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Pre- and post-treatment malnutrition in head and neck cancer patients

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Jager-Wittenaar, H. (2010). *Pre- and post-treatment malnutrition in head and neck cancer patients*. [s.n.].

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Download date: 03-06-2022

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The research described in thesis was financially supported by a grant from the UMCG.

The printing and distribution of this thesis was financially supported by:
Fam. Jager
Abbott B.V.
Dental Union
Fresenius Kabi
Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie (NVMKA)
Nestlé Nutrition
Nutricia Advanced Medical Nutrition
Rijksuniversiteit Groningen
Sorgente B.V.
Straumann B.V.
Universitair Medisch Centrum Groningen

Cover design: P. van der Sijde en H. Jager-Wittenaar, Groningen
Lay out: P. van der Sijde en H. Jager-Wittenaar, Groningen
Printing: GVO drukkers & vormgevers B.V. | Ponsen & Looijen, Ede

ISBN: 978-90-367-4403-4
978-90-367-4410-2 (digitaal)

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RIJKSUNIVERSITEIT GRONINGEN

Pre- and post-treatment malnutrition in head and neck cancer patients

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 8 september 2010
om 13.15 uur

door

Harriëtte Jager-Wittenaar

geboren op 24 mei 1974
te Hoogezand-Sappemeer

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Beoordelingscommissie: Prof. dr. R. de Bree
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Prof. dr. ir. E. Kampman

Aan Harold

"If you enter this world knowing you are loved
and you leave this world knowing the same,
then everything that happens in between can be dealt with."

Michael Jackson, 29 augustus 1958 – 25 juni 2009

Paranimfen: Mw. S. Huitema
Mw. dr. M. van Rijn

CONTENTS

Chapter 1

Introduction

INTRODUCTION

Head and neck cancer

Head and neck cancer is an umbrella term to describe a range of malignant tumors originating from the upper aerodigestive tract, including the mouth (oral cavity), throat (pharynx), larynx, nasal cavity and paranasal sinuses (Figure 1). The most common type of cancer in the head and neck is squamous cell carcinoma, and less common types include salivary gland tumors and sarcomas. The age-adjusted incidence of head and neck cancer in the Netherlands is about 14 new patients per 100,000 inhabitants per year (Table 1).[1] Major risk factors for developing a squamous cell carcinoma in the head and neck region are excessive use of tobacco and alcohol.[2] Alcohol and tobacco are synergistic in causing head and neck cancer.[2] Due to excessive alcohol use and smoking, nutritional deficits are not uncommon in head and neck cancer patients.[3-5] Consumption of fruit and vegetables may reduce the risk for developing head and neck cancer.[6]

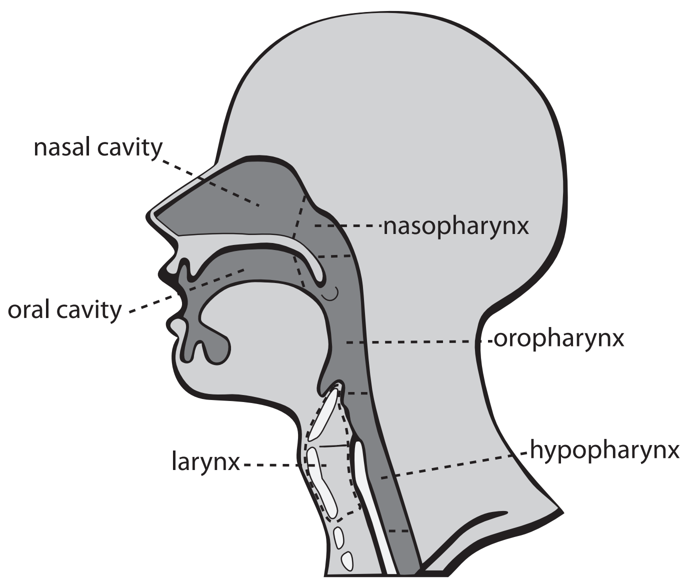

Figure 1. Head and neck anatomy. Printed with permission.[57]

Table 1. Age-adjusted incidence per 100,000 of head and neck cancer in The Netherlands in 2007 (The Netherlands Cancer Registry).[1]

	Men	*Women*	*Total*
Head and neck cancer	19.0	8.3	13.8
Oral cavity	5.4	3.8	4.6
Pharynx	4.1	1.7	2.9
Larynx	5.8	1.1	3.5

Curing the patient is the primary goal of treatment, but preserving function and esthetics are also important aspects in choice of treatment. Besides tumor stage, choice of treatment depends on overall condition and preferences of the patient. Whereas head and neck cancer used to be treated by surgery and/or radiotherapy, nowadays combined treatment modalities including chemotherapy are frequently applied, such as radiotherapy with chemotherapy (chemoradiation) and surgery plus chemoradiation. All these regimens have their side effects, which are considered a hazard for maintaining a good nutritional status.

Treatment of head and neck cancer is complex as it affects airway, chewing, taste, salivary gland function, swallowing and speech. Furthermore, head and neck cancer treatment may mutilate the appearance of the face, neck and shoulder. As a result, head and neck cancer treatment is incriminating for the patient and many patients are at risk to become handicapped socially. Whereas surgical treatment may result in esthetic mutilation, radiotherapy and chemoradiation are considered tissue preserving in this respect. However, these treatment modalities are not less aggressive and are accompanied by considerable damage to healthy tissues. These damages will result in mucositis, loss of taste, impaired salivary gland function and swallowing problems due to fibrosis, which may have a major impact on the patients' nutritional status. Furthermore, radiation-induced fatigue may have a negative impact on maintaining an adequate nutritional status.[7]

Oral symptoms and their impact on oral feeding

Head and neck cancer patients are a nutritionally vulnerable group of patients. In addition to general symptoms caused by cachexia, such as loss of appetite, early satiety and changes in smell and taste[8,9], head and neck cancer patients often suffer from oral symptoms, caused by the tumor, or as a side effect of head and neck cancer treatment.[10,11] The most common oral symptoms include swallowing problems, chewing problems, hyposalivation, pain in the mouth or throat, taste disturbances and trismus.[10,11]

Swallowing problems include difficulty with swallowing and pain during swallowing. In head and neck cancer patients, swallowing problems may be present in both pre-and post-treatment period. Before treatment, swallowing problems are frequently observed in patients with a tumor in the oral cavity, oropharynx, hypopharynx and supraglottic larynx. Furthermore, all treatment modalities may compromise swallowing function to some degree.[12] The extent of resection of structures vital to bolus formation, bolus transit and airway protection (such as oral tongue, tongue base or arytenoid cartilages) has a great impact on postsurgical swallowing function.[13] Postoperative radiotherapy fibrosis further negatively affects swallowing function.[12] Moreover, radiation induced mucositis contributes to impaired swallowing function after radiotherapy or chemoradiation.[11,13] Additionally, swallowing may be impeded by radiation-induced hyposalivation, due to insufficient moistening of food by saliva.[11]

Chewing problems may be the result of pain due to the tumor localization, side effects of radiotherapy, poor dental status or trismus. Tumors in the oral cavity, for example in the mandible or maxilla, often cause pain, especially during chewing. Furthermore, chewing may be compromised by tumor resections of the mandible or maxilla and floor of the mouth.[14]

Besides the aimed effect on tumor tissue, radiotherapy (in)directly affects healthy tissues that are located in proximity to the tumor tissue, such as the salivary glands, oral mucosa, bone, masticatory musculature, and dentition. As a result, hyposalivation and trismus may occur, both may possibly induce problems with chewing. In addition, to prevent osteoradionecrosis, a late side-effect of radiotherapy, permanent teeth with a doubtful prognosis are removed prior to radiotherapy.[15] These dental extractions may exaggerate the chewing problems, also because wearing a denture is often accompanied by symptoms in the radiated patients. Furthermore, after radiotherapy or chemoradiation, edentulous patients have to wait for a new prosthesis, and thus remain edentulous, for at least 3 to 6 months, as oral mucosa needs this period to fully recover from radiotherapy.

Hyposalivation is the result of radiation-induced damage to salivary glands. Hyposalivation results, amongst others, in dry mouth (xerostomia), sticky saliva, changes in taste, difficulty in wearing a prosthesis and chewing problems.[11] Besides reduced quantity of saliva, head and neck cancer patients treated with radiotherapy suffer from a changed composition of saliva, resulting in a shift in oral microflora toward cariogenic bacteria and yeasts.[11]

Taste disturbances in head and neck cancer patients are characterized by decrease in taste acuity (i.e. decreased sensitivity to or absence of taste perception) and a change in taste quality (i.e. mainly unpleasant taste).[16] Taste disturbances may be caused by release of tumor-induced pro-inflammatory cytokines[17] and cancer treatment. Radiotherapy causes damage to taste buds and hyposalivation, both resulting in taste abnormalities.[11,16] Patients treated with radiotherapy or chemotherapy have a decreased ability to identify the basic tastes bitterness, sourness, saltiness and sweetness.[16,18] Furthermore, these patients may perceive a metallic or bitter taste, or aftertaste.[16] Taste disturbances may be that severe that food aversion is inevitable.[16] Loss of taste is usually temporary and usually gradually returns to normal or near-normal levels within the first year after radiotherapy. However, for some patients these taste disturbances are permanent.[11]

Trismus, a severely restricted mouth opening, is a common problem in patients with head and neck cancer, with a prevalence ranging from 5% to 38%.[19,20] Trismus may result from tumors infiltrating or irritating mouth closing muscles, from scar tissue formation as a result of surgery and from irradiation injury.[11,21-23] Trismus may hinder eating, especially large boluses of solid food. To enable determination of therapeutic effects of anti-trismus treatment, reliability of these mouth opening measurements needs to be investigated.

All of the above mentioned oral symptoms have the potential to compromise mandibular functioning, patient's nutritional status and quality of life.[24,25] Previous studies on the relationship between oral or oropharyngeal cancer treatment and oral symptoms have focused on 1 or 2 specific symptoms, such as swallowing and/or chewing problems after surgery and/or radiotherapy.[14,26] Previous studies also focused on functional outcome after specific types of treatment, for instance radial forearm free flap reconstruction.[27-29] However, so far it is unclear how oral symptoms impact mandibular function and nutritional status.

Malnutrition

As is obvious from the previous 2 paragraphs, it is not uncommon that malnutrition develops in head and neck cancer patients. Malnutrition has been defined as 'a subacute or chronic state of nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity has led to a change in body composition and diminished function'.[30] In this definition, body function refers to muscle function (strength), cognitive function and immune function.

Prevalence of severe weight loss, an indicator of malnutrition, in head and neck cancer patients at diagnosis varies from about 30% to 55%.[31-34] Prevalences of severe weight loss vary due to differences in timing of nutritional assessment, differences in operationalization of severe weight loss, and differences in study populations regarding tumor localization. Due to this heterogeneity, numbers of studied patients with oral or oropharyngeal cancer are small. Furthermore, follow up of the studies on malnutrition in head and neck cancer published in literature to date was limited to 6 months after treatment.[31-37] As a result, little is known about prevalence of malnutrition in head and neck cancer patients in the long-term period (more than 6 months) after treatment.

Generally, head and neck cancer patients are at risk for malnutrition from diagnosis to their remaining life after treatment (Figure 2). In the period before treatment, a major cause of malnutrition is insufficient food intake related to mechanical obstruction of food or pain caused by the tumor. Cancer cachexia, a complex

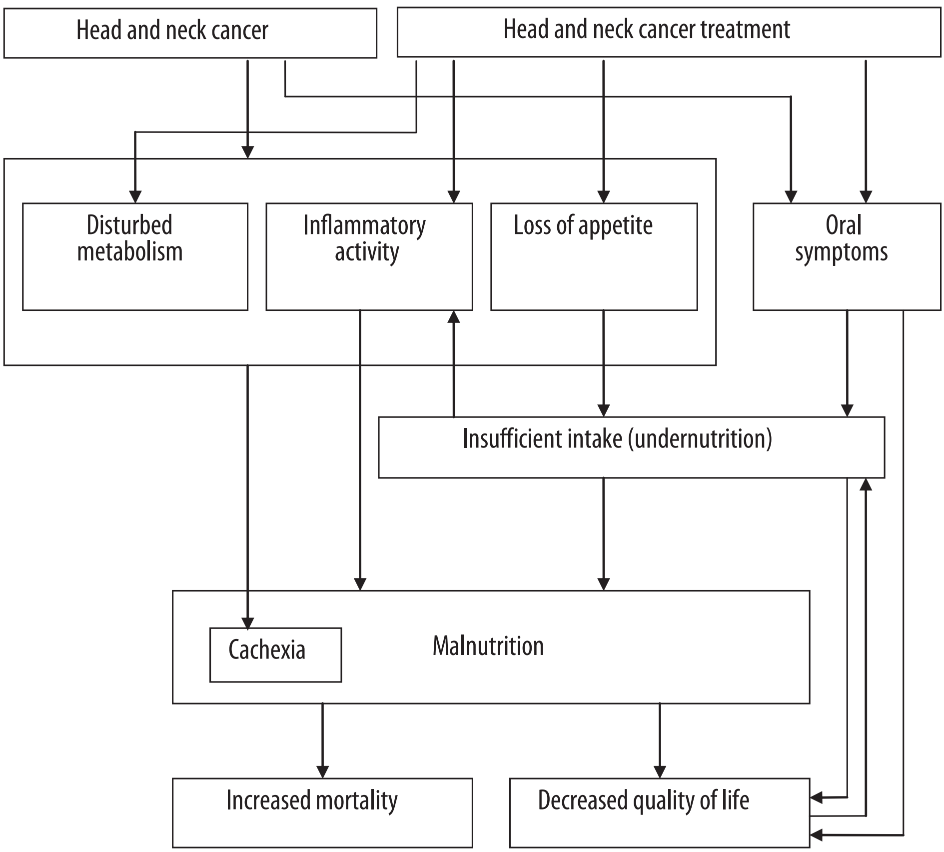

Figure 2. Causes and consequences of malnutrition in head and neck cancer patients. Modified after Soeters et al.[30]
Malnutrition in head and neck cancer patients may be caused by both cancer itself and its treatment. Cancer may be accompanied by disturbed metabolism, inflammatory activity and loss of appetite. These factors combined may cause cachexia, a subtype of malnutrition. Furthermore, the localization of the tumor may cause oral symptoms that hamper food intake. Treatment related symptoms, such as swallowing problems, chewing problems, dry mouth and changes in smell and taste may hinder food intake as well, possibly resulting in insufficient food intake. Malnutrition may result in decreased quality of life and increased mortality.

metabolic syndrome associated with the underlying disease and characterized by loss of appetite and inflammatory activity, may contribute to malnutrition in this period.[30,38,39] During and after head and neck cancer treatment, malnutrition may develop or aggravate. First, head and neck cancer treatment induces inflammation. Second, treatment-related oral symptoms may hamper eating and drinking, which in turn may result in insufficient energy and protein intake. Although all of these oral symptoms are risk factors for malnutrition, it is not clear which oral symptoms are most strongly related to malnutrition, both at time of diagnosis and in the period after treatment.

Malnutrition is associated with increased morbidity and mortality.[34,40-44] The associated decreased immune function is expressed by an increased complication rate, such as impaired wound healing, and decreased tolerance to surgery, radiotherapy and chemotherapy.[34,40,43,45] Malnutrition also impairs response to cancer treatment[46] and has a negative impact on quality of life.[35,44,47-49]

As malnutrition may affect patients' outcome, it is of clinical importance to know which factors are most strongly related to malnutrition risk in head and neck cancer patients. Knowledge on risk factors for malnutrition may contribute to effective treatment of or even prevention of malnutrition in these patients.

Body composition

At present, changes in body weight are widely used to both assess malnutrition and monitor nutritional status. Weight loss is an accepted and valid indicator of malnutrition, as it is related to postoperative complications, mortality and quality of life.[34,40,42-44,47,49] Whereas disease related weight loss is known to be characterized by loss of both fat mass and lean mass (i.e. muscle mass, cutaneous mass, visceral mass)[30,50,51], so far it is unknown which body compartments increase in head and neck cancer patients that manage to gain body weight after treatment. The pitfall is that gain of body weight is characterized by gain of mainly fat mass, whereas gain of muscle mass (indicated by lean mass) is aimed for. Muscle mass is considered the crucial body compartment of lean mass, as it furnishes the substrate to fuel and supports the acute phase response (inflammatory activity) during disease or treatment.[30] Obviously, to maintain immune status and physical function, loss of lean mass should be prevented as much as possible. It would be of great clinical importance to have insight into changes in body composition during and after head and neck cancer treatment.

Dietary treatment

Dietary treatment in patients with head and neck cancer aims to optimize or maintain nutritional status.[46] In underweight patients dietary treatment aims to improve both fat and lean mass, whereas in normal weight or overweight patients improvement of primarily lean mass is aimed for.[52]

Evidence suggests that during and shortly after head and neck cancer treatment, energy and protein requirements increase.[53,54] Surgery and radiotherapy are accompanied by increased inflammatory activity, possibly resulting in an elevated resting energy expenditure.[53] The combination of reduced oral functioning and increased nutritional requirements makes it difficult to consume a sufficient amount of energy and protein when using oral food only. Although patients are advised to use high-calorie and high-protein products in a soft, mashed or liquid diet, a large subset of the patients needs additional liquid dietary supplements. In a smaller subgroup of patients oral symptoms cause such a burden to the patient that additional or complete tube feeding is required (temporarily), for example during radiotherapy or chemoradiation.

Quality of life

Health-related quality of life is a multidimensional concept that reflects the psychological, physical and social effects of disease and its therapy.[55] Age, gender, tumor localization, tumor size, treatment modality, oral symptoms, emotional status, smoking and alcohol consumption, marital status, income and performance status have all been shown to affect overall health related quality of life in patients with head and neck cancer.[56] The awareness that malnutrition is an important endpoint in the outcome of head and neck cancer treatment, and thus might have a significant impact on quality of life too, is growing. Previous studies have demonstrated that malnutrition has a negative impact on quality of life.[35,47-49] However, these studies were heterogeneous regarding tumor localization, resulting in a small number of included patients with oral or oropharyngeal cancer.[35,47-49] Furthermore, in these studies malnutrition and quality of life were assessed during and shortly after treatment. Thus, it remains unclear how malnutrition relates to quality of life in patients after treatment for oral or oropharyngeal cancer, and more specific in the long-term period after treatment.

Aim of the thesis

The general aim of this thesis was to explore pre- and post-treatment malnutrition in head and neck cancer patients. Specific aims of this thesis were to assess nutritional status during the various phases of the treatment head and neck cancer patients are subjected to, viz. from diagnosis up to the period after completion of cancer treatment, and to identify risk factors for malnutrition that occur during these various phases. Therefore we:

- assessed prevalence of malnutrition in head and neck cancer patients at diagnosis and identified risk factors underlying this malnutrition (Chapter 2);
- assessed prevalence of malnutrition and dietary intake in patients treated for oral or oropharyngeal cancer and explored the relationship between malnutrition and oral symptoms (Chapter 3) and quality of life (Chapter 4);
- assessed changes in nutritional status and dietary intake during and after head and neck cancer treatment (Chapter 5);
- explored oral symptoms in patients treated for oral or oropharyngeal cancer and assessed its impact on mandibular functioning (Chapter 6);
- assessed variation in repeated mouth opening measurements in head and neck cancer with and without trismus, to enable determination of therapeutic effects of anti-trismus treatment (Chapter 7).

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Chapter 2

Critical weight loss in patients with head and neck cancer - prevalence and risk factors at diagnosis: an explorative study

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Support Care Cancer 2007: 15: 1045-50

ABSTRACT

Background & Aims

Critical weight loss (≥5% in 1 month or ≥10% in 6 months) is a common phenomenon in head and neck cancer patients. It is unknown which symptoms are most strongly related to critical weight loss in head and neck cancer patients at the time of diagnosis. The aim of this explorative study was to assess prevalence of critical weight loss and to analyze risk factors for critical weight loss in head and neck cancer patients before treatment.

Methods

Critical weight loss and factors reducing dietary intake were assessed in 447 patients referred to an ear, nose and throat clinic at the time of diagnosis.

Results

In total, data of 407 patients were analyzed. Critical weight loss was present in 19% of the patients. Patients with cancer in the hypopharynx, oropharynx/oral cavity and supraglottic larynx had the highest risk for critical weight loss. Loss of appetite, dysphagia/passage difficulties and loss of taste/aversion were significantly ($p<0.05$) associated with critical weight loss.

Conclusion

Already before treatment, critical weight loss is a considerable problem in head and neck cancer patients. Critical weight loss is frequently observed in patients with cancer in the hypopharynx, oropharynx/oral cavity and supraglottic larynx.

INTRODUCTION

Critical weight loss (CWL), defined as the involuntary weight loss of ≥5% in 1 month or ≥10% in 6 months, is a common phenomenon in head and neck cancer patients because it is present in about 30% to 55% of these patients.[1-4] CWL is clinically of utmost importance. It is associated with increased morbidity and mortality. CWL may result in an increased complication rate, such as impaired wound healing, reduced immune function and decreased tolerance to surgery, radiotherapy and chemotherapy.[4-6] CWL also reduces disease-related quality of life and functional status.[7]

Head and neck cancer patients often experience symptoms related to the localization of the tumor, such as dysphagia, odynophagia, passage difficulties and pain in the mouth.[8-12] Furthermore, systemic effects of the tumor may result in changes in taste or appetite.[13,14] These symptoms may result in difficulties with nutritional intake leading to CWL. It is unknown, however, which symptoms are most strongly related to CWL in head and neck cancer patients at the time of diagnosis.

The aim of this explorative study was to assess the prevalence of CWL and to analyze the risk factors for CWL before treatment in head and neck cancer patients referred to the ear, nose and throat (ENT) department of the University Medical Center Groningen (UMCG).

PATIENTS AND METHODS

Patients with a newly diagnosed tumor in the head and neck region, either a (second) primary or a recurrent tumor, were screened according to the UMCG Head and Neck Clinical Screening Tool (UMCG H&N CST) as a part of a routine clinical procedure at the ENT department of the UMCG. The screening was performed by an ENT physician or a nurse, at the first visit at the ENT department or at the time of endoscopic diagnostic investigation, usually about 2 weeks after the first visit.

The UMCG H&N CST consisted of 2 parts. The first part assessed CWL, defined as weight loss of ≥5% in 1 month or ≥10% in 6 months.[4-6,15-17] Assessment of CWL was based upon the formula [(normal weight (kg) – actual weight (kg)) / normal weight (kg)] × 100. CWL was recorded as a dichotomous variable (present/absent). The second part of the UMCG H&N CST assessed symptoms that may lead to difficulties with nutritional intake, including loss of appetite, dysphagia, passage difficulties, pain in the throat, loss of taste/aversion, dry mouth and pain in the mouth. These symptoms were recorded also dichotomously (present/absent). In addition, tumor localization and tumor size of each patient were obtained from the medical records after diagnostics.

The data of 447 consecutive patients with a tumor in the head and neck region, screened between November 2001 and August 2004, were used for this study. For data analysis, SPSS version 12.0 (SPSS, Chicago) was used. Descriptive statistics were used to assess the prevalence of CWL. Stepwise multivariate logistic regression was used to identify risk factors for CWL. The presence or absence of CWL was used as the dependent variable, and the symptoms possibly influencing nutritional status were used as the independent variables. The influence of the tumor size (T) on CWL was calculated by means of chi-square analysis. A p-value <0.05 was considered statistically significant.

RESULTS

Data of 407 patients out of 447 (91%) of the UMCG H&N CST were complete. Patient characteristics of patients with complete (91%) and incomplete (9%) data sets are summarized in Table 1. Significantly more patients with a tumor of the hypopharynx, oropharynx/oral cavity or supraglottic larynx had an incomplete data set compared to patients with other tumor localizations (p=0.038) and significantly more patients with a T3 or T4 tumor had an incomplete data set compared to patients with a T1 or T2 tumor (p=0.003). CWL was present

Table 1. Patient characteristics.

Patient characteristics (n=447)	*Patients with complete data (n=407)*		*Patients with incomplete data (n=40)*	
Age (yr, mean±SD)	63.3±13.8		65.3±12.4	
	%	*n*	*%*	*n*
Gender				
Male	74	302	80	32
Female	26	105	20	8
Tumor type[a]				
Primary tumor	91	371	83	33
Recurrent tumor	9	36	18	7
Tumor localization[a,b]				
Larynx	31	125	28	11
Supraglottic larynx	9	38	13	5
Glottic larynx	26	107	8	3
Sub-/transglottic larynx	2	9	8	3
Oropharynx	15	62	23	9
Hypopharynx	12	49	20	8
Nasopharynx	3	14	10	4
Oral Cavity	2	6	3	1
Other[c]	30	122	18	7
Tumor size[a,d]				
T1	20	82	13	5
T2	19	77	5	2
T3	8	32	18	7
T4	18	75	30	12
Not recorded[e]	35	141	35	14

a. Total percentage is not similar to 100, due to rounding off. Percentages are column percentages.
b. Significantly more patients with a tumor of the hypopharynx, oropharynx/oral cavity or supraglottic larynx had an incomplete data set compared to patients with other tumor localizations (p=0.038).
c. Carcinoma in the ear, salivary gland, nose/paranasal cavity, esophagus, thyroid gland, skin, eye, lymphoma and unknown primary.
d. Significantly more patients patients with a T3 or a T4 tumor had an incomplete data set compared to patients with a T1 or a T2 tumor (p=0.003).
e. From the tumors listed as 'other', no classifications of tumor size were made.

in 19% (77/407) of the patients. Prevalence of CWL did not differ significantly between patients with a newly diagnosed primary tumor (19%, 71/371 CWL) and patients with a recurrent tumor (17%, 6/36 CWL).

Critical weight loss related to tumor localization

CWL related to tumor localization is presented in Table 2. Tumor localizations in which CWL was present in more than 30% of the patients were the oropharynx/oral cavity, nasopharynx and hypopharynx. Although prevalence of CWL in patients with laryngeal cancer was low (12%, 18/154), within this group of patients, patients with supraglottic laryngeal cancer had CWL more frequently (34%, 13/38).

In total, 122 patients had a tumor at 1 of the following sites: ear, salivary gland, nose/paranasal cavity, esophagus, thyroid gland, skin, eye or lymphoma or had an unknown primary tumor. If this group of patients with tumor localizations registered as 'other' was excluded from the analysis, the prevalence of CWL increased to 24% (67/285).

Table 2. Prevalence of critical weight loss per tumor localization.

Tumor localization	*Prevalence of critical weight loss*	
	%	*n*
Larynx	12	18
Supraglottic larynx	34	13
Glottic larynx	3	3
Sub-/transglottic larynx	22	2
Hypopharynx	43	21
Oropharynx/oral cavity	34	23
Nasopharynx	36	5
Other[a]	8	10

a. Carcinoma in the ear, salivary gland, nose/paranasal cavity, esophagus, thyroid gland, skin, eye, lymphoma and unknown primary.

Predictive symptoms for critical weight loss

Dysphagia and/or passage difficulties were most frequently reported in patients with hypopharyngeal cancer and the group of patients with cancer in the oropharynx/oral cavity (Table 3). Dysphagia and/or passage difficulties, loss of taste/aversion and loss of appetite were significantly associated ($p<0.05$, logistic multivariate regression analysis) with CWL (82% correctly predicted) (Table 4).

