

**From recognition of malnutrition to
improvement of dietary counseling for patients
with head and neck cancer**

Manon van den Berg

COLOFON

ISBN: 978-90-820955-3-1

Copyright © 2014 Manon van den Berg, Nijmegen, The Netherlands

All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior written permission of the author or from the publisher holding the copyright of the published articles.

Cover design and book lay-out: Bas van Rens
Printed by: Bas van Rens

Financial support by Fresenius Kabi Nederland BV, Sorgente BV, Nestlé Health Science, Nederlandse Vereniging van Diëtisten, Nutricia Advanced Medical Nutrition, B. Braun Medical BV, Mediq tefa and Stichting Klankbord for publication of this thesis is gratefully acknowledged.

From recognition of malnutrition to improvement of dietary counseling for patients with head and neck cancer

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op woensdag 5 februari 2014
om 12.30 uur precies

door

Manon Gertruda Allegonda van den Berg

geboren op 13 juli 1976
te Nijmegen

Promotoren

Prof. dr. M.A.W. Merkx

Prof. dr. J.H.A.M. Kaanders

Prof. dr. J.P.H. Drenth

Copromotor

Dr. G.J.A. Wanten

Manuscriptcommissie

Prof. dr. T. van Achterberg

Prof. dr. E. Kampman (WUR)

Prof. dr. H.A.M. Marres

TABLE OF CONTENTS	Page
CHAPTER 1 General Introduction	6
CHAPTER 2 A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis treatment and revalidation	20
CHAPTER 3 A prospective study on malnutrition and quality of life in patients with head and neck cancer	32
CHAPTER 4 Supportive care in early rehabilitation for advanced-stage radiated head and neck cancer patients	46
CHAPTER 5 Comparison of the effect of individual dietary counseling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy	60
CHAPTER 6 Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: A cross-sectional study	74
CHAPTER 7 Normalcy of food intake in head and neck cancer patients supported by combined dietary counseling and swallowing therapy: A Randomized clinical trial	88
CHAPTER 8 Summary, general discussion and future perspectives	106
Samenvatting	122
Dankwoord	130
Publications	136
Curriculum Vitae	140

1

General introduction



Head and neck cancer

Head and neck cancer is a serious healthcare problem that poses a considerable challenge to patients and health care providers. Head and neck cancers have an estimated yearly incidence worldwide of more than 600.000 new cases, and are among the most common cancers in men.¹ The mortality related to this cancer type is high and about 250.000 patients die each year.

The yearly incidence of head and neck cancers in the Netherlands is about 2800 and still growing.(Fig.1) Head and neck cancers are associated with lifestyle and environmental risk factors. Tobacco and alcohol use are the most important causative factors for developing head and neck cancer.² The sexually transmitted human papilloma virus is also a risk factor for head and neck cancer, especially for oropharyngeal carcinomas.³

Intake of non-starchy vegetables and fruits in general may protect against cancers of the mouth, pharynx and larynx.^{4,5}

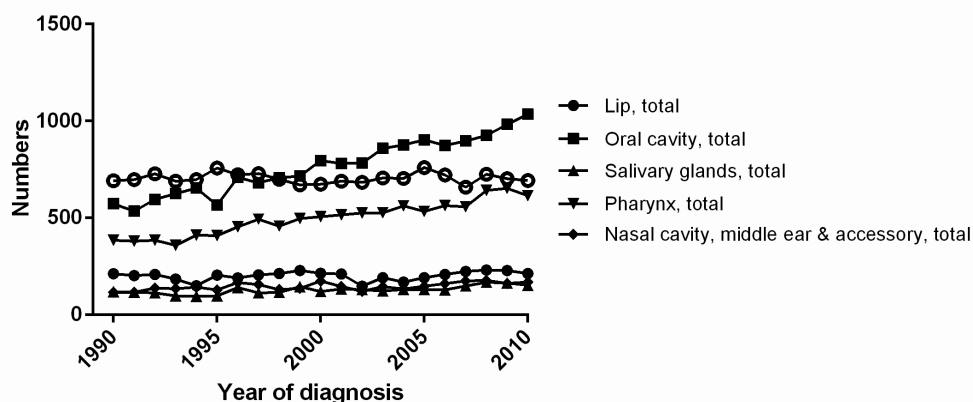


Figure 1. Incidence by tumor location for head and neck cancers from 1990 to 2010. (The Netherlands Cancer Registry. www.cijfersoverkanker.nl)

The locations of head and neck cancer include nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, nasal cavity and paranasal sinuses and salivary glands.(Fig. 2)

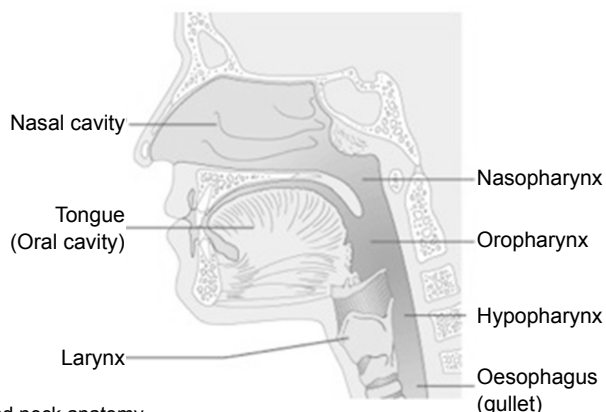


Figure 2. Head and neck anatomy.

An important component in head and neck cancer diagnosis, is tumor staging. The TNM system is an uniform instrument for oncology health professionals and serves as a basis for decision making on management of individual patients. Each individual aspect of TNM is termed in categories: T category describes the size and extensions of the primary tumor site, N category describes the regional lymph node involvement and M category describes the presence of distant metastatic spread. TNM combinations correspond to one of six stages.⁶(Fig. 3)

	T ₁	T ₂	T ₃	T _{4a}	T _{4b}
N ₀	I	II			
N ₁			III		
N ₂				IVa	
N ₃					IVb
M ₁			IVc		

Figure 3. UICC tumor staging.⁶

The type of treatment given for head and neck cancer depends on the tumor location, stage, histology and the condition of the patient. Potential curative treatment consists of surgery, radiotherapy, and/or chemotherapy. Over the last decade, new treatment protocols have arisen such as surgical approaches based on pre-operative imaging facilities and image and function based reconstructive techniques.^{7,8} Also non-surgical (combined) treatment modalities, such as intensity modulated radiotherapy, accelerated radiotherapy, radiotherapy with hypoxic modification, concomitant chemoradiation and radiotherapy combined with targeted therapies have been developed.⁹⁻¹¹(Fig. 4) These therapies are beneficial in terms of locoregional tumor control and some also for overall survival.^{12,13} Chemoradiation is the recommended therapy for more advanced tumors (T₃₋₄).^{14,15} Although this therapy offers increased organ preservation and is associated with progression-free and overall survival, it also increases toxicity and can compromise organ function. Dysphagia is one of the most recognized toxicities, which affects eating ability, and can lead to malnutrition.¹⁶⁻¹⁹

