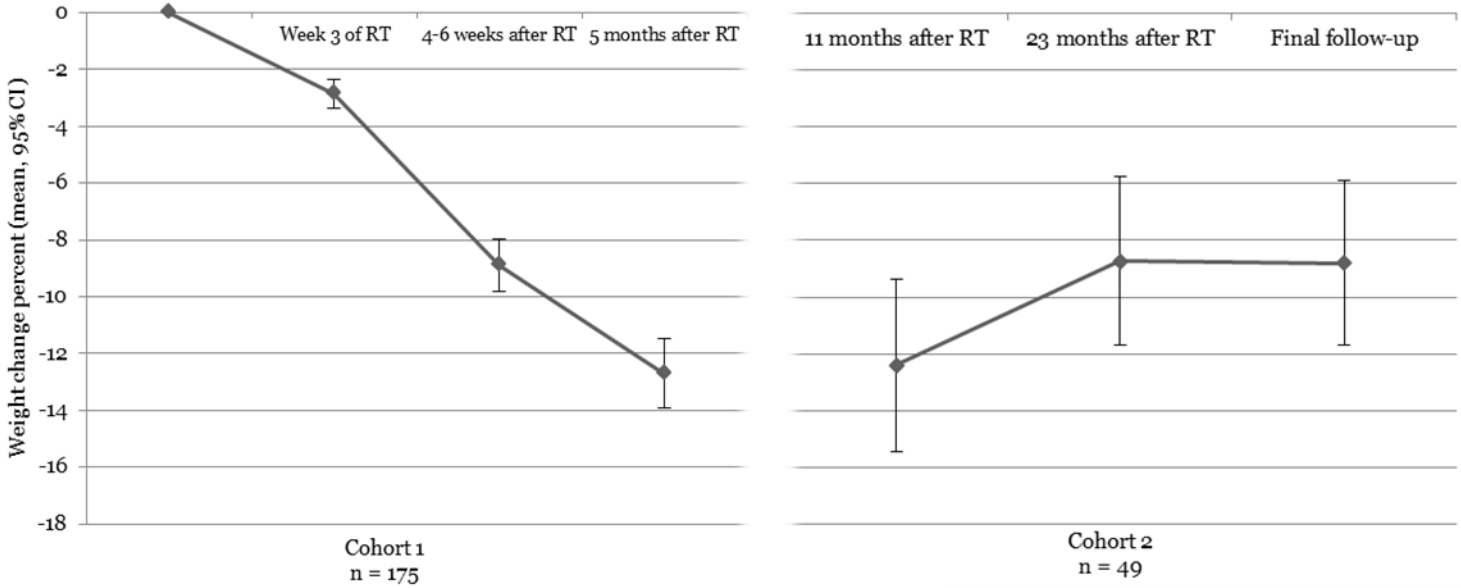

Figure 11. Weight change percent (mean, 95% CI) from the start of radiation therapy (RT) (reference point) up to different time points during and after RT with the Final follow-up at a mean of 69.3 ±29.6 months, i.e. >5 years after the termination of RT in patients with head and neck cancer (Cohort 1: n = 175, Cohort 2: n = 49).

Predictive factors for weight loss and body mass index

Weight change from the start of RT up to five months after the termination of RT (Paper I and II) and to the Final follow-up (Paper III) was analyzed in relation to patient, tumor, treatment, nutritional, and clinical parameters in univariate and multivariate analyses. The results from the multivariate analyses are shown in **Tables 7 - 9**. Tumor site (oropharyngeal cancer) (Papers I and III), a high BMI at the start of RT (Papers I and III), absence of TF at the start of RT (Papers I and II), larger $TV_{64.6\ Gy}$ and $TV_{43.7\ Gy}$ (Paper II), and presence of post-treatment aspiration (Paper III) were parameters significantly related to of a higher weight loss. No significant difference in weight loss was seen between patients treated with CF or AF at five months ($p = 0.839$) (Paper I).

BMI at the Final follow-up was analyzed in relation to patient, tumor, treatment, nutritional, and clinical parameters in univariate and multivariate analyses (Paper III). The results from the multivariate analysis are shown in **Table 9**. Post-treatment aspiration was significantly related to a reduced BMI at the Final follow-up ($p < 0.001$).

Table 7. Result from a multiple linear regression analysis ($R^2 = 0.278$, $p < 0.001$) showing predictive factors for weight loss from the start of radiation therapy (RT) up to five months after the termination of RT (n = 230) (Paper I).

Characteristics		**B** (95% CI)**	**p**
Intercept		-12.96 (-16.14 - -9.78)	<0.001
Age	*<65 years*	Ref	
	≥65 years	-0.58 (-2.74 – 1.59)	0.601
Tumor site	*Oropharynx*	Ref	
	Hypopharynx	1.66 (-1.59 – 4.91)	0.316
	Larynx	3.63 (0.96 – 6.29)	**0.008**
	Oral cavity	3.79 (0.67 – 6.91)	**0.018**
BMI RT start*	*Overweight/obese*	Ref	
	Normal weight	4.22 (2.16 – 6.28)	**<0.001**
	Underweight	10.06 (6.52 – 13.60)	**<0.001**
Karnofsky Performance Status	*<80*	Ref	
RT start	*≥80*	3.73 (-1.95 – 9.42)	0.197
Tube feeding use RT start	*No*	Ref	
	Yes	6.43 (1.84 – 11.01)	**0.006**
Dysphagia RT start	*No*	Ref	
	Yes	-4.74 (-9.73 – 0.24)	0.062
Mucositis RT end	*No*	Ref	
	Yes	-2.76 (-5.72 – 0.21)	0.068

*Body mass index (BMI). Underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 – 25 kg/m² (BMI 22 – 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).
**The regression coefficients (B) represent the increase (positive values) or a decrease (negative values) in weight (percentage points).

Table 8. Result from two multiple linear regression analyses showing predictive factors for weight loss from the start of radiation therapy (RT) up to five months after the termination of RT in patients with oropharyngeal cancer (n = 228) (Paper II). Treated volume (TV) was used as a measure of the radiation dose burden. $TV_{64.6\ Gy}$ was used as one of the independent variables in the first analysis ($R^2 = 0.084$, $p < 0.001$) and $TV_{43.7\ Gy}$ in the second analysis ($R^2 = 0.142$, $p < 0.001$).