Loss of taste/aversion was significantly ($p<0.05$) more frequently present in patients with tumor sizes 3 and 4 (11%, 11/102) than in patients with tumor sizes 1 and 2 (3%, 4/143). Patients with tumor sizes 3 and 4 also reported significantly ($p<0.001$) more frequently loss of appetite (28%, 28/102) than patients with tumor sizes 1 and 2 (5%, 7/143).

Finally, CWL was significantly ($p<0.001$) more frequently present in patients with tumor sizes 3 and 4 (43%, 46/107) than in patients with tumor sizes 1 and 2 (7%, 12/159).

Table 3. Reported symptoms per tumor localization.

	Loss of appetite %[a] (n)	Loss of taste and/or aversion %[a](n)	Dysphagia and/or passage difficulties %[a](n)	Pain in throat %[a](n)	Dry mouth and/or pain in mouth %[a](n)
Larynx (n=139)	6 (8)	4 (6)	16 (22)	17 (23)	7 (10)
Supraglottic larynx (n=34)	12 (4)	9 (3)	47 (16)	47 (16)	12 (4)
Glottic larynx (n=96)	3 (3)	2 (2)	3 (3)	5 (5)	6 (6)
Sub-/transglottic larynx (n=9)	11 (1)	11 (1)	33 (3)	22 (2)	0 (0)
Hypopharynx (n=47)	23 (11)	9 (4)	62 (29)	47 (22)	15 (7)
Oropharynx and oral cavity (n=66)	29 (19)	9 (6)	53 (35)	38 (25)	15 (10)
Nasopharynx (n=12)	8 (1)	0 (0)	42 (5)	17 (2)	17 (2)
Other[b] (n=109)	11 (12)	6 (6)	14 (15)	9 (10)	6 (7)

a. Percentages are row percentages.
b. Carcinoma in the ear, salivary gland, nose/paranasal cavity, esophagus, thyroid gland, skin, eye, lymphoma and unknown primary.

Table 4. Logistic multivariate regression analysis on critical weight loss.

Variable	*ß*	*SE ß*	*OR*	*95% CI of OR*
Loss of appetite[a]	0.87	0.43	2.38	1.03 to 5.47
Loss of taste and/or aversion[a]	1.33	0.64	3.80	1.08 to 13.36
Dysphagia and/or passage difficulties[a]	2.95	0.35	19.12	9.63 to 37.97
Constant	-3.08	0.29	0.05	0.03 to 0.08

ß = Regression Coefficient; SE ß = Standard Error of ß; OR = Odds Ratio = $e^{ß}$; 95% CI of OR = 95% Confidence Interval of Odds Ratio.
a. 0 = absent; 1 = present.

DISCUSSION

In the current study, CWL was present in one-fifth of all patients. Other studies in which CWL was assessed in head and neck cancer patients before treatment reported prevalences varying from 31% to 57%.[2-4] Our lower prevalence may be explained by the timing of the assessment. In our study, CWL was assessed at the time of diagnosis, while patients in the other studies were assessed on starting radiotherapy or on the day before surgery. Initial surgery or radiotherapy is usually 2 to 6 weeks after diagnosis, while post-operative radiotherapy is usually 4 to 6 weeks after surgery. The extent of the weight loss may increase in the period between diagnosis and start of the treatment, specifically if dysphagia or passage difficulties are present.

Distribution of tumor localization in the current study differed from those reported in previous studies. In 2 of the 3 studies in which CWL was studied before treatment, significantly more patients with cancer in the oral cavity were included (respectively 10% and 43% instead of 1% in our study).[2,3] In the other study, distribution of tumor localizations was not given.[4] In the UMCG, patients with cancer in the oral cavity are predominantly treated at the oral and maxillofacial surgery department and only a few of these patients are treated at the ENT department. This phenomenon may have resulted in an underestimation of the prevalence of CWL in head and neck cancer patients, because patients with cancer in the oral cavity are at risk for CWL due to dysphagia and chewing problems. No information was given about the prevalence of CWL within the various tumor localizations in previous studies.[2-4] This information is relevant as we showed that prevalence of CWL varies greatly between various tumor localizations. Therefore, it is not known if differences in distribution of tumor localizations can explain the differences between total prevalences of CWL reported in the other studies.

In the current study, data were incomplete of only 9% of the patients. More data were incomplete in patients with a tumor in the hypopharynx, oropharynx/oral cavity and supraglottic larynx and in patients with T3/T4 tumors than in patients with tumors at the other localizations studied or with T1/T2 tumors. These tumor localizations and tumor sizes were identified in our study as risk factors for CWL. Although the differences between complete and incomplete data sets were significant for tumor site and tumor localization, the absolute numbers are small. As a result, the prevalence of CWL in the current study is slightly underestimated.

With regard to tumor localization, almost one-third of the whole population was categorized as 'other' indicating cancer in the ear or nose or esophagus or salivary glands, etc. As expected, prevalence of CWL in this specific group was low (8%) because the majority of these tumor localizations does not affect the swallowing function and therefore seldom leads to CWL, except for carcinoma in the esophagus. Only 3 patients with carcinoma in the esophagus were present in the current study, of which 2 had CWL. If the group categorized as 'other' was excluded from analysis, the prevalence of CWL in the remaining group of head and neck cancer patients increased to 24%. In our opinion, patients with carcinoma in areas not directly localized in the upper digestive tract do not need to be screened routinely for CWL at the time of diagnosis.

CWL was present in almost one-fifth of the patients. This prevalence may be lowered if the patient is already screened for CWL at the general practitioner. In The Netherlands, CWL during illness is generally poorly recognized and only half of the malnourished patients are referred to a dietitian.[18] More attention has to be put into screening in the general practitioner's office because a longer period of nutritional intervention may result in effective weight gain and a more positive effect on treatment-related morbidity and mortality.

Patients with a tumor in the hypopharynx, oropharynx/oral cavity and supraglottic larynx had the highest risk for CWL, probably related to dysphagia, which was frequently present in these patient groups in the current study. About 34% of the patients with oral or oropharyngeal cancer report dysphagia before the start of the treatment.[8] Cancer in the glottic larynx rarely impairs swallowing function. Therefore, cancer in this localization is seldom associated with CWL as confirmed by the results of the current study. Prevalence of CWL was high (36%) in patients with cancer in the nasopharynx. However, in our study, only 14 patients had nasopharyngeal cancer. The high prevalence might be the result of sample variation.

Loss of taste/aversion and loss of appetite were significantly associated with CWL in the logistic multivariate regression analysis. Loss of taste/aversion and loss of appetite may be symptoms of the cancer anorexia–cachexia syndrome.[19,20] This syndrome is the result of a multifactorial process involving cytokines, hormones and neuropeptides.[13,14,20] It was suggested that patients with head and neck cancer may have an elevated cytokine production related to tumor stage.[21,22] Future prospective studies should point out whether CWL at diagnosis is the result of starvation due to dysphagia and passage difficulties or the result of the systemic effects of the cancer anorexia–cachexia syndrome, because the effectiveness of the nutritional intervention may depend on the underlying mechanisms of the weight loss.

The symptom 'pain in throat' was not significantly related to CWL. This finding may be the result of difficulty in distinguishing 'dysphagia' from 'pain in throat' by the observer or patient. These 2 symptoms overlap. The symptoms 'dry mouth and/or pain in mouth' were not significantly related to CWL either, possibly because the screening was performed at the time of diagnosis, whereas xerostomia is to be expected during and after treatment with radiotherapy or chemoradiation.[23]

Prevalence of CWL was highest in patients with a tumor in the hypopharynx, oropharynx/oral cavity and supraglottic larynx, especially in patients with larger tumors. Nowadays, tumors with tumor size 3 and 4 are mainly treated with (accelerated) radiotherapy or chemoradiation. These treatment modalities are accompanied by dysphagia, odynophagia, xerostomia, taste disorders and loss of appetite. The results of our study have shown that most of these symptoms are predictive for CWL at the time of diagnosis. If no nutritional intervention takes place, body weight will further decline during cancer treatment. Prophylactic placement of a gastrostomy tube is effective in reducing weight loss during treatment with radiotherapy and chemoradiation.[24-26] When CWL is present at the time of diagnosis, placement of a gastrostomy tube in these patients in the period before the start of the treatment should be considered to optimize nutritional status.

CWL was dichotomized to be able to perform a risk analysis on clinically relevant weight loss. A gold standard for the assessment of malnutrition unfortunately does not exist currently. Weight loss is one of the criteria commonly used for assessment of the risk for malnutrition. Weight loss of ≥5% in 1 month or ≥10% in 6 months is a generally accepted cutoff for clinically relevant weight loss. Weight loss of ≥5% in 1 month or ≥10% in 6 months is associated with increased morbidity such as impaired wound healing, reduced immune function and decreased tolerance to surgery, radiotherapy and chemotherapy and with increased mortality.[4-6] Besides that, weight loss of ≥5% in 1 month or ≥10% in 6 months has a negative impact on disease-related quality of life and functional status.[7] The cutoff point used was adopted by ASPEN to define 'nutritionally at risk adults'.[15]

In the current study, the patient was asked for his or her body weight. Generally, men overestimate body weight (mean 0.42 kg), whereas women tend to underestimate their body weight (mean 1.41 kg).[27] This discrepancy is related to age. With an increase of age, more body weight is overestimated by men. Women tend to underestimate their weight less as age increases.[27,28] In our study population, the majority (75%) of patients was male and the median age in men was 64 years. Men in the age range of 60 to 69 years overestimate their weight with an average of 0.31 kg (SD 5.1 kg).[28] These findings indicate that the prevalence of CWL in the current study is probably slightly underestimated.

Although the UMCG H&N CST is valuable, it was not validated yet. We used involuntary weight loss of ≥5% in 1 month or ≥10% in 6 months as the cutoff point for CWL because it appeared to be of great prognostic value in the occurrence of major post-operative complications and is associated with higher mortality and complication rate.[4-6] CWL is an indicator of recently developed malnutrition risk.[15,16] Chronic malnutrition risk can be detected by the body mass index (BMI, weight/height^2).[29,30] Patients with head and neck cancer are at risk for chronic malnutrition as a result of bad dietary habits due to excessive drinking and smoking.[31] Therefore, the body mass index should be added to the screening tool in future studies.

In conclusion, CWL is already a considerable problem in head and neck cancer patients at the time of diagnosis. CWL is in particular frequently observed in patients with cancer in the hypopharynx, oropharynx/oral cavity and supraglottic larynx. Symptoms that were strongly related to CWL were dysphagia/passage difficulties, loss of taste/aversion and loss of appetite.

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Chapter 3

Malnutrition in patients treated for oral or oropharyngeal cancer - prevalence and relationship with oral symptoms: an explorative study

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Submitted

ABSTRACT

Background & Aims

This study aimed to assess prevalence of malnutrition after treatment for oral/oropharyngeal cancer and to explore how oral symptoms relate to malnutrition after treatment.

Methods

In this cross-sectional study, malnutrition (weight loss ≥10% in 6 months or ≥5% in 1 month), oral symptoms (EORTC QLQ-H&N35 questionnaire and additional questions to assess chewing problems), dental status, trismus and dietary intake were assessed in 116 adult patients treated for oral/oropharyngeal cancer.

Results

Prevalence of malnutrition was 16% (95%CI: 10% to 23%). Prevalence of malnutrition in the period 0-3 months after treatment was significantly higher (25%) than in the periods >3-12 months (13%) and >12-36 months after treatment (3%, p=0.008). Logistic multivariate regression analysis revealed that swallowing problems (p=0.021) and insufficient protein intake were significantly related to malnutrition (p=0.016).

Conclusion

In conclusion, malnutrition is a considerable problem in patients treated for oral/oropharyngeal cancer, shortly after treatment. Of all oral symptoms, only swallowing problems were significantly related to malnutrition in the period after treatment for oral/oropharyngeal cancer.

INTRODUCTION

Malnutrition has been defined as a subacute or chronic state of nutrition, in which a combination of undernutrition (insufficient food intake) and inflammation has led to a decrease in muscle mass, fat mass, and diminished function, i.e. immune function, cognitive function and muscle strength.[1] In the period before head and neck cancer treatment, prevalence of severe weight loss, an indicator of malnutrition, varies from 19% to 45%.[2-5]

Malnutrition in head and neck cancer patients may have multiple causes. In the period before treatment, a major cause of malnutrition is insufficient food intake, related to mechanical obstruction of food or pain caused by the tumor. In addition, inflammatory activity induced by the tumor or cancer treatment, leading to catabolism of body cell mass may contribute to malnutrition.[1] During and after treatment, malnutrition may develop or aggravate as a result of oral symptoms related to treatment, such as chewing and swallowing problems, pain, dry mouth, sticky saliva and taste disturbances.[6]

Although malnutrition or weight loss in the period before head and neck cancer treatment is often reported[2,4,7], few data are available on prevalence of malnutrition after treatment for oral/oropharyngeal cancer. Previous studies in head and neck cancer patients treated with radiotherapy reported that prevalence of malnutrition is highest during radiotherapy and declines during the first 3 months after radiotherapy.[8,9] These studies were heterogeneous regarding tumor localization and follow-up was limited to the first 6 months after treatment. Consequently, prevalence of malnutrition in the long-term period after treatment for oral/oropharyngeal cancer is unclear.

It is well known that oral symptoms are risk factors for malnutrition.[6] In the period before treatment, swallowing problems and pain in the mouth are identified as main risk factors for malnutrition in head and neck cancer patients.[2,10] Besides swallowing problems, patients treated for oral/oropharyngeal cancer may also suffer from chewing problems, due to either poor dental status or trismus. Edentulous patients often cannot wear their prosthesis for about 3 months after surgery and not uncommonly even up to 6 months after radiotherapy or chemoradiation, due to either radiation-induced mucositis, oral edema, tender oral mucosal surfaces, surgically induced changes in anatomy, or time needed to manufacture a new prosthesis. Additionally, trismus may result from scar tissue formation, as a result of surgery and from radiotherapy.[11-13] The relationship between poor dental status and trismus and malnutrition in patients treated for oral/oropharyngeal cancer has not been studied before. Thus, it is unclear which oral symptom(s) are risk factors for malnutrition in the period after treatment for oral/oropharyngeal cancer.

The primary aim of this study was to test the hypothesis that prevalence of malnutrition in patients treated for oral/oropharyngeal cancer declines in the period after treatment. The secondary aim of the study was to test the hypothesis that swallowing problems, poor dental status and trismus are risk factors for malnutrition in the period after treatment for oral/oropharyngeal cancer.

PATIENTS AND METHODS

A convenience sample of 185 consecutive adult patients was asked to participate in this cross-sectional study between October 2004 and February 2006. These patients had been treated for oral or oropharyngeal cancer at the University Medical Center Groningen (UMCG), the Netherlands. Patients willing to participate underwent assessment after their visit to the physician. Diagnosis and treatment information were retrieved from medical records (Table 1). The study was approved by the Ethics Committee of the UMCG. Informed consent was obtained from all participants.

Inclusion criteria were: age ≥18 years and completed treatment for oral/oropharyngeal cancer ≤3 years before study measurement. Treatment modalities were: surgery (local tumor excision and/or neck dissection); surgery and radiotherapy; radiotherapy (conventional or accelerated scheme); or radiotherapy with concomitant chemotherapy (carboplatin and 5-FU). Exclusion criteria were: a recurrent, residual or newly diagnosed tumor within 3 months after study measurement; edema due to liver, kidney or cardiac disease, to eliminate confounding by edema on body weight; uncontrolled diabetes mellitus to eliminate possible confounding in risk factors for weight loss.

Patients received dietary counseling from a dietitian working at the UMCG at time of diagnosis, during admission for surgery and weekly during radiotherapy. Duration of dietary counseling was generally limited to the first half year after treatment.

Assessment of malnutrition

Actual body weight (kilogram) was measured on a calibrated Seca 701 scale (Medical scales & Measuring Systems Seca Ltd., UK). Patients were measured in indoor clothing without shoes, after voiding the bladder. Weight for clothing (1.0-1.5 kg) was deducted from measured weight and this corrected weight was used for further analysis. Patients were asked for their body weight 1 and 6 months before study measurement. Pretreatment body weight was retrieved from medical records. Height was measured by a stadiometer (Seca 222, Medical scales & Measuring Systems Seca ltd., UK).

Percentage weight loss was calculated as: [(normal body weight - actual body weight) / normal body weight] x 100. Normal body weight was defined as body weight 1 month, or 6 months ago, or prior to treatment. Malnutrition was defined as weight loss ≥10% in 6 months or ≥5% in 1 month.[4,14-18] BMI (kg/m^2) was calculated as actual body weight / body height^2.

Assessment of oral symptoms

The EORTC QLQ-H&N35 questionnaire was used to assess pain in mouth or throat, swallowing problems, senses problems, dry mouth and sticky saliva.[19] Scale scores were calculated according to the manual and range from 0 to 100.[20] In addition, 3 questions regarding chewing problems were asked: 1) How much difficulty did you experience while eating solid food (like meat/solid bread)?; 2) How much difficulty did you experience while eating dry food (like cookies)?; 3) How much difficulty did you experience while eating soft food (like soft bread)? Possible answers to the additional questions were: 1) no difficulty; 2) little difficulty; 3) much difficulty; and

4) so much difficulty that eating was impossible. Answers 3) and 4) were dichotomized to 'chewing problems' and answers 1) and 2) to 'no chewing problems'. Time frame for all questions was the week prior to assessment.

Dental status was assessed by number of natural teeth and/or presence or absence of a dental prosthesis. Dental status was considered poor if: edentate without prosthesis, edentate plus prosthesis in upper/lower jaw, or 1 edentulous jaw without prosthesis and 1-16 elements in the other jaw, otherwise dental status was considered acceptable.

Maximal mouth opening was measured 3 times using 2 calibrated callipers, 1 for edentates or partially dentate patients wearing their prosthesis and 1 for edentates not wearing their prosthesis. Trismus was defined as mean mouth opening ≤35 mm.[21]

Dietary intake and requirements

Dietary intake of the last week before measurement was assessed by means of dietary history, by a registered dietitian (HJ).[22] Energy and protein intake were calculated using food calculation software (JOULE v.02r80 by iSOFT, The Netherlands). Nutritional requirements were estimated conform practical guidelines used in the UMCG: 30 or 35 kcal and 1.0 or 1.5 gram protein per kg actual body weight for well-nourished and malnourished patients respectively.[23] For patients with a BMI>27, body weight equivalent to BMI=27 was calculated and used in the calculations, to correct for the relatively lower metabolic active muscle mass.[24] Energy or protein intake <90% of requirements was considered insufficient.

Patients were asked if they (partly) mashed or grinded their food. Patients not using oral food were able to answer with 'not applicable'.

Statistical analysis

Statistical analyses were performed using SPSS 16.0 for Windows software (SPPS Inc., Chicago, IL, USA). Interval after treatment (months) was categorized into 0-3 months after treatment, >3-12 months after treatment and >12-36 months after treatment. An independent samples Student's t-test was used to test differences in continuous variables between 2 groups. A paired sample Student's t-test was used to test differences in the mean of a continuous variable between 2 related groups. The Mann-Whitney U test was used to test differences in continuous variables between 2 groups if not distributed normally and in ordinal variables. The chi-square test was used to test differences between categorical variables. The Fisher's exact test was used for categorical variables if ≥20% of the cells had an expected count less than 5, in 2 x 2 tables.

The relationship between oral symptoms and malnutrition was analyzed in a multivariate logistic regression analysis. Malnutrition (yes/no) was entered as outcome variable. Age (years), gender (male versus female), tumor size (T1/T2 versus T3/T4), treatment with or without radiotherapy (surgery alone versus radiotherapy, surgery and radiotherapy or chemoradiation), single or combined treatment modality (surgery alone or radiotherapy alone versus surgery and radiotherapy or chemoradiation), interval after treatment (continuous variable (months)), dental status (poor versus acceptable), chewing problems (yes versus no), trismus (yes versus no), energy intake (sufficient versus insufficient), protein intake (sufficient versus insufficient), EORTC QLQ-H&N35 scale scores on swallowing problems, sticky saliva, senses problems, dry mouth, and pain in mouth or throat were entered in the logistic regression analysis (method stepwise backward), entry criterion $p \leq 0.05$, removal criterion $p > 0.10$.

The relationship between percentual decline in pretreatment body weight and interval after treatment (categorical variable) was analyzed by one-way analysis of variance (ANOVA).

In all analyses, statistical significance was set at $p < 0.05$.

RESULTS

Patients

Of the 185 eligible patients, 63 patients declined participation. Reasons to decline participation were: not interested in the study (33%, 23/63), fatigue (14%, 9/63), time investment too long (17%, 11/63) and unknown reasons (32%, 20/63). One-hundred and twenty-one patients were included in the study. Six patients had to be excluded because of either still being under treatment (n=1), tumor recurrence shortly after inclusion (n=1), or not being able to undergo nutritional assessment (n=4). Data of the remaining 116 patients (Table 1) were used in the various analyses on malnutrition, unless stated otherwise. Data on pretreatment body weight were complete in 112 patients.

Nutritional assessment

Overall prevalence of malnutrition was 16% (18/116, 95%CI: 10% to 23%). Prevalence of malnutrition in the period 0-3 months after treatment was significantly higher (25%, 13/53) than in the periods >3-12 months after treatment (13%, 4/32) and >12-36 months after treatment (3%, 1/31) ($p=0.008$). Mean pretreatment body weight significantly declined from 78.7±13.4 kg to 75.9±14.0 kg post-treatment ($p<0.001$) (mean decline 2.8±5.9 kg). Mean percentual decline in pretreatment body weight was 3.4±7.3% and no significant differences in percentual decline in pretreatment body weight between the 3 intervals after treatment were found ($p=0.220$). Mean pretreatment BMI declined from 26.3±4.0 kg/m^2 to 25.4±4.0 kg/m^2 post-treatment ($p<0.001$) (mean decline 1.0±2.0 kg). Five percent (6/114) of all patients had a BMI<18.5 kg/m^2.

Prevalence of malnutrition per treatment modality is presented in Table 2. Analyzed univariately, no differences in age (years), gender, tumor size (T1/T2 versus T3/T4), number of treated head and neck tumors and localization of last tumor (oral cavity versus oropharynx) were found between malnourished and well-nourished patients.

Oral symptoms

Analyzed univariately, malnourished patients scored worse on swallowing problems ($p=0.005$), dry mouth ($p=0.032$) and sticky saliva ($p=0.011$) compared to well-nourished patients (Table 3).

Dietary intake

Ninety-six percent of all patients (111/115) used an oral diet, either with (3%, 3/115) or without tube feeding (94%, 108/115) (Table 1). Of the patients using oral food (with or without tube feeding), 87% (97/111) used a

Table 1. Patient characteristics (n=116).

Age (years), mean±SD		59.7±11.7
	n	%[a]
Gender		
Male	72	62
Female	44	38
Number of treated head and neck tumors		
1	90	77
2	24	21
3	2	2
Last treated tumor		
Squamous cell carcinoma	103	89
Salivary gland tumor	10	9
Other	3	3
Size of last treated tumor		
T1	53	46
T2	34	29
T3	3	3
T4	13	11
Unknown	13	11
Localization of last treated tumor		
Oral cavity	82	71
Oropharynx	30	26
Other[b]	4	3
Treatment of last tumor		
Surgery	62	53
Surgery + radiotherapy	35	30
Radiotherapy	12	10
Chemoradiation	7	6
Interval after treatment		
0 – 3 months	53	46
>3 – 12 months	32	28
>12 – 36 months	31	27
Type of diet[c]		
Oral diet only	75	65
Oral diet with liquid dietary supplements	33	29
Oral diet and tube feeding	3	3
Tube feeding only	4	3
Interval between end of treatment and assessment (months), median (IQR[d])		4.3 (1.4; 12.6)

a. Sum of percentages may be dissimilar to 100%, due to rounding.
b. Neck metastasis, maxillary sinus, unknown primary.
c. N=115.
d. IQR: Interquartile range.

solid diet and 13% (14/111) a liquid/mashed diet. Patients using a liquid/mashed diet were significantly more often malnourished (36%, 5/14) than patients using a solid diet (11%, 11/97, p=0.003).

Mean actual intake was 2185±699 kcal and 83±24 gram protein. No significant differences were found in intake between malnourished and well-nourished patients. Frequency of insufficient protein intake, related to requirements, was significantly higher in malnourished patients (65%, 11/17) than in well-nourished patients (29%, 27/92 p=0.011).

Table 2. Prevalence of malnutrition related to last type of head and neck cancer treatment.

Type of treatment (n)	*Malnutrition*	
	n	*%*[a]
Surgery (62)	5	8
Treatment including radiotherapy (54)	13	24[b]
Radiotherapy (12)	3	25
Surgery and radiotherapy (before or after surgery) (35)	9	26
Chemoradiation (7)	1	14

a. Percentages are row percentages.
b. Prevalence of malnutrition in patients treated with radiotherapy, surgery and radiotherapy, or chemoradiation is significantly higher than in patients treated with surgery alone (p=0.034), analyzed by chi-square test.

Table 3. Univariate analysis on malnutrition and oral symptoms.

Oral symptoms (n)[a]	*Malnutrition*		*No malnutrition*		*p*
	n	*%*[b]	*n*	*%*[b]	
Chewing problems (31/116)	7	23	24	77	0.248[c]
Trismus (30/116)	7	23	23	77	0.239[c]
Poor dental status (37/116)	9	24	28	76	0.129[d]
	median	*IQR*[e]	*median*	*IQR*	*p*
Pain in mouth / throat (113)	25.0	14.6; 37.5	16.7	0.0; 25.0	0.092[f]
Swallowing problems (113)	29.2	0.0; 52.1	0.0	0.0; 25.0	**0.005**[f]
Senses problems (113)	16.7	0.0; 37.5	0.0	0.0; 16.7	0.211[f]
Dry mouth (113)	66.7	33.3; 100.0	33.3	0.0; 66.7	**0.032**[f]
Sticky saliva (113)	66.7	0.0; 100.0	0.0	0.0; 66.7	**0.011**[f]

a. Number of valid observations (patients with this symptom/total number of patients).
b. Percentages are row percentages.
c. Analyzed by Fisher's exact test.
d. Analyzed by chi-square analysis, with continuity correction.
e. Interquartile range.
f. Analyzed by Mann-Whitney U test.

Multivariate logistic regression analysis

Swallowing problems and insufficient protein intake were significantly related to malnutrition in the logistic multivariate regression analysis (Table 4).

Table 4. Results of multivariate logistic regression analysis on malnutrition and oral symptoms.

Variable	*ß*	*SE ß*	*OR*	*95% CI of OR*	*p*
Swallowing problems	0.03	0.01	1.03[a]	1.01 to 1.06	**0.021**
Insufficient protein intake[b]	1.60	0.66	4.93	1.35 to 18.06	**0.016**
Interval after treatment (months)	-0.13	0.06	0.89	0.79 to 1.00	0.057
Constant	-2.37	0.64	0.09		**<0.001**

ß = Regression Coefficient; SE ß = Standard Error of ß; OR = Odds Ratio = $e^{ß}$; 95% CI of OR = 95% Confidence Interval of Odds Ratio.

a. A difference, for instance of 20 points in swallowing problems assessed by EORTC QLQ-H&N35, between 2 patients results in an OR for malnutrition of 1.82.
(20 x ß = 20 x 0.03 = 0.06 → $e^{0.06}$ = 1.82).

b. 0 = absent; 1 = present.