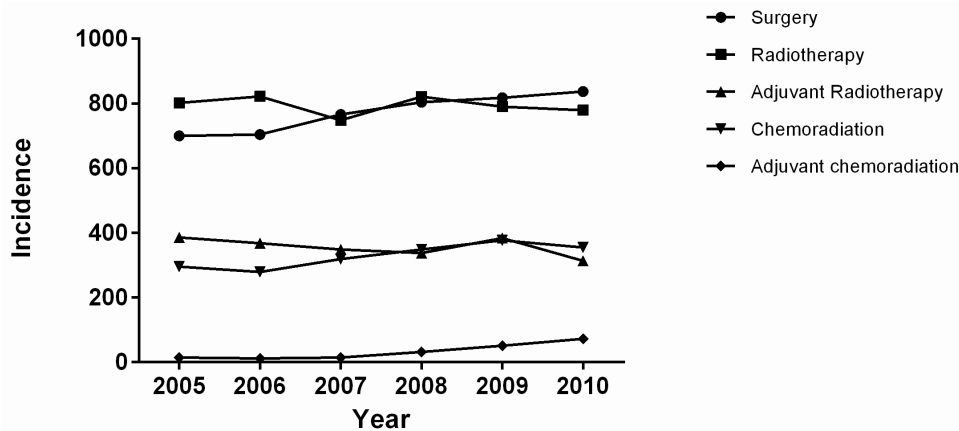


Figure 4. Incidence of treatment strategies for head and neck cancers from 2005 to 2010 (tumor stages >I)⁶ (The Netherlands Cancer Registry)

Malnutrition in cancer patients

Malnutrition is a nutritional status in which a deficiency or imbalance of energy, protein, and other nutrients has measurable adverse effects on tissue/body form (shape, size, and composition), function, and clinical outcome.²⁰ The prevalence of malnutrition in oncologic patients varies from 0 to 60%, depending on various oncology-related factors (tumor type, stage, treatment, treatment phase). Figures also depend on the criteria used for malnutrition, such as weight loss, low body mass index (BMI), decreased fat-free mass, diminished dietary intake, deteriorated biochemical values or a combination of these.²¹⁻²⁴ The most frequently used definition for malnutrition is $\geq 5\%$ weight loss in 1 month and/or $\geq 10\%$ weight loss in 6 months, and/or a BMI of $\leq 18.5 \text{ kg/m}^2$ (for age ≥ 65 years, $\text{BMI} \leq 20 \text{ kg/m}^2$), and/or in combination with decreased nutritional intake. Discussions in expert meetings on which criteria are essential to define malnutrition are ongoing.^{23,24}

There are a number of factors that lead to a compromised nutritional health status in patients with cancer. Nutritional intake in patients with a malignancy is negatively affected by factors such as anorexia, pain, fatigue, and anxiety. Depending on tumor location and treatment, gastrointestinal symptoms such as nausea, vomiting, restrictions in food passage, constipation, diarrhea, and altered absorption may also be present.^{25,26} Apart from inadequate food intake, cachexia plays a role in malnutrition due to the cancer. Cancer can, in some ways, be compared with chronic inflammation. A malignant tumor can produce cytokines, like interleukins (IL-1, IL-6) and TNF- α and the liver responds to these cytokines with increased acute-phase proteins, like C-reactive protein (CRP). These elevated CRP concentrations are correlated with weight loss, hypermetabolism, anorexia and decreased muscle volume and function, known as cancer cachexia. The precise mechanism is still unclear.²⁷⁻²⁹ In general, cancer patients lose weight due to a combination of inadequate food intake and changed metabolism, depending on the tumor location, stage, and treatment.

Malnutrition in head and neck cancer patients

Patients with head and neck cancer are specifically at risk for malnutrition. Symptoms such as dysphagia, mastication problems, mucositis, xerostomia, changed and/or decreased smell and taste, nausea, and trismus due to tumor location and/or treatment side effects are frequently seen. These symptoms increase the risk of developing malnutrition.³⁰ The incidence of malnutrition in patients with head and neck cancer is 30–57%.³¹⁻³³

The incidence is the highest in patients with malignant tumors of the pharynx and oral cavity.^{34,35} Patients with stage III/IV tumors have more weight loss than patients with stage I/II tumors.^{34,36} Little is known about the presence of unintended weight loss/malnutrition and energy intake from diagnosis until rehabilitation and the differences between treatment strategies. This is of special interest, because cancer therapies have changed over the last decade, and patients at risk for malnutrition should be identified in order to offer optimal nutritional intervention to decrease malnutrition.

Quality of life and malnutrition in head and neck cancer patients

Health-related quality of life (QoL) is a multi-dimensional concept which comprises physical and psychological functioning, social interaction, and disease- and treatment-related symptoms.³⁷ QoL is increasingly being recognized as an important issue in oncology, especially since

cancer, in general, is becoming a more chronic disease. In addition to traditional clinical outcomes, such as tumor response and survival, health-related QoL is a respectable outcome measurement in clinical research, representing the patient's perspective.³⁸ QoL in head and neck cancer patients is characterized by a significant decrease in physical functioning, increased fatigue and a decrease in appetite. Also disease specific QoL symptoms are reduced, from diagnosis till 6 months after treatment and thereafter like trismus, dry mouth, sticky saliva, altered taste and/or smell, less (enjoyment in) social eating, and difficulty in swallowing.³⁹⁻⁴¹ There is a negative relationship between unintended weight loss and QoL.^{42,43} Patients who develop $\geq 10\%$ weight loss after treatment score lower on items such as role functioning, fatigue, loss of appetite, global QoL, sticky saliva, and swallowing, at diagnosis.⁴⁴ As such, QoL assessment could identify patients at risk of severe weight loss during and after treatment. Knowledge of the relationship between malnutrition and QoL functional and symptoms scores before, during and after treatment could help to guide the direction of malnutrition prevention and management.

Nutritional intervention

Over the last decade, clinical research has shown that unintended weight loss and malnutrition in head and neck cancer patients have a negative impact on treatment outcomes. There are associations with decreased treatment tolerance, increased postoperative complications, higher mortality and morbidity rates, shorter failure-free survival and poorer QoL.^{32,43,45-47} Nutritional intervention in head and neck cancer patients has been proven to be beneficial to prevent unintended weight loss.⁴⁸⁻⁵⁰ Periods of tube feeding (nasogastric or gastrostomy tubes), use of oral nutritional supplements and/or food modification are necessary to ensure nutrient intake in order to maintain or improve nutritional status.⁵¹ Despite the recognized importance of nutritional care, scientific data on the benefits of dietary counseling in maintaining stable weight and decreasing malnutrition are still scarce. A critical view on the effect of dietary counseling in head and neck cancer patients is lacking, but would be of great interest in common practice, to offer the optimal nutritional support.