Characteristics		**B* (95% CI)**	**p**
Intercept		-10.68 (-14.10 - -7.27)	<0.001
Clinical stage	*I+II*	Ref	
	III-IV	1.34 (-2.15 – 4.83)	0.449
Tube feeding use RT start	*No*	Ref	
	Yes	4.95 (0.48 – 9.41)	**0.030**
$TV_{64.6\ Gy}$		-0.008 (-0.012 - -0.004)	**<0.001**
Intercept		-9.04 (-12.44 - -5.64)	<0.001
Clinical stage	*I+II*	Ref	
	III+IV	2.59 (-0.83 – 6.01)	0.138
Tube feeding use RT start	*No*	Ref	
	Yes	5.25 (0.93 – 9.57)	**0.017**
$TV_{43.7\ Gy}$		-0.005 (-0.007 - -0.003)	**<0.001**

*The regression coefficients (B) represent the increase (positive values) or a decrease (negative values) in weight (percentage points).

Table 9. Result from two multiple linear regression analyses showing predictive factors for weight loss from the start of radiation therapy (RT) up to the Final follow-up (mean 69.3 ±29.6 months, i.e. >5 years) ($R^2 = 0.462$, $p < 0.001$) and body mass index (BMI) at the Final follow-up ($R^2 = 0.421$, $p < 0.001$) (Paper III) (n = 101).

		Weight loss	
Characteristics		**B** (95% CI)**	**p**
Intercept		-4.04 (-8.22 – 0.12)	0.058
BMI RT start*	*Overweight/obese*	Ref	
	Normal weight	4.42 (0.88 - 7.96)	**0.015**
	Underweight	8.95 (2.18 – 15.72)	**0.010**
Surgery	*No*	Ref	
	Yes	-1.55 (-5.33 – 2.23)	0.417
Post-treatment	*No*	Ref	
aspiration	*Yes*	-7.28 (-10.65 - -3.91)	**<0.001**
Sex	*Female*	Ref	
	Male	-3.60 (-0.25 – 7.46)	0.066
Tumor site	*Oropharynx*	Ref	
	Hypopharynx	13.40 (7.05 – 19.75)	**<0.001**
	Larynx	6.92 (1.27 – 12.57)	**0.017**
	Oral cavity	2.99 (-1.41 – 7.39)	0.180
		BMI	
		B (95% CI)**	**p**
Intercept		27.49 (26.51 – 28.46)	<0.001
BMI RT start*	*Overweight/obese*	Ref	
	Normal weight	-3.52 (-4.86 - -2.18)	**<0.001**
	Underweight	-7.02 (-9.49 - -4.54)	**<0.001**
Post-treatment	*No*	Ref	
aspiration	*Yes*	-2.62 (-3.86 - -1.38)	**<0.001**

*Underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 – 25 kg/m² (BMI 22 – 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).

**The regression coefficients (B) represent the increase (positive values) or a decrease (negative values) in weight (percentage points) or BMI.

Weight change and body mass index in relation to survival in head and neck cancer

Weight change up to five months after the termination of RT (<10%, ≥10%) and BMI at the start of RT (underweight, normal weight or overweight/obese) were analyzed together with five-year overall survival in patients with oropharyngeal cancer (Paper II). BMI at the start of RT was shown to be significantly associated with five-year overall survival ($p < 0.001$), whereas weight change was not ($p = 0.708$). **Table 10** shows the hazard ratios for BMI from the Cox regression analysis when controlling for age, sex, clinical stage, RT schedule, and surgery.

Table 10. Cox regression analysis of the association between five-year overall survival and body mass index (BMI) at the start of radiation therapy (RT) (n = 203).

BMI, start RT*	*HR† (95% CI)*	*p-value*
Overweight/obesity	-	-
Normal weight	2.57 (1.43 - 4.62)	**0.002**
Underweight	3.78 (1.46 - 9.75)	**0.006**

*Underweight: BMI <20 kg/m² (BMI <22 kg/m² if ≥70 years of age), normal weight: BMI 20 – 25 kg/m² (BMI 22 – 27 kg/m² if ≥70 years of age), overweight/obese: BMI >25 kg/m² (BMI >27 kg/m² if ≥70 years of age).
†Hazard Ratios (HRs) are adjusted for age, sex, clinical stage (strata), RT schedule, and surgery.

The experience of food, eating and meals following radiation therapy

The patients' experience of food, eating and meals in a long-term perspective after the termination of RT could be captured in the following six categories: "A new way of eating", "Eating without satisfaction", "Challenging meals outside the family", "A long journey – taking small steps to an uncertain future", "Support and information – the key to a successful journey", and "The creation and acceptance of a new normal".

Despite the remaining sequelae of treatment described by the respondents, they still managed to eat sufficiently by altering the food choices and food textures, all part of the strategies used by the respondents to facilitate eating after treatment. The meals were also described as time-consuming as the respondents needed to carefully chew and clean the mouth afterwards due to food sticking in the mouth. The limited food alternatives gave less variety and thus less satisfaction in food and eating. Also, some of the respondents experienced taste losses and/or taste changes, which also altered the overall satisfaction with food; many ate because they had to, not because the felt any pleasure in food and eating.

> *"You have another relation to food today, you look for the nutritional aspects; earlier you could eat because you thought it tasted good." (Stig, 47 years)*

The limited food choices and the remaining sequelae (dysphagia with coughing) also made it more difficult for the respondents to eat with others than the closest family; feeling embarrassed when not being able to eat the food served and not being able to eat in a socially accepted way.

"If you are invited to a dinner party, you wonder what food they are going to serve." (Hans, 61 years)

The time after the termination of treatment was described as a long unpredictable journey where the respondents were taking small steps in their recovery. Although the respondents were satisfied with the information given during and after treatment, some had hoped for better knowledge on how long the journey should be, whereas others were happy that they did not know beforehand.

"It was for the best that I did not know because then it would have felt impossible that I should be sick until June; that would have been hard. I thought all the time – next Friday it will be better." (Klas, 55 years)

Many of the respondents expressed an uncertainty about the future, still hoping that the remaining sequelae would resolve and things would return to normal, i.e. a situation similar to that before treatment. In parallel with these thoughts came an acceptance of the new way of living.