DISCUSSION

The results of our study demonstrate that 1 out of 6 patients is malnourished after treatment for oral/oropharyngeal cancer, with the highest prevalence of malnutrition shortly after treatment (1 out of 4 patients). The decline in prevalence of malnutrition within the first year after treatment in our study is in accordance with results of other studies.[8,9,25]

Very limited data are available on prevalence of malnutrition after treatment for oral/oropharyngeal cancer. In a randomized clinical trial 48% of the patients was malnourished 3 months after start of radiotherapy. If patients received dietary counseling during and shortly after radiotherapy this percentage was 24%.[8] In a study in head and neck cancer patients, in which malnourished patients received tube feeding during and after radiotherapy, prevalence of malnutrition was 27% and 6% in the third and sixth month after start of radiotherapy, respectively.[25] Other studies on malnutrition in head and neck cancer patients focused on changes in nutritional status during and after treatment. In another randomized clinical controlled trial, performed in head and neck cancer patients treated with radiotherapy, nutritional status was deteriorated 3 months after treatment in all patients, but if patients received dietary counseling during radiotherapy this frequency was limited to 12%.[9] In head and neck cancer patients not receiving dietary counseling during and after treatment, mean body weight significantly declined with 2.3 ±4.0 kg during treatment and 2.2±5.5 kg in the period after treatment.[5] In all of these studies prevalence of malnutrition declined in the first 6 months after treatment in patients receiving dietary intervention.[8,9,25]

Of all oral symptoms, swallowing problems was the only one related to malnutrition in the logistic multivariate regression analysis. Although swallowing problems may be present in the long-term period after treatment for oral or oropharyngeal cancer[26], swallowing problems are most severe during and shortly after treatment, due to radiation-induced mucositis and reduced mobility of the tongue due to surgery.[6,27] Probably swallowing problems will cause malnutrition predominantly during treatment, and to a lesser extent in the period after treatment.

Poor dental status, trismus and chewing problems were no risk factors for malnutrition in the multivariate regression analysis. The multiple regression analysis corrected for confounders like change in diet and dietary treatment. Patients having chewing problems often change their diet into a soft, mashed or liquid diet. As nutritional density of a mashed or liquid diet is lower than that of a solid diet, these patients also are advised to use energy- and protein enriched liquid dietary supplements. Use of these supplements increases energy and protein intake and in turn decreases the risk for malnutrition. Only 1 other study assessed the relationship between dental status and malnutrition, but this study was performed in the period before treatment.[10] In the latter study also no significant relationship between these variables was found.[10]

No significant relationship was found between percentual decline in body weight and interval after treatment. Mean decline in pretreatment body weight was limited to 3%. However, this 3% weight loss may be additional to weight loss that already may have developed before start of treatment. At time of diagnosis, 34% of patients with oral/oropharyngeal cancer have already lost ≥10% of body weight in 6 months or ≥5% in 1 month.[2] Additionally, in the current study difference between pretreatment and actual body weight ranged widely, indicating that a subgroup of patients fails to regain body weight to pre-illness or even pretreatment level.

Although patients treated with radiotherapy were significantly more frequently malnourished than patients treated with surgery alone in the univariate analysis, treatment with any type of radiotherapy was not significantly related to malnutrition in the multivariate logistic regression analysis. In a prospective study on weight loss in head and neck cancer patients not receiving dietary counseling, patients treated with any type of radiotherapy lost significantly more body weight than patients treated with surgery alone.[5] In the current study, swallowing problems and insufficient intake were more strongly related to malnutrition than type of treatment, in the period after treatment.

Averagely, both malnourished and well-nourished patients seemed to have a rather adequate intake of energy and protein. However, insufficient protein intake related to requirements was significantly related to malnutrition. Energy and protein intake of our patients were similar to intake reported in other studies in head and neck cancer patients.[5,8,9] On the other hand, mean body weight of our patients was higher than reported in 2 of these studies[5,9], suggesting that dietary requirements of our patients were higher as well. As the 95% confidence interval of the odds ratio of insufficient protein intake was wide, the significant relationship found between insufficient protein intake and malnutrition should be interpreted with caution. This wide confidence interval may be the result of insufficient power due to the relatively low prevalence of malnutrition. On the other hand, the effect of protein intake on malnutrition may vary per patient. As malnutrition is the result of a combination of insufficient intake and inflammatory activity[1], inflammatory activity may have continued in the period after treatment.

Unfortunately, currently a gold standard for the assessment of malnutrition does not exist.[1] Weight loss is one of the criteria commonly used for assessment of malnutrition.[18] Weight loss of ≥10% in 6 months/≥5% in 1 month is a generally accepted cutoff for clinically relevant weight loss. Such a weight loss is associated with increased morbidity, such as impaired wound healing and reduced immune function.[28,29] Besides that, weight loss of ≥10% in 6 months/≥5% in 1 month has shown to be of great prognostic value in the occurrence of major postoperative complications and has been associated with higher mortality and reduced quality of life.[4,14,16,17,28-31] The cutoff point used in the current study was adopted by ASPEN to define 'nutritionally at risk adults'.[32]

Whereas weight loss reflects acute malnutrition, underweight reflects chronic malnutrition.[33,34] Cutoff values for BMI varying from 18.5 to 20.0 kg/m^2 have been used as an indicator of chronic malnutrition.[18,35] If a BMI<18.5 kg/m^2 was added to our criteria for malnutrition, total prevalence of malnutrition would have risen to 19% (22/116). Prevalence of malnutrition in the period 0-3 months after treatment (28%, 15/53) also would have been significantly higher than in the periods >3-12 months and >12-36 months after treatment (16%, 5/32 and 7%, 2/31, p=0.012). If this cutoff for BMI is increased to BMI<20 kg/m^2, total prevalence of malnutrition would have increased further to 22% (25/116). Prevalence of malnutrition per interval after treatment would have been 32% (17/53), 16% (5/32) and 10% (3/32) respectively (p=0.012). These findings indicate that the choice of the cutoff values is of the utmost importance for assessment of malnutrition. Obviously, a gold standard for the assessment of malnutrition is required.

To test the hypothesis that prevalence of malnutrition declines after treatment, we classified patients into 3 groups: 0-3 months after treatment, >3-12 months after treatment and >12-36 months after treatment. We chose these cutoff values, to distinguish between acute and late side effects of head and neck cancer treatment. Radiation induced acute side-effects, such as mucositis, will diminish in the first 3 months after treatment.[6,36] In the period between 3 months and 1 year after treatment, existing oral symptoms may recover or may become chronic, as oral symptoms present 1 year after treatment usually do not recover in the period after that.[27,37] Furthermore, in the short-term period after treatment, inflammatory activity related to treatment may still be present.[38-40] One year after treatment, it is expected that patients reach a 'steady state' with regard to their nutritional problems.

A limitation of this study is the modest participation rate of 66%. In 14% of the patients not willing to participate fatigue has played a major role in the decision to refuse participation in the study. As it cannot be excluded that fatigue was the result of malnutrition, the modest participation rate may have resulted in underestimation of malnutrition.

Another limitation of the study is the use of prediction equations to estimate nutritional requirements.[41-43] Indirect calorimetry is the gold standard to assess energy requirements.[44] However, for practical reasons it was not possible to perform indirect calorimetry in the current study. Therefore, energy requirements had to be estimated. We have chosen to compare energy intake to energy recommendations conform clinical practice in the UMCG. Use of prediction equations to predict energy expenditure may lead to prediction errors.[41-43] Such prediction errors may vary from 235 to 425 kcal, which is about 15-30% of resting energy expenditure as measured by indirect calorimetry.[43] Therefore, evaluation of dietary intake in relation to requirements requires further research.

In conclusion, malnutrition is a considerable problem in patients treated for oral/oropharyngeal cancer, shortly after treatment. Of all oral symptoms, only swallowing problems were significantly related to malnutrition in the period after treatment for oral/oropharyngeal cancer.

ACKNOWLEDGEMENTS

This study was financially supported by a grant from the Stimulation Fund of the UMCG, Groningen, the Netherlands. The study sponsor did not have any involvement in the study design, data collection, analysis and interpretation of data, the writing of the manuscript, and in the decision to submit the manuscript for publication.

The authors thank Greet van Rijn and Sietske Huitema for reviewing the manuscript.

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Chapter 4

Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer

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Head Neck: in press

ABSTRACT

Background & Aims

This study assessed whether malnourished patients score lower on quality of life after treatment for oral/oropharyngeal cancer.

Methods

Malnutrition (weight loss ≥10% in 6 months/≥5% in 1 month) and quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire) were assessed cross-sectionally in patients treated for oral/oropharyngeal cancer. Interval after treatment varied from 1 day to 3 years. The relationship between malnutrition and quality of life was analyzed univariately (Mann-Whitney U test) and multivariately (linear regression analyses). Statistical significance was set at $p<0.05$.

Results

Prevalence of post-treatment malnutrition was 16% (18/115, 95%CI: 9-23%). Analyzed univariately, malnourished patients scored significantly worse on physical functioning ($p=0.007$) and fatigue ($p=0.034$) than well-nourished patients. Multivariate analysis revealed that malnutrition was significantly related to physical functioning ($p=0.015$).

Conclusion

Malnourished patients treated for oral/oropharyngeal cancer score lower on quality of life scales related to physical fitness.

INTRODUCTION

Malnutrition has been defined as a subacute or chronic state of nutrition, in which a combination of undernutrition (insufficient food intake) and inflammation leads to a decrease in muscle mass, fat mass, and diminished body function.[1] In this definition, body function includes muscle function, cognitive function and immune function. In the period before treatment, prevalence of malnutrition in head and neck cancer patients ranges from 19% to 57%.[2-4] Patients with oral or oropharyngeal cancer are at risk for malnutrition, due to oral symptoms caused by either the tumor localization or sequalae of treatment (Figure 1). Furthermore, inflammatory activity may contribute to malnutrition, either indirectly as a result of undernutrition, or directly mediated by the tumor or treatment.[1-3]

Malnutrition is associated with increased morbidity and mortality. Malnutrition may result in an increased complication rate, including impaired wound healing, reduced immune function and decreased tolerance

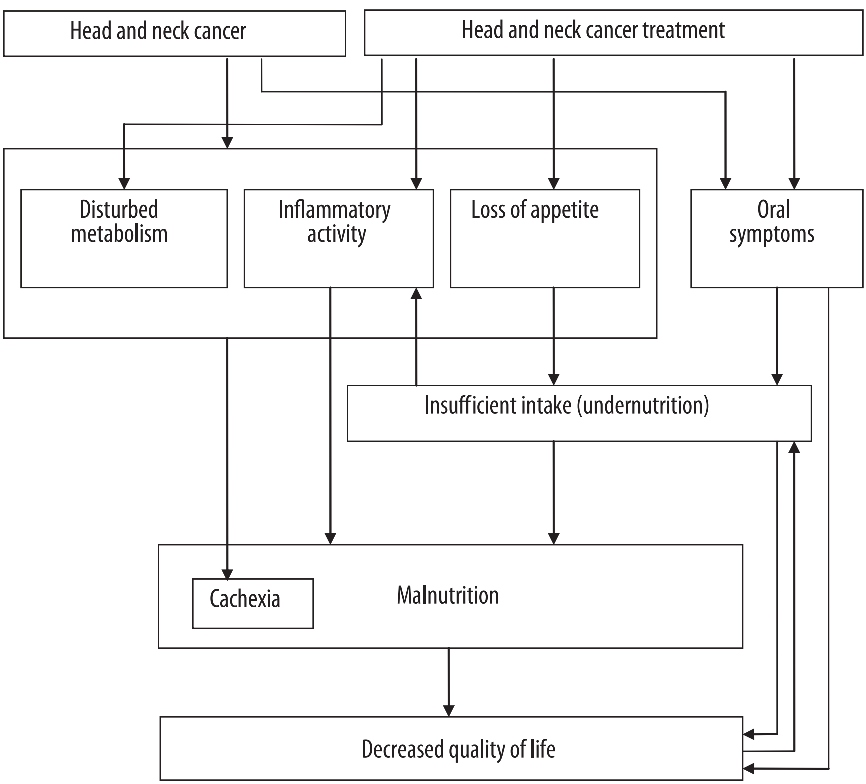

Figure 1. Causes and consequences of malnutrition in head and neck cancer patients. Modified after Soeters et al.[1]
Malnutrition in head and neck cancer patients may be caused by both cancer itself and its treatment. Cancer may be accompanied by disturbed metabolism, inflammatory activity and loss of appetite. These factors combined may cause cachexia, a subtype of malnutrition. Furthermore, the localization of the tumor may cause oral symptoms that hamper food intake. Treatment related oral symptoms, such as swallowing problems, chewing problems, dry mouth and changes in smell and taste may hinder food intake as well, possibly resulting in insufficient food intake. Malnutrition may result in decreased quality of life.

to surgery, radiotherapy and chemotherapy.[4-6] Additionally, malnutrition has a negative impact on disease-related quality of life.[7] Although cancer stage is the major determinant of patients' overall quality of life, the impact of malnutrition combined with insufficient food intake on quality of life has been shown to be more important than the stage of the disease process.[8]

The negative influence of malnutrition on quality of life has already been demonstrated in head and neck cancer patients in the period before, during and shortly after treatment.[9-12] However, heterogeneous populations regarding tumor localization were studied and follow up was limited to 6 months after treatment. Consequently, the relationship between malnutrition and quality of life in the long-term period after treatment for oral or oropharyngeal cancer remains unclear. Therefore, the aim of our study was to test the hypothesis that in the period after treatment for oral or oropharyngeal cancer, malnourished patients experience a lower quality of life than well-nourished patients.

PATIENTS AND METHODS

A convenience sample of 185 consecutive adult patients was asked to participate in the study between October 2004 and February 2006. These patients had been treated for oral or oropharyngeal cancer within the setting of the multidisciplinairy head and neck cancer group of the University Medical Center Groningen (UMCG), the Netherlands. Patients willing to participate underwent assessment after their scheduled visit to the physician. The study was approved by the Ethics Committee of the UMCG. Informed consent was obtained from all participants.

In this cross-sectional study, nutritional status and quality of life were assessed once after head and neck cancer treatment. Interval between day of assessment and last day of head and neck cancer treatment varied from 1 day to 3 years. Patients were classified into 3 groups in accordance with interval between end of treatment and time of study measurement: 0-3 months after treatment; >3-12 months after treatment; and >12-36 months after treatment.

Inclusion criteria were a completed head and neck cancer treatment, speaking Dutch language, and capable of completing a questionnaire. Treatment modalities were surgery (local tumor excision and/or neck dissection), surgery followed by radiotherapy, radiotherapy alone (either a conventional fractionated or accelerated scheme) or radiotherapy with concomitant chemotherapy (carboplatin and 5-fluoroucil). Exclusion criteria were patients with a recurrent, residual or newly diagnosed tumor within 3 months after study measurement, patients with edema due to liver, kidney or cardiac disease, to prevent influence of co-morbidities on hydration status, and patients with uncontrolled diabetes mellitus to prevent possible confounding in risk factors for weight loss.

All patients were routinely referred to a dietitian working at the UMCG. Patients received dietary counseling at time of diagnosis, during admission for surgery and weekly during radiotherapy. Duration of dietary counseling after treatment was generally limited to the first half year after treatment. During dietary counseling, nutritional requirements were estimated: 30 or 35 kcal and 1.0 or 1.5 gram protein per kg actual body weight for well-nourished and malnourished patients respectively.[13] For patients with a Body Mass Index

(BMI)>27 (n=37), a body weight equivalent to BMI=27 was calculated and used in the calculations, to correct for the relatively lower metabolic active muscle mass in overweight patients.[14]

Diagnosis and treatment information were retrieved from medical records and included the number of primary tumors, localization of each primary tumor, size of each primary tumor, tumor type of the last primary tumor, number and type of head and neck cancer treatment(s) the patient had undergone, and dates of start and ending of each treatment. Pretreatment body weight (i.e. body weight at start of treatment) was retrieved from the medical records as well.

Assessment of nutritional status

Actual body weight (kilogram) was measured on a calibrated Seca 701 scale (Medical scales & Measuring Systems Seca Limited, United Kingdom). Patients were allowed to eat and drink before assessment. Patients were measured in indoor clothing without shoes, after voiding the bladder. Either 1 kg (for light clothes) or 1.5 kg (for jeans and sweater) was deducted from the measured weight and this corrected weight was used for further analysis. This weight is referred to as post-treatment body weight. Patients were asked for their normal body weight (without clothes and shoes), i.e. body weight of 1 and 6 months before study measurement. Height was measured by a stadiometer (Seca 222, Medical scales & Measuring Systems Seca Limited, United Kingdom).

Percentage weight loss was calculated as: [(normal body weight - actual body weight) / normal body weight] x 100. Malnutrition was defined as weight loss ≥10% in 6 months or ≥5% in 1 month.[4-6,15-17] BMI (kg/m^2) was calculated as actual body weight / (body height^2).

Quality of life assessment

Quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire (EORTC QLQ-C30).[18] This self-rating questionnaire contains 30 items, including 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), a global health scale, and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhoea, and financial difficulties). In addition, the EORTC head and neck module (EORTC QLQ-H&N35) was used to assess pain in mouth or throat, swallowing problems, senses problems, dry mouth, sticky saliva, trouble with social eating and trouble with social contact. Missing data were imputed in accordance with the guidelines in the manual.[19] Linear transformation to '0–100' scales were carried out in accordance with the EORTC QLQ-C30 scoring manual.[19] For the functioning scales and the global quality of life scale a high score represents a better level of functioning. For the symptom scales and the single item questions a high score represents a high level of problems.

In addition, 3 questions regarding chewing problems were asked: 1) How much difficulty did you experience while eating solid food (like meat/hard bread)?; 2) How much difficulty did you experience while eating dry food (like cookies)?; 3) How much difficulty did you experience while eating soft food (like soft bread)? Possible answers to the additional questions were: 1) no difficulty; 2) little difficulty; 3) much difficulty; and 4) so much difficulty that eating was impossible. Answers 3) and 4) were dichotomized to 'chewing problems' and answers

1) and 2) to 'no chewing problems'. The time frame for all questions was the week prior to assessment.

Dental status was considered poor if: patients were edentate without prosthesis or edentate plus prosthesis in upper or lower jaw, or had 1 edentulous jaw without prosthesis and 1-16 elements in the other jaw, otherwise dental status was considered acceptable.

Maximal mouth opening was measured 3 times using 2 calibrated callipers, 1 for edentates or partially dentate patients wearing their prosthesis and 1 for edentates not wearing their prosthesis. Trismus was defined as mean mouth opening ≤35 mm.[20,21]

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 16.0 for Windows software (SPPS Incorporated, Chicago, Illinois). Interval after treatment (months) was categorized into 0-3 months after treatment, >3-12 months after treatment, and >12-36 months after treatment. Differences in gender, tumor size and type of treatment (surgery alone versus radiotherapy, surgery and radiotherapy, or chemoradiation) and interval after treatment (0-3 months after treatment, >3-12 months after treatment, and >12-36 months after treatment) between malnourished and well-nourished patients were univariately analyzed by chi-square test. Differences in age between malnourished and well-nourished patients were analyzed by independent samples Student's t-test. Scores on the EORTC scales and items were compared between malnourished and well nourished patients by Mann-Whitney U test.

The relationship between malnutrition and quality of life was analyzed in linear regression analyses. Scales of the EORTC QLQ-C30 that were related to malnutrition were entered as outcome variables. The relationship between the EORTC scales and cancer treatment was explored in a regression analysis using 3 dummy variables: (1) chemoradiation (yes, no); (2) radiotherapy (yes, no); and (3) surgery and radiotherapy (yes, no). In this way surgery alone was the 'reference' therapy. Cancer treatment did not contribute significantly to the regression equation. Therefore type of cancer treatment was dichotomized into: radiotherapy, yes (including radiotherapy, surgery and radiotherapy, or chemoradiation) and no (surgery).

In the final regression analyses, malnutrition (malnutrition versus no malnutrition), gender (male versus female), age (years), tumor size (T1/T2 versus T3/T4), radiotherapy (yes, no), interval after treatment (months), pain in mouth or throat, swallowing problems, senses problems, dry mouth, sticky saliva, trouble with social eating, trouble with social contact, chewing problems (yes, no), poor dental status (yes, no) and trismus (yes, no) were entered as predictors in the linear regression analyses (method stepwise backward), entry criterion $p \leq 0.05$, removal criterion $p > 0.10$. In all analyses, statistical significance was set at $p < 0.05$.

RESULTS

Patients

Of the 185 eligible patients, 63 declined participation. Reasons to decline participation were: not interested in the study (33%, 23/63), fatigue (14%, 9/63), time investment too long (17%, 11/63), or unknown reason (32%, 20/63). In total, 121 patients were included in the study. Six patients had to be excluded because of either still being under treatment (n=1), tumor recurrence shortly after inclusion (n=1), or not being able to undergo nutritional assessment (n=4). Data of malnutrition and quality of life were complete in 115 patients. Characteristics of these 115 patients are shown in Table 1. Data of the 115 patients were used in the various analyses, unless stated otherwise. Twenty-three percent (26/115) of the patients had previously been treated for a primary tumor in the head and neck region.

Table 1. Patient characteristics.

Age (years), mean±SD		59.5±11.6
	%[a]	*n*
Gender		
Male	62	71
Female	38	44
Last treated tumor		
Squamous cell carcinoma	89	102
Salivary gland tumor	9	10
Other	3	3
T classification of last treated tumor		
T1	46	53
T2	29	33
T3	3	3
T4	11	13
Unknown	11	13
Site of last treated tumor		
Oral cavity	70	81
Oropharynx	26	30
Other[b]	3	4
Treatment of last tumor		
Surgery	53	61
Surgery + radiotherapy	30	35
Radiotherapy	10	12
Chemoradiation	6	7
Interval between end of treatment and assessment (months), median (IQR[c])		4.2 (1.4; 12.6)

a. Sum of percentages may be dissimilar to 100%, due to rounding.
b. Neck metastasis, maxillary sinus, unknown primary.
c. IQR: Interquartile range.

Nutritional assessment

Overall, prevalence of post-treatment malnutrition was 16% (18/115, 95%CI: 9-23%). In the periods 0-3 months, >3-12 months and >12-36 months after treatment prevalence of malnutrition reduced from 25% (13/53) to 13% (4/32) and 3% (1/30) respectively (p=0.009). Prevalence of malnutrition was significantly

Table 2. Scores on EORTC QLQ-C30 of malnourished and well-nourished patients.

Scale or item (n)	*Malnourished patients (n=18)*		*Well-nourished patients (n=97)*		*p*[b]
	median	*IQR*[a]	*median*	*IQR*[a]	
GHSQOL (113)	66.7	50.0; 83.3	83.3	66.7; 91.7	0.061
Physical functioning (115)	60.0	40.0; 80.0	100.0	60.0; 100.0	**0.007**
Role functioning (115)	66.7	50.0; 100.0	100.0	66.7; 100.0	0.106
Emotional functioning (114)	83.3	64.6; 100.0	91.7	75.0; 100.0	0.221
Cognitive functioning (114)	83.3	62.5; 100.0	100.0	83.3; 100.0	0.079
Social functioning (113)	91.7	62.5; 100.0	100.0	83.3; 100.0	0.326
Fatigue (115)	33.3	19.4; 55.6	22.2	0.0; 33.3	**0.034**
Nausea/vomiting (115)	0.0	0.0; 4.2	0.0	0.0; 0.0	0.354
Pain (115)	25.0	0.0; 50.0	0.0	0.0; 33.3	0.062
Dyspnoea (115)	0.0	0.0; 33.3	0.0	0.0; 8.3	0.219
Insomnia (115)	0.0	0.0; 41.7	0.0	0.0; 33.3	0.630
Loss of appetite (115)	0.0	0.0; 41.7	0.0	0.0; 0.0	0.236
Constipation (115)	0.0	0.0; 33.3	0.0	0.0; 0.0	0.245
Diarrhoea (115)	0.0	0.0; 0.0	0.0	0.0; 0.0	0.251
Financial difficulties (112)	0.0	0.0; 8.3	0.0	0.0; 0.0	0.449

(n) number of valid observations.
a. Interquartile range.
b. Analyzed by Mann-Whitney U test.

Table 3. Results of multivariate linear regression analysis (stepwise backward) to predict scores on EORTC QLQ-C30 scales.

EORTC scale	*Predictor*	*ß*	*SE ß*	*95% CI*	*p*
Physical functioning					
	Malnutrition[a]	-15.0	6.1	-27.1 to -3.0	**0.015**
	Treatment including radiotherapy[b]	14.6	4.9	4.9 to 24.3	**0.004**
	Dry mouth	-0.2	0.1	-0.3 to -0.03	**0.021**
	Trouble with social eating	-0.3	0.1	-0.6 to -0.1	**0.003**
	Constant	86.8	3.4	80.1 to 93.6	**<0.001**
Fatigue					
	Dry mouth	0.2	0.1	0.09 to 0.3	**0.001**
	Pain in mouth or throat	0.4	0.1	0.2 to 0.6	**<0.001**
	Trouble with social contact	0.6	0.1	0.03 to 0.9	**<0.001**
	Constant	4.0	3.1	-2.2 to 10.2	0.203

ß = Regression Coefficient; SE ß = Standard Error of ß; 95% CI = 95% Confidence Interval.
a. Yes = 1; no = 0.
b. Yes (including radiotherapy, surgery and radiotherapy, or chemoradiation) = 1; no (surgery) = 0.

higher in patients treated with primary radiotherapy, surgery plus radiotherapy, or chemoradiation (24%, 13/54), when compared to patients treated with surgery alone (8%, 5/61, p=0.037).

Pretreatment body weight and BMI data were available for all patients. Body weight declined from 78.7±13.4 kg pretreatment to 76.0±14.0 kg post-treatment (mean difference -2.8±5.9 kg, p<0.001). Mean percentual decline in pre- and post-treatment body weight was 3.4±7.3% and no significant differences in percentual decline in pretreatment body weight between the 3 intervals after treatment were found (p=0.220). Pretreatment BMI declined from 26.3±4.0 kg/m^2 to 25.4±4.0 kg/m^2 post-treatment (p<0.001).

No significant differences were found in age, gender and tumor size (T1/T2 versus T3/T4) between malnourished and well-nourished patients.

Quality of life

Analyzed univariately, median score of malnourished patients on global health status / quality of life was lower (66.7) than that of well-nourished patients (83.4), but this difference did not reach statistical significance (p=0.061). Median scores of malnourished patients on physical functioning (p=0.007) and fatigue (p=0.034) were significantly lower than those of well-nourished patients. Median scores, interquartile ranges and p-values on the EORTC QLQ-C30 of malnourished and well-nourished patients are presented in Table 2.

Analyzed multivariately, malnutrition, treatment with radiotherapy, dry mouth and trouble with social eating were significantly related to physical functioning (p<0.05; Table 3). Malnutrition was not significantly related to fatigue in the multivariate linear regression analysis.