Food intake and malnutrition in long-term survivors

Chemoradiotherapy is the current standard of care for advanced tumors, but is associated with significant early side effects, including mucositis, radiation dermatitis, xerostomia and dysphagia^{12,17}, while dysphagia, xerostomia, osteoradionecrosis, trismus and oesophageal strictures are known late side effects.^{52,53} Independent risk factors for severe late toxicity are older age, advanced tumor stage, and larynx or hypopharynx tumors.⁵⁴ Dysphagia appears to be one of the most important late complications of chemoradiation that impacts nutritional intake.^{18,55,56} Regarding nutrition, the reported incidence of tube feeding (mostly by means of gastrostomy tubes) more than 1 year after chemoradiation varies between 6 and 31%.⁵⁷⁻⁵⁹ After therapy, tube feeding is a strong negative predictor of QoL.^{60,61} Reports on long-term weight loss/malnutrition and nutritional intake after head and neck cancer treatment are scarce but necessary to fully understand the impact of these intensive therapies.

Nutrition and dysphagia

In current practice, individual dietary counseling is standard in order to optimize or maintain nutritional status.^{62,63} Tube feeding via nasogastric and gastrostomy tubes (30–70%), energy drinks (30–50%), and modified foods (30–60%) are frequently necessary in head and neck cancer patients to ensure optimal nutritional intake during treatment and rehabilitation.^{64–66}

These alternative means of nutritional intake have an enormous impact on daily life experiences, such as decreased enjoyment in eating, increased eating time and messiness, inability to eat in public, and special food preparation, overall resulting in decreased QoL.^{67,68} Dysphagia is significantly related to malnutrition in the period after treatment.⁶⁹ and is obviously one of the most severe and determining factors, besides mucositis, pain, and xerostomia, in alternative food intake and decreased QoL for stage II–IV head and neck cancer patients treated with radiotherapy or chemoradiotherapy.^{59,66,70} An important focus of today's progress in head and neck cancer patients' treatment is improving their QoL. From a paramedical multidisciplinary point of view, there seems to be an opportunity to improve "normalcy of food intake". Clinical studies indicate that preventive swallowing strategies may be useful in decreasing dysphagia, reducing the need for tube feeding, and improving functional oral intake in treated head and neck cancer patients.^{71–74} However, no randomized controlled trials have been carried out. Novel strategies are essential to decrease the uncomfortable experiences with regard to means of food intake of head and neck cancer patients during and after treatment. The dietician might possibly contribute to innovating strategies to improve "normalcy of food intake" by warranting nutritional requirements and offering possibilities in food assortment and the speech language pathologist by individual swallowing therapy.

Aims and scope of this thesis

The overall aim of the research described in this thesis is to improve nutritional care for head and neck cancer patients.

Dieticians working with head and neck cancer patients need more knowledge on the severity of weight loss/malnutrition and tools to better identify patients at risk. Therefore a prospective observational study on weight loss, energy intake and quality of life in head and neck cancer patients was performed from diagnosis until revalidation. Subsequently, the lack of evidence on the added value of individual dietary counseling above standard nutritional care led to a new prospective cohort study on the effect of individual dietary counseling on weight loss and malnutrition.

After analysis of the acute and long term QoL issues we found that dysphagia was one of the most restrictive symptoms which limited (perception of) food intake and caused weight loss/malnutrition. In the light of this we looked for a novel paramedical intervention that could address this problem. A randomized controlled trial was undertaken in order to investigate whether a multidisciplinary approach with individually dietary counseling and individual swallowing therapy could improve restrictions in food intake.

This thesis incorporates a total of six successive studies based on progressive understanding of malnutrition and nutritional related problems in head and neck cancer patients with the aim to improve nutritional care for head and neck cancer patients.

Chapter 2 describes a prospective observational study on the onset and extent of weight loss and energy intake in patients with head and neck cancer undergoing different treatment to identify the patients at risk. This study describes weight change and energy intake in time, from baseline until six months after treatment to determine critical moments of weight loss and energy intake.

Chapter 3 evaluates the relation between malnutrition ($\geq 10\%$ unintended weight loss within 6 months) and specific QoL parameters during diagnosis, treatment, and rehabilitation in head and neck cancer patients.

Chapter 4 provides a descriptive analysis of QoL issues for the different treatment strategies, one month after treatment, to improve quality of care. A reflection of these QoL issues at this time point provides a start point to determine the content and intensity of supportive care follow-up.

Chapter 5 reports on the results of a prospective clinical cohort study on the value of dietary counseling. This study compared individual dietary counseling by a dietitian against standard nutritional care by a nurse on weight loss, body mass index and malnutrition from start of radiotherapy until two months after treatment.

Chapter 6 describes a cross-sectional study on nutritional status, food intake, and dysphagia in head and neck cancer survivors treated by chemoradiotherapy with the aim to understand the long term nutritional consequences of chemoradiotherapy.

Chapter 7 describes a randomized controlled trial of combined individual dietary counseling and individual swallowing therapy versus usual individual dietary counseling. This study was performed in stage II-IV head and neck cancer patients treated with (adjuvant) (chemo) radiation with the aim to investigate if this combined therapy can improve 'normal food intake' and decrease dysphagia, malnutrition and improve QoL.

Chapter 8 provides the summary, general discussion and future perspectives.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010 15;127(12):2893-917.
2. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18(2):541-50.
3. Bisht M, Bist SS. Human papilloma virus: A new risk factor in a subset of head and neck cancers. *J Cancer Res Ther* 2011;7(3):251-5.
4. World Cancer Research Fund AlFCR. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective; 2010. World Cancer Research Fund 2012 Available from: URL: http://www.dietandcancerreport.org/expert_report/report_contents/index.php
5. Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 2012;23(1):69-88.
6. UICC TNM Classification of Malignant Tumours 7th Edition, 2011.
7. Scully C, Bagan JV. Recent advances in oral oncology 2008; squamous cell carcinoma imaging, treatment, prognostication and treatment outcomes. *Oral Oncol* 2009;45(6):e25-e30.
8. Boyapati RP, Shah KC, Flood V, Stassen LF. Quality of life outcome measures using UW-QOL questionnaire v4 in early oral cancer/squamous cell cancer resections of the tongue and floor of mouth with reconstruction solely using local methods. *Br J Oral Maxillofac Surg* 2013;51(6):502-7.
9. Kaanders JH, Bussink J, van der Kogel AJ. ARCON: a novel biology-based approach in radiotherapy. *Lancet Oncol* 2002;3(12):728-37.
10. Bernier J, Dommange C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350(19):1945-52.
11. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354(6):567-78.
12. Blanchard P, Hill C, Guihenneuc-Jouyaux C, Baey C, Bourhis J, Pignon JP. Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. *J Clin Epidemiol* 2011;64(9):985-92.
13. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011;100(1):33-40.
14. Hypopharynxcarcinom. Nation wide evidence based guideline. www.oncoline.nl 2010
15. Larynxcarcinom. Nation wide evidence based guideline. www.oncoline.nl 2010