"It is now after one year that the reality strikes you, that it is in this way things are going to be. Earlier you were in another phase, you fought, you thought everything was going to be ok - after two months I am going to be fine, nothing happens, it is the same thing, you are even more tired… it can take one year, two years, to accept it, that is not easy." (Sture, 64 years)

Discussion

Main findings

The papers in this thesis have focused on the impact of the disease and treatment on body weight and eating in patients with HNC treated with RT as the single modality treatment or as preoperative RT. One main finding in patients with oropharyngeal cancer was that a high BMI at the start of RT had beneficial effects on survival. In contrast, weight loss during and after RT was not correlated to survival in the same study cohort receiving nutritional surveillance according to the local guidelines for nutritional support applied during the ARTSCAN trial. Different predictive factors for weight loss during and after RT have also been outlined from the papers presented in this thesis. Patients with oropharyngeal cancer and patients treated with larger TV, as a measure of the radiation dose burden, had the highest weight loss up to five months after the termination of RT. Another finding from the present thesis was the delayed effects of nutritional deterioration that the patients experienced. Nadir of weight loss occurred at five month after the termination of RT, and when analyzing swallowing dysfunction it was shown that post-treatment aspiration was an important predictive factor for weight loss and BMI in a long-term perspective. Patients with aspiration lost weight between 23 months after the termination of RT and the Final follow-up (mean 69.3 ±29.6 months, i.e. >5 years) in addition to the acute weight lost during and after RT. The patients' own narratives showed that many patients still suffered from treatment sequelae nine months after the termination of RT.

Impact of weight loss and body mass index on survival in head and neck cancer

There are numerous studies investigating nutritional-related prognostic factors for survival in patients with HNC. However, small studies and methodological concerns make it difficult to come to any conclusions about the level of nutritional deterioration that might lead to poorer survival. In Paper II, it was shown that patients with a high BMI at the start of RT had a better five-year overall survival, whereas no relation was shown between weight loss and survival, which are results that are in line with previous research. Pai et al. (114) came to the same conclusion, i.e. that a high BMI pre-treatment is of greater prognostic value for survival than weight loss *per se*. There are also other studies on patients with HNC that have shown the same relation between BMI and survival (46, 115, 116), especially BMI > 25 kg/m^2 (115). The research available on weight loss in relation to survival in HNC does not give the same clear-cut patterns. Some studies have shown a negative

effect of weight loss on survival (69, 117-123), whereas others have not (55, 124, 125). The results are, however, leaning toward that weight loss prior to RT (117, 118, 123) or weight loss in recurrent disease (119, 122) may be of importance for survival. Opposite to the results from Paper II, Langius et al. (123) found in a large prospective study on 1340 patients with HNC that patients with critical weight loss during RT (defined as >5% during RT or >7.5% until week 12) had a poorer survival. Methodological and cohort differences may perhaps explain the difference in result between Langius et al. and Paper II. For example, in Paper II only patients that survived up to five months post-treatment were analyzed. Also, by the results from Langius et al. it can be speculated that a rapid weight loss during a short period of time, i.e. >5% during RT or >7.5% until week 12 after RT, might be more "critical" in respect to outcome than the weight loss investigated in Paper II (≥10% between the start of RT up to five months after the termination of RT).

Besides weight loss and BMI that were investigated in Paper II, there might be other important factors to consider for nutritional deterioration. For instance, earlier studies have examined different biochemical parameters (116, 124) and used methods for analyzing body composition (126). These nutritional-related factors would also have been valuable to investigate in relation to survival. Therefore, many questions still remain on this topic. However, the result from Paper II showed no correlation between ≥10% weight loss from the start of RT up to five months after the termination of RT and survival in patients with oropharyngeal cancer receiving nutritional support. Instead, a high BMI at the start of RT was shown to correlate to increased survival. The amount of adipose tissue available is thus an important factor determining the amount of FFM that can be spared during negative energy balance (79), i.e. the protective effect on FFM when more adipose tissue is available may have important clinical implications. The fact that the majority of patients in the ARTSCAN trial had a BMI within or above the normal range at the start of RT can therefore be seen as a favorable nutritional status when starting treatment for HNC. Even long ago Hippocrates is reported to have said: *"In the face of disease, thin people do badly",* and in the light of previous and current research this seems to be applicable to patients with HNC. This finding indicates that patients with a low BMI should be encouraged to gain weight before RT start. Intervention studies for nutritional support are needed as we do not yet know if nutritional interventions can increase survival in patients with an unfavorable nutritional status at the start of RT.

How to find patients at nutritional risk

Early identification and treatment of patients at nutritional risk may reduce the risk of malnutrition. Nutritional screening can be initiated at the start of RT to find patients in need of early reactive or proactive nutritional interventions or patients that should be monitored closely during RT. Since the treatment in HNC may lead to further nutritional deterioration, predictive factors for anticipated weight loss during RT is information that can be obtained during patient history in addition to the nutritional screening. In Papers I - II, we found that tumor site and TV were factors of importance for weight loss up to five months after the termination of RT. These results add to the growing literature showing clinically examined predictive factors for weight loss in HNC (**Table 1**).

Tumor site was shown to be of significant importance for weight loss (Paper I). Patients with tumor of the oropharynx lost more weight up to five months after the termination of RT compared to patients with tumors of the larynx or oral cavity. Various tumor sites have earlier been stated in the literature as risk sites for weight loss depending on the time period used to define significant weight loss. Tumors of the oropharynx/oral cavity, hypopharynx and supraglottic larynx have been correlated with increased weight loss prior to treatment (42), whereas tumors of the nasopharynx, hypopharynx and oropharynx have been shown to be of importance for weight loss during RT (51, 57). Moreover, patients with oropharyngeal cancer are reported to have more dysphagia after treatment (127, 128). Murry and co-workers found, for example, that patients with oropharyngeal cancer reported more dysphagia at six months after the termination of treatment when compared to patients with tumors of the larynx and hypopharynx (127). In Paper III, patients with oropharyngeal cancer had the largest weight loss up to the Final follow-up. It is evident that patients with HNC are a nutritionally vulnerable group and that some sites display a higher frequency of nutritional deterioration compared to others, with oropharyngeal cancer being one site that requires extra attention.

TV was another factor shown to be of significant importance for weight loss up to five months after the termination of RT in patients with oropharyngeal cancer (Paper II). In previous research, clinical stage has been shown to be an important factor for weight loss both before and during RT (48, 49, 53-55). However, since clinical stage was a variable controlled for in the multivariate analysis together with TV, it seems to be other explanatory factors behind the increasing weight loss in patients with larger TV. For example, larger TV can impact nutritional status both by local (15, 25) and systemic effects (38). That is, larger TV can result in more treatment toxicities and induce a larger cytokine response, both of which are correlated to a poor appetite and a

reduced food intake (36, 47). Mallick et al. (57) studied PTV instead of TV in relation to weight loss during RT and found a significant impact of larger PTV on weight loss. Thus, this result together with the result from Paper II suggests that more specific RT parameters should be considered in the attempt to find patients at risk for weight loss during and after RT and that may be in need of early nutritional interventions. However, this relationship needs further investigation before it can be implemented in clinical practice.