DISCUSSION

Our study is the first to assess the relationship between malnutrition and quality of life, assessing both the short-term and long-term period after treatment for oral or oropharyngeal cancer. Whereas malnutrition was already established as important determinator of quality of life in head and neck cancer patients in the period before, during and shortly after treatment[9-12], it was still unclear how malnutrition relates to quality of life in the long-term period after head and neck cancer treatment. Furthermore, the relationship between malnutrition and quality of life in patients treated for oral or oropharyngeal cancer in particular was unknown, given that previous studies were performed in heterogeneous head and neck cancer populations in which only a small number of patients with oral or oropharyngeal cancer were included.[11,12] The current study showed that malnutrition significantly pointed towards a worse physical functioning in patients treated for oral or oropharyngeal cancer.

The lower score of malnourished patients on physical functioning in our study is considered clinically relevant, because the difference in score on physical functioning between malnourished and well-nourished patients was ≥10 points.[22] The relationship between malnutrition and physical functioning has been previously reported in other studies with respect to patients with head and neck cancer. In a prospective observational study in head and neck cancer patients treated with surgery, surgery and radiotherapy, radiotherapy or chemoradiation, malnourished patients scored clinically relevant, but not significantly worse on physical functioning compared to well-nourished patients, 6 months after end of treatment.[12] Another study in head and neck cancer patients treated with radiotherapy demonstrated a significant positive effect of intensive dietary counseling on physical function, whereas in patients not receiving intensive dietary counseling physical functioning deteriorated significantly.[11] The relationship between malnutrition and physical functioning can be ascribed to decreased muscle mass and muscle function. In malnourished patients, atrophy of mainly type II muscle fibres results in muscle fatigue and an altered pattern of muscle contraction and relaxation.[23]

Although in our study prevalence of malnutrition was significantly higher in the period 0-3 months after treatment compared to longer periods after treatment, the relationship between malnutrition and physical functioning was not confounded by interval after treatment. Interval after treatment was not significantly related to physical functioning in the multivariate linear regression analysis. However, the low prevalence of malnutrition in the long-term period after treatment indicates that malnutrition is not a factor affecting quality of life in the long-term period after treatment for oral or oropharyngeal cancer.

Besides malnutrition, treatment with radiotherapy, dry mouth and trouble with social eating were shown to be related to physical functioning in the multivariate linear regression analysis as well. Unfortunately, dry mouth and trouble with social eating are direct and usually long lasting sequelae of head and neck cancer treatment and are difficult to treat.[24] However, in contrast to these problems, malnutrition can be treated effectively, for example by intensive dietary counseling including advice on liquid dietary supplements[11] and/or tube feeding by a percutaneous endoscopic gastrostomy.[25]

Analyzed univariately, malnutrition was significantly related to fatigue. However, when analyzed multivariately, no significant relationship between these variables was found. Dry mouth, pain in the mouth or throat, and trouble with social contact appeared to be more strongly related to fatigue than malnutrition was.

Although we found a clinically relevant worse score of malnourished patients on global health status / quality of life, this difference did not reach statistical significance. One study found a significant relationship between malnutrition and global health status / quality of life, both during and after treatment for head and neck cancer.[12] Other studies in this patient group focused on the impact of intensive dietary counseling during radiotherapy on quality of life. These studies demonstrated a positive effect of intensive dietary counseling on global health status / quality of life.[10,11] As in our study prevalence of malnutrition was highest shortly after treatment, it is unlikely that coping strategies have played a role in the lack of a significant relationship between malnutrition and global health status / quality of life. The lack of statistical significance may be the result of insufficient power, due to the relatively low prevalence of malnutrition.

The results of our study indicate that a subgroup of patients does not sufficiently gain weight to pretreatment level, given the 3.4±7.3% decline in pre- and posttreatment body weight. Prospective studies are needed to examine if such a failure to gain weight in the long-term period after treatment for oral or oropharyngeal cancer affects quality of life and increases the risk for late complications.

Unfortunately, currently a gold standard for the assessment of malnutrition does not exist.[26] Weight loss is one of the criteria commonly used for assessment of malnutrition.[17] Weight loss of ≥10% in 6 months or ≥5% in 1 month is a generally accepted cutoff for clinically relevant weight loss. Such a weight loss is associated with increased morbidity, such as impaired wound healing and reduced immune function.[27,28] Besides that, weight loss of ≥10% in 6 months or ≥5% in 1 month has shown to be of great prognostic value in the occurrence of major postoperative complications and has been associated with higher mortality.[4-6,27,29,30] The cutoff point used was adopted by the American Society for Parenteral and Enteral Nutrition to define 'nutritionally at risk adults'.[15]

Health-related quality of life is a complex, multidimensional concept that reflects the psychological, physical and social effects of disease and its therapy.[31] Besides age, gender, tumor localization, tumor size and treatment modality, also emotional status, smoking and alcohol consumption, marital status and income are known to influence overall health related quality of life in patients with oral or oropharyngeal cancer.[32] In the current study we did not measure lifestyle and socioeconomic variables, which may have acted as confounders in the relationship between malnutrition and quality of life. As a result, the relationship between malnutrition and quality of life might be overestimated.

The current study has some limitations. The first one is the modest participation rate of 66%. In 14% of the patients not willing to participate in this study, fatigue played a major role. For this reason it cannot be excluded that fatigue was the result of malnutrition. Furthermore, 32% of non-participants did not report a reason for no participation. Since patients in the current study were informed and recruited after they had finished treatment, we speculate that patients in this phase of treatment are less motivated to participate in studies that they deemed no longer had a clear benefit for themselves. Furthermore, there is still a general belief among patients that only underweight patients may suffer from malnutrition. Because most of the patients were not underweight, these patients may have believed that participation in the current study was not relevant. Consequently, the modest participation rate may have resulted in underestimation of prevalence of malnutrition.

The second limitation is the use of a cross-sectional study design. As patients were assessed only once after treatment, individual pre-illness scores on quality of life are unknown. Therefore, in the chosen study design we limited our analysis to test interindividual differences after treatment. Prospective studies are needed to confirm or to refute our findings. In addition, the use of a cross-sectional study design did not allow us to identify cause-effect relationships. Previous prospective studies have demonstrated a positive relationship between deterioration of nutritional status and impairment of quality of life.[11,12] Thus, we assume that malnutrition is more likely to be the cause than consequence.

In conclusion, the results of our study indicate that malnourished patients score lower on quality of life scales related to physical fitness, especially in the period shortly after treatment.

ACKNOWLEDGEMENTS

This study was financially supported by a grant from the Stimulation Fund of the UMCG, Groningen, the Netherlands. The study sponsor did not have any involvement in the study design, data collection, analysis and interpretation of data, the writing of the manuscript, and in the decision to submit the manuscript for publication.

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Chapter 5

Changes in nutritional status and dietary intake during and after head and neck cancer treatment

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Head Neck: accepted for publication

ABSTRACT

Background & Aims

This study aimed to test whether nutritional status of head and neck cancer patients changes during and after treatment.

Methods

Nutritional status (including body weight, lean mass and fat mass) and dietary intake were assessed in 29 head and neck cancer patients. Patients were assessed 1 week before, and 1 and 4 months after treatment (radiotherapy, either alone or combined with chemotherapy or surgery).

Results

During treatment, body weight (-3.6±5.3 kg, p=0.019) and lean mass (-2.43±2.81 kg, p=0.001) significantly declined. Patients with sufficient intake (≥35 kcal and ≥1.5 gram protein/kg body weight) lost less body weight and lean mass than patients with insufficient intake (mean difference -4.0±1.9 kg, p=0.048 and -2.1±1.0 kg, p=0.054 respectively). After treatment, only patients with sufficient intake gained body weight (2.3±2.3 kg) and lean mass (1.2±1.3 kg).

Conclusion

Head and neck cancer patients fail to maintain or improve nutritional status during treatment, despite sufficient intake.

INTRODUCTION

Malnutrition has been defined as a subacute or chronic state of nutrition, in which a combination of undernutrition (insufficient food intake) and inflammation has led to a decrease in muscle mass and fat mass, and diminished immune function, cognitive function and muscle strength.[1] Malnutrition is a common problem in head and neck cancer patients. Pretreatment prevalence of severe weight loss, an indicator of malnutrition, ranges from 19% to 57%.[2-4]

Malnutrition may have multiple causes in head and neck cancer patients. In the period before treatment, a major cause of malnutrition is insufficient food intake, related to mechanical obstruction of food or pain related to the tumor. In addition, cancer cachexia may contribute to malnutrition.[1] Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[5] During and after treatment, malnutrition may develop or aggravate as a result of reduced dietary intake due to treatment related oral symptoms, such as chewing and swallowing problems, pain, dry mouth, sticky saliva and taste disturbances.[6] Furthermore, cancer treatment may induce inflammation, either directly due to surgery[7], or indirectly due to (chemo)radiation induced mucositis.[8] This inflammation may in turn result in (further) loss of muscle mass.[9,10]

Little is known about changes in body composition in head and neck cancer patients. Assessment of changes in body composition is of clinical importance. In malnourished patients, lean mass depletion, i.e. muscle mass depletion, is responsible for the impaired immune function, which in turn results in a higher risk for postoperative complications and reduced response to cancer treatment.[11] Moreover, lean mass depletion is associated with reduced physical activity, reduced quality of life and prolonged length of hospital stay.[1,12]

In previous prospective studies on malnutrition in head and neck cancer patients, various methods to assess nutritional status have been used. In some studies, nutritional status was assessed by means of changes in body weight[13] or Patient Generated Subjective Global Assessment (PG-SGA).[14,15] The PG-SGA is a nutritional assessment tool that assesses changes in body weight, presence of symptoms and evaluates changes in dietary intake and body composition. These studies demonstrated improvement in nutritional status in patients receiving dietary counseling during radiotherapy[14,15] and deterioration of nutritional status in patients not receiving dietary intervention.[13-15] It is unknown, however, if and to what extent lean mass changed in these studies. Two other studies assessed body composition prospectively in head and neck cancer patients.[16,17] In both studies, body weight and lean mass declined significantly during head and neck cancer treatment despite dietary counseling.[17] Another study assessed lean mass and PG-SGA prospectively in a mixed group of patients with head and neck cancer or gastrointestinal cancer receiving radiotherapy.[14] In that study, patients randomised to dietary counseling had significantly smaller deterioration of PG-SGA than patients not receiving dietary counseling, but they had no significant improvement in body weight and lean mass during treatment.[14] Validity of assessment of lean mass in that study was limited, due to use of foot-to-foot bioelectrical impedance analysis. This method leads to unacceptable errors in predicting lean mass.[18] Currently, it remains unclear whether improvement of nutritional status or body weight in head and neck cancer patients is characterized by improvement of lean mass. The pitfall is that gain of body weight is characterized by mainly fat mass, whereas improvement in lean mass is aimed for.

The primary aim of this prospective cohort study was to test whether nutritional status, including lean mass, changes during and after head and neck cancer treatment including radiotherapy or chemoradiation. The secondary aim was to assess energy and protein intake, grip strength, phase angle and performance status during and after treatment, since these variables are related to nutritional status.[19-22]

PATIENTS AND METHODS

A consecutive series of 59 adult patients was asked to participate in this prospective study between March 2008 and September 2009. All patients were treated for head and neck cancer within the setting of the multidisciplinairy head and neck cancer group of the University Medical Center Groningen and Medical Center Leeuwarden, the Netherlands. Patients willing to participate were assessed after a scheduled visit at the hospital. Diagnosis and treatment information were retrieved from medical records and included tumor localization, tumor size, type of head and neck cancer treatment, date of start and ending of head and neck cancer treatment. The study was approved by and performed according to standards of the Ethics Committee of the University Medical Center Groningen and Medical Center Leeuwarden. Informed consent was obtained from all participants.

Inclusion criteria were: age ≥18 years; primary or recurrent squamous cell carcinoma in the oral cavity, oropharynx, hypopharynx or larynx; treatment with curative radiotherapy (including uni- or bilateral neck irradiation) either alone, or in combination with chemotherapy or following surgery.

Exclusion criteria were: secondary tumor in another region than the head or neck; a recurrent, residual or new tumor diagnosed within study period. Comorbidity also may have a significant impact on nutritional status and thus might serve as a possible confounding risk factor for weight loss or lean mass depletion. Therefore, patients with edema due to liver, kidney or cardiac disease, muscular disease and uncontrolled diabetes mellitus were also excluded.

All patients received individual dietary counseling during the study period, on admission for surgery and weekly during radiotherapy. Dietary counseling included advice on modification of food texture to alleviate treatment related oral symptoms like pain and dry mouth. To meet nutritional objectives of 35 kcal/kg body weight and 1.5 gram protein/kg body weight[11,23], tube feeding or liquid dietary supplements were prescribed, either post-surgery or during radiotherapy or in post-treatment period.

Study measurements

Study assessments were carried out 3 times. First study measurement (T_0) was performed in the week before start of treatment. In this study measurement, body height, body weight, lean mass, fat mass, phase angle, grip strength, performance status and dietary intake were assessed. Second (T_1) and third (T_2) study measurement were performed 1 month and 4 months after end of treatment respectively. At these time points, assessment of all variables were repeated, except for body height.

Patients were not allowed to eat and drink during 4 hours preceding the measurements. Patients were measured in underwear and without shoes, after voiding the bladder. Body height was measured by a stadiometer (Seca 222, Medical scales & Measuring Systems Seca ltd., United Kingdom). Body weight was measured on a calibrated Seca 701 scale (Medical scales & Measuring Systems Seca ltd., United Kingdom) to the nearest 0.1 kg.

Patients were asked for their body weight (without clothes and shoes) 6 months and 1 month before start of treatment. Percentage weight loss in the last month was calculated as (body weight 1 month ago – actual body weight / body weight 1 month ago) x 100. Percentage weight loss in last 6 months was calculated as (body weight 6 months ago – actual body weight / body weight 6 months ago) x 100. Malnutrition was defined as weight loss ≥10% in last 6 months or ≥5% in last month.[4,24-26] Body Mass Index (BMI, kg/m^2) was calculated as actual body weight / height^2. BMI was classified as: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–25 kg/m^2), overweight (BMI >25-30 kg/m^2) or obese (BMI>30 kg/m^2).[27]

Dual energy x-ray scans were performed to measure lean mass, fat mass and bone mineral content, with a Hologic Discovery A (Hologic Inc., Bedford, MA, USA). Changes in total lean mass, total fat mass, as well as changes in regional lean mass and fat mass (arms, legs and trunk) were analyzed. Lean mass index (kg/m^2) was calculated as lean mass / (height)^2.[12] Fat mass index (kg/m^2) was calculated as fat mass / (height)^2.[12] Change in body weight and lean mass of ≥0.5 kg were considered clinically relevant. Lean mass and fat mass depletion were defined as lean mass index and fat mass index <10th percentile.[28] Lean mass index eliminates differences in lean mass associated with height.

Grip strength was measured as operationalization of muscle strength, by means of a hydraulic hand dynamometer (Jamar®) in a sitting position, on the non-dominant hand, with the elbow fixed at 90 degrees. The mean of 3 readings was used in the analysis.[29]

Bioelectrical impedance analysis was used to measure resistance and reactance, using Bodystat® QuadScan 4000 (Bodystat Ltd.). Patients were in a supine position 15 minutes before measurement. Phase angle was calculated as arc-tangent (reactance / resistance) x 180º / π and expressed in degrees. A smaller phase angle, as observed in malnourished patients, suggests decreased cell integrity or cell death, whereas a larger phase angle suggest large quantities of intact cell membranes.[21] Besides the function as nutritional indicator[21,30,31], phase angle is a prognostic indicator as well.[21,30,32] Phase angle is independent of regression equations and can be performed even in situations in which bioelectrical impedance analysis assumptions are not valid.[30]

Performance status was graded by WHO score.[33] Grades vary from 0 ('Fully active, able to carry on all pre-disease performance without restriction') to 4 ('Completely disabled. Cannot carry on any selfcare. Totally confided to bed or chair').

Dietary intake of the last week before study measurement was assessed by a registered dietitian (HJ), by means of dietary history.[34] Energy and protein intake were calculated using food calculation software (JOULE v.02r80 by iSOFT, The Netherlands). Intake of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight was considered sufficient.[11,23]

Statistical analysis

Statistical analyses were performed using SPSS 16.0 for Windows software (SPPS Inc., Chicago, IL, USA).

Descriptive statistics were used to summarize baseline patient characteristics. Results are expressed as mean±SD, unless stated otherwise. Changes in body weight, lean mass, lean mass index, fat mass, fat mass index, grip strength, and phase angle over time were analyzed by General Linear Model repeated measures, using type of treatment (surgery and radiotherapy/chemoradiation versus radiotherapy/chemoradiation) as within-subject factor. In case of deviation from sphericity a Greenhouse Geisser correction for degrees of freedom was used. Changes in performance status over time were analyzed by Wilcoxon's rank sum test. Differences in continuous variables between 2 groups were analyzed by independent sample t-tests and one-way ANOVA between 3 groups. Pearson's correlation coefficient r was used to analyze the relationship between 2 continuous variables. In all analyses, statistical significance was set at $p<0.05$.

RESULTS

Thirty-five patients could be included in the study (59% participation rate). The main reason for not willing to participate in the study was expected physical or mental burden of participation (n=16). Other reasons for no participation were: too busy due to disease itself (n=6) and not interested (n=2). No significant differences in body weight and BMI were found between participants and non-participants. However, significantly more non-participants were treated with primary radiotherapy/chemoradiation (71%, n=17) than participants (31%, n=9; $p=0.004$).

During the study period 1 patient was excluded because no indication for postoperative radiotherapy existed anymore. During the study period, 5 patients dropped out. Between T_0 and T_1, 1 malnourished patient died and 3 patients, of which 2 were malnourished, dropped out due to fatigue. Between T_1 and T_2, a well-nourished patient died. Twenty-nine patients completed all measurements.

Phase angle measurements were performed in 27 patients, because in 2 patients bio-electrical impedance analysis could not be performed due to presence of metal prostheses. In all other measurements data of 29 patients were used in the analysis.

Baseline patient characteristics are shown in Table 1. Body weight of patients treated with surgery and radiotherapy/chemoradiation was significantly higher (79.5±18.0 kg) than of patients treated with primary radiotherapy/chemoradiation (69.0±20.2 kg).

Pretreatment prevalence of malnutrition was 17% (5/29). Malnourished patients had cancer in the supraglottic larynx (n=2), tongue (n=1) and hypopharynx (n=2). Four malnourished patients had received dietary intervention before T_0.

Five patients (25%) treated with surgery and radiotherapy/chemoradiation and 6 patients treated with primary radiotherapy/chemoradiation (67%) had received dietary counseling before start of treatment. In total, 13 patients (45%) were (partially) fed by tube feeding during radiotherapy. Twelve patients (41%) had received a prophylactic gastrostomy prior to start of treatment, of which 3 patients were treated with surgery and radiotherapy, 5 patients with primary chemoradiation and 4 patients with surgery and chemoradiation. Two patients (7%) that were treated with surgery and chemoradiation did not use their gastrostomy. One of these 2 patients did not want to use tube feeding and in the other patient the gastrostomy had to be removed

Table 1. Baseline patient characteristics at T_0.

Age (years), mean±SD		60.6±10.0
	n	%[a]
Gender		
Male	23	79
Female	6	21
Tumor localization		
Larynx	7	24
Hypopharynx	2	7
Oropharynx	10	35
Oral cavity	10	35
Tumor size		
T1	1	3
T2	7	24
T3	8	28
T4	13	45
Type of treatment		
Radiotherapy	3	10
Surgery + radiotherapy	16	55
Chemoradiation	6	21
Surgery + chemoradiation	4	14
WHO Performance status		
0	20	69
1	7	24
2	1	3
3	1	3
Malnutrition		
Yes	5	17
No	24	83
BMI (kg/m^2)		
<18.5 (underweight)	5	17
18.5-25 (normal weight)	13	45
>25-30 (overweight)	6	21
>30 (obese)	5	17
BMI, mean±SD (kg/m^2)		
Men		24.7±5.2
Women		21.8±5.8
Lean mass index, mean±SD (kg)		
Men		17.9±2.5
Women		14.2±2.4
Fat mass index, mean±SD (kg)		
Men		6.2±3.0
Women		7.2±3.4

a. Sum of percentages may be dissimilar to 100%, due to rounding.

early due to infection. One patient (3%) used tube feeding by a nasogastric tube during treatment with chemoradiation, because prophylactic placement of a gastrostomy was not possible. One patient (3%) received therapeutic tube feeding by a nasogastric tube during radiotherapy.

Table 2. Changes in nutritional status during and after head and neck cancer treatment.

	T_0	T_1	T_2	p
Body weight (kg), mean±SD	76.3±19.0	72.7±16.5	73.0±15.0	**0.019**[a,b]
Body mass index (kg/m²), mean±SD	24.1±5.4	23.0±4.6	23.1±4.0	**0.024**[a,b]
Lean mass (kg), mean±SD	54.6±11.4	52.1±10.7	52.3±10.3	**0.001**[b,c]
Lean mass index (kg/m²), mean±SD	17.2±2.9	16.5±2.5	16.6±2.3	0.065[b,d]
Fat mass (kg), mean±SD	20.0±9.8	18.9±8.1	19.0±7.0	0.298[b]
Fat mass index (kg/m²), mean±SD	6.4±3.1	6.1±2.5	6.1±2.2	0.502[b]
Grip strength (kg), mean±SD	39.8±12.8	35.3±12.2	37.0±12.2	**<0.001**[b,e]
Phase angle (°), mean±SD	6.3±0.8	5.8±0.1	6.0±1.4	0.077[f]

a. $P<0.05$ (T_0 - T_1).
b. Analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation versus radiotherapy/chemoradiation) as within-subject factor. A Greenhouse Geisser correction for degrees of freedom was used because of deviation from sphericity.
c. $P<0.05$ (T_0 - T_1; T_0 - T_2).
d. Interaction between time and type of treatment (patients treated with surgery plus radiotherapy/ chemoradiation versus patients treated with radiotherapy/chemoradiation) ($p<0.05$).
e. $P<0.05$ (T_0 - T_1; T_1 - T_2; T_0 - T_2).
f. Analyzed by Wilcoxon's rank sum test.

Table 3. Changes in dietary intake during and after head and neck cancer treatment.

	T_0	T_1	T_2	p^a
Total energy (kcal), mean±SD	2448.7±769.3	2540.6±745.5	2652.8±795.1	0.849
Energy/body weight (kcal/kg), mean±SD	34.2±13.9	36.2±11.6	37.9±14.2	0.853
Energy/lean mass (kcal/kg), mean±SD	46.9±17.6	49.4±14.5	52.3±17.7	0.749
Total protein (gram), mean±SD	90.1±29.0	98.9±30.2	102.3±31.5	0.596
Protein/body weight (gram/kg), mean±SD	1.3±0.5	1.4±0.5	1.5±0.5	0.416
Protein/kg lean mass (gram/kg), mean±SD	1.7±0.6	1.9±0.6	2.0±0.7	0.372

SD = standard deviation.
a. Analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation versus radiotherapy/chemoradiation) as within-subject factor.

Changes in nutritional status and performance status

As shown in Table 2, body weight, BMI and lean mass significantly declined during treatment ($p<0.05$). In this period patients lost 3.6±5.3 kg body weight, which was 4.7% of pretreatment body weight. Sixty-two percent of weight loss was loss of lean mass (2.4±2.8 kg), which was 4.5% of pretreatment lean mass. Lean mass declined significantly in all body regions (arms, legs $p<0.001$; trunk $p<0.05$). Prevalence of malnutrition shortly after treatment (at T_1) increased to 52% (15/29).

Overall, no significant changes in body weight, BMI and lean mass were found between first and second post-treatment assessment (between T_1 and T_2, Table 2). Ten patients (34%) lost body weight and lean mass both during and after treatment. At second post-treatment assessment, 11 patients (38%) had returned their body weight to pretreatment level. Prevalence of malnutrition at second post-treatment assessment declined to 24% (7/29).

In male, lean mass tended to be depleted pretreatment and was depleted post-treatment (lean mass index<17.6 for men aged 35-74 years, Table 2).[28] In women, lean mass depletion (lean mass index<14.6-14.7 for women aged 35-74 years)[28] was observed both pre- and post-treatment. Neither in male or female fat mass depletion was observed. A higher fat mass at T_0 was significantly related to loss of lean mass during treatment (r=0.51, p=0.005).

Loss of body weight and lean mass during and after treatment did not significantly differ per age (≥65 years versus <65 years), gender, tumor size (T1/T2 versus T3/T4), type of treatment (primary radiotherapy or chemoradiation versus surgery and radiotherapy or surgery and chemoradiation), baseline nutritional status (malnutrition yes/no) and use of tube feeding (yes/no). However, a significant interaction between time and type of treatment was observed for changes in lean mass index over time (p<0.048).

Grip strength significantly declined during treatment and significantly increased after treatment (p<0.001, Table 2). Decline in grip strength during treatment was significantly related to decline in body weight (r=0.42, p=0.023) and decline in lean mass (r=0.49, p=0.007) in this period. Such a relationship was not found after treatment (between T_1 and T_2).

Phase angle did not significantly change over time (Table 2). However, decrease in phase angle during treatment was significantly related to decrease in lean mass in this period (r=0.51, p=0.007).

Median performance status significantly decreased during treatment from 0 ('Able to carry out all normal activity without restriction') to 1 ('Restricted in physically strenuous activity but ambulatory and able to carry out light work') (p=0.013), and significantly recovered to 0 in the period after treatment (p=0.003).

Dietary intake

As shown in Table 3, energy and protein intake did not change over time. However, a significant interaction between time and type of treatment was observed for changes in energy intake over time (p=0.033, Figure 1).

Patients with a sufficient intake during treatment lost significantly less body weight (mean difference 4.0±1.9 kg, p=0.048) and lean mass (mean difference 2.1±1.0 kg, p=0.054) than patients with an insufficient intake (Table 4). Furthermore, patients with a sufficient intake in the period after treatment gained body weight and lean mass, whereas patients with an insufficient intake lost body weight (mean difference 3.7±0.9 kg, p<0.001) and lean mass (2.0±0.6 kg, p=0.001) in this period.

No significant differences in dietary intake were found between patients with and without tube feeding during radiotherapy/chemoradiation. Five out of 13 patients (39%) using tube feeding had sufficient intake during radiotherapy/chemoradiation.

Frequency of insufficient intake was significantly higher in overweight/obese patients (91%) than in normal weight (54%) or underweight patients (20%) (p=0.021).

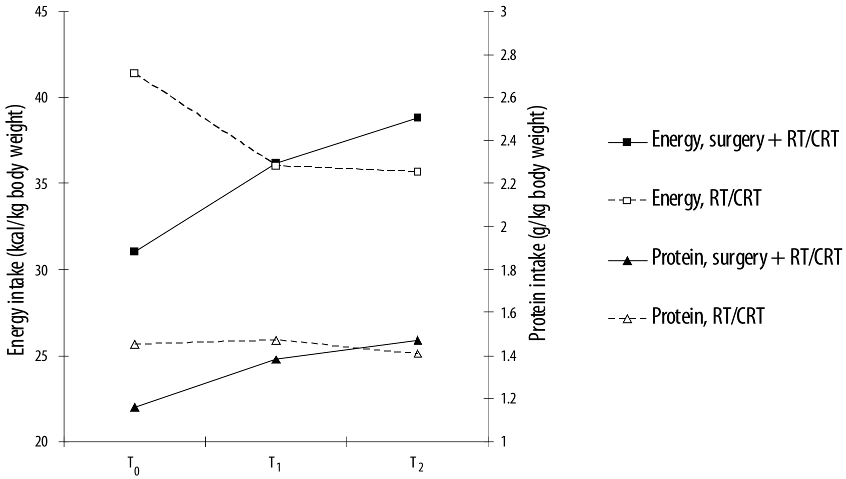

Figure 1. Changes in dietary intake, as expressed by energy end protein intake during and after treatment, per type of treatment.