16. List MA, Siston A, Haraf D, Schumm P, Kies M, Stenson K, et al. Quality of life and performance in advanced head and neck cancer patients on concomitant chemoradiotherapy: a prospective examination. *J Clin Oncol* 1999;17(3):1020-8.
17. Allen AM, Elshaikh M, Worden FP, Bradford CR, Teknos TN, Chepeha DB, et al. Acceleration of hyperfractionated chemoradiation regimen for advanced head and neck cancer. *Head Neck* 2007;29(2):137-42.
18. Platteaux N, Dirix P, Dejaeger E, Nuyts S. Dysphagia in head and neck cancer patients treated with chemoradiotherapy. *Dysphagia* 2010;25(2):139-52.
19. Pauloski BR, Rademaker AW, Logemann JA, Newman L, MacCracken E, Gaziano J, et al. Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. *Head Neck* 2006;28(12):1069-76.
20. Stratton R.J., Green C.J., Elia M. Disease-Related Malnutrition: an evidence-based approach to treatment. 2003.
21. Bozzetti F. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. *Support Care Cancer* 2009;17(3):279-84.
22. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. *Nutrition* 2010;26(3):263-8.
23. Meijers JM, van Bokhorst-de van der Schueren MA, Schols JM, Soeters PB, Halfens RJ. Defining malnutrition: mission or mission impossible? *Nutrition* 2010;26(4):432-40.
24. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN J Parenter Enteral Nutr* 2010;34(2):156-9.
25. Grant M, Kravits K. Symptoms and their impact on nutrition. *Semin Oncol Nurs* 2000;16(2):113-21.
26. Vogel J, Beijer S, Doornink N., Wipkink A. Handboek Voeding bij kanker. 2012.
27. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nutr* 2008;27(6):793-9.
28. Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. *JPEN J Parenter Enteral Nutr* 2009;33(4):361-7.
29. Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumour interaction? *Clin Nutr* 2007;26(6):667-76.
30. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;14(3):199-212.
31. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care (Engl)* 1998(3):133-6.
32. van Bokhorst-de van der Schueren MA, van Leeuwen PA, Sauerwein HP, Kuik DJ, Snow GB, Quak JJ. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck* 1997;19(5):419-25.

33. Hammerlid E, Wirblad B, Sandin C, Mercke C, Edstrom S, Kaasa S, et al. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck* 1998;20(6):540-8.
34. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: an explorative study. *Support Care Cancer* 2007;15(9):1045-50.
35. De Luis DA, Izaola O, Aller R. Nutritional status in head and neck cancer patients. *Eur Rev Med Pharmacol Sci* 2007;11(4):239-43.
36. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol* 2003;15(8):443-50.
37. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality-of-life assessment in cancer clinical trials. *Recent Results Cancer Res* 1988;111:231-49.
38. Rogers SN, Ahad SA, Murphy AP. A structured review and theme analysis of papers published on 'quality of life' in head and neck cancer: 2000-2005. *Oral Oncol* 2007;43(9):843-68.
39. de Graeff A, de L, Jr., Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. A prospective study on quality of life of patients with cancer of the oral cavity or oropharynx treated with surgery with or without radiotherapy. *Oral Oncol* 1999;35(1):27-32.
40. Bjordal K, hlner-Elmqvist M, Hammerlid E, Boysen M, Evensen JF, Biorklund A, et al. A prospective study of quality of life in head and neck cancer patients. Part II: Longitudinal data. *Laryngoscope* 2001;111(8):1440-52.
41. de Graeff A, de L, Jr., Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head Neck* 2000;22(4):398-407.
42. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. *Head Neck* 2011;33(4):490-6.
43. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer - a systematic review of the epidemiological literature. *Nutr J* 2012;11(1):27.
44. Petruson KM, Silander EM, Hammerlid EB. Quality of life as predictor of weight loss in patients with head and neck cancer. *Head Neck* 2005;27(4):302-10.
45. Liu SA, Tsai WC, Wong YK, Lin JC, Poon CK, Chao SY, et al. Nutritional factors and survival of patients with oral cancer. *Head Neck* 2006;28(11):998-1007.
46. Nguyen TV, Yueh B. Weight loss predicts mortality after recurrent oral cavity and oropharyngeal carcinomas. *Cancer* 2002;95(3):553-62.
47. van Bokhorst-de van der Schuer, van Leeuwen PA, Kuik DJ, Klop WM, Sauerwein HP, Snow GB, et al. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. *Cancer* 1999;86(3):519-27.
48. Chasen MR, Bhargava R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. *Support Care Cancer* 2009;17(11):1345-51.

49. Rabinovitch R, Grant B, Berkey BA, Raben D, Ang KK, Fu KK, et al. Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: a secondary analysis of RTOG trial 90-03. *Head Neck* 2006;28(4):287-96.
50. Goncalves Dias MC, de Fatima Nunes MM, Nadalin W, Waitzberg DL. Nutritional intervention improves the caloric and proteic ingestion of head and neck cancer patients under radiotherapy. *Nutr Hosp* 2005;20(5):320-5.
51. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clin Nutr* 2006;25(2):245-59.
52. Ang KK, Harris J, Garden AS, Trotti A, Jones CU, Carrascosa L, et al. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation therapy oncology group phase II trial 99-14. *J Clin Oncol* 2005;23(13):3008-15.
53. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008;26(21):3582-9.
54. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008;26(21):3582-9.
55. Rutten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijackers AF, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. *Int J Radiat Oncol Biol Phys* 2011;81(4):923-9.
56. Pauloski BR, Rademaker AW, Logemann JA, Newman L, MacCracken E, Gaziano J, et al. Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. *Head Neck* 2006;28(12):1069-76.
57. Akst LM, Chan J, Elson P, Saxton J, Strome M, Adelstein D. Functional outcomes following chemoradiotherapy for head and neck cancer. *Otolaryngol Head Neck Surg* 2004;131(6):950-7.
58. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50(5):1161-71.
59. Shiley SG, Hargunani CA, Skoner JM, Holland JM, Wax MK. Swallowing function after chemoradiation for advanced stage oropharyngeal cancer. *Otolaryngol Head Neck Surg* 2006;134(3):455-9.
60. Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, et al. Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2004;130(4):401-8.
61. Paleri V, Patterson J. Use of gastrostomy in head and neck cancer: a systematic review to identify areas for future research. *Clin Otolaryngol* 2010;35(3):177-89.
62. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clin Nutr* 2006;25(2):245-59.