A diverse number of factors may be used in HNC to find patients with anticipated weight loss during and after RT and thus patients at nutritional risk. Predictive factors for weight loss from previous studies have primarily been clinical stage, pre-treatment weight loss and presence of different treatment toxicities (**Table 1**). In Papers I – II, patients with oropharyngeal cancer and patients receiving larger TV had the highest weight loss and may therefore be pointed out as patients at risk of nutritional deterioration and in need of continuous nutritional monitoring and follow-up. The increasing research available today on factors for nutritional deterioration in this group of patients brings us one step closer to finding a predictive model that can be used at the start of RT during patient history to rapidly find patients at risk of nutritional deterioration and in need of early and proactive nutritional interventions.

Is weight loss in head and neck cancer of clinical importance?

Severe weight loss may be used as an indicator of malnutrition (54, 68). However, malnutrition is more than a reduction in a patients' nutritional status (2), and hence not all patients with weight loss develop malnutrition. Unintentional weight loss during disease is mainly in the form of FFM (67, 82) and this loss rather than the loss of fat mass may lead to the reduced function related to malnutrition. Earlier studies on patients with HNC have shown a significant decrease in both weight and FFM during RT (67, 82, 129, 130), and between 60 - 70% of the body weight lost has been shown to be FFM (67, 82). This reduction of FFM may have important clinical implications. For example, in studies on patients with HNC reduced FFM has been correlated to impaired physical performance (67, 82, 131), decline in independence of activities of daily living (67), reduced muscle strength (131), and impaired hand grip strength (82).

Different cut-offs for weight loss are used in the literature to define patients at nutritional risk, which makes it hard to find a specific cut-off correlated to a poorer function (as proposed by the definition of malnutrition, see Glossary). For patients in general, a previous weight loss of 5 - 10% during 3 - 6 months

is stated to be “critical”, and thus of significant relevance (2). A number of earlier studies on patients with HNC have investigated either ≥5% weight loss during 3 months (81) or ≥10% weight loss during 6 months (68, 80, 85-87) in relation to different outcome parameters such as immune function, postoperative complications, and QoL. All studies showed a negative impact of critical weight loss on the outcome parameters of interest.

When taking the joint results of previous studies into consideration, the suggested cut-off (5 - 10% during 3 - 6 months) is a cut-off that also seems to be applicable for patients with HNC. In addition to this, the available research is also suggesting that a modest weight loss is of less clinical importance in patients with HNC.

Nutritional deterioration in the study cohort

The information on weight change (%) and BMI used in the present thesis is not enough to assess a patients’ nutritional status but may be used to find patients at nutritional risk (76, 88). On a group level, the patients in the ARTSCAN trial lost weight despite receiving nutritional support according to the local guidelines used at each treatment center, i.e. the patients did not reach energy balance, which might be due to inadequate administration of nutritional support, difficulties to give the prescribed nutrients due to treatment toxicities, insufficient medical treatment, complications related to the nutritional support or poor patient compliance. During the period from the start of RT up to five months after the termination of RT, almost two-thirds of the patients had a weight loss of ≥10% and more than 10% of the patients had a weight loss of ≥20%. In comparison, in a study by Silander et al. (56) 66% of the patients had a weight loss of >10% after 6 months from diagnosis and in a study by Langius et al. (73) every fourth patient had a weight loss of ≥10% from the start of RT up to 12 weeks post-RT. These numbers highlights the increased frequency of at risk patients that evolves during and after RT, probably due to treatment toxicities.

The average BMI on a group level was at the start of RT slightly above the cut-off for normal weight, which is in line with previous research (43, 45, 46, 54, 55, 67, 75), and the number of patients with overweight/obesity at the start of RT (53.5%) is similar with the numbers found in other Swedish cohorts of HNC patients (55, 75). Furthermore, in Papers I and III it was shown that patients with overweight/obesity at the start of RT displayed the largest weight loss both in the short (up to five months after the termination of RT) and a long-term perspective (up to the Final follow-up). It was further shown that patients with overweight/obesity at the start of RT still displayed the highest BMI at the Final follow-up despite the larger weight loss (Paper III).

Table 6 also shows the similar pattern, i.e. that it seems like the patients are able to recover their BMI at the Final follow-up, despite the weight lost during and after RT. However, it is unclear if this gain in weight is in the form of fat mass in favor of FFM.

When taking all aspects into consideration, the period from the start of RT up to five months after the termination of RT seems to be the most nutritionally vulnerable period. The majority of patients had a weight loss ≥10% and despite a normal BMI, the patients may have lost FFM instead of fat mass (67, 82). It is not clear how weight loss over a longer time-period (>5 years) should be assessed. The literature suggests that a low BMI may be used to indicate chronic changes in nutritional status (2). It may therefore be speculated that the frequency of patients at nutritional risk was low at the Final follow-up (Paper III), since few patients were underweight as a result of a previous large weight loss. This implies that patients adapt to and find strategies to be able to eat sufficient despite any remaining sequelae. However, to be able to elaborate on this statement correctly, information on when and for how long the weight loss was displayed, i.e. if the patients at the Final follow-up are weight stable or continuous to lose weight involuntary needs to be considered.

"A long journey"

Both the quantitative and qualitative parts of this thesis make it evident that patients that get HNC are in for a long journey – both physiologically and psychologically. Paper I presented the nadir of weight loss at five months after the termination of RT for the group in total, which also confirms previous research (55, 70, 74).

The slow recovery process was further confirmed in Paper III, which showed that post-treatment aspiration led to long-term weight loss and a lower BMI at the Final follow-up and that patients with post-treatment aspiration lost weight after 23 months following treatment. The reason to why aspiration impact weight loss and BMI might have both physical and psychological explanations. Swallowing dysfunction may lead to restricted food intake and TF dependence and psychosocial concerns during mealtimes (61, 132, 133), which in turn may impact nutritional status. The results from Paper III suggest that the treatment toxicities may remain for a long period of time after the termination of treatment. Some studies even indicate that the treatment toxicities may deteriorate further after the termination of treatment or that the onset of the treatment sequelae may be delayed up to several years post-treatment (134-136). These results imply that patients with swallowing dysfunction should be the target for a prolonged nutritional follow-up post-treatment. Furthermore, the main focus for the health-care professionals is to

cure the patient from HNC and swallowing dysfunction may therefore be an untreated and overlooked long-term consequence of treatment. Hence, these data also suggest that continued weight loss and a low BMI post-treatment can be used as a warning sign for possible swallowing dysfunction with silent aspiration in patients with HNC.