RT = radiotherapy.

CRT = chemoradiation.

a. A significant interaction between time and type of treatment was found in changes in energy intake over time (p=0.033), analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation versus radiotherapy/ chemoradiation) as within-subject factor.

Table 4. Changes in nutritional status related to dietary intake during and after head and neck cancer treatment.

	Energy intake ≥35 kcal/ kg BW	*Energy intake <35 kcal/ kg BW*	*Protein intake ≥1.5 gram/ kg BW*	*Protein intake <1.5 gram/ kg BW*	*Energy intake ≥35 kcal/ kg BW and protein intake ≥1.5 gram/ kg BW*	*Energy intake <35 kcal/kg BW and/or protein intake <1.5 gram/ kg BW*
Change between T_0 and T_1						
Number of patients	*n=16*	*n=13*	*n=12*	*n=17*	*n=11*	*n=18*
Body weight (kg), mean±SD	-1.1±4.8	-6.7±4.4[a]	-1.2±5.2	-5.3±4.8[b]	-1.1±5.5	-5.1±4.8[b]
Lean mass (kg), mean±SD	-1.4±2.8	-3.7±2.4[a]	-1.2±3.1	-3.3±2.3[b]	-1.2±3.3	-3.2±2.2
Fat mass (kg), mean±SD	0.3±2.4	-3.0±2.7[a]	0.1±2.5	-2.0±3.1	0.1±2.6	-1.9±3.0
Change between T_1 and T_2						
Number of patients	*n=16*	*n=13*	*n=15*	*n=14*	*n=14*	*n=15*
Body weight (kg), mean±SD	2.2±2.2	-1.9±2.1[c]	1.9±2.7	-1.3±2.4[a]	2.3±2.3	-1.5±2.3[c]
Lean mass (kg), mean±SD	1.1±1.3	-1.0±1.7[a]	1.0±1.6	-0.7±1.7[a]	1.2±1.3	-0.8±1.7[a]
Fat mass (kg), mean±SD	0.1±1.5	-1.1±2.3[a]	1.0±1.6	-0.8±2.3[b]	1.2±1.5	-0.8±2.3[a]

BW = body weight.

a. $P<0.01$, analyzed by independent samples t-test.

b. $P<0.05$, analyzed by independent samples t-test.

c. $P<0.001$, analyzed by independent samples t-test.

DISCUSSION

Our study is one of the few studies that longitudinally performed advanced nutritional assessments in head and neck cancer patients and related nutritional status to dietary intake. Patients in the current study were not able to maintain or improve lean mass during head and neck cancer treatment. Instead, patients lost about 5% of their pretreatment body weight, of which nearly two-third was loss of lean mass.

Generally, loss of body weight and lean mass are known to be the result of negative energy and protein balance.[9,11] The observed loss of body weight and lean mass during cancer treatment may point towards insufficient dietary intake. Whereas dietary intake of our patients was in line with the current recommendations of 30-35 kcal/kg and 1.2–2.0 gram protein/kg body weight[11], and whereas protein intake of 1.5-1.7 gram/kg body weight has generally been proposed as 'optimal' to preserve lean mass in ambulant patients[23], the optimal amount of energy and protein to preserve lean mass in head and neck cancer patients is still unknown. In the current study, patients with an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg still had their lean mass declined (1.2±3.3 kg). Post-hoc analysis revealed that if the cutoff score for sufficient protein intake was raised to 1.7 gram/kg body weight, the accompanied decline in body weight and lean mass were not significantly or clinically relevantly smaller than when using the cutoff score of 1.5 gram protein/body weight. As the number of patients with an intake of >1.7 gram protein/kg body weight was rather small (n=8), this finding should be validated, as well as that the current recommendations for dietary intake proposed in the literature need reappraisal.

Dietary intake of the patients in the current study was higher than patients in other head and neck cancer studies.[14-17] Only 1 of these studies reported improvement in nutritional status during treatment with radiotherapy after induction chemotherapy.[15] Unfortunately, in that study body composition was not assessed. As a result, it cannot be ruled out that increase in fat mass, rather than lean mass, was responsible for the gain in body weight observed in that study.

Inflammatory activity related to disease or treatment may increase energy expenditure and protein breakdown. Additionally, physical inactivity may hamper protein synthesis.[9,11] Since intake of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight could not preserve lean mass during treatment but could so in post-treatment period, it may be assumed that head and neck cancer patients subjected to intensive cancer treatment are physically inactive due to fatigue, or suffer from inflammatory activity. During treatment patients were restricted in physically strenuous activity, but remained ambulant and were still able to carry out light work. This moderate deterioration of performance status may have contributed to loss of lean mass during treatment.

Literature on inflammatory activity in head and neck cancer patients points towards presence of inflammatory activity during radiotherapy. Increased C-reactive protein (CRP) levels have been reported in head and cancer patients during and shortly after radiotherapy.[8,35,36] Furthermore, elevated levels of interleukin-1ß, interleukin-6, interleukin-8, and CRP were found in head and neck cancer patients before and shortly after treatment with induction chemotherapy followed by chemoradiation.[17] In the latter study, post-treatment levels of inflammatory markers were not significantly higher than pretreatment levels. Increased inflammatory activity during radiotherapy has been associated with radiation-induced mucositis.[35,37] More knowledge concerning the level and duration of inflammatory activity per treatment modality is needed. Furthermore, more insight in the effect of inflammatory activity on energy expenditure and protein breakdown in head and neck cancer patients is needed.

In the current study, lean mass depletion (lean mass index <10th percentile) was observed despite normal BMI values, similar to previous findings.[38] Additionally, our study demonstrated that despite a substantial decrease in prevalence of malnutrition in the first 4 months post-treatment, patients fail to regain lean mass during this period. Obviously, body composition measurements provide valuable information about nutritional status in addition to more general and less specific methods as body weight and BMI.

In the current study, even in absence of a specific physical exercise training gain of lean mass was observed in patients having a sufficient intake (≥35 kcal/kg and ≥1.5 gram protein/kg body weight) between the first and fourth month after treatment. Protein anabolism may be stimulated by physical exercise, as physical exercise ameliorates the efficiency in using dietary protein.[9] In survivors of haematological malignancies and breast cancer who suffered from severe weight loss during high-dose chemotherapy followed by stem cell transplantation, a 12-week physical exercise program resulted in an increase of lean mass of more than 6 kg, in contrast to the control group.[39] Although sample size in that study was small, the observed effect of physical exercise on gain of lean mass is encouraging, and may be beneficial for head and neck cancer patients.

Surprisingly, more than one-third of the patients using tube feeding did not meet the nutritional goals of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight. The majority of the patients using tube feeding was treated with chemoradiation (77%). Insufficient intake in these patients may be related to nausea. Nausea is frequently present in patients treated with chemoradiation and is less frequently present in patients treated with radiotherapy alone.[40] More insight is needed in factors contributing to insufficient intake in patients using tube feeding.

Grip strength and performance status decreased during treatment and increased after treatment. These changes in grip strength were positively related to changes in lean mass during treatment, but not after treatment. Improvement of muscle strength in absence of improvement in lean mass is also seen in obese subjects[41] and in patients with anorexia nervosa[42], during refeeding after a period of hypocaloric feeding. It has been suggested that nutrition exerts effects on muscle strength independently of muscle mass.[26] Additionally, a negative association between grip strength and inflammatory activity has been reported.[20,43] Therefore, the observed increase in grip strength in post-treatment period may reflect decreased inflammatory activity.

Whereas a relationship between phase angle and nutritional status has been demonstrated in other studies[21,31,44], our study is the first that found a relationship between changes in phase angle and changes in lean mass during head and neck cancer treatment.

The current study has some limitations. First, the participation rate (59%) was lower than expected, mainly due to expected physical or mental burden of repeated study measurements (67%). Furthermore, 60% of the patients that dropped out due to fatigue or death were malnourished. As a result, prevalence of malnutrition is underestimated. Second, energy expenditure was not measured in our study. Unfortunately, it was not feasible to perform indirect calorimetry measurements in the current study protocol, as we needed to minimize burden (e.g. duration of fasting) to patients, who are already in an aggravating phase of their lives. As a result, we had to estimate energy requirements. Use of prediction equations to predict energy expenditure may lead to prediction errors.[45,46] Such prediction errors may vary from 235 to 425 kcal, which is about 15-30% of resting energy expenditure as measured by indirect calorimetry.[46]

In conclusion, loss of body weight and lean mass during intensive head and neck cancer treatment occurred despite internationally recommended energy and protein intake. The results of this study illustrate that more insight in total and resting energy expenditure, and insight in the effect of inflammatory activity and reduced physical activity on loss of lean mass in head and neck cancer patients during and after treatment is needed.

ACKNOWLEDGEMENTS

This study was financially supported by a grant from the Stimulation Fund of the UMCG, Groningen, the Netherlands. The study sponsor did not have any involvement in the study design, data collection, analysis and interpretation of data, the writing of the manuscript, and in the decision to submit the manuscript for publication.

HJ was involved in the study design and concept, carried out the study, performed the statistical analysis, data analysis and interpretation of data and drafted the manuscript. JLNR and PUD were involved in the study design and concept, analysis and interpretation of data, and revision of the manuscript. AV was involved in the analysis and interpretation of data and revision of the manuscript. JAL, BFAM and JP participated in the interpretation of data, and were involved in acquisition of data and the revision of the manuscript. All authors read and approved of the final manuscript.

All authors have no conflict of interest.

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Chapter 6

Oral symptoms and functional outcome related to oral and oropharyngeal cancer

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ABSTRACT

Background & Aims

This study aimed to assess oral symptoms of patients treated for oral or oropharyngeal cancer, to assess how patients rank burden of oral symptoms, and to analyze the impact of the tumor, symptoms, and treatment on functional outcome.

Methods

Eighty-nine patients treated for oral or oropharyngeal cancer were asked for treatment related symptoms regarding mouth opening, dental status, oral sensory function, tongue mobility, salivary function and pain, and to rank these symptoms. The mandibular function impairment questionnaire (MFIQ) was filled out to assess functional outcome. In multivariate linear regression analyses variables univariately related to MFIQ score ($p \leq 0.10$) were entered as predictors and MFIQ-score was entered as outcome variable.

Results

Lack of saliva (52%), restricted mouth opening (48%) and restricted tongue mobility (46%) were the most frequently reported symptoms. Lack of saliva was most frequently (32%) ranked as most burdening oral symptom, followed by restricted mouth opening (14%) and restricted tongue mobility (14%). For radiated patients not being able to wear a dental prosthesis, T3 or T4 classification and a higher age resulted in poorer functional outcome. For non-radiated patients restricted mouth opening, not being able to wear a dental prosthesis, restricted tongue mobility and surgery of the mandible resulted in poorer functional outcome.

Conclusions

Lack of saliva, not only was the most frequently reported symptom after treatment for oral or oropharyngeal cancer, but was the most burdening symptom as well. Functional outcome is strongly influenced by not being able to wear a prosthesis in both radiated and non-radiated patients.

INTRODUCTION

After oral and oropharyngeal cancer treatment patients may report several oral symptoms, such as restricted mouth opening, lack of saliva, not being able to wear a dental prosthesis or lack of retention of the prosthesis, loss of oral sensory function, and restricted tongue mobility.[1-3] These symptoms may influence functional outcome negatively.

Functional outcome after treatment of oral or oropharyngeal cancer is related to tumor site, tumor size and type of treatment.[4-8] In a study in patients treated for tongue base cancer, surgery including the mandible (mandibulectomy or mandibulotomy) reduced functional outcome significantly more than surgery in which the mandible was not included.[5] In that study, functional outcome was determined by assessing eating, speech, and diet (eating in public and normalcy of diet). Furthermore, reconstruction with free tissue transfer results in a significantly worse functional outcome compared to direct reconstruction.[5,6,8] Additionally, higher T classification (T3 or T4) and larger resection size are also associated with poorer functional outcome.[4-6,8]

Besides tumor and treatment characteristics, oral symptoms may influence functional outcome as well. A restricted mouth opening may impede mandibular functions, including chewing, eating and swallowing. Furthermore, a restricted mouth opening may impede oral hygiene, dental treatment, and oncological follow-up.[9] Lack of saliva, which may result from radiation-induced damage to the salivary glands or from removal of a salivary gland, negatively influences consolidation of a food bolus and reduces functional outcome significantly.[10,11] Lack of retention of the prosthesis and pain may hamper edentulous or partially dentate patients wearing a dental prosthesis, resulting in problems with biting and chewing food.[1] Patients who are fitted a dental prosthesis are known to have a better functional outcome than those who are not fitted a prosthesis.[10] Additionally, it is clinically assumed that pain in the mouth or also reduces functional outcome.

To study the symptoms related to oral and oropharyngeal cancer and their association with functional outcome, 3 aims were formulated. The first aim of this study was to assess symptoms of patients treated for oral or oropharyngeal cancer. Before treatment of oral or oropharyngeal cancer most patients rank being cured as most important, followed by living as long as possible and having no pain. Fewer patients rank normal swallowing, normal taste, and normal salivation as most important.[12,13] Currently, it is not clear which oral symptoms burden patients most after treatment of oral and oropharyngeal cancer. Therefore, the second aim of this study was to assess how patients rank burden of their oral symptoms. Additionally, as mentioned above, oral and oropharyngeal cancer itself and the consequences of treatment can influence mandibular functioning (Figure 1). However, it is unclear which factors have the largest impact on functional outcome. Hence, the third aim of this study was to analyze the impact of the tumor, cancer treatment, and oral symptoms on functional outcome.

PATIENTS AND METHODS

Patients aged ≥18 years, treated for oral or oropharyngeal cancer at the department of Oral and Maxillofacial Surgery, Division Oncology, of the University Medical Center Groningen (UMCG), the Netherlands, were invited

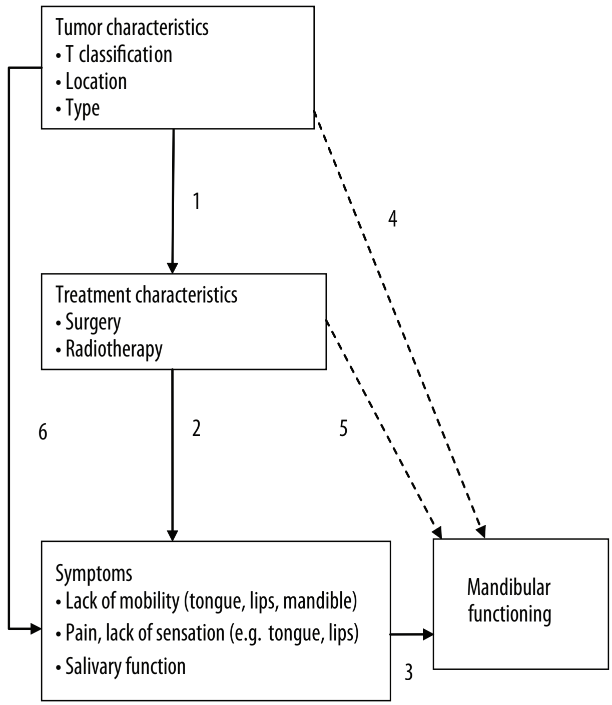

Figure 1. Clinical model of factors influencing mandibular functioning.
Within this study a clinical model of factors influencing mandibular functioning was hypothesized and analyzed: 1) Tumor characteristics determine treatment modalities (extent of surgery, dose of radiotherapy etc.). 2) Besides anti-tumor effects treatments also induce adverse effects, resulting in symptoms in the oral region. 3) These symptoms may result in restrictions in mandibular functioning. 4,5) However, it is possible that some tumor characteristics or treatment characteristics influence mandibular functioning directly without actually resulting in specific symptoms. 6) Finally, tumor characteristics may induce symptoms directly.

to participate in this cross-sectional study. Patients were informed about this study by means of a letter 1 week prior to their regular follow-up appointment. During this appointment the physician informed the patient again and invited the patient to participate. The assessments were performed after written informed consent.

Included in the study were patients that had completed their treatment for oral or oropharyngeal cancer, consisting of surgery or a combination of surgery and radiotherapy, at least 6 months before study assessment. Excluded were patients who did not understand Dutch sufficiently to be interviewed, or patients who were physically or mentally not fit enough to participate.

Information regarding type and localization of the tumor, TN classification, and type of treatment (surgery, radiotherapy) was retrieved from the medical records.

Symptoms and functional outcome

Assessment of symptoms after treatment for oral or oropharyngeal cancer was performed by 1 observer (PMH), who asked if patients:

- experienced a restricted mouth opening (yes/no);
- were able to wear the dental prosthesis in case of an edentulous mandible or maxilla or a partially dentate mandible or maxilla (yes/no);
- experienced lack of retention of the dental prosthesis (yes/no);
- experienced loss of sensory function of the tongue (yes/no), lips (yes/no) or elsewhere in mouth (yes/no);
- experienced a restricted mobility of the tongue (yes/no), or lips (yes/no);
- experienced lack of saliva (yes/no);
- experienced too much saliva (yes/no);
- experienced pain in the mouth (yes/no);
- experienced other problems and if so, what kind of problems.

These questions were the result of a consensus between 2 experts (RPO, oral maxillofacial prosthetist and JLNR, oral maxillofacial surgeon oncologist). These experts were asked to list the most frequently reported symptoms of patients being treated for oral and oropharyngeal cancer. Additionally, the patients were asked to rank burden of their oral symptoms. The 3 most burdening symptoms were recorded.

Functional outcome was assessed by the Mandibular Function Impairment Questionnaire (MFIQ), which was filled in by the patients. This questionnaire consists of 11 items assessing perceived difficulties in mandibular functioning during social activities: speaking, taking a large bite, chewing hard food, chewing soft food, work and/or daily activities, drinking, laughing, chewing resistant food, yawning and kissing. Additionally, 6 items assess perceived difficulties in mandibular functioning during eating (taking a bite, chewing and swallowing) a hard cookie, eating meat, eating a raw carrot, eating French bread, eating peanuts/almonds, and eating an apple. Possible answers were 0) no difficulty, 1) a little difficulty, 2) quite a bit difficulty, 3) much difficulty and 4) very much difficulty or impossible without help. The scores are added up to a sum score (range 0 - 68). A higher score indicates more perceived impairments and a MFIQ score of '0' indicates no impairment of functional outcome. Internal consistency of the questionnaire ranges between 0.80 and 0.95.[14] The outcome of the questionnaire is independent of the method applied, interview or filled out by the patient (r=0.95).[14] The MFIQ has been used previously to assess mandibular function after treatment of chronic closed lock, subacute non-specific temporomandibular disorders, painful disc displacement and to determine a functional cutoff point for trismus.[15-18]

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Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows software (SPPS Inc., Chicago, IL, USA). Statistical analysis included univariate analyses and multivariate linear regression analyses. In the univariate analyses the association between MFIQ scores and possible predictors were analyzed by means of independent samples t-test and Pearson's correlation coefficient (*r*). Possible predictors were age, gender, dental status, T classification (T1/T2 versus T3/T4), radiotherapy (yes, no), surgery of the mandible (yes, no), interval between last oncology treatment and study assessment (years), and the experienced symptoms: lack of saliva, restricted mouth opening, reduced tongue mobility, lack of retention of the prosthesis, reduced sensation of the lips, not being able to wear a prosthesis, reduced sensation of the tongue, restricted mobility of the lips, reduced sensation elsewhere in mouth, pain in the mouth, too much saliva, and swallowing problems (yes,no). In the multivariate linear regression analysis functional outcome (MFIQ score) was entered as outcome variable. Variables related to MFIQ score in the univariate analyses ($p \leq 0.10$) were entered as predictors in the multivariate linear regression analysis (method stepwise backward, entry criterion $p \leq 0.05$, removal criterion $p > 0.10$). Interaction effects between predictor variables were explored.

RESULTS

Of the 101 patients who were asked to participate, 12 patients did not fulfill the inclusion criteria or refused to participate in the study. In total 89 patients (88%) participated in the study.

Descriptive statistics with respect to patients, tumor type, tumor localization, and treatment are presented in Table 1. Median interval (inter quartile range) between last oncology treatment and study assessment was 1.7 years (0.9; 4.1). The mean MFIQ score was 24.3±16.9. Mean MFIQ score of radiated patients (28.9±14.9) was significantly higher than that of non-radiated patients (16.7±17.6, $p = 0.001$). Most patients (76%) were treated for a squamous cell carcinoma, most frequently in the tongue (36%). In total, 63% of the patients were treated with radiotherapy.

Dental status is reported in Table 2. Twenty patients (22%) did not wear their dental prosthesis during the assessment, of which 8 patients did not wear their upper dentures and 12 patients did not wear their lower dentures. Five patients wore neither their upper or lower dentures.

TN classification is summarized in Table 3. For 75% of the patients the TN classification could be found in the medical records. Patients of whom TN classification was missing were treated longer ago (mean 4.4±4.2 years) than patients of whom the TN classification was present (mean 2.8±3.9 years, $p = 0.138$). Patients of whom the TN classification was missing were also more often treated in another hospital previously.

Reported symptoms are shown in Table 4. Lack of saliva was the most frequently reported symptom (52%), followed by restricted mouth opening (48%) and restricted tongue mobility (46%). Lack of saliva was ranked as most burdening oral symptom by 32% of the patients. Restricted tongue mobility and restricted mouth opening were both ranked as most burdening by 14% of the patients.

In the data analysis, a significant interaction between radiotherapy and restricted mouth opening was found to predict MFIQ scores. Therefore, the relationship between predictive variables and MFIQ scores were analyzed for radiated and non-radiated patients separately. In radiated patients, the variables age, gender, restricted mouth opening, not being able to wear a dental prosthesis, surgery of the mandible, being fully edentulous, and T classification were significantly related to MFIQ scores ($p \leq 0.10$). In non-radiated patients, the variables restricted mouth opening, restricted tongue mobility, reduced sensation elsewhere in mouth than tongue or lip, restricted lip mobility, reduced tongue sensation, not being able to wear a dental prosthesis, surgery of the mandible, and being fully edentulous were significantly related to MFIQ scores ($p \leq 0.10$). Additionally, 2 regression analyses were performed, 1 for radiated patients and the other for non-radiated patients (Table 5). For radiated patients, not being able to wear a dental prosthesis, T classification (T3/T4), and higher age resulted in higher MFIQ scores. For non-radiated patients, a restricted mouth opening, not being able to wear a dental prosthesis, restricted tongue mobility, and surgery of the mandible resulted in higher MFIQ scores.

Table 1. Patient, tumor and treatment characteristics (n=89).

Age (years, mean±SD)		61.0±14.0
Interval between last oncology treatment and assessment (years, median (IQR[a]))		1.7 (0.9; 4.1)
MFIQ Score (scoring range 0 to 68) (mean±SD)		24.3±16.9
	%	*n*
Gender		
Male	57	51
Female	43	38
Tumor type		
Squamous cell carcinoma	76	68
Salivary gland tumor	18	16
Other	6	5
Tumor localization[b]		
Tongue	36	32
Alveolar process of the mandible	24	21
Floor of mouth	19	17
Alveolar process of the maxilla	11	10
Salivary gland	11	10
Soft palate	11	10
Lip	10	9
Pharyngeal arch	8	7
Cheek	7	6
Base of the tongue	7	6
Tonsil	5	4
Lateral and dorsal wall of the oropharynx	2	2
Buccogingival vault of the maxilla	1	1
Buccogingival vault of the mandible	1	1
Other[c]	1	1
Radiotherapy		
Yes	63	56
No	37	33
Surgery of the mandible		
Yes	28	25
No	72	64

a. IQR: Interquartile range.
b. N=137. In 67% of the patients the tumor was located on 1 site. In the other patients the tumor extended over several regions. Therefore, the total number of localizations exceeded the total number of patients.
c. Nasopharynx.

Table 2. Dental status.

Dental status	*Mandible dentate*	*Mandible partially dentate*	*Mandible edentulous*	*Total*
Maxilla dentate	13	5	-	18
Maxilla partially dentate	5	9	3	17
Maxilla edentulous	-	8	46	54
Total	18	22	49	89

Table 3. TN classification on the basis of the pathology report.

Status	*T1*	*T2*	*T3*	*T4*	*Total*
N0	20	13	5	8	46
N1	2	1	2	1	6
N2	1	-	-	-	1
N2b	1	4	1	6	12
N2c	-	-	-	1	1
N3	-	1	-	-	1
Total	24	19	8	16	67

TN classification was present in de medical records of 67 patients (75%).

Table 4. Oral symptoms in 89 patients with oral or oropharyngeal cancer.

Symptom	*% (n)*	*Most burdening symptom (n=88)*	*Second most burdening symptom (n=72)*	*Third most burdening symptom (n=56)*
Lack of saliva	52 (46)	32%	11%	5%
Restricted mouth opening	48 (42)	14%	14%	18%
Reduced tongue mobility	46 (41)	14%	24%	13%
Lack of retention of the prosthesis	39 (34)	9%	10%	5%
Reduced sensation of the lips	30 (27)	6%	11%	7%
Not being able to wear a prosthesis	28 (25)	9%	7%	9%
Reduced sensation of the tongue	27 (24)	7%	8%	13%
Restricted mobility of the lips	25 (22)	3%	6%	9%
Reduced sensation elsewhere in the mouth	23 (20)	5%	4%	9%
Pain in the mouth	17 (15)	2%	4%	5%
Too much saliva	6 (5)	-	-	-
Swallowing problems	6 (5)	-	-	-

Some patients reported only the most important symptom (n=88) whereas others also reported the second most or third most important symptoms.

Table 5. Results of multivariate linear regression analyses to predict the score on the Mandibular Function Impairment Questionnaire (MFIQ).

MFIQ score (scale range 0-68)	*β*	*95% CI β*
Radiated patients		
Not being able to wear a dental prosthesis[a]	10.5	2.1 to 18.9
T classification[b]	6.9	-1.5 to 15.3
Age[c]	0.5	0.2 to 0.8
Constant	-7.8	-24.9 to 9.4
r^2=0.45		
Non-radiated patients		
Restricted mouth opening[a]	22.9	14.9 to 30.9
Not being able to wear a dental prosthesis[a]	14.3	4.4. to 24.3
Restricted tongue mobility[a]	13.0	5.2 to 20.9
Surgery of the mandible[a]	12.8	-0.1 to 25.7
Constant	1.5	-3.7 to 6.7
r^2=0.72		

β: Regression Coefficient; 95% CI β: 95% Confidence Interval of the regression coefficient; r^2: explained variance of the regression model.
a. Yes=1; no=0.
b. T3/T4 = 1; T1/T2=0.
c. Per year.