63. National Working group Dieticians Oncology (LWDO). guideline: malnutrition in patients with cancer. Oncoline 2012 Available from: URL: <http://www.oncoline.nl/index.php?language=nl>
64. Locher JL, Bonner JA, Carroll WR, Caudell JJ, Keith JN, Kilgore ML, et al. Prophylactic percutaneous endoscopic gastrostomy tube placement in treatment of head and neck cancer: a comprehensive review and call for evidence-based medicine. *JPEN J Parenter Enteral Nutr* 2011;35(3):365-74.
65. Rademaker AW, Vonesh EF, Logemann JA, Pauloski BR, Liu D, Lazarus CL, et al. Eating ability in head and neck cancer patients after treatment with chemoradiation: a 12-month follow-up study accounting for dropout. *Head Neck* 2003;25(12):1034-41.
66. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Mittal B, Gaziano J, et al. Xerostomia: 12-month changes in saliva production and its relationship to perception and performance of swallow function, oral intake, and diet after chemoradiation. *Head Neck* 2003;25(6):432-7.
67. McQuestion M, Fitch M, Howell D. The changed meaning of food: Physical, social and emotional loss for patients having received radiation treatment for head and neck cancer. *Eur J Oncol Nurs* 2011;15(2):145-51.
68. Larsson M, Hedelin B, Johansson I, Athlin E. Eating problems and weight loss for patients with head and neck cancer: a chart review from diagnosis until one year after treatment. *Cancer Nurs* 2005;28(6):425-35.
69. Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan BF, Roodenburg JL. Malnutrition in patients treated for oral or oropharyngeal cancer--prevalence and relationship with oral symptoms: an explorative study. *Support Care Cancer* 2011;19(10):1675-83.
70. Langendijk JA, Doornaert P, Verdonck-de L, I, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26(22):3770-6.
71. Mittal BB, Pauloski BR, Haraf DJ, Pelzer HJ, Argiris A, Vokes EE, et al. Swallowing dysfunction--preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. *Int J Radiat Oncol Biol Phys* 2003;57(5):1219-30.
72. Roe JW, Ashforth KM. Prophylactic swallowing exercises for patients receiving radiotherapy for head and neck cancer. *Curr Opin Otolaryngol Head Neck Surg* 2011;19(3):144-9.
73. Crary MA, Carnaby Mann GD, Groher ME, Helseth E. Functional benefits of dysphagia therapy using adjunctive sEMG biofeedback. *Dysphagia* 2004;19(3):160-4.
74. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Nguyen PD, et al. Impact of swallowing therapy on aspiration rate following treatment for locally advanced head and neck cancer. *Oral Oncol* 2007;43(4):352-7.

2

A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis treatment and revalidation

M.G.A. van den Berg

E.L. Rasmussen-Conrad

G.M. Gwasara

P.F.M. Krabbe

A.H.J. Naber

M.A.W. Merkx

Clinical Nutrition. 2006;25:765-772



Abstract

Background & aims

Patients with head and neck carcinomas often lose a significant percentage of weight, which correlates with the complications rate. Only limited information is available on the moment and extent of weight loss and energy intake in time and the relation with type of treatment. The aim of this study was to describe the moment and extent of weight loss and nutritional energy intake in patients with tumors in oral cavity, oropharynx and hypopharynx during diagnosis, treatment and revalidation.

Methods

An observational, prospective study on weight changes and nutritional intake in these patients was carried out during diagnosis, treatment and revalidation in relation to the type of treatment.

Results

Forty-seven patients successfully completed the study. A significant difference in mean bodyweight was found for patients treated by radiotherapy during treatment (-3.3 kg, $p=0.01$) and the early revalidation period (-3.4 kg, $p=0.01$) and for patients treated with surgery during diagnoses (-1.5 kg, $p=0.001$) and early revalidation period (1.6 kg, $p=0.02$). Overall patients lowered their energy intake by 122 kcal/day followed by a significant increase in energy intake during revalidation 326 kcal/day ($p=0.04$).

Conclusions

The radiotherapy and the concomitant radio-chemotherapy group lost most body weight during treatment and early revalidation. All treatment groups experienced a decrease in energy intake during treatment followed by a significant increase during revalidation.

Introduction

Squamous cell carcinoma (SCC) in the upper digestive tract is the fourth most common cancer type among men in the European community, after cancer of the lung, colorectal and prostate. Women in the European community have a lower incidence compared to men. The overall annual standardized incidence rate in the European community has been estimated at 26.0 per 100.000 in men and 3.1 per 100.000 in women.¹ Tobacco and alcohol consumption are major risk factors. In the Netherlands, the total number of head and neck SCC amounted to 2400 and 2300 in the years 2001 and 2002 respectively.²

The most common treatment modalities for head and neck cancer patients are surgery, radiotherapy, chemotherapy or a combination of these treatments. Despite new techniques in treatment, the overall survival rate of this group of patients has not improved for the last two decades.³ Weight loss has been implicated as an important prognostic indicator of malnutrition in most of the cancers in the Western world.⁴ Accordingly the progress and outcome of treatment in terms of minimizing weight loss, deterioration in nutritional status, global quality of life and physical function is due to nutritional status before, during and after treatment.⁴⁻¹⁰ Malnutrition, specified as loss of weight $\geq 5\%$ in 1 month and/or $\geq 10\%$ in 6 months, is a common problem in head and neck SCC and is present in 30-50% of these patients.^{11,12} Patients with SCC in the oral cavity, oropharynx and hypopharynx (OOH) are specifically at risk due to nutritional problems like pain, nausea, dry mouth, ageusia, hyposmia and trismus induced by tumor location and/or treatment side effects. Besides the use of tobacco and alcohol these patients have less healthy food habits, which predispose for malnutrition.¹³ Only limited information is available on the moment and extent of weight change and energy intake in relation to the type of treatment in the interval of time of diagnosis, treatment and revalidation in patients with OOH. This information is important to decide the optimal moment and sort of nutritional intervention.

Therefore, it was the aim of this study to describe the moment and extent of weight loss and nutritional energy intake in patients with tumors in oral cavity, oropharynx and hypopharynx during diagnosis, treatment and revalidation in relation to the type of treatment.

Methods and Material

Study population

An observational, prospective study on weight change and nutritional intake in patients with SCC of the OOH carcinomas was carried out during diagnoses, treatment and revalidation in the Radboud University Nijmegen Medical Centre (RUNMC).

The study was approved by the Committee on Research Involving Human Subjects of the RUNMC. All participants signed an informed consent.

Admission criteria included age ≥ 18 years, primary tumour stage II-IV (UICC TNM-tumor classification) in oral cavity, oropharynx, hypopharynx and primary curative treatment intentions.¹⁴ Patients were treated by different treatment methods depending on stage, location and general health conditions: surgery, radiotherapy, combined surgery-radiotherapy and concomitant radio-chemotherapy.

Table 1 Characteristics at baseline of the study subjects and the excluded patients.

Variabel	Total included (n=47)	Total drop-outs (n=21)
Age (years)	60.0±9.0 ^a	58±11.7 ^a
Height (m)	1.72±0.09 ^a	1.72±0.09 ^a
Weight (kg)	69.9±14.0 ^a	74.6±16.7 ^a
Tumour stage (n)		
T ₂	29	8
T ₃	12	7
T ₄	6	6
Tumor Location (n)		
Oral cavity	24	12
Oropharynx	18	7
Hypopharynx	5	2
Mode of treatment (n)		
Radiotherapy	19	6
Surgery	15	4
Chemotherapy/Radiotherapy	3	7
Surgery/Radiotherapy	10	4
Body mass index (kg/m2) (n)		
<18.5	6	3
18.5 – 25.0	26	11
>25.0	15	7
Age groups (years)		
30-60	25	14
>60	22	7
Baseline weight status (kg)		
Stable weight	34	12
Weight loss 5-10%	13	9

T₂ = tumour larger than 2 centimetres but smaller than 4 centimetres and has not spread to lymph nodes.