There is a substantial amount of research available showing the frequency of late and chronic treatment toxicities in HNC (15, 25, 28, 30, 31). However, less research has been done on how the remaining sequelae affect the patients in their daily living. In Paper IV, the majority of the respondents experienced treatment sequelae at the time of the interview (approximately nine months after the termination of RT) and in order to be able to eat sufficient, they had to alter their food choice and the food texture. The rehabilitation period was described by the respondents as long and unpredictable, as they were taking small steps toward improvement. The slow recovery process after HNC treatment has been shown to give fear about the long-term and permanent changes to treatment (61) and may result in depression (137). Also, many patients miss regular support and contact with the health-care professionals in the period after treatment (58, 60). It was previously shown that patients satisfied with their post-treatment period had continued access to the specialist multi-professional HNC team (39). Hence, many earlier studies have highlighted the importance of having a health-care professional available for questions and support in the period after treatment (39, 58, 60, 62).

Nutritional follow-up in head and neck cancer

Guidelines for nutritional surveillance and treatment of patients receiving RT and patients with HNC states that patients should be followed by a dietitian weekly during RT (90), thereafter up to six weeks post RT and up to six months or longer for certain high-risk patients (patients with severe weight loss and/or remaining treatment toxicities) (90, 95). This type of follow-up has been shown to reduce weight loss post-treatment. Isenring and coworkers (138) showed that patients that were followed weekly during RT by a dietitian and thereafter every other week up to 12 weeks post-treatment had significantly less weight loss compared to patients receiving standard care. Paper I together with previous studies confirm that the period up to 5 - 6 months post-treatment seems to be the most critical in terms of weight loss (55, 70, 74). Which patients that are at nutritional risk during the post-treatment period needs further investigation, but the results found in Paper III suggest that patients with post-treatment aspiration require prolonged nutritional follow-up after the termination of RT.

Individualized information during the trajectory of care

It was earlier shown that proper and sufficient information during treatment reduce anxiety (39) and make the patients feel safe and secure (59). Despite this, it was also shown that the information given to patients with HNC on the long-term treatment impact is not enough (139). The difficulty in delivering the proper information to the patient is the wide range of treatment toxicities that patients may develop from the same treatment. One important finding in Paper IV was that the respondents described a desire of more individualized information from the health-care professionals. For example, some patients wanted more information about the journey to come, whereas others were glad that they did not know beforehand how tough the treatment and the convalescent period were going to be. Thus, how do we provide information that is individualized and suited for the patient? The current evidence supports the notion that information needs to be given to fit the patients' expectations (61, 139). McQuestion et al. (61) states that patients with HNC need to be more prepared for the period after treatment and the slow recovery so that they have more realistic expectations of the time to come. This means that the health-care professionals should give information with the patients' thoughts about the treatment and the convalescent period as the starting point to be able to narrow the gap between the patients' expectations and the actual experience.

Nutrition and its role in head and neck cancer

Increasing research makes it possible to develop evidence based guidelines for nutritional support in patients with cancer that can be used in clinical practice (90, 94-96). These guidelines are generally developed for patients in a curative state since nutrition in patients in a late palliative phase has a more reserved position. It is evident that patients with HNC should be the target for individualized nutritional treatment due to their multifaceted needs. In the present study cohort, some patients gained weight, whereas others had a weight loss of ≥20% up to five months after the termination of treatment and the majority of patients were overweight or obese. Due to this heterogeneity, different nutritional approaches are necessary. In patients with underweight and weight loss, the nutritional treatment should be given to reduce weight loss and promote weight stability or gain (90, 94). In patients with normal BMI, it seems unnecessary to further increase body weight and instead, the nutritional treatment should focus on the increase in FFM in favor of fat mass since FFM depletion may be present despite a normal BMI (82).

The nutritional treatment approach in patients with HNC is nutritional counseling, use of oral nutritional supplements, TF and/or parenteral

nutrition. Although all members of the multi-professional team are responsible for acknowledging nutritional deterioration and should give general advice on food intake, more specific nutritional interventions rely on the dietitians' knowledge about assessing nutritional status and implementing nutritional patient oriented interventions. In fact, individualized nutrition counseling by a dietitian has been shown to increase energy and protein intake, minimize weight loss and thus deteriorations in nutritional status, and also give pronounced effects on QoL and physical function in cancer patients in general (138, 140, 141). In patients with HNC, early and intensive nutrition support may minimize weight loss and loss of FFM when compared to standard care (142). Also, the implementation of guidelines for nutritional treatment with a dietitian in the multi-professional team can improve nutritional management of patients with HNC (143).

Tube feeding

The use of TF through a PEG or nasogastric tube is a nutritional regime that allows administration of energy and nutrients to patients not able to eat sufficiently, for example, patients with swallowing dysfunction. The common ground today in the use of prophylactic PEG vs. installation of a feeding tube when indicated is diverse and largely determined on an institutional level. In Sweden, most treatment centers wait to introduce a feeding tube until there is an indication. In the ARTSCAN trial, only 10.7% of the patients received TF at the start of RT, whereas 47.1% received TF at the end of RT. This indicates that most of the feeding tubes were installed due to treatment toxicities and the indication for installation may have been extensive weight loss and/or poor food intake. There are both pros and cons for choosing one treatment approach over the other. Important aspects to consider when placing a gastrostomy are the risk of complications, with the most common severe complication being wound infection (144). Unnecessary placement of a prophylactic PEG to patients that do not require it also needs to be considered, which might be as many as 50% (145). Some patients may also experience difficulties in obtaining the prescribed amount of nutrition. Silander et al. (146) showed, for example, that 10 – 18% of the recommended energy requirement was not met in patients with a feeding tube present, and in a study by Jager-Wittenaar et al. (82) more than one-third of the patients with TF did not reach their nutritional goals. TF use and nothing by mouth have also been argued to result in prolonged TF dependence and post-treatment swallowing dysfunction due to limited rehabilitation of the swallowing muscles (70, 147, 148). However, the results from Paper III do not support such findings as there was no significant difference in previous TF use between patients with and without aspiration. Contrary to the negative aspects that may be linked to TF and prophylactic feeding, previous studies