DISCUSSION

The current study demonstrated that lack of saliva was not only the most frequently reported oral symptom in patients treated for oral or oropharyngeal cancer, but also the symptom that burdened these patients most. Nearly one-third of the patients ranked lack of saliva as most burdening symptom. Lack of saliva is known as one of the most common symptoms of head and neck cancer patients after treatment with radiotherapy.[19] Radiotherapy causes damage to the salivary glands, resulting in an altered volume and composition of saliva.[3] Saliva changes from thin to thick secretions with reduced pH and buffering capacity.[3,19] Besides dryness of the mouth and thirst, lack of saliva may cause mucus accumulation, burning sensation, taste disturbances, and difficulties in oral functioning and wearing dentures.[3]

Restricted mouth opening and restricted tongue mobility were also reported by nearly 1 out of 2 patients. Both symptoms are known to occur frequently after treatment for oral or oropharyngeal cancer.[20,21] These symptoms were also reported among the 3 symptoms burdening patients most.

Remarkably, lack of saliva was not predictive for functional outcome in the multivariate regression analysis, despite the fact that this symptom was most frequently mentioned and was ranked as symptom that burdened most by a substantial percentage of patients. Generally, lack of saliva is perceived as very inconvenient. However, to overcome this inconvenience, patients may compensate lack of saliva by taking artificial saliva or drinking during meals.[4,22] Most patients prefer water as a lubricant.[3] It might also be possible that the influence of lack of saliva on the regression analyses was obscured by the different analyses for radiated and non-radiated patients.

In the current study, a mean MFIQ score of 24.3 was found, indicating a substantial reduction of functional outcome after oncological treatment. As described previously[23], radiated patients had a poorer functional outcome than non-radiated patients. However, for radiated patients and non-radiated patients the MFIQ scores were predicted by different factors. The only factor in common in the regression analyses was not being able to wear dental prosthesis, but in non-radiated patients the impact of not being able to wear a prosthesis on functional outcome was slightly larger ($\beta=14.3$) than in radiated patients ($\beta=10.5$). Edentulous or partially dentate patients may not be able to wear a dental prosthesis, because of lack of retention due to the surgically induced anatomical changes. Moreover, pain may prevent patients from wearing their dentures, resulting in problems with biting and chewing of food.[1] Patients who are fitted a dental prosthesis are known to have a better functional outcome than those who are not fitted a prosthesis, based on List's Performance Status Scale.[10]

In the current study a higher T classification was associated with poorer functional outcome. As this relationship was found in radiated patients only, T classification may have acted as confounding variable. Especially in larger tumors generally combined treatment consisting of surgery and postoperative radiotherapy results in more tissue damage and scar formation, reducing mandibular functioning. In patients with smaller tumors a single treatment modality, i.e. surgery or radiotherapy alone have comparable chance of curation. Surgery has the advantage of a better functional outcome. In radiated patients we also found a relationship between higher age and poorer functional outcome. This relationship might be explained by comorbidity, which is known to be present more frequently as age increases. Comorbidity has been negatively associated with swallowing function after surgical treatment for advanced oral or oropharyngeal cancer.[23]

Whereas we expected a restricted mouth opening to be a strong predictor of reduced functional outcome in radiated patients[24], this symptom appeared to be the best predictor in non-radiated patients instead. Nevertheless, restricted mouth opening, as well restricted tongue mobility, are well known factors negatively affecting oral functioning.[21,25]

Clinical consequences

Based on the results of the regression analysis it is clear that not being able to wear a dental prosthesis deteriorates mandibular functioning substantially. Therefore, providing patients, both radiated and non-radiated, a dental prosthesis with an optimal retention is important to reduce mandibular impairment. Additionally, for non-radiated patients treatment of a restricted mouth opening and a restricted tongue mobility may reduce mandibular impairment.

Rehabilitation of patients after treatment for oral or oropharyngeal cancer should focus on preserving tongue mobility and mouth opening. However, preservation of mouth opening after radiation therapy is difficult, since the average reduction of mouth opening after radiation ranges from 18% to 32%, with the greatest decrease in 1 to 9 months after radiotherapy.[26,27] The currently frequently applied intensity-modulated radiotherapy reduces mouth opening less than conventional radiotherapy.[28] Once mouth opening has decreased it is difficult to increase it again, since effects of exercises on a restricted mouth opening after oral or oropharyngeal cancer are limited (mean increase 5 to 6 mm).[29] Only a Therabite® seems to be effective.[30] Restricted tongue mobility may be improved by speech therapy, including range of motion exercises.[31-33]

Strengths of the study were the use of a standardized valid and reliable mandibular function questionnaire, and the assessment of multiple symptoms related to oral and oropharyngeal cancer. Limitations of the current study were the relatively small sample size hampering statistical analysis, the cross-sectional study design and the substantial number of missing data regarding T classification in the medical records.

More insight in development of symptoms and functional outcome is needed to determine which symptoms should be prevented, to maintain mandibular function and achieve optimal functional outcome.

Conclusion

Lack of saliva, not only was the most frequently reported symptom after treatment for oral or oropharyngeal cancer, but was the most burdening symptom as well. Functional outcome is strongly influenced by not being able to wear a prosthesis in both radiated and non-radiated patients.

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Chapter 7

Variation in repeated mouth opening measurements in head and neck cancer patients with and without trismus

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Int J Oral Maxillofac Surg 2009 Jan;38(1):26-30

ABSTRACT

Background & Aims

Trismus after head and neck cancer treatment may severely limit mandibular functioning. Interventions aimed at reducing trismus can only be evaluated when the amount of variation associated with these measurements is known. The aim of this study was to analyze the variation in mouth opening measurements in patients treated for head and neck cancer, with and without trismus.

Methods

Maximal mouth opening was measured in 120 patients in 2 sessions of 3 repeated measurements by 1 observer. To analyze the influence of interobserver variation on mouth opening measurements a subgroup of 30 patients was measured by a second observer. The standard deviation of the 6 measurements per patient was used as the variation in measurements of maximal mouth opening.

Results

No significant difference was found in maximal mouth opening in patients with (n=33) or without (n=87) trismus. The interobserver intraclass correlation coefficient (ICC) was 0.98. Intraobserver ICC and intersession ICC reliabilities both were 0.99. The variation in the mean values of the 3 measurements was only slightly smaller than the variation of the single measurements.

Conclusion

Variation in maximal mouth opening in patients with trismus does not differ from variation in maximal mouth opening in patients without trismus. Interobserver variation is limited.

INTRODUCTION

Trismus, severely restricted mouth opening, is a common problem in patients with head and neck cancer. The prevalence of trismus after head and neck cancer ranges from 5% to 38%.[1,2] Trismus may result from tumors infiltrating or irritating mouth closing muscles, from scar tissue formation as a result of surgery and from irradiation injury.[3-5] Trismus may impair the quality of life as it impedes food intake, chewing, swallowing and oral hygiene including dental care. Current treatment for trismus in head and neck cancer patients consists of exercises with or without the assistance of incentives or mouth opening devices.[6,7]

Changes in maximal mouth opening may reflect the impact of the disease activity, scar formation due to surgery or radiotherapy and the effects of interventions.[8] To detect changes in maximal mouth opening, consistency in the measurement results is required. Measurements are influenced by the patient, time of measurement, measurement device, observers and interaction between these factors; random errors may also occur.

It can be hypothesized that measurements of maximal mouth opening in patients with structurally restricted mouth opening may be accompanied by less variation than measurements in patients with no structural restriction. Substantial variation in the measurement results renders them unreliable and makes detection of small therapeutic effects impossible.

The aim of this study was to assess the influence of trismus on the variation in repeated mouth opening measurements in patients treated for cancer in the oropharynx or oral cavity. The secondary aim was to analyze intra- and interobserver variation in mouth opening in this group of patients.

PATIENTS AND METHODS

Subjects

A consecutive series of 192 patients, aged ≥18 years, curatively treated for head and neck cancer at the Department of Oral and Maxillofacial Surgery or the Department of Otorhinolaryngology of the University Medical Center Groningen (UMCG), the Netherlands, were recruited between October 2004 and February 2006. Patients were informed about the study by means of a letter received 1 week prior to their regular follow-up appointment. During this appointment, the physician explained the study and invited the patient to participate. The study was conducted as a cross-sectional study, in which the time interval between study and ending of cancer treatment varied from 1 week to 3 years.

Patients were included if they had been treated for cancer at 1 of the following sites: tongue, base of tongue, floor of mouth, cheek, lip, alveolar process of mandible or maxilla, buccogingival vault of the mandible or maxilla, tonsil, palate, lateral and dorsal wall of the oropharynx, retromolar trigonum, pharyngeal arch and maxillary sinus. Patients who did not understand Dutch sufficiently to be interviewed, or who were physically or mentally not fit enough to participate were excluded.

The following information was obtained from the medical records: type and site of tumor, tumor size, type and date of end of cancer treatment.

All participants gave their written informed consent. The study was approved by the medical ethical committee of the UMCG.

Measurement procedure

Maximal mouth opening was measured using 2 calibrated calipers; 1 for dentates or partial dentates wearing their prosthesis and 1 for edentates not wearing their prosthesis. All patients were measured with their heads supported in a neutral position. Patients were asked to open their mouth as wide as possible, while avoiding excessive pain. The dental status of the patients during measuring maximal mouth opening was similar to the dental status of the patients during eating or drinking. Dental status did not change during the measurements. In case of complete frontal dentition the maximal inter-incisal distance (11–41) was measured. In patients with an edentulous mandible, not wearing dentures, the distance between the incisal edge of 11 and the alveolar ridge of the mandible (location 41) was measured. In patients with an edentulous maxilla, not wearing dentures, the distance between the incisal edge of 41 and the alveolar ridge (location 11) was measured. In edentulous patients wearing dentures the distance between the upper and lower dentures was measured, or if the patient did not wear dentures the maximal distance between the 2 alveolar ridges (location 11–41) was measured.

The measurements were performed by a dietitian (HJ) and a student (master) in dental sciences (PN), who were trained how to perform the measurements on 15 healthy volunteers before measuring the study subjects. All patients were measured 6 times in 2 sessions of 3 measurements by the first observer (HJ). The interval between sessions was 45 min.

Additionally, a part of the study population (n=30) was measured in a similar way by a second observer (PN). In this study, patients were classified as having trismus if the mean of the 6 measurements performed by observer 1 was ≤35 mm.[9]

Statistical analysis

Statistical analysis was performed in SPSS 12.0 for Windows. A normal probability plot and a one-sample Kolmogorov–Smirnov test were used to check the normal distribution of the data. The standard deviation (SD) of the 6 measurements per patient was used as the variation in measurements of maximal mouth opening. To analyze variation in measurements of maximal mouth opening in patients with and without trismus, an independent samples Student's t-test was performed on those SDs. A correlation was calculated between interval after treatment and SD of the mouth opening measurements. To analyze whether dental status (fully dentate, partial dentate and edentate) influenced the variation in measurement results an ANOVA was performed.

A scatterplot of the mean SD of the mean of 6 measurements and the mean maximal mouth opening of 6 measurements was drawn, to assess visually the influence of the magnitude of mouth opening on variation in mouth opening. To analyze the influence of mouth opening on the SD of the measurements a linear regression analysis was performed, with mouth opening as predictor and SD as an outcome variable.

Intraobserver variability (HJ) was analyzed by means of a series 4 dependent Student's t-tests to compare:

the differences between the means of 3 measurements of session 1 and session 2; the differences between the first measurement of session 1 and the first measurement of session 2; the differences between the second measurement of session 1 and the second measurement of session 2; the differences between the third measurement of session 1 and third measurement of session 2. The smallest real differences (SRD) were calculated as 1.96 x SD of mean difference between the means of the sessions and the first, the second and the third measurement of each session. SRD is the change in mouth opening that should occur before one knows that there is a statistically significant increase or decrease in mouth opening.

Variance components were calculated for main effects and two-way interactions of patient, observer, session and measurement. Intraclass correlation coefficients (ICCs) were calculated to determine intra- and interobserver reliability.[10] ICCs were interpreted as follows: 0.00–0.10 virtually no reliability; 0.11–0.40 slight reliability; 0.41–0.60 fair reliability; 0.61–0.80 moderate reliability; and 0.81–1.00 substantial reliability.[11] The level of significance was set at 0.05.

RESULTS

In total, 122 patients (64%) participated in the study. In 2 patients the data were incomplete so statistical analysis was performed on the data obtained from 120 patients. Patient characteristics and data on the tumor and cancer treatment are summarized in Table 1. Mouth opening data met the criteria for a normal distribution. In total, 33/120 (28%) patients had a mean maximal mouth opening ≤35 mm and were thus classified as having trismus.

No influence of dental status on variation in measurement results was found ($F_{2,117}$=0.689; p=0.504). No relationship between measurement variation and interval after treatment was found either (Pearson's r= 0.028, p=0.760).

Influence of trismus on variation in maximal mouth opening

The SDs for patients with trismus (mean SD 1.3, SD 0.8) did not differ significantly from patients without trismus (mean SD 1.4, SD 0.6, 95% CI difference -0.27 to 0.34) (p=0.83). There is no funnel pattern in the scatterplot, indicating that variation in mouth opening measurements (SD of mean of 6 measurements) was not related to the magnitude of the mouth opening (Figure 1). In the regression analysis, mouth opening could not significantly predict SD of measurements (p=0.317).

The maximum difference between the measurements in session 1 and the measurements in session 2 was 5.7 mm. Results of the measurements performed by observer 1 are shown in Table 2. The mouth opening in session 2 was significantly larger than that in session 1. The mean difference ranged between -0.5 to -0.8. The SRD between the mean of session 1 and the mean of session 2 was 3.4 mm, whereas the SRD between the first measurements of the sessions was 4.7 mm.

Intraclass correlations

Interobserver reliability of the measurements in 30 patients, measured by both observers, expressed as ICC was

Table 1. Patient (n=120), tumor and treatment characteristics.

Variables		
Age (years), mean±SD		60.3±11.8
Time interval after last cancer treatment (months), median (IQR)		4.3 (1.2; 12.6)
Mouth opening (mm), mean±SD[a]		40.1±11.5
	%	*n*
Gender		
Male	62	74
Female	38	46
Trismus[b]		
Yes	28	33
No	73	87
Number of primary tumors[b]		
1	87	104
2	13	15
3	1	1
Tumor type of last treated tumor[b]		
Squamous cell carcinoma	89	107
Salivary gland tumor	8	10
Other	2	3
Tumor size of last treated tumor		
T1	44	53
T2	30	36
T3	3	3
T4	12	15
Unknown	11	13
Tumor site of last treated tumor		
Tongue	31	38
Base of tongue	6	7
Floor of mouth	15	18
Cheek	9	11
Lip	4	5
Mandible	5	6
Maxilla	1	1
Tonsil	5	6
Palate	6	7
Dorsal wall of the oropharynx	2	2
Retromolar trigonum	3	4
Pharyngeal arch	3	4
Maxillary sinus	3	3
Vallecula	1	1
Other	6	7
Cancer treatment		
Radiotherapy	13	16
Surgery	44	53
Surgery + radiotherapy	37	44
Chemoradiation	3	4
Surgery + chemoradiation	3	3

IQR: Interquartile range.

a. Mean±SD based upon the first measurement in the first session of observer 1.

b. Total percentages do not add up to 100%, due to rounding off.

0.98. Intraobserver reliability and intersession reliability expressed as ICC were both 0.99. Between-patient variance accounted for 97% of total variance. Absolute error variance (i.e. observer, session, measurement and their two-way interactions) accounted for 3% of total variance. Patient–observer interaction accounted for 47% of the absolute error variance (4.26).

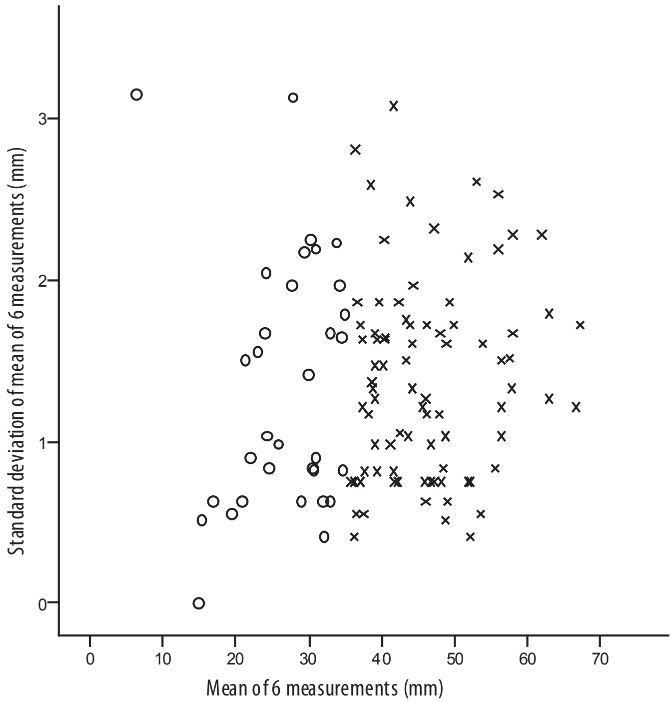

Figure 1. A scatterplot of the mean of 6 measurements and standard deviation of the mean of 6 measurements (n=120).
O trismus
X no trismus

Table 2. Repeated measurements performed by observer 1 (n=120).

	Mean difference[a]	*SD of difference*[a]	*SRD*[b]
Difference in mean mouth opening of the 2 sessions	- 0.6[c]	1.72	3.4
Difference in mouth opening between the first measurement of the sessions	- 0.5	2.42	4.7
Difference in mouth opening between the second easurement of the sessions	- 0.6	2.04	4.0
Difference in mouth opening between the third measurement of the sessions	- 0.8	1.90	3.7

a. In mm.
b. SRD: Smallest Real Difference = ± 1.96 x standard deviation of the difference (SD).
c. Value of first measurement minus value of second measurement.

Table 3. Results of analysis of variance components.

Source	*Variance components*		*% Total variance*	*% Error variance*
Patient	123.95		96.7	
Error	4.26			
Observer		0.00		0.00
Session		0.15		3.57
Measurement		0.07		1.67
Patient x observer		1.98		46.58
Patient x session		0.65		15.29
Patient x measurement		0.09	3.3	2.2
Observer x session		0.04		0.9
Observer x measurement		0.01		0.3
Session x measurement		0.00		0.0
Residual error		1.27		29.9
Total	128.21			

DISCUSSION

The variation in the mouth opening measurements in patients treated for head and neck cancer did not depend on the range of mouth opening. In patients with a mouth opening ≤35 mm one might expect structural limitations in mouth opening due to scar formation and or fibrosis. Scar formation and fibrosis largely consist of collagen fibres that are not stretched easily. The authors' hypothesis was that in these patients variation in mouth opening was less than in 'non-trismus' patients in which these structural limitations may not be present. This assumption was based on the observation that in patients with myogenous temporomandibular disorders, in which no structural limitation exists in mouth opening, the SRD (1 day, 1 observer, 3 repetitions) was 8.1 mm.[12]

The SRD is the change in mouth opening that should occur before one knows that there is a statistically significant change (increase or decrease) in mouth opening. The SRD in patients with myogenous temporomandibular disorders reflected a substantial amount of variation in measurement results. It is possible that the SRD in the latter patients was partly influenced by the pain experienced during mouth opening measurements (mean intensity assessed on a VAS was 27 mm). In the current study, the authors asked the patient to open the mouth as wide as possible without provoking excessive pain, thus they were not able to analyze the influence of pain.

The aim of this study was to analyze the influence of the magnitude of mouth opening on the variation in measurement results, therefore dental status was kept the same during the measurements. Although the authors recognize that wearing dentures or not influences maximal mouth opening, it can be seen from the results of the regression analysis and the scatterplot that the magnitude of mouth opening did not influence the magnitude of the difference, independent of where the cutoff point for trismus is set. The criterion for trismus of 35 mm or less was also developed on the basis of the dental status the patient presented to the observer.[9]

SRDs of 5 mm (in case of 1 single measurement) and 4 mm (using the mean of 3 measurements) were found. No other study on the SRD of maximal mouth opening in head and neck cancer patients has been performed. When maximal mouth opening measurements are repeated twice, the SRD can be reduced from 5 to 4 mm. Both SRDs are low and a reduction in SRD of 1 mm is clinically too low to make repetition of the measurements necessary in the authors' opinion.

It was not feasible to repeat the measurement sessions on separate days because the patients lived too far away from the hospital and some patients were not in good health. For the convenience of the patients it was decided to perform the measurements on the same day as the regular follow-up appointment with the physician. The standard time interval between 2 regular follow-up appointments is 3–6 months, which is too long for a reliability study.[10] If the measurements had been performed on more occasions (for example 1 month apart) it is possible that mouth opening would have changed because of late radiation effects. This change would have influenced the reliability of the measurements negatively.

The measurements of maximal mouth opening in this study had excellent reliability, indicated by the ICCs for interobserver and intraobserver reliability (ICC >0.95). Absolute error variance was low (3%) and the measurement facet 'patient' accounted for 97% of total variance. This means that patients could be distinguished from each other very well on the basis of mouth opening measurement and the contribution of facets other than 'patient' was very small. Almost half of the error variance was due to the measurement facet 'patient–observer interaction' (46%), but because the absolute error variance of 'patient–observer interaction' was very low (4.26), this component is clinically negligible. Measurement facet 'observer–session interactions' accounted for only 0.04 of absolute error variance, meaning that both observers perform similarly over both sessions.

Mouth opening measured in the second session was significantly larger than in the first. This increase may be interpreted as a (small) training effect. Clinically this increase is small and hardly relevant.

In conclusion, maximal mouth opening can be assessed reliably, regardless of the observer in head and neck cancer patients. Variation in measurements of maximal mouth opening in patients with head and neck cancer with trismus did not differ from that of patients without trismus. Overall variation in maximal mouth opening in head and neck cancer patients was low, enabling good monitoring of the patients' response to anti-trismus treatment. During treatment, an improvement of maximal mouth opening of at least 5 mm has to be measured to be statistically significant.

ACKNOWLEDGEMENTS

This study was financially supported by a grant from the Stimulation Fund of the University Medical Center Groningen, Groningen, The Netherlands. We thank Pieter Nijenhuis (PN) for his participation in this study as the second observer.

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Chapter 8

General discussion

INTRODUCTION

In the late 1970's, Sobol et al.[1] stressed that head and neck patients are at high risk for malnutrition. The authors recognized tumor- and treatment-related symptoms, and cachexia as risk factors for malnutrition in this group of patients. However, studies on malnutrition in head and neck cancer patients remained scarce until the late 1990's. Since then interest on this topic is growing. Currently, still many head and neck cancer patients are subjected to their cancer treatment in an already malnourished state, and because of that malnourished state have a higher risk for developing postoperative complications[2], a decreased tolerance or response to cancer treatment[3] and a reduced quality of life.[4-7] Previous studies in head and neck cancer patients have focused on criteria for assessment of malnutrition[2,8], the effect of immunonutrition on immune status[9-12], the relationship between nutritional status and quality of life during and shortly after treatment[6,7], and the effectiveness of placement of a prophylactic gastrostomy tube on nutritional status.[13-15] Although these studies have increased knowledge on nutritional status in head and neck cancer patients prominently, basic knowledge on prevalence of malnutrition before and after cancer treatment, identification of the main risk factors for malnutrition, insight in how body composition changes during and after cancer treatment and the relationship between malnutrition and quality of life in the period after head and neck cancer treatment is still lacking. Such knowledge is of utmost importance to determine if current (dietary) intervention needs reappraisal. In this thesis we investigated these topics.

MAIN FINDINGS

The main findings of this thesis are:

- pretreatment prevalence of malnutrition in head and neck cancer patients is 19%;
- overall post-treatment prevalence of malnutrition in patients treated for oral or oropharyngeal cancer is 16%. In the first 3 months post-treatment this percentage is 25% and declines to 3% in the second and third year post-treatment;
- patients lose a significant amount of their pretreatment body weight (5%) during head and neck cancer treatment, of which two-third is loss of lean mass. In the early post-treatment period, patients do not regain this body weight and lean mass;
- an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight does not preserve lean mass during head and neck cancer treatment, but it does enable improvement of lean mass in the early post-treatment period;
- loss of appetite and loss of taste/aversion are risk factors for pretreatment malnutrition. Swallowing problems are a risk factor for both pre- and post-treatment malnutrition;
- malnutrition is associated with the quality of life domain physical functioning in patients treated for oral or oropharyngeal cancer;
- lack of saliva is the most frequently reported symptom resulting from treatment for oral or oropharyngeal cancer, and burdens patients most after treatment for oral or oropharyngeal cancer;

- not being able to wear a dental prosthesis impacts mandibular functioning most after treatment for oral or oropharyngeal cancer.

INTERPRETATION OF THE MAIN FINDINGS AND CLINICAL IMPLICATIONS

Malnutrition

The studies described in this thesis demonstrate that head and neck cancer patients are nutritionally at risk before, during and shortly after cancer treatment. Both the study on pretreatment malnutrition (Chapter 2) and the study on changes in nutritional status and dietary intake during and after head and neck cancer treatment (Chapter 5) revealed that about 1 out of 5 patients is malnourished before start of cancer treatment. This prevalence of malnutrition is lower than reported in previous studies in head and neck cancer patients, in which prevalence numbers varied from 31% to 57%.[2,16,17] In the study described in Chapter 2, timing of assessment may be responsible for our lower prevalence of malnutrition. In our study, malnutrition was assessed in the early diagnostic phase, whereas in the other studies malnutrition was assessed shortly before start of treatment. Thus, in this study assessment of malnutrition may have been 2 to even 6 weeks earlier than in other studies. In this period patients may continue losing weight, either due to oral symptoms or cachexia.

Furthermore, differences in tumor localization might have played a role in our lower pretreatment prevalence of malnutrition. In the study described in Chapter 2 only few patients with oral cancer were included (1%), as this study was performed at the department of Otorhinolaryngology and this type of cancer is rarely diagnosed and treated at this department in our University Medical Center (these patients are predominantly treated at the department of Oral and Maxillofacial Surgery in our setting). In 2 of the 3 other studies reported in the literature, more patients with cancer in the oral cavity were included, respectively 10% and 43% of total included patients.[16,17] Patients with oral cancer are at risk for malnutrition, as these patients may suffer from swallowing problems and chewing problems.[18,19] In the other studies, prevalence of malnutrition was not differentiated per type of treatment. As a result, it remains unclear to what extent prevalence of malnutrition may have been underestimated due to low number of included patients with oral cancer. In the study described in Chapter 5, effect of pretreatment dietary intervention (in 37% of our patients) may have acted as a confounder in prevalence of pretreatment malnutrition.

The prospective study described in Chapter 5 also demonstrated that prevalence of malnutrition has more than tripled (from 17% to 52%) shortly after treatment. Subsequently, prevalence of malnutrition substantially decreases to 24% during the first 4 months after treatment, a percentage that was also found in the cross-sectional study on prevalence of malnutrition after treatment of oral and oropharyngeal cancer (Chapter 3).