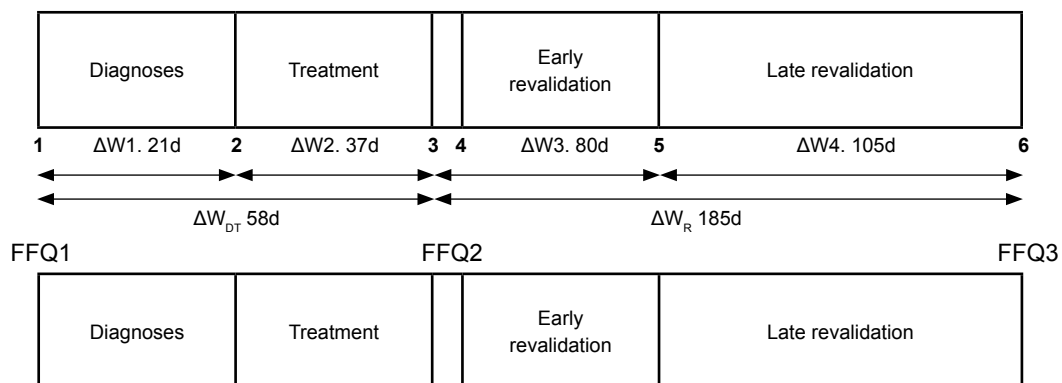
T₃ = tumour larger than 4 centimetres or any size and spread to one of the lymph nodes.

T₄ = tumour of any size but invades adjacent structures.

BMI (kg/m2): <18.5=Underweight; 18.5-25.0=Healthy weight; >25.0=Overweight (WHO).

^a = Mean±Standard deviation.

Weight



Energy intake

Figure 1. Study design: Weight (1-6) and energy intake (FFQ1-FFQ3) measurements during diagnosis, treatment and revalidation. ΔW= time period between measurements, d=mean days between screening.

Weight change and energy intake were registered during the different phases. The time schedule of each treatment was different so measurements took place during the specific phases of diagnosis, treatment and revalidation for each therapy (Fig. 1).

Usual medical and nutritional care was provided. The standard procedure for dietetic intervention was maintained. Weight loss and oral supplementation and or tube feeding in patients receiving radiotherapy were evaluated by a nurse of the radiation department.

Measurements on age, sex, length and usual weight were taken at the first visit. Height was measured with a Seca-scale in meters (two decimals). Patients were asked to recall their usual weight at their first visit in kilograms.

Nutritional assessment

Weight loss of $\geq 5\%$ in one month and/or $\geq 10\%$ in six months is a well-accepted criterion for malnutrition in head and neck cancer patients.^{4,6,8,11} Therefore, change in body weight has been assessed each visit on a calibrated scale (one decimal Seca-scale) while wearing lightweight clothing without shoes. All these measurements were taken six times on defined intervals shown as ΔW for each treatment process (Fig. 1).

Energy intake

Nutritional intake was measured three times by a trained dietician: at the first visit, the end of treatment and 6 months after treatment by a Food Frequency Questionnaire (FFQ) which assesses nutritional intake over the previous month.¹⁵ Questions on food consistency were added on account of nutritional problems of these patients. Food consumption was measured by standard household portion sizes. Food items were coded according to the NeVo 2001, The Netherlands.¹⁶ Food calculation software was used to calculate nutritional energy intake in kcal per day (Vodisys 1.3 Medical Software Infacom IT Consultants b.v.). Changes in energy intake over time are defined as ΔWDT (during diagnoses and treatment) and $\Delta W R$ (during revalidation) (Fig. 1). Energy intake was also calculated in kcal per kg actual body weight and compared with energy requirements according to theoretical data (30-40 kcal per kg body weight a day).

Statistical Analyses

The changes in body weight (kg) and energy intake (kcal/day) were expressed as mean \pm SD. The distribution of variables was evaluated by a Kolmogorov-Smirnov test. The changes in energy intake (kcal/day) and body weight (kg) were compared using the Wilcoxon signed rank test.

The relation between changes in energy intake (kcal/day) and body weight change was carried out with the Spearman rank correlation coefficient. Difference in weight loss under the types of treatment was performed with the Friedman test. Statistical tests were considered to be significant at a two-sided $p < 0.05$. Data analyses were carried out with the Statistical Package for Social Sciences (SPSS) version 12.1 (SPSS Corporation, Chicago, IL, USA).

Results

Between May 2002 and May 2004, 47 of 68 patients with SCCOOH met the criteria and successfully completed the study, with a male-female ratio of 28:19 and a mean age of 60 years (30-83). All patients received their tumour treatment at RUNMC. Twenty-one subjects finally were excluded from the study (nine dropped out, 12 died during the study). Nine patients dropped out because they were too ill to continue the study ($n=6$), two patients did not show up anymore, one patient stopped participation in the study because he had other things on his mind. Twelve patients died due to the tumor or the tumor related side effects. Characteristics of the dropped out patients are shown in table 1. At baseline characteristics of the study population and the patients who dropped out are not statistically different. ($\chi^2 r=8.3$, $p=0.51$) Based on treatment strategy patients were classified in four groups: radiotherapy ($n=19$), surgery ($n=15$), concomitant radio-chemotherapy ($n=3$) and combined surgery radiotherapy ($n=10$). At baseline, patients had a mean bodyweight of 69.9 kg (41.2 -116 kg). Among them, 26 patients (55.3 %) started treatment having a body mass index (BMI) in the range of 18.5 to 25 kg/m² (WHO), which is the recommended BMI range for a healthy person. Based on their self-reported usual weight, 13 patients (27.7%) had lost 5-10% of their body weight in a period of one to 6 months prior to their first visit at the clinic (Table 1).

Weight change

In general, patients suffered significant weight loss during treatment ($\Delta W2$: $-2.3 \text{ kg} \pm 4.0$, $p=0.001$) which continued till revalidation (ΔWR : $-2.2 \text{ kg} \pm 5.5$, $p=0.07$).