have highlighted the benefits of TF given with a prophylactic intent (75, 149-152). In Papers I and II, use of TF at the start of RT was shown to reduce weight loss up to five months after the termination of RT, both when studying all HNC sites (Paper I) and when studying oropharyngeal cancer in particular (Paper II), which are results that confirms previous research (149-151). Use of TF from the start of RT also is reported to result in fewer treatment interruptions (149, 150) and improved QoL (75, 152). Hence, it appears to be both advantages and disadvantages with the use of prophylactic TF in HNC. Guidelines on nutritional treatment for cancer patients states that: "nutrition support therapy should not be used routinely in patients undergoing head and neck irradiation" (96). Evidentially, the heterogeneous character of patients with HNC makes it impossible to treat all patients with a uniform approach. The use of TF should therefore be given based on an individual examination simultaneously considering the patients' autonomy. In the evaluation, one must take into account the balance between the risks of complications related to TF vs. the risk of malnutrition. A basic principle in the decision to give TF is to evaluate both the nutritional status and the expected nutritional deterioration. In Paper I, we found several factors associated with the use of TF that are in line with factors found in previous studies (51, 151). The increasing research for factors associated with TF use can therefore give some support for the health-care professionals in the decision making of which patients should receive nutritional support through TF.

Nutritional treatment given with a holistic approach

In Paper IV, it was evident that physical, psychological and social dimensions of food, eating and meals got affected in a longer perspective by the remaining sequelae. Larsson et al. (59) have previously shown that patients struggle with both physical and psychological aspects of food and eating during treatment, and that the treatment toxicities diminish the will and desire to eat. The respondents in Paper IV needed to alter their food choice to be able to eat sufficient which changed the enjoyment of food and eating. Not being able to eat everything served and not being able to eat in a "socially acceptable" way made the respondents less willing to eat together with others than the closest family. The meal-time was earlier described by patients with HNC as a ritual unifying family and friends, and thus to avoid eating with others leads to loss of togetherness (59) and a changed meaning of food (61). Hence, the growing literature on the HNC patients' experience are leaning toward that many aspects of food and eating get affected by the disease and treatment. To increase the support to the patient, McQuestion and coworkers (61) suggests that the dietitian at the patients' community should be involved in the aftercare, giving support in food preparation and food selection to facilitate food intake and eating in social settings. Hence, the nutritional treatment

administered to this group of patients needs to be given with a holistic approach, that is, patients need support to be able to eat sufficient, to find variation in food choices and guidance in eating outside the closest family.

Methodological considerations

The ARTSCAN database contains a rich amount of information on treatment, tumor and patient parameters, which has enabled an investigation of predictive factors for weight loss in a broad perspective. Despite the high number of variables available for the statistical analyses, the multiple linear regression model in Paper I explained a rather low variation in weight loss from the included variables. This can mostly be explained by the fact that weight loss is a complex problem and that the ARTSCAN trial did not include all characteristics important for weight loss in patients with HNC. The ARTSCAN trial was not primarily designed with the main aim of studying nutritional aspects and this has resulted in less information available on nutritional parameters, that is, more information on the amount of nutritional guidance and support administered during the study would have been desirable information to include in the analyses of predictive factors for weight loss from the ARTSCAN trial.

As the ARTSCAN trial was not designed with nutrition as one of the primarily outcomes, the information available on anthropometric measures such as weight was limited at follow-up. This was due to death and residual/recurrent disease but most important owing to missing weight data registrations at follow-up. In Paper I, weight data were available for 60.7% patients at follow-up and the corresponding number for Paper II was 65.0%. Of the missing data, 49.3% (Paper I) and 57.6% (Paper II), these were due to missing weight data registrations at follow-up. In follow-up studies on cancer patients, missing data are a common problem that cannot be ignored as there always is a risk to get skewed selections by chance when analyzing incomplete data from a larger study cohort. Restricting the analysis to include only completers might therefore offer data that give a more optimistic picture. In the ARTSCAN trial, no information was available on patient drop-out, but earlier studies have shown a lower clinical stage in study completers (153), and that almost half of the drop-outs are disease or treatment related (154).

In Paper II, we found that patients with a high BMI at the start of RT had a better five-year overall survival. Although this result confirms previous research (46, 114-116), it needs to be interpreted in the light of factors that could have influenced the result. Clinical stage is a well-known prognostic factor for survival in HNC (12), and a low BMI has been shown to be correlated with a more advanced disease (114). However, in Paper II, BMI remained an

independent factor for survival in patients with oropharyngeal cancer when also controlling for clinical stage in the cox regression. It has further been shown that patients with advanced disease and a low BMI display poorer survival compared with patients with advanced disease and a high BMI (114), which implies that the initial nutritional status is of importance beyond the disease effect. It can also be speculated that the prevalence of HPV infection and unhealthy lifestyle habits such as smoking might have been confounding factors in the relation between BMI and survival. HPV infection has been shown to be a favorable prognostic factor in oropharyngeal cancer (6, 12), whereas smoking may have the opposite effect (155). Patients with a low BMI have been shown to have a significantly higher frequency of smoking history than patients with a high BMI (114). However, when controlling for smoking in the multivariate analysis, McRackan et al. (115) still found a significant impact from BMI on survival. As for now, it is difficult to decipher whether patients with a low BMI have worse survival due to the poor nutritional status, *per se*, or if other patient, disease or treatment related factors are the main cause of this relation. However, the current research strongly leans toward the importance of a balanced nutritional status at the start of RT for patients with HNC.

The patients in the ARTSCAN trial were given RT with 3-DCRT and/or IMRT techniques. IMRT has been shown to result in less treatment toxicities compared to 3-DCRT (156). Since the study was completed, the IMRT technique has been further introduced in clinical settings resulting in more refined treatment approaches to minimize the treatment burden. This implies a lower frequency of treatment toxicities nowadays compared with the frequencies seen in the ARTSCAN trial. Also, improved and better use of medications may reduce the impact of the treatment toxicities on food intake. This together with new and improved treatment methods are therefore important steps to be able to reduce the amount of nutritional deterioration seen in patients with HNC.