Both our cross-sectional (Chapter 3) and prospective study (Chapter 5) showed that prevalence of malnutrition declines in post-treatment period. However, although the prospective study (Chapter 5) demonstrated a decline in prevalence of malnutrition during the first 4 months post-treatment, unfortunately body weight, lean mass and fat mass did not improve in this period. The decline in prevalence of malnutrition is related to the operationalization of malnutrition. In the various studies reported in this thesis, malnutrition was defined as weight loss ≥10% in 6 months or ≥5% in 1 month. When malnutrition is assessed repeatedly, intervals in which weight loss is calculated will move, because the <10% or <5% weight loss are calculated for different periods. For example, malnourished patients that stabilize their body weight in the next 4 months after treatment are classified as well-nourished, because in post-treatment period weight loss is <10% in last 6 months or <5% in last month, although their nutritional status may not have improved. In other words, prevalence data should not be used to show whether patients have become well-nourished post-treatment.

Additionally, the study on prevalence of malnutrition after treatment for oral or oropharyngeal cancer revealed that post-treatment body weight is 3% below pretreatment level (Chapter 3). This weight loss is not only present shortly post-treatment, but also exists during the long-term post-treatment period. Therefore, our findings suggest that in the long-term body weight does not return to pre-illness level. As our data on post-treatment malnutrition are retrieved from a cross-sectional study, this assumption needs to be confirmed in a prospective study with a long-term follow up. At the same time, clinical consequences of long-term decline in body weight are unclear. Since in our study on post-treatment malnutrition both pre- and post-treatment BMI was normal, it seems unnecessary to further improve body weight. Instead, improvement of lean mass in favour of fat mass may be required.

Nutritional assessments, including longitudinal body composition measurements (lean mass and fat mass), have additional value to current practice of measurement of body weight and BMI alone. The pitfall in current practice is that body weight may remain stable despite decline in lean mass, indicating gain of fat mass or edema. Furthermore, similar to previous findings[20], in our study on changes in nutritional status during and after treatment (Chapter 5), we demonstrated that lean mass depletion may be present despite normal BMI.

Besides body composition measurements, changes in grip strength provide valuable information about changes in nutritional status. Measurement of grip strength is an operationalization of muscle function, which reflects nutritional status as well. Already in the early stage of malnutrition, electrolytic composition of cells alters, which affects contractive capacity of muscle fibers.[21] Hand grip strength is not only positively related with lean mass, as demonstrated in Chapter 5, but is also negatively related to inflammatory activity[22] and improves even before changes in lean mass are observed. Therefore, in post-treatment period, hand grip strength may reflect the shift from catabolism to anabolism.

Dietary intake

In both the study on post-treatment malnutrition (Chapter 3) and the study on changes in nutritional status during and after head and neck cancer treatment (Chapter 5), a relationship was found between insufficient dietary intake and malnutrition. Patients with an intake of <35 kcal/kg and <1.5 gram protein/kg body weight lost more body weight and lean mass during cancer treatment than patients with an intake of ≥35 kcal and ≥1.5 g protein/kg body weight (Chapter 5). Furthermore, patients with an intake of <35 kcal/kg and <1.5 gram protein/kg body weight continued losing weight and lean mass in the early post-treatment period, whereas patients with an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight managed to gain body weight and lean mass in this period. However, although considered sufficient[23,24], an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight could not prevent loss of body weight and lean mass in our patients undergoing head and neck cancer treatment. In malnutrition, protein breakdown is the result of a combination of reduced intake and inflammatory activity. As intake of our patients is considered sufficient, the results of our study indirectly suggest that head and neck cancer patients suffer from inflammatory activity during and shortly after treatment. Inflammation is a known risk factor for malnutrition by causing protein breakdown despite sufficient intake of energy and protein.[25] Elevated inflammatory markers have been observed in head and neck cancer patients undergoing radiotherapy, indicating inflammatory activity.[26-28] Apparently, the loss of body weight and lean mass observed in our study, despite sufficient intake, supports the assumption that loss of lean mass is unavoidable during acute illness and cancer.[25]

The study on changes in nutritional status and dietary intake (Chapter 5) revealed that tube feeding did not have a beneficial effect on energy and protein intake during radiotherapy or chemoradiation. We expected these patients to have a sufficient intake during radiotherapy or chemoradiation, as the majority (77%) had a prophylactic gastrostomy tube. Previous studies that compared prophylactic placement of a gastrostomy tube to therapeutic placement of a nasogastric tube or gastrostomy tube demonstrated significantly lower rates of weight loss in patients with a prophylactically placed gastrostomy tube.[29,30] The majority of the patients using tube feeding in our study was treated with chemoradiation (62%). Nausea is a common side-effect of chemoradiation[31,32] and may therefore have played a role in insufficient intake. Factors contributing to insufficient intake in patients using tube feeding need to be elucidated.

Risk factors for malnutrition

As stated in the Introduction of this thesis, illness and treatment related symptoms are potential risk factors for malnutrition. In the study on prevalence of malnutrition before the onset of treatment in head and neck cancer patients referred to the department of Otorhinolaryngology of the UMCG (Chapter 2), swallowing/passage difficulties were identified as symptoms strongly related to malnutrition. Such a relationship was also found in the study on post-treatment malnutrition in patients treated for oral or oropharyngeal cancer (Chapter 3). Thus, in head and neck cancer patients swallowing problems are a risk factor for malnutrition in all phases of disease and treatment. Other authors have also identified swallowing problems as a predictor for malnutrition or weight loss, not only in pretreatment period[33], but also during treatment, for example during radiotherapy.[34,35]

In the study on prevalence of malnutrition of patients treated for oral or oropharyngeal cancer (Chapter 3), a higher prevalence of malnutrition in patients using a liquid or mashed diet (36%) than in patients using a solid diet (11%) was found. Generally, a liquid or mashed diet contains less energy and protein than a solid diet and may therefore cause malnutrition. Although patients using a liquid or mashed diet are often advised to use additional liquid dietary supplements, reaching sufficient intake is still difficult for patients using a liquid or mashed diet. Early satiation, taste disturbances and a feeling of mucus in the mouth or throat caused by these supplements may hamper sufficient intake of these supplements.

Treatment of swallowing problems in head and neck cancer patients needs a multidisciplinary approach. Dietary counseling is required to advise the patient on meal texture modification and nutritional content of meals.[36] Additionally, the speech therapist can advise the patient on feeding strategies and exercises to improve swallowing.[36-38] Swallowing rehabilitation after head and neck cancer treatment has shown to be effective in improving this function.[39] The reinforcement of the teamwork between the dietitian and speech therapist may reduce the contribution of swallowing problems to development of malnutrition.

Surprisingly, in the study on post-treatment malnutrition (Chapter 3) no relationship was found between malnutrition and oral symptoms like dry mouth, chewing problems, poor dental status and trismus. In our study on oral symptoms and functional outcome (Chapter 6), it was found that not being able to wear a dental prosthesis influenced mandibular functioning most. Therefore, we expected poor dental status also to be strongly related to malnutrition. Modification of food texture may prevent deterioration of nutritional status in patients with chewing problems, poor dental status and trismus, but not in patients with swallowing problems.

Besides oral symptoms, the general symptoms loss of appetite and loss of taste/aversion were identified as pretreatment risk factors for malnutrition (Chapter 2). Loss of appetite has previously been associated with weight loss (2-2.9% in 1 month or 2-5.9%% in 6 months) in head and neck cancer patients in pretreatment period.[33] As loss of appetite and loss of taste/aversion are frequently observed in patients with cachexia[40-42], it is hypothesized that head and neck cancer may suffer from cachexia. If this hypothesis is true, treatment of malnutrition should specifically address the problem of cachexia to be able to effectively prevent or limit deterioration of nutritional status in pretreatment period.

Quality of life

The study on malnutrition and quality of life (Chapter 4) demonstrated that post-treatment malnutrition is related to reduced physical functioning. The quality of life domain physical functioning refers to the ability to perform intensive daily activities, need for assistance in daily activities, taking a short or long walk, and restriction to bed or chair by day.

It is of clinical importance to prevent deterioration of nutritional status as much as possible. Malnourished patients may end up in a vicious circle of loss of lean mass and physical inactivity, as physical inactivity is known to contribute to muscle atrophy itself as well.[25] The relationship between post-treatment malnutrition and physical functioning stresses the role of malnutrition as comorbid condition in head and neck cancer or its treatment.

Methodological considerations: criteria for malnutrition

During the period this research was performed, there was no consensus on a definition of malnutrition and gold standard for the operationalization of malnutrition. In all studies, we have chosen to use a weight loss ≥10% in 6 months or ≥5% in 1 month as criteria for malnutrition. This amount of weight loss is generally accepted as criteria for malnutrition[21], because this weight loss is associated with increased morbidity, increased mortality and reduced quality of life.[2,7,8,11,43-46] The study on changes in nutritional status and dietary intake during and after head and neck cancer treatment (Chapter 5) demonstrated that about two-third of weight loss is loss of lean mass. This loss of lean mass is responsible for the negative outcome.[47] Another reason to choose weight loss ≥10% in 6 months or ≥5% in 1 month as criteria for malnutrition was to enable comparison between results of our studies and other studies reported in the international literature. Besides the criteria used in our studies, the only other method used in studies to which we compared our results was the Patient Generated Subjective Global Assessment (PG-SGA).[6,48] In this tool, evaluation of nutritional status also largely depends on severe weight loss, with similar cutoff scores as used in our study.[49] Additionally, the PG-SGA assesses presence of symptoms and evaluates changes in dietary intake and body composition.

Whereas weight loss reflects acute malnutrition, underweight, as operationalized by low Body Mass Index (BMI), may reflect chronic malnutrition.[50,51] Cutoff values for BMI varying from 18.5 to 20.0 kg/m^2 have been used as an indicator of chronic malnutrition.[21,52] If a BMI<18.5 kg/m^2 was added to the criteria for malnutrition in our study on post-treatment malnutrition (Chapter 3), prevalence of malnutrition would have risen from 16% to 19%. If this cutoff for BMI is increased to BMI<20 kg/m^2, prevalence of malnutrition would have increased further to 22%. Obviously, the criteria weight loss ≥10% in 6 months or ≥5% in 1 month contribute more to prevalence of malnutrition than BMI<18.5 kg/m^2 or BMI<20 kg/m^2. In the study on post-treatment malnutrition (Chapter 3) pretreatment BMI was 26.3±4.0 kg/m^2 and decreased to 25.3±4.0 kg/m^2 post-treatment. In the study on changes in nutritional status and dietary intake (Chapter 5) lower, but normal BMI values were found. In this study pretreatment BMI was 24.1±5.4 kg/m^2 and decreased to 23.1±4.0 kg/m^2 4 months post-treatment. Both of these BMI values are well within the range of normal BMI values (20-25 kg/m^2). Thus, prevalence of chronic malnutrition seems to be low in the studied population.

Recently new definitions for malnutrition have been developed and efforts have been made to reach consensus on a definition for malnutrition. Soeters et al.[47] proposed a definition that includes both inflammation and body function: 'Malnutrition is a subacute or chronic state of nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity has led to a change in body composition and diminished function'. The International Consensus Guideline Committee managed to reach consensus on 3 definitions for malnutrition based upon etiology[53]:

- 'starvation-related malnutrition', which reflects prolonged insufficient intake without inflammation;
- 'chronic disease-related malnutrition', which refers to chronic diseases or conditions that impose sustained inflammation of a mild to moderate degree;
- 'acute disease or injury-related malnutrition', which refers to acute disease or injury states with severe inflammation.

If these definitions should be applied to the patients studied in this thesis, the following classification of malnutrition is proposed:

- 'starvation-related malnutrition': malnutrition that develops in head and neck cancer patients as a result of insufficient intake due to factors not directly related to underlying illness, for example chewing problems caused by not wearing a dental prosthesis;
- 'chronic disease-related malnutrition': malnutrition that develops in head and neck cancer patients in the period >3 months after treatment, either caused by insufficient intake, or increased nutritional requirements, or both;
- 'acute disease or injury-related malnutrition': malnutrition that develops in head and neck cancer patients in the period before or during treatment, or in the short-term recovery period (i.e. during the first 3 months after treatment), either caused by insufficient intake, or increased nutritional requirements, or both.

In addition to a proposed definition of malnutrition, that hopefully will be commonly accepted, international consensus on operationalization of malnutrition is also needed to enable determination of efficacy of treatment of malnutrition, as well as to allow for a better comparison of study results. Soeters et al. proposed to include assessment of nutrient balance, body composition, inflammatory activity and measurement of muscle function in the operationalization of malnutrition.[47]

Future research

Besides providing answers to the research questions, this thesis also raises new questions. As malnutrition may develop during all phases of disease and treatment, future research should address factors contributing to malnutrition in the period before, during and after head and neck cancer treatment.

First, the role of cachexia in the etiology of malnutrition in head and neck cancer patients needs to be elucidated. Presence of cachexia in head and neck cancer patents may explain the difficulty in restoring lean mass in these patients in pretreatment period and during radiotherapy or chemoradiation. Unfortunately, cachexia cannot be effectively treated by dietary intervention as monotherapy.[54,55] Treatment of cachexia requires a multimodal approach, including drug intervention and physical exercise.[54,55] Future research should validate the hypothesis that head and neck cancer patients may suffer from cachexia. If head and neck cancer do suffer from this syndrome, future research should aim for development of an effective anticachectic treatment specifically designed for head and neck cancer patients. For example, since these patients suffer from oral symptoms in addition to general cancer related symptoms, special attention should be paid to texture of the anticachectic diet.

Second, more insight is needed in energy and protein requirements of head and neck cancer patients. To reduce prediction errors in estimation of energy requirements, insight in resting energy expenditure in all phases of head and neck cancer treatment, differentiated per type of treatment is needed. Furthermore, it is unclear to what extent the several head and neck cancer treatment modalities induce inflammatory activity. Knowledge on this topic is of clinical importance, because inflammatory activity influences energy expenditure and causes protein breakdown,[25] and therefore is a determinator of effectiveness of dietary intervention. Furthermore, inflammation-induced malnutrition may compromise clinical response to cancer treatment.[53]

Third, insight is needed in level of physical activity of head and neck cancer patients. We hypothesize that head and neck cancer patients are physically not very active. It is known from research in patients with haematological malignancies and patients with breast cancer that after a period of severe weight loss due to treatment with high-dose chemotherapy followed by stem cell transplantation, a training programme including aerobic training and resistance training has positive effects on lean mass.[56] Such effects of exercise training on lean mass are encouraging for other populations, such as ours. From a meta-analysis of randomized clinical trials predominantly performed in breast cancer and prostate cancer patients it was concluded that a physical exercise programme, supervised as well as home based, during adjuvant cancer treatment is feasible.[57] In the studied trials, adherence ranged from 39% of the patients who visited at least 70% of the supervised exercise sessions to 100% completion of a home-based walking programme. Studies are needed to determine feasibility of physical exercise programs in head and neck cancer patients and to evaluate effectiveness of such training on lean mass in this patient population.

Fourth, strategies to minimize the role of swallowing problems as risk factor for malnutrition should be explored. For example, the nowadays common application of 'intensity modulated radiotherapy' (IMRT) has resulted in a significantly less impairment of swallowing function compared to three-dimensional conventional radiotherapy.[58] Such a reduction might reduce the risk for developing or aggravating malnutrition during radiotherapy as well. Furthermore, the assumed efficacy of multidisciplinary treatment of cancer treatment related swallowing problems needs to be investigated.

More insight in the above mentioned topics contributes to a more purposeful treatment of malnutrition. Hopefully, in the future head and neck cancer patients will be able to improve nutritional status already before start of treatment and maintain or further improve that status during and after treatment. This would be an important achievement as an improved nutritional status will reduce treatment related morbidity and mortality, and will improve quality of life.

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Summary

Malnutrition has been defined as a subacute or chronic state of nutrition, in which a combination of undernutrition (insufficient food intake) and inflammation has led to a decrease in muscle mass, fat mass, and diminished function, i.e. immune function, cognitive function and muscle strength. Malnutrition is not uncommon in head and neck cancer patients. In the period before head and neck cancer treatment, prevalence of severe weight loss, an indicator of malnutrition, has been reported to vary from 30% to 55%.
Malnutrition in head and neck cancer patients may have multiple causes. In the period before treatment, a major cause of malnutrition is insufficient food intake, related to mechanical obstruction of food or pain caused by the tumor. Cancer cachexia, a complex metabolic syndrome associated with the underlying disease and characterized by loss of appetite and inflammatory activity, may contribute to malnutrition in this period. During and after treatment, malnutrition may develop or aggravate as a result of treatment-related oral symptoms, such as swallowing and chewing problems, pain, hyposalivation, sticky saliva, taste disturbances and trismus (a severely restricted mouth opening). These symptoms may hamper eating and drinking and therefore may result in insufficient intake of energy and protein. Moreover, head and neck cancer treatment may induce inflammatory activity, leading to catabolism of muscle mass.

This thesis aimed to assess malnutrition during the various phases of the treatment head and neck cancer patients are subjected to, viz. from diagnosis up to the period after completion of cancer treatment, and to identify risk factors for malnutrition that occur during these phases.

In **Chapter 2**, prevalence of pretreatment malnutrition was assessed and risk factors for pretreatment malnutrition were analyzed. In this study, malnutrition (i.e. weight loss ≥10% in 6 months or ≥5% in 1 month) was assessed in a mixed population of 407 newly diagnosed head and neck cancer patients that were to be treated at the department of Otorhinolaryngology in the University Medical Center Groningen. Symptoms that may lead to difficulties with nutritional intake (loss of appetite, dysphagia, passage difficulties, pain in the throat, loss of taste/aversion, dry mouth and pain in the mouth) were assessed by the UMCG Head and Neck Clinical Screening Tool. Pretreatment prevalence of malnutrition was 19%, indicating that already before start of cancer treatment, malnutrition is a considerable problem. Malnutrition was associated with localization of the tumor in the hypopharynx, oropharynx/oral cavity or supraglottic larynx. Furthermore, the symptoms dysphagia/passage difficulties, loss of taste/aversion and loss of appetite were related to pretreatment malnutrition. The relationship found between loss of taste/aversion and loss of appetite and malnutrition suggests that pretreatment malnutrition in head and neck cancer patients may not only be the result of reduced dietary intake as result of oral symptoms, but may also be the result of cancer cachexia.

In **Chapter 3**, prevalence of post-treatment malnutrition and its relationship with oral symptoms were assessed cross-sectionally in 116 patients treated for oral or oropharyngeal cancer. Malnutrition (i.e. weight loss ≥10% in 6 months or ≥5% in 1 month) was assessed once after treatment. Interval between end of cancer treatment and study measurement varied from 1 day to 3 years, enabling assessment of malnutrition in both short-term and long-term period after treatment. Oral symptoms were assessed by means of the EORTC QLQ-H&N35 questionnaire and some additional questions. Furthermore, dental status was evaluated and mouth opening was measured. Energy and protein intake were assessed as well, and an intake <90% of requirements was considered insufficient. In this study post-treatment prevalence of malnutrition in patients treated for oral or oropharyngeal cancer was 16%. Prevalence of malnutrition was highest in the first 3 months after treatment (25%) and lowest in the second and third year after treatment (3%). Similar to findings in the study described in Chapter 2, swallowing problems were related to post-treatment malnutrition, as well as insufficient protein intake.

In addition to the relationship between malnutrition and oral symptoms as described in Chapter 3, the relationship between malnutrition and quality of life was explored in the same study population and is described in **Chapter 4**. In this study, quality of life was assessed by the EORTC QLQ-C30. Malnutrition was associated with reduced physical functioning, especially in the period shortly after treatment.

In **Chapter 5** changes in nutritional status of head and neck cancer patients during and after cancer treatment were assessed longitudinally. Twenty-nine head and neck cancer patients were assessed 1 week before, and 1 and 4 months after head and neck cancer treatment. Besides assessment of malnutrition (i.e. weight loss ≥10% in 6 months or ≥5% in 1 month), advanced nutritional assessments including assessment of lean mass (which includes muscle mass) and fat mass, grip strength and phase angle measurement (an indicator of decreased cell integrity or cell death) were performed. Additionally, performance status and dietary intake were assessed. During treatment, patients lost a considerable amount of body weight and lean mass. Subgroup analysis revealed that patients with an intake of <35 kcal and <1.5 gram protein/kg body weight lost nearly 5 times more body weight and nearly 3 times more lean mass than patients with an intake of ≥35 kcal and ≥1.5 gram protein/kg body weight. After treatment, only patients with an intake of ≥35 kcal and ≥1.5 gram protein/kg body weight gained body weight and lean mass. Decreases in phase angle and grip strength during treatment were related to decrease in lean mass in this period. Furthermore, performance status decreased during treatment and recovered in the period after treatment. The findings of this study illustrate that even patients with a generally considered sufficient intake of energy and protein failed to maintain body weight and lean mass during head and neck cancer treatment. This finding suggests that malnutrition in head and neck cancer patients may not only be caused by tumor-related or treatment-related oral symptoms, but to systemic effects such as inflammatory activity as well.

Obviously, oral symptoms have the potential to compromise mandibular functioning and patient's nutritional status. However, so far it was unclear how the various oral symptoms affect mandibular function and nutritional status. The cross-sectional study described in **Chapter 6** aimed to assess oral symptoms of 89 patients treated for oral or oropharyngeal cancer, to assess how patients rank burden of oral symptoms, and to analyze the impact of the tumor, symptoms, and treatment on mandibular functioning. Lack of saliva, restricted mouth opening and restricted tongue mobility were the most frequently reported symptoms. Lack of saliva was most frequently ranked as most burdening oral symptom, followed by restricted mouth opening and restricted tongue mobility. In radiated patients, not being able to wear a dental prosthesis, a larger tumor size (T3 or T4 classification) and a higher age resulted in poorer functional outcome. In non-radiated patients, restricted mouth opening, not being able to wear a dental prosthesis, restricted tongue mobility and surgery of the mandible resulted in poorer functional outcome. It was concluded from this study that lack of saliva not only was the most frequently reported symptom after treatment for oral or oropharyngeal cancer, but was the most burdening symptom as well. Mandibular functioning is strongly influenced by not being able to wear a prosthesis in both radiated and non-radiated patients.

Trismus, a severely restricted mouth opening, is one of the oral symptoms that may compromise nutritional status, because trismus may hinder eating, especially large boluses of solid food. To enable determination of therapeutic effects of anti-trismus treatment, reliability of these mouth opening measurements needed to be investigated. In **Chapter 7** variation in mouth opening measurements in patients treated for oral or oropharyngeal cancer, both with and without trismus, was analyzed. Therefore, maximal mouth opening was measured in 120 patients in 2 sessions of 3 repeated measurements by 1 observer. To analyze the influence of interobserver variation on mouth opening measurements a subgroup of 30 patients was measured by a second observer. Variation in maximal mouth opening in patients with trismus did not differ from variation in maximal mouth opening in patients without trismus. Furthermore, both intra- and interobserver reliability of mouth opening measurements were very good, enabling good monitoring of the patients' response to anti-trismus treatment.

In **Chapter 8**, the main findings of this thesis and their clinical implications are discussed. The studies described in this thesis demonstrate that head and neck cancer patients are nutritionally at risk in all phases of head and neck cancer treatment. Although prevalence of malnutrition gradually declines in the period after treatment, this decline is not accompanied by improvement in lean mass. From the studies described in this thesis, it can be concluded that swallowing problems are an important risk factor for malnutrition in head and neck cancer patients in both pretreatment and post-treatment period. Furthermore, the loss of appetite and loss of taste/aversion reported by head and neck cancer patients at diagnosis point towards presence of cachexia. Finally, it is concluded that even an intake of energy and protein which is generally considered sufficient cannot prevent loss of body weight and lean mass during head and neck cancer treatment.

To be able to improve patients' nutritional status already before start of treatment, in order to reduce treatment related morbidity and mortality, and improve quality of life, additional research is needed. This research should provide more insight into the role of cachexia in the etiology of malnutrition in head and neck cancer patients, as cachexia cannot be effectively treated with current dietary interventions. Additionally, the effect of inflammatory activity and physical inactivity on energy expenditure and protein requirements, during all phases of diagnosis and treatment of head and neck cancer needs to be elucidated. Finally, strategies to minimize the role of swallowing problems as risk factor for malnutrition should be explored. For example, the assumed efficacy of multidisciplinary treatment of cancer treatment related swallowing problems needs to be investigated.

Samenvatting

Ondervoeding is gedefinieerd als een subacute of acute voedingstoestand waarbij een combinatie van onvoldoende voedingsinname en ontstekingsactiviteit heeft geleid tot een afname van de spier- en vetmassa en een verminderde functie (lichamelijke afweer, denkvermogen en spierkracht). Ondervoeding komt vaak voor bij hoofd-halskankerpatiënten. In de literatuur wordt gesteld dat bij 30% tot 55% van de hoofd-halskankerpatiënten al in periode voorafgaand aan de behandeling sprake is van ernstig gewichtsverlies, een indicator voor ondervoeding.

Ondervoeding kan bij hoofd-halskankerpatiënten door meerdere factoren worden veroorzaakt. Een belangrijke factor voor het ontstaan van ondervoeding in de periode voor de behandeling is onvoldoende voedselinname als gevolg van mechanische obstructie van voeding door de tumor of pijn gerelateerd aan de in het hoofd-halsgebied gelegen tumor. Daarnaast kan cachexie, een complex metabool syndroom dat is gerelateerd aan de onderliggende ziekte, bijdragen aan het ontstaan van ondervoeding in deze periode. Cachexie wordt o.a. wordt gekenmerkt door verlies van eetlust en ontstekingsactiviteit. Tijdens en na de hoofd-halskankerbehandeling kan ondervoeding ontstaan of verergeren door bijwerkingen van de behandeling, zoals slik- en kauwproblemen, pijn, een verminderde speekselvloed, taai speeksel, smaakveranderingen en trismus (ernstig beperkte mondopening). Deze problemen kunnen het eten en drinken bemoeilijken en kunnen daardoor resulteren in onvoldoende inname van energie en eiwit. Bovendien kan de behandeling van de tumor in het hoofd-halsgebied ontstekingsactiviteit veroorzaken, die kan leiden tot afbraak van spierweefsel.

Het doel van dit proefschrift was het bepalen van het vóórkomen van ondervoeding bij patiënten met een tumor in het hoofd-halsgebied in de verschillende fasen in het diagnose-behandeltraject en het identificeren van risicofactoren voor ondervoeding in deze verschillende fasen.

In **Hoofdstuk 2** is een studie beschreven waarin de prevalentie van ondervoeding in de periode voor de behandeling werd bepaald en risicofactoren voor ondervoeding in deze periode werden geanalyseerd. In dit onderzoek is ondervoeding (≥10% gewichtsverlies in 6 maanden of ≥5% gewichtsverlies in 1 maand) bepaald bij 407 patiënten met verschillende typen nieuw gediagnosticeerde tumoren in het hoofd-halsgebied, die behandeld zouden gaan worden op de afdeling Keel-, Neus- en Oorheelkunde van het Universitair Medisch Centrum Groningen. Symptomen die kunnen leiden tot problemen met de voedselinname (verminderde eetlust, slikklachten, passageklachten, pijn in de keel, smaakverlies/aversie, verminderde speekselvloed en pijn in de mond) werden onderzocht met behulp van de UMCG Head and Neck Clinical Screening Tool. In dit onderzoek was de prevalentie van ondervoeding in de periode voor de behandeling 19%, wat aangeeft dat ondervoeding al voorafgaand aan de behandeling een aanzienlijk probleem is. Ondervoeding in deze periode bleek samen te hangen met een tumor in het onderste deel van de keelholte, de mond-/mond-keelholte of het strottenhoofd (boven de stembanden). Daarnaast bleken slik-/passageklachten, smaakverlies/aversie en verminderde eetlust samen te hangen met ondervoeding in de periode voor de behandeling. De relatie tussen smaakverlies/aversie en verminderde eetlust en ondervoeding suggereert dat ondervoeding bij hoofd-halskanker in de periode voor de behandeling vermoedelijk niet alleen het gevolg is van verminderde inname door orale symptomen, maar mogelijk ook het gevolg is van cachexie.