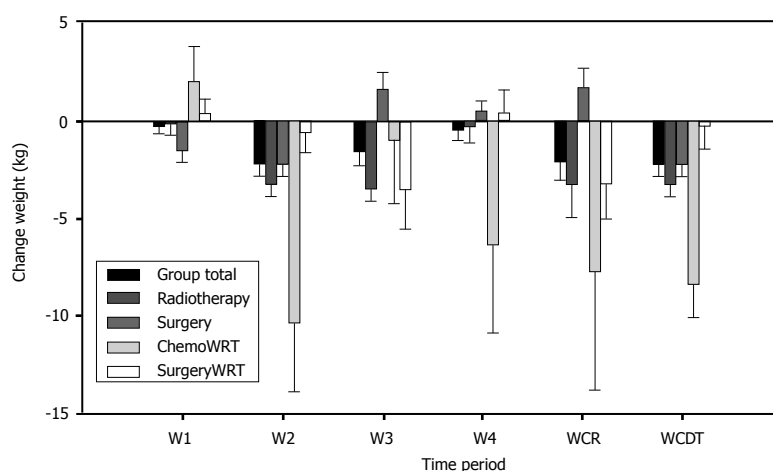
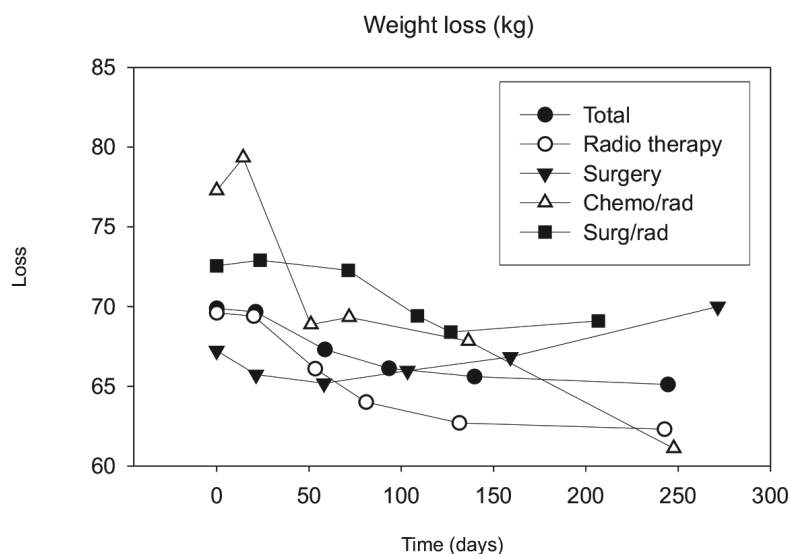
Treated by surgery alone patients lost significant body weight ($\Delta W1$: $-1.5 \text{ kg} \pm 2.0$ $p=0.01$) during diagnosis followed by weight gain after surgery throughout the early revalidation period ($\Delta W3$: $1.6 \text{ kg} \pm 3.5$, $p=0.02$) (Table 2, Figs. 2 and 3). A significant difference in mean body weight was found for the patients treated by radiotherapy during treatment and the early revalidation period ($\Delta W2$: $-3.3 \text{ kg} \pm 3.0$ and $\Delta W3$: $-3.4 \text{ kg} \pm 2.9$, $p=0.01$). Patients treated by a combination of surgery and radiotherapy showed a decline in body weight in the early revalidation period ($\Delta W3$: $-3.6 \text{ kg} \pm 6.2$)

A distinct pattern of change in body weight was found for patients treated by concomitant chemo- radiotherapy. A steep decline in body weight was found during treatment ($\Delta W2$: $-10.5 \text{ kg} \pm 6.0$) followed by a body weight that was more stable in the early revalidation period ($\Delta W3$: $-1.0 \text{ kg} \pm 5.6$). Body weight decreased again in the late revalidation period ($\Delta W4$: $-6.7 \text{ kg} \pm 7.9$). (Table 2, Figs. 2 and 3)

Comparisons of changes in body weight (kg) over time between the treatment groups revealed that during diagnosis ($\Delta W1$), the patients treated by surgery showed a significant difference compared to other treatment methods. Body weight decreased during treatment for patients in all methods of treatment ($\Delta W2$, $p=0.001$) and in the early recovery period ($\Delta W3$, $p=0.03$). A significant difference in weight loss under the different types of treatment ($\chi^2 r=10.8$, $p=0.00013$) was found.

Table 2 Mean (SD) weight during diagnosis, treatment and revalidation.

Mean weight per measurement	Total (n=47)	Radiotherapy (n=19)	Surgery (n=15)	Chemo/Rad (n=3)	Sur/Rad (n=10)
Weight 1	69.9±13.6	69.6±14.8	67.2±9.5	77.3±8.4	72.5±17.7
Weight 2	69.6±14.2	69.4±14.9	65.7±10.6	79.3±5.4	72.9±18.4
Weight 3	67.3±13.1	66.1±13.1	65.2±9.7	68.9±11.2	72.3±18.1
Weight 4	66.1±11.5	64.0±11.9	66.0±10.4	69.3±4.6	69.4±14.0
Weight 5	65.6±11.7	62.7±12.3	66.8±11.2	67.8±8.3	68.4±12.7
Weight 6	65.1±12.1	62.3±11.8	70.0±10.7	61.1±7.7	69.1±15.2

**Figure 2.** Mean (SD) weight change in kg between screening moments: during diagnoses treatment and revalidation by treatment therapy.**Figure 3.** Mean (SD) weight change in kg during diagnoses treatment and revalidation by treatment therapy in time.

Changes in energy intake

Energy intake (kcal) and energy intake in kcal per kg body weight were measured (Table 3 and 4). The overall change in energy intake decreased for the whole group from baseline through treatment (ΔWDT : 122 kcal/day \pm 850), followed by a significant increase in energy intake (ΔWR : 326 kcal/day \pm 819, $p=0.04$) during revalidation. Patients treated by radiotherapy decreased their energy intake from baseline throughout treatment (ΔWDT : 267 kcal/day \pm 864). Thereafter they had a significant increase in energy intake throughout the revalidation period (ΔWR : 498 kcal/day \pm 835, $p=0.03$). The patients with concomitant radio-chemotherapy had a decreased energy intake from baseline throughout treatment (ΔWDT : 1234 kcal/day \pm 412). In the revalidation period they had an increase of energy intake amounting (ΔWR : 1141 kcal/day \pm 1852). In the other two groups more modest changes were seen. Patients treated with surgery hardly changed their energy intake all the way through. The patients treated by surgery and radiotherapy had a slight increase in energy intake from baseline up to the treatment period (ΔWDT : 308 kcal/day \pm 812) followed by a small fall in energy intake in the revalidation period (ΔWR : 31 kcal/day \pm 576). (Fig. 4)

Changes in energy intake (kcal) per kg body weight were measured between the different screening moments for each type of treatment (Table 4). For all types of treatment energy intake in kcal per kg body weight was between the 30-40 kcal per kg body weight. Except for the concomitant radio-chemotherapy group during the treatment period the energy intake was 19 kcal/kg body weights.

The relationship between mean change in energy intake and mean weight

The correlation between changes in energy intake and bodyweight were analysed using Spearman's correlation. For all patients, a positive significant correlation between changes in energy intake (kcal/day) and bodyweight (kg) from baseline through treatment ΔWDT ($r_s=0.39$, $p=0.01$). During the revalidation period no correlation was found anymore ΔWR ($r_s=-0.29$) between the change in energy intake and body weight. In this period, weight declined despite an increase in energy intake.

Table 3 Mean (SD) energy intake in kcal during diagnoses, treatment and revalidation for each type of treatment.

Energy intake per measurement (kcal)	Total (n=47)	Radiotherapy (n=19)	Surgery (n=15)	Chemo/Rad (n=3)	Sur/Rad (n=10)
FFQ1	2199 \pm 721	2347 \pm 773	1891 \pm 676	2525 \pm 977	2280 \pm 543
FFQ2	2077 \pm 600	2080 \pm 430	1889 \pm 689	1292 \pm 565	2587 \pm 328
FFQ3	2399 \pm 879	2578 \pm 901	2060 \pm 780	2433 \pm 2022	2556 \pm 430

Table 4 Energy in kcal/kg bodyweight (SD) for each treatment modality during diagnoses, treatment and revalidation.

Energy intake (kcal) per kg bodyweight per measurement	Total (n=47)	Radiotherapy (n=19)	Surgery (n=15)	Chemo/Rad (n=3)	Sur/Rad (n=10)
FFQ 1/Weight 1	32 \pm 11	35 \pm 12	28 \pm 10	33 \pm 13	33 \pm 10
FFQ 2/Weight 3	32 \pm 11	33 \pm 11	29 \pm 11	19 \pm 8	37 \pm 9
FFQ 3/Weight 6	38 \pm 16	43 \pm 18	31 \pm 11	37 \pm 29	39 \pm 11

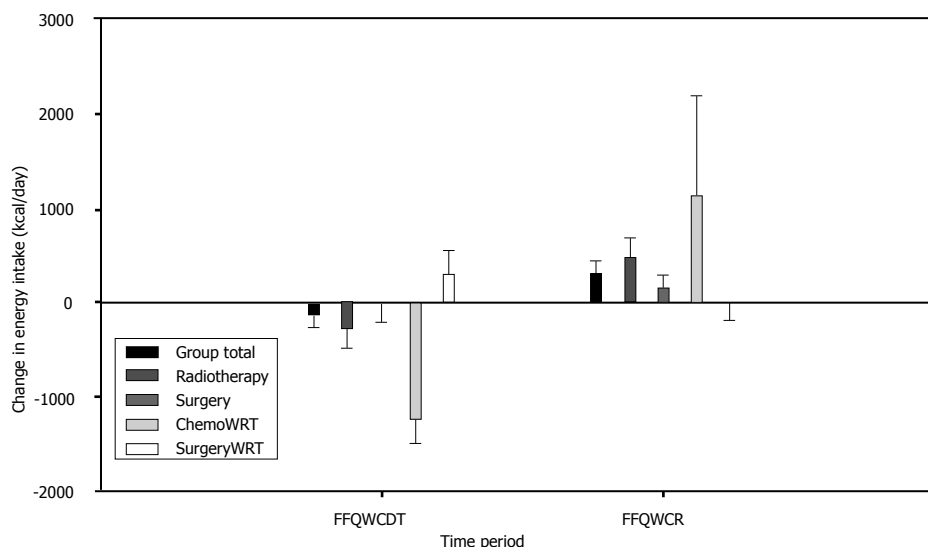


Figure 4. The mean (SD) change in energy intake during diagnoses, treatment and revalidation by type of treatment

Discussion

It is well known that patients with SCCOOH often lose a significant percentage of weight, which correlates with the prognosis of the patients in time.⁴⁻¹⁰

Only limited information is available on the moment and extent of malnutrition and energy intake in time and the relation with treatment strategy to determine where and when intensive nutritional intervention is needed. This prospective observational study analysed the change in body weight (kg)/malnutrition and energy intake (kcal/day) during diagnosis, treatment and revalidation for SCCOOH patients who undergone different treatment modalities. The pattern of change in bodyweight/malnutrition and energy intake differed among sub-groups.

Not only treatment modality may influence energy intake and weight changes. However parameters as tumor stage, tumor location, baseline weight status, baseline BMI, age and gender showed no significant difference.

A significant weight loss was found for the entire group during treatment and the early revalidation period. Specified for each type of treatment, a significant loss of body weight during diagnoses was only found in the surgery group with the exception that this group showed an increase in body weight during revalidation. A significant difference in mean bodyweight was found for patients treated by radiotherapy during treatment and early revalidation period. Lees⁸ found during radiotherapy -6,5 kg weight loss in patients with larynxcarcinoma. Beaver et al.⁹ also found significant weight loss in patients with oral cavity/oropharynxcarcinoma during radiotherapy. A distinct pattern of change in body weight was found for the patients treated by

concomitant chemo-radiotherapy. During treatment, all patients showed a decrease in body weight, this was faster, not significant, for the three patients treated with concomitant chemo-radiotherapy. In this limited group of patients, all patients started treatment with advanced tumour stage, which made them more vulnerable for weight loss.

Almost all treatment groups experienced a decrease in energy intake during treatment followed by an significant increase in the revalidation period. More pronounced negative changes in energy intake from baseline through treatment were found for the subgroups of patients treated by radiotherapy and the concomitant radio-chemotherapy followed by a significant increase for the radiotherapy patients and for the concomitant radio-chemotherapy group during revalidation.

Consistent with a review study by Tschudi et al.¹⁷ on patients who had carcinoma of oropharynx, the group of patients who were treated by surgery alone or a combination of surgery and radiotherapy did not decrease their energy intake after initiation of treatment.

The increase in energy intake in the revalidation period did not correspond with the change in body weight. Although the energy intake increased during the late revalidation period, a decline in body weight was found for patients treated with radiotherapy and concomitant radio-chemotherapy. Kenway et al.¹⁸ in their study in Nasopharynx cancer patients treated by radiotherapy found progressive weight loss and a significant increased total energy expenditure between the end of treatment and during revalidation. Bosaeus et al.¹⁹ in their study on unselected cancer patients found that progressive weight loss was significantly related to elevated resting energy expenditure and not with energy intake.

Although the group of patients in this study is limited, these findings imply a negative energy balance after treatment. Metabolic dysbalance may contribute to progressive weight loss due to altered responses on body functions. Although nutrition supply is important in this period also in relation to complications and quality of live, its supply might be of less benefit to maintain stable weight change due to metabolic dysfunction? Further research on this is necessary.

Acknowledgements

This work was funded by College of health care insurance (CVZ) Association of academic efficacy programs (VAZ)

We are grateful to Nienke van der Veer (RN), Maurice van Dongen (RN) and Marianne Arts (clinical nurse specialist) of the Oral and Maxillofacial Surgery and Otorinolaryngology Department RUNMC for helping to include patients. Thanks are also due to Jacqueline Arnts (RN) and Heleen Lintz-Luidens (nurse specialist) of the Radiotherapy Department RUNMC for helping to collect data on weight. We are also very grateful to Dr. Lisette de Groot, Department of Human Nutrition Wageningen University and Research Centre.

References

1. Berrino F, Gatta G, Eurocare Working Group. Variation in survival of patients with head and neck cancer in Europe by the site of origin of the tumors. *Eur J cancer* 1998;34: 2154-2161.
2. Incidence of cancer in the Netherlands 1989/2002. Netherlands cancer Registry.
3. Schliephake H, Jamil MU. Prospective evaluation of quality of life after oncologic surgery for oral cancer. *Int J Oral Maxillofac Surg* 2002;31:427-433.
4. American Institute for Cancer Research. World cancer research fund food, nutrition and the prevention of cancer: a global perspective. Washington: American Institute for Cancer Research; 1997.
5. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91:447-452.
6. Nguyen TV, Yueh B. Weight loss predicts mortality after recurrent