Study sample

Papers I - III

The patients in the ARTSCAN trial constituted a somewhat different patient population compared with data from the Swedish Head and Neck Cancer Register (113) on tumors of the oropharynx, hypopharynx, larynx, and oral cavity (**Table 5**). Overall, more men were represented in the ARTSCAN trial, and there were higher frequencies of stage III-IV disease and oropharyngeal cancer and a lower frequency of cancer in the oral cavity when compared with the corresponding tumor sites from the Swedish Head and Neck Cancer

Register. The treatment approach in Sweden for oropharyngeal cancer is mainly RT, in some cases combined with neck dissection and/or anticancer drugs, whereas oral tumors are primarily treated with surgery alone or combined with RT. Since the main aim of the ARTSCAN trial was to compare the effect of AF vs. CF, it seems reasonable that the study population consisted of more patients with oropharyngeal cancer and less patients with tumors of the oral cavity. Of the tumor locations studied in the ARTSCAN trial, tumors of the oral cavity are the most common tumor site in women (113) and therefore this might be the reason to why fewer women were represented in the ARTSCAN trial. Oral cancer may affect swallowing function and lead to nutritional problems (157, 158). Hence, the low number of patients with oral cancer may have reduced the prevalence of weight loss in the study cohort. Contrarily, since the risk of weight loss increases with the severity of the disease (48, 54, 55) it seems reasonable to speculate that the higher frequency of stage III and IV tumors in the ARTSCAN trial might have increased the frequency of weight loss in the study cohort.

Paper IV

Within qualitative research it is important to display a variance within the study participants (112, 159). In Paper IV, patients with different tumors and hence different treatment approaches were studied at approximately nine months after the termination of RT. The experience of food, eating and meals described by women and palliative patients was poorly addressed as the true distribution of men vs. women in HNC (12), and only patients with a curative treatment intent were included in the study. Transferability instead of generalization is the preferable concept used for results generated by qualitative research (112). Patients with tumor of the head and neck are a group with specific nutritional problems due to tumor burden and treatment toxicities. Nevertheless, there are also other diseases that affect many aspects of food intake and some of the concepts of the results from Paper IV may therefore be transferred to other patient groups experiencing similar symptoms.

Difficulties in studying the "real" effect of nutritional status and nutritional support

The need of nutrition in human is unquestionable and therefore nutritional treatment is part of a standard care approach. Hence, it is not ethical to randomize patients for whether to receive nutritional support or not, which makes it difficult to find straightforward multiple lines of evidence for the effect of nutritional support in HNC. Consequently, few studies have been conducted using a randomized methodology. Those found have usually been

performed investigating the effect of a nutritional intervention vs. standard care (75, 138, 141, 146, 152, 160, 161). In a Swedish study, patients with HNC were randomized to either prophylactic PEG or a nutritional regime according to standard care (75). The authors found a higher health-related QoL in the study group receiving prophylactic PEG. Another highly debated study on patients with HNC showed that nutritional support given before treatment was associated with inferior treatment outcome (162). However, because of its non-randomized character, it is difficult to interpret if confounding factors might have biased the results.

Nutritional status may be assessed using different tools (76, 91, 92). However, besides these objective measures, other factors, such as the intensity of supportive care, can also have an influence. Thus, the effect of the nutritional support cannot be "taken away" when studying the correlation between nutritional status and outcome. The patients in the ARTSCAN trial were given nutritional support when indicated according to local guidelines at the treatment centers. Therefore, when interpreting the results from Papers I - III that show predictive factors for weight loss and BMI in HNC, it is important to recognize the synonymously use of nutritional support. For example, the use of TF might provide an explanation to why no significant difference was found in weight loss between the two fractionation schedules since patients treated with AF received TF more frequently (Paper I). That is, patients with AF did not have significantly more weight loss compared to patients treated with CF, although patients with AF had more treatment toxicities. Unfortunately, this could not be adjusted for using significant interaction effects between TF and the other variables in the multivariate model due to poor statistical power since few patients received TF at the start of RT. Although it is possible to use statistical methods to control for the effect of the nutritional support, it is still a matter of methodological concern. Thus, the synonymous use of nutritional support should be acknowledged when interpreting research within this area.

Another question of concern when studying the effect of nutritional support in HNC is how patients receiving nutritional support differ from patients that not receiving nutritional support. Results from Paper I and previous studies showed that older patients, patients with larger clinical stage, patients with low BMI or low KPS, patients with higher pre-treatment weight loss or patients with more treatment toxicities received TF more frequently (51, 151). Therefore, it is easy to speculate that patients with high morbidity and/or poor nutritional status receive nutritional support more frequently and this selection bias is important to consider in studies investigating the effect of nutritional support vs. outcome.

Trustworthiness

There are different concepts used within qualitative research to ensure trustworthiness. Credibility relates to how well the data and process of analysis reflect the focus of the study, i.e. the choice of method and study participants as well as different decisions made during the analysis process (112, 163). A qualitative method and in-depth semi-structured interviews were chosen in Paper IV since the research question was poorly described in previous research and because of the interest to investigate patients' experience. The analysis was continuously discussed between the presenting authors to come to an agreement on how the data should be sorted and labeled (112). Reflexivity deals with the authors pre-knowledge (159, 163). The first author has a background as a dietitian constituting knowledge of the concepts of this patient group from daily clinical practice, and this means that it is impossible for the first author to not have any preconceived pictures of the phenomenon in question. To deal with this, the pre-knowledge was thoughtfully recognized and "set-aside" during the analysis process and notes were taken after each of the interviews where the first author reflected over the interview and the interaction with the respondent. Dependability is another concept that deals with data consistency over time, and therefore information about the data collection and analysis should be clearly defined (112, 163). To ensure that all respondents were presented with similar questions, a semi-structured topic-guide that had been tested through two initial pilot interviews was used. To further ensure dependability, a code-recode approach was used (163), and the analysis and result were continuously discussed between the presenting authors.

Suggested recommendations for nutritional surveillance based on findings from Papers I - IV

Recommendations for nutritional surveillance pre and post-treatment in patients with HNC receiving RT as the single modality treatment or as preoperative RT based on findings from this thesis have been summarized in **Figure 12**. For nutritional guidelines during RT see (90, 95).