Hoofdstuk 3 beschrijft een studie naar het vóórkomen van ondervoeding in de periode na de behandeling en de relatie tussen ondervoeding en klachten in de mond of keel. Dit dwarsdoorsnede-onderzoek was uitgevoerd bij patiënten die waren behandeld voor een tumor in de mond of mond-keelholte. Ondervoeding (≥10% gewichtsverlies in 6 maanden of ≥5% gewichtsverlies in 1 maand) werd eenmalig na de behandeling bepaald, waarbij de tijd tussen het einde van de behandeling en de onderzoeksmeting varieerde van 1 dag tot 3 jaar. Deze variatie in tijd tussen behandeling en onderzoeksmeting maakte het mogelijk om inzicht te krijgen in het vóórkomen van ondervoeding in zowel de korte termijnperiode als lange termijnperiode na de behandeling. Aanwezigheid van klachten in de mond of keel werd bepaald met behulp van de EORTC QLQ-H&N35 vragenlijst en een aantal aanvullende vragen. De gebitstoestand werd beoordeeld en de grootte van de mondopening werd gemeten. Ook werd de energie- en eiwitinname bepaald, waarbij een inname van 90% of minder van de behoefte werd beschouwd als onvoldoende. Uit dit onderzoek kwam naar voren dat 16% van de patiënten die waren behandeld voor een tumor in de mond-/mond-keelholte ondervoed was. Ondervoeding kwam het meest frequent voor in de eerste 3 maanden na de behandeling (25%) en het minst vaak in het tweede en derde jaar na de behandeling (3%). Slikklachten en onvoldoende eiwitinname bleken samen te hangen met ondervoeding in de periode na de behandeling.

Naast de relatie tussen ondervoeding en klachten in de mond of keel, zoals beschreven in Hoofdstuk 3, is de relatie tussen ondervoeding en kwaliteit van leven in dezelfde onderzoekspopulatie onderzocht en beschreven in **Hoofdstuk 4**. De kwaliteit van leven is bepaald met behulp van de EORTC QLQ-C30 vragenlijst. Ondervoeding bleek gerelateerd te zijn aan verminderd lichamelijk functioneren, vooral in de periode kort na de behandeling.

In **Hoofdstuk 5** is een studie beschreven waarin veranderingen in de voedingstoestand tijdens en na de hoofd-halskankerbehandeling zijn onderzocht. In totaal werden 29 patiënten driemaal onderzocht, namelijk 1 week voorafgaand aan de behandeling, 1 maand na de behandeling en 4 maanden na de behandeling. Naast het bepalen van ondervoeding (≥10% gewichtsverlies in 6 maanden of ≥5% gewichtsverlies in 1 maand) werden de vetvrije massa (waar de spiermassa deel van uitmaakt) en vetmassa bepaald, evenals de handknijpkracht en de phase angle (een methode die wordt gebruikt als indicator voor verminderde celintegriteit of celdood). Daarnaast werden de performance status (maat voor het zelfstandig functioneren) en de energie- en eiwitinname bepaald. Patiënten bleken een aanzienlijke hoeveelheid lichaamsgewicht en vetvrije massa te verliezen tijdens de behandeling. Subgroepanalyse liet zien dat patiënten met een inname van <35 kcal en <1.5 gram eiwit/kg lichaamsgewicht bijna 5 keer zoveel lichaamsgewicht en bijna 3 keer zoveel vetvrije massa verloren als patiënten met een inname van ≥35 kcal en ≥1.5 gram eiwit/kg lichaamsgewicht. In de periode na de behandeling slaagden alleen patiënten met een inname van ≥35 kcal en ≥1.5 gram eiwit/kg lichaamsgewicht erin om het lichaamsgewicht en de vetvrije massa te laten toenemen. De daling van de handknijpkracht en phase angle tijdens de behandelingsperiode waren gerelateerd aan de afname van de vetvrije massa in deze periode. De performance status daalde tijdens de behandeling en steeg weer in de periode na de behandeling. De resultaten van dit onderzoek laten zien dat patiënten met een tumor in het hoofd-halsgebied, ondanks een inname van energie en eiwit die in het algemeen als voldoende wordt beschouwd, er niet in slaagden het lichaamsgewicht en de vetvrije massa tijdens de behandeling te handhaven. Deze bevinding suggereert dat ondervoeding bij hoofd-halskankerpatiënten niet alleen kan worden veroorzaakt door tumorgerelateerde of behandelingsgerelateerde factoren, maar mogelijk ook door systemische effecten zoals ontstekingsactiviteit.

Vanzelfsprekend kunnen mondklachten het mandibulair functioneren (functies waarbij activiteit van het kaakgewricht en de kauwspieren nodig is) en de voedingstoestand van de patiënt negatief beïnvloeden. In welke mate dit gebeurt was echter onduidelijk. In het dwarsdoorsnede-onderzoek dat is beschreven in **Hoofdstuk 6** zijn deze mondklachten onderzocht in een groep van 89 patiënten, die waren behandeld voor een tumor in de mond-/mond-keelholte. Daarnaast werd onderzocht hoe patiënten deze klachten rangschikken op de mate waarin deze klachten last geven. Tevens werden de invloed van de tumor, de klachten en de behandeling op het mandibulair functioneren onderzocht. Gebrek aan speeksel, een beperkte mondopening en een beperkte beweeglijkheid van de tong werden het vaakst genoemd als klachten. Van de klachten die de patiënten het meest hinderen in hun functioneren werd gebrek aan speeksel het vaakst genoemd, gevolgd door een beperkte mondopening en beperkte beweeglijkheid van de tong. Bij bestraalde patiënten resulteerden het niet kunnen dragen van een gebitsprothese, een grotere tumor (T3 of T4 classificatie) en een hogere leeftijd in een slechtere mandibulaire functie. Bij niet-bestraalde patiënten resulteerden een beperkte mondopening, het niet kunnen dragen van een gebitsprothese en chirurgie van de onderkaak in een slechtere mandibulaire functie. Op basis van de resultaten van dit onderzoek werd geconcludeerd dat gebrek aan speeksel niet alleen de meest frequent genoemde klacht na behandeling van een tumor in de mond-/mond-keelholte is, maar ook de meest hinderlijke klacht. Zowel bij bestraalde als niet-bestraalde patiënten blijkt dat het mandibulair functioneren het meest beïnvloed wordt door het niet kunnen dragen van een gebitsprothese.

Trismus, een sterk beperkte mondopening, kan de voedingsinname bemoeilijken, vooral de inname van grote stukken vaste voeding. Daardoor kan trismus de voedingstoestand negatief beïnvloeden. Om de effectiviteit van een anti-trismusbehandeling te kunnen beoordelen, diende de betrouwbaarheid van het meten van de mondopening te worden onderzocht. In **Hoofdstuk 7** is een studie beschreven waarin de betrouwbaarheid van mondopeningmetingen was onderzocht bij patiënten die waren behandeld voor een tumor in de mond-/mond-keelholte. In dit onderzoek werden zowel patiënten met als zonder trismus onderzocht. Hiertoe werd bij 120 patiënten in 2 sessies van elk 3 metingen de maximale mondopening gemeten, door 1 onderzoeker. Bij een subgroep van 30 patiënten werden deze 2 sessies door een tweede onderzoeker herhaald. De variatie in maximale mondopening van patiënten met trismus verschilde niet van die van patiënten zonder trismus. Metingen van de maximale mondopening bleken zeer betrouwbaar te zijn, zowel binnen als tussen beoordelaars, wat een goede beoordeling van het effect van antri-trismusbehandeling mogelijk maakt.

In **Hoofdstuk 8** worden de belangrijkste bevindingen die uit dit proefschrift naar voren zijn gekomen en hun klinische consequenties besproken. Zo laten de verschillende studies uit dit proefschrift zien dat hoofd-halskankerpatiënten tijdens alle fasen van het diagnose-behandelingstraject ondervoed kunnen raken. Hoewel het vóórkomen van ondervoeding geleidelijk daalde in de eerste 3 maanden na de behandeling, ging deze daling niet gepaard met een toename van de vetvrije massa. Daarnaast kan worden geconcludeerd dat slikklachten een belangrijke risicofactor vormen voor ondervoeding bij hoofd-halskankerpatiënten, zowel in de periode voor als na de behandeling. Het gebrek aan eetlust, smaakverlies en aversie wijzen op mogelijke aanwezigheid van cachexie. Tenslotte kan worden geconcludeerd dat zelfs een energie- en eiwitinname die gewoonlijk als voldoende wordt beschouwd, verlies van lichaamsgewicht en vetvrije massa tijdens de behandelingsperiode niet kan voorkomen.

Om de voedingstoestand al in de periode voorafgaand aan de behandeling te kunnen verbeteren, om vervolgens de behandelingsgerelateerde morbiditeit en mortaliteit te verlagen en de kwaliteit van leven te verhogen, is nader onderzoek nodig. Toekomstig onderzoek moet meer inzicht geven in de rol van cachexie bij het ontstaan van ondervoeding in deze patiëntengroep. Dergelijk onderzoek is van groot belang, omdat is gebleken dat met de huidige dieetinterventies cachexie niet effectief kan worden behandeld. Daarnaast dient het effect van ontstekingsactiviteit en lichamelijke inactiviteit op het energieverbruik en de eiwitbehoefte tijdens alle fasen van het diagnose-behandelingstraject van hoofd-halskankerpatiënten te worden onderzocht. Tenslotte dienen strategieën te worden bedacht om de rol van slikklachten als risicofactor voor ondervoeding te verkleinen. Onder andere dient de veronderstelde effectiviteit van multidisciplinaire behandeling van behandelingsgerelateerde slikklachten te worden onderzocht.

Dankwoord

Met het verschijnen van dit proefschrift is mijn promotietraject afgesloten. Op deze periode kijk ik met ontzettend veel plezier terug! In de afgelopen 6 jaren heb ik me echt kunnen verdiepen in het fenomeen ondervoeding, bij een zeer boeiende patiëntengroep.
Gedurende het promotietraject heb ik met veel mensen plezierig samengewerkt en hebben veel mensen mij geholpen. Graag wil ik iedereen die heeft bijgedragen aan de totstandkoming van mijn proefschrift dan ook heel hartelijk bedanken!

Een aantal mensen wil ik in het bijzonder bedanken, te beginnen met mijn promotoren, oftewel mijn 'dreamteam'.
Prof. dr. J.L.N. Roodenburg, beste Jan, ik weet nog als de dag van gisteren hoe onze onderzoekssamenwerking begon. In 2003 mailde je mij met de mededeling dat je had vernomen dat ik graag onderzoek wilde doen. "Fantastisch!" vond je dit. Ik had me geen enthousiastere reactie kunnen wensen. Jouw enthousiasme heeft me in het gehele onderzoekstraject erg geïnspireerd.
Je expertise als kaakchirurg-oncoloog was essentieel in alle fasen van het onderzoek. Maar daarnaast waren je helikopterview, je klinische blik, je luisterend oor en je relativeringsvermogen, alles gehuld in een flinke dosis humor, voor mij erg belangrijk! Als er 'beren op de weg kwamen' zorgde je er wel voor dat ze snel weer verdwenen.
Een van de hoogtepunten was het gezamenlijke congresbezoek met Pieter in Toronto!
Ik wil je heel hartelijk bedanken voor alles wat je voor me hebt gedaan en in het bijzonder voor het vertrouwen om mij zonder wetenschappelijke vooropleiding promotieonderzoek te laten doen. Ik hoop dat we het onderzoek naar ondervoeding bij hoofd-halskankerpatiënten nog lang mogen voortzetten.

Prof. dr. P.U. Dijkstra, beste Pieter, je hebt mij met je heldere uitleg wegwijs gemaakt in het land van de methodologie en statistiek, wat zelfs in een 'statistisch artikel' heeft geresulteerd! Ik ben je erg dankbaar voor alle tijd die je in mijn begeleiding hebt gestoken. Van je kritische opmerkingen bij de manuscripten heb ik veel geleerd. Daarnaast hebben je humor en relativeringsvermogen me altijd gauw opgebeurd als ik even een 'dipje' had. Je met het beroemde zakmes geschilde appels hebben daarbij positief bijgedragen aan mijn eigen voedingstoestand!

Prof. dr. A. Vissink, beste Arjan, onze samenwerking begon met het schrijven van een hoofdstuk over smaak- en reukstoornissen. Ik had destijds niet kunnen bedenken dat je niet lang daarna mijn promotor zou worden!
Je kritische vragen op het gebied van (onder)voeding en methodologie en je interesse voor voeding waren erg inspirerend. Voor al je hulp tijdens het onderzoek, inclusief je 'reviewersblik' en de prettige samenwerking wil ik je heel hartelijk bedanken.

Dr. R.P. van Oort, beste Rob, onze samenwerking is begonnen met de CBO-richtlijn Mondholte-orofarynxcarcinoom, waarbij je al gauw in de gaten had dat ik geïnteresseerd was in het doen van onderzoek. Ik wil je heel hartelijk bedanken voor je enthousiasme en inzet bij de totstandkoming van ons onderzoek.

Ook wil ik je graag bedanken voor je hulp bij het beoordelen van de gebitstoestand en het analyseren van de gebitsgegevens. Ik vond het erg leuk om een kijkje te nemen in de keuken van de tandarts.

Patiënten zijn uiteraard onmisbaar bij het uitvoeren van klinisch onderzoek. Alle patiënten die bereid waren om mee te werken aan de verschillende studies wil ik dan ook heel hartelijk bedanken. Ik heb veel waardering voor het feit dat u allen, in de zware tijd van ziekte en behandeling, toch de tijd en moeite heeft genomen om mee te doen aan wetenschappelijk onderzoek.

De leden van de beoordelingscommissie, **prof. dr. R. de Bree**, **prof. dr. J.A. Gietema** en mw. **prof. dr. ir. E. Kampman**, graag wil ik u heel hartelijk bedanken voor de kritische beoordeling van het manuscript.

Een paramedicus laten promoveren is niet de normaalste zaak van de wereld. Echter, voor de afdeling Kaakchirurgie lijkt dit bijna traditie te worden. **Prof. dr. L.G.M. de Bont**, **dr. F.K.L. Spijkervet** en **dhr. R.M. Rolvink**, oftewel het dagelijks bestuur van de Kaakchirurgie, ik wil u allen heel hartelijk bedanken dat u mij de mogelijkheid heeft geboden om promotieonderzoek binnen de afdeling Kaakchirurgie te doen. Ook ben ik erg dankbaar voor de kansen die ik heb gekregen om onze onderzoeksresultaten nationaal en internationaal te presenteren en daar waar nodig internationaal kennis te 'halen'. Vanaf de eerste minuut heb ik me erg thuis gevoeld bij de Kaakchirurgie en ik hoop dat we het onderzoek naar ondervoeding bij hoofd-halskankerpatiënten de komende jaren op dezelfde prettige wijze kunnen voortzetten.

De prettige sfeer op de afdeling wordt uiteraard ook bepaald door de collega's. Alle **stafleden**, **onderzoekers**, **arts-assistenten (i.o.)**, **polikliniekmedewerkers**, **mondhygiënisten** en alle **(oud-)kamergenoten van de voormalige flexkamer van de Kaakchirurgie** wil ik dan ook graag hartelijk bedanken voor de gezelligheid en interesse in mijn onderzoek. Hoewel ik als paramedicus een beetje een vreemde eend in de bijt was heb ik me nooit een vreemde een in de bijt gevoeld.

Mw. H. van der Lei-Groenewegen, beste Hester, bedankt voor alle gezellige momenten, niet alleen die op de derde verdieping en bij de koffiecorner op de Radiotherapie, maar zeker ook die tijdens de treinreizen naar Utrecht voor de CBO-richtlijn en onze overnachting in Utrecht.

Mw. J.M. Baldi-Ekelhoff, beste Judith, bedankt voor je gezelligheid en mental support.

Mw. dr. M.A. Stokman, beste Monique, bedankt voor alle tips en adviezen die je me hebt gegeven, daar was ik erg blij mee.

Mw. M. Popma, beste Madelon, het is alweer even geleden dat we kamergenootjes waren, maar ik vond het een leuke tijd.

Mw. M. Hoff, beste Margriet, bedankt voor je betrokkenheid en niet te vergeten je 'stiekeme' foto's!

Met gezelligheid kom je er natuurlijk niet alleen. Gelukkig kon ik ook altijd een beroep doen op verschillende mensen.
Dhr. H.B. de Jonge, beste Harrie, bedankt dat je me altijd snel kon helpen, niet alleen met administratieve en ICT-gerelateerde zaken, maar bijvoorbeeld ook met het snel vervangen van een lege batterij zodat ik weer verder kon met mijn metingen.

Mw. N.E. Jaeger, mw. L. Kempers, mw. K. Wolthuis, mw. D.V. Barelds en mw. **S. Wiersema**, beste Nienke, Lisa, Karin, Debby en Fieke, hartelijk dank voor jullie ondersteuning en prettige samenwerking.

Mw. C.H. Hagenus, mw. J.A. van den Akker, mw. E. Wartena, mw. H.C. Bouma, mw. K.E. Kreeft, beste Corriet, Jenny, Esther, Hilde en Karien, bedankt voor jullie enthousiaste medewerking bij de verschillende studies.

Alle **dames van de zorgadministratie van de polikliniek Kaakchirurgie** wil ik graag bedanken voor het opvragen van de statussen.

Mw. R.J.M. Dopheide, beste Rachel, graag wil ik je heel hartelijk bedanken voor je inspanningen als voormalig leidinggevende bij de totstandkoming van mijn promotietraject. Je was vanaf het begin erg enthousiast en betrokken, waar ik je erg dankbaar voor ben. Ik vind het erg leuk dat je nu zelf ook deel uitmaakt van de hoofd-halsoncologische zorg!

Dhr. L.A.M. van Zoggel en **mw. drs. M.R.M. Felten**, beste Bert en Marja, als voormalige en huidige leidinggevende hebben jullie mij en mijn promotietraject overgenomen. Ik wil jullie graag bedanken voor jullie medewerking ten aanzien van mijn detachering bij de Kaakchirurgie. Hierdoor heb ik dit promotietraject, ondanks de reorganisatie, kunnen afmaken.

Prof. dr. B.F.A.M. van der Laan en **prof. dr. J.A. Langendijk**, ik wil u beiden hartelijk danken voor de enthousiaste participatie in de verschillende studies.

Dr. J. Pruim, hartelijk dank voor uw enthousiaste medewerking aan de LISAH-studie.

Dr. H. Groen, beste Henk, hartelijk dank voor al je hulp bij het formuleren van de aanvragen en het verkrijgen van de subsidies voor de verschillende studies.

Prof. dr. P.J.J. Sauer, ook u wil ik hartelijk bedanken voor uw hulp en suggesties en de beoordeling van de subsidieaanvraag voor de LISAH-studie.

Mw. M.E. Duits en **mw. E.R. Baldal**, beste Marianne en Rebecca, hartelijk dank voor al jullie medewerking bij de inclusie van patiënten en het opvragen van statussen.

Dr. J.G.A.M. de Visscher, **mw. K. Rozema** en **mw. W. van Abbema**, beste Jan, Klaske en Wilma, hartelijk dank voor jullie enthousiaste participatie in de LISAH-studie.

Alle **medewerkers van de Nucleaire Geneeskunde** wil ik graag bedanken voor alle vriendelijke medewerking bij het plannen en uitvoeren van de DEXA scans.

(Oud-)medewerksters van de Patiëntenservice Radiotherapie, beste Antje, Hilda, Janneke, Janny, Jeanet en Tea, hartelijk dank voor feit dat ik jullie ondanks jullie eigen drukte toch heb mogen bestoken met logistieke vragen ten behoeve van de LISAH-studie.

Mw. drs. M.E.M.C. Christianen, beste Miranda, bedankt voor de prettige samenwerking. De 'concurrentie' ten aanzien van het includeren van patiënten heeft onze samenwerking niet in de weg gestaan!

Dr. F.R. Burlage, **dr. H.P. Bijl** en **mw. drs. O. Hoegen**, beste Fred, Henk en Olga, bedankt voor jullie medewerking bij de patiënteninclusie ten behoeve van de LISAH-studie.

Ook de **dames van de medische administratie van de Radiotherapie** wil ik graag bedanken voor het opvragen van de medische statussen.

Dr. M.J.H. Witjes en **dr. K.P. Schepman**, beste Max en Kees Pieter, bedankt voor de prettige samenwerking in de hoofd-halsoncologische zorg.

Alle verpleegkundigen, voedingsassistenten en **medewerksters van de zorgadministratie van de verpleegafdelingen A1VA, D2VA en L4VA** wil ik graag bedanken voor de prettige samenwerking ten behoeve van de LISAH-studie.

Mw. S. Bunskoek, beste Sophie, ook jou wil ik bedanken voor de logistieke afstemming in het kader van de LISAH-studie.

Mw. S. Keizer, beste Sanne, bedankt voor het aankondigen van de geplande opnames van de TLE-patiënten.

Dhr. P.A.M. Nijkrake, hartelijk dank voor uw bereidheid om een onderzoeksruimte namens de afdeling Revalidatie ter beschikking te stellen. Ik zou niet weten waar ik de metingen anders had moeten doen.

De **dames van de zorgadministratie van de Polikliniek Revalidatie** wil ik graag bedanken voor de gastvrijheid op de poli.

De **Radiotherapie Zwolle** wil ik graag bedanken voor het zo nu en dan faciliteren van een onderzoeksruimte.

Dr. G. Dijkstra, beste Gerard, hartelijk dank voor je enthousiaste participatie in de LISAH-studie. Omdat de subsidiëring van de serologische bepalingen pas in de eindfase van het promotietraject is rondgekomen valt dit gedeelte van de LISAH-studie buiten dit proefschrift. De komende maanden krijgt dit zijn vervolg!

Dhr. H. Breukelman, **mw. dr. J. Westra** en **dhr. J. Bijzet**, hartelijk dank voor al uw hulp en ondersteuning ten aanzien van de serologische bepalingen.

Mw. J.H. Kuipers en **mw. S. Huitema**, beste Sietske en Jolanda, jullie zijn mijn directe collega's in de patiëntenzorg. Ik wil jullie heel hartelijk bedanken voor de prettige samenwerking. Ons team is 'klein maar fijn'! Dankzij jullie kon ik me ook in drukke tijden in de patiëntenzorg focussen op onderzoek.

Alle **collega's van de Sectorondersteuning Sector Oncologie** en **dr. J.W. Hesselink** wil ik heel erg bedanken voor alle interesse in mijn onderzoekstraject. Op de boot naar Schiermonnikoog is dankzij jullie de promotiedatum 8-9-'10 ontstaan…. en het is gelukt!

Collegadiëtisten van Sector B, graag wil ik jullie bedanken voor jullie medewerking om het LISAH-onderzoek binnen het zorgtraject hoofd-halsoncologie te kunnen laten plaatsvinden.

De **overige collegadiëtisten uit het UMCG** wil ik bedanken voor de belangstelling voor mijn onderzoeksactiviteiten. Daarnaast heb ik ook dankbaar 'gebruik' van jullie gemaakt om te oefenen met de nutritional assessment-metingen. **Mw. L.G. Swart**, beste Linda, bedankt voor je instructies.

De **collega's uit diëtetiek(Neder)land** wil ik bedanken voor ieders enthousiasme en belangstelling voor mijn onderzoeksactiviteiten. Er is na vandaag weer een gepromoveerd diëtist bijgekomen!

Mw. N. Doornink en **mw. A. van Stijgeren**. Beste Niki, zoals je ziet: je staat inderdaad in het Dankwoord! Maar volkomen terecht. Je hebt me niet alleen 'gevoerd' met nieuwe artikelen, maar vooral met je droge humor en gezelligheid!
Beste Ans, ons eerste gezamenlijk geschreven hoofdstuk 'Voeding en dieettherapie' in de richtlijn 'Mondholte-/orofarynxcarcinoom' bleek achteraf ook een belangrijke stap richting mijn promotieonderzoek. Ik heb niet alleen genoten van onze samenwerking, maar ook van de 'jaarlijkse' dagen die we met Niki op stap zijn geweest. Niki en Ans, ik hoop dat we deze gezellige 'culturele bijscholing' de komende jaren voortzetten!

Mw. S. Huitema en **mw. dr. M. van Rijn**, beste Sietske en Greet. Jullie treden op als (ik citeer Sietske) "komisch duo". Ik vind het ontzettend leuk dat jullie naast me staan als paranimfen! Maar daarnaast hadden jullie ook een belangrijke rol in mijn onderzoekstraject, namelijk het geven van inhoudelijke feedback. Daar wil ik jullie ook graag voor bedanken!

Trotse **pap en mam**, bedankt voor jullie onvoorwaardelijke steun en de vrijheid die jullie me altijd hebben gegeven.

Lieve Harold, vanaf dag één was je vol trots en je hebt me altijd aangemoedigd mijn ambities te realiseren. Niets was jou daarbij teveel. Je onvoorwaardelijke liefde, je steun en je humor hebben er voor gezorgd dat ik dit intensieve traject heb kunnen doorlopen. Daarnaast heb je me met je inlevingsvermogen en je interesse voor voeding en de medische wereld ook inhoudelijk kunnen helpen. Lieve Harold, ik hou van je en geniet elke dag van ons samenzijn. Dit proefschrift draag ik aan jou op!

About the author

Harriët Jager-Wittenaar was born on May 24th 1974 in Hoogezand-Sappemeer. After finishing athenaeum, she started studying 'English Language and Literature' at the University of Groningen. After 1 year she switched to the study 'Nutrition & Dietetics' at the Hanzehogeschool Groningen. After 4 years she graduated in 1997 and started to work as a clinical dietitian in the University Medical Center Groningen.
She has been an active member of the 'National Working Group of Oncology Dieticians' (LWDO) and the 'Supportive Care Working Group Head and Neck Oncology' (PWHHT). Currently, she is an active member of the 'Dutch Working Group on Malnutrition' (DON).
She has translated her clinical experience into evidence based guidelines, for example in the multidisciplinary guidelines 'Cancer in the oral cavity or oropharynx' (2004) and 'Hypopharyngeal cancer' (2007). Furthermore, she has written book chapters on dietary treatment of cancer patients.
Moreover, she has lectured at the University of Groningen and on several national and international congresses. In 2004 she started her part-time PhD research work at the Department of Oral and Maxillofacial Surgery at the University Medical Center Groningen, which has resulted in this thesis.

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Jager-Wittenaar H, Dijkstra PU, Langendijk JA, van der Laan BFAM, Pruim J, Roodenburg JLN. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *[Head Neck: accepted for publication]*

Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan BFAM, Roodenburg JLN. Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. *[Head Neck: in press]*

Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan BFAM, Roodenburg JLN. Malnutrition in patients treated for oral or oropharyngeal cancer – prevalence and relationship with oral symptoms: an explorative study. *[submitted]*

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