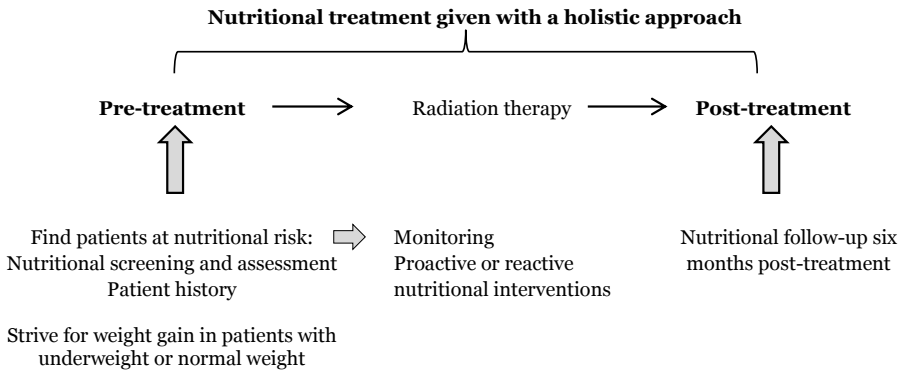

Figure 12. Suggested recommendations for nutritional surveillance pre and post-treatment for patients with head and neck cancer.

Pre-treatment

Patients with HNC are a nutritionally heterogeneous group. Some patients will have a substantial weight loss during and after RT, whereas others will remain stable or even gain weight. It is therefore imperative to sort out patients at nutritional risk, i.e. to find patients in need of early active or proactive nutritional interventions. On the other hand, we do not want to create unnecessary anxiety in non-risk patients. This is an important aspect to consider in clinical work that requires a delicate touch by the physician and dietitian. To be able to provide nutritional actions in time to the right patients, nutritional screening and assessment together with patient history should be included as early as possible during the pre-treatment period. Information on involuntary weight loss in combination with information about BMI and eating difficulties (76, 88) or the use of MUST (89) are two examples of tools recommended in the literature that can be used during nutritional screening and for the nutritional assessment, PG-SGA has been suggested for patients with HNC (90, 95). During patient history, presence of predictive factors for anticipated weight loss during RT should be considered. The result from the present thesis indicates that tumor site, and more specific RT parameters, may be of importance, i.e. patients with oropharyngeal cancer or patients receiving

larger TV. Once at-risk patients have been found, they should be referred to a dietitian for nutritional assessment and treatment so that their nutritional status can be optimized before starting RT. This approach is supported by the results from the present thesis together with previous research that strongly indicates that a high BMI at the start of RT may be of importance for survival in patients with HNC. Therefore, it is suggested that patients with a low BMI should be encouraged to gain weight before RT start.

Post-treatment

The papers in this thesis make it evident that many patients deal with the sequelae of their disease and treatment during a long period of time after the termination of treatment. With the routines for follow-up used during the ARTSCAN trial, patients continued to lose weight after RT with a nadir at five months after the termination of RT. Many of the guidelines for nutritional treatment available today focus on the short term impact of treatment, and thus there is less information available on how these patients should be followed in a long-term perspective and which particular patients are at nutritional risk post-treatment. The papers in this thesis together with previous research have shown that patients with HNC may be at nutritional risk up to 5 - 6 months after the termination of RT, which emphasize the need of additional and prolonged nutritional surveillance and support following RT. The results specially highlight patients with severe post-treatment swallowing dysfunction as a group of patients that requires extra nutritional attention in the post-treatment period.

Holistic approach

The present thesis highlights that the consequences of HNC and related treatment have a substantial impact on the patients' daily life both in the short and long term. The nutritional treatment given therefore needs to be encompassing all aspects of food, eating and meals, i.e. the nutritional treatment should be given with a holistic approach to meet the multifaceted needs patients with HNC experience. During the whole treatment period, but especially after six months post-treatment, more focus should be given on factors that may increase the patients' satisfaction in food and eating. This includes guidance in food selection and strategies that can be used when eating in social environments. Thus, the dietitian may have an important role to play for the HNC survivor when it comes to increasing the pleasure in food and eating and for guidance in the new way of living.

Implications for further research

In most of the research available today on patients with HNC, there are diverse ways used to describe and define the nutritional status. A review addressing this problem showed that some studies assess malnutrition by a single descriptor, whereas other studies have used multiple domains (164). Therefore, when studying the effect of nutritional deterioration on outcome parameters, an agreement on how to define nutritional deterioration need to be established. Also, when designing studies on nutritional status vs. outcome, the pathophysiological factors of the nutritional deterioration need to be better identified. More information is, for example, attained on the patients' nutritional status when including measures on body stores since loss of FFM is of greater significance than loss of adipose tissue (79). It is desirable that larger prospective studies are performed where the nutritional status is uniformly assessed to be able to reach comparable and reproducible results, more truthful prevalence numbers, and more clear-cut and unanimous description of nutritional status in the HNC literature.

It is evident that HNC signifies a long journey that many patients do not fully recover from. However, the guidelines available for nutritional treatment for patients with cancer focus on the time during treatment and there is currently weak guidance on how patients should be monitored after the termination of treatment and which patients are of particular nutritional risk. Therefore, more studies are needed where the outcome of nutritional support and time of follow-up are investigated in different sub-groups of HNC patients to establish evidence based guidelines that can be implemented in everyday clinical work.

The research available today confirms the multifactorial nature of nutritional deterioration in HNC, and hence more information is needed to be able to put more pieces together in this complex puzzle. In an ongoing study (the quantitative data collection as a part of the care development project) we will be able to investigate inflammatory activity in relation to nutritional status, food intake and energy expenditure, and the change from the pre-treatment to the post-treatment period. Hopefully, this can make it possible to further address which components are of greatest importance for an energy balance in patients with HNC.

Conclusions

Based on the results from Papers I - IV, the following conclusions can be made:

I. Weight loss up to five months after the termination of RT in HNC was found to have a multifactorial etiology. Patients with oropharyngeal cancer and patients with overweight/obesity had the highest weight loss, and patients with TF at the start of RT lost less weight than patients without TF. No significant difference in weight loss could be seen between patients treated with AF or CF. On a group level, patients lost weight during and after RT with a nadir at five months after the termination of RT.

II. Larger treated volume, as a measure of the radiation dose burden, was shown to be correlated with a higher weight loss up to five months after the termination of RT in patients with oropharyngeal cancer. Furthermore, a high BMI at the start of RT was shown to increase five-year overall survival in the same study cohort, whereas the same relation was not found between weight loss and survival.

III. Presence of post-treatment aspiration was correlated with increased weight loss and a lower BMI in HNC survivors and patients with aspiration lost weight from 23 months after the termination of RT. Despite a high frequency of post-treatment aspiration, few patients in the study cohort were defined as being at nutritional risk.

IV. The patients' own narratives showed that all aspects of food, eating and meals were affected by the remaining sequelae. The acceptance of a new normal and the use of strategies facilitated food intake and social interaction during meal-time. HNC signifies a long journey where support and proper information are essential parts during treatment and the rehabilitation period.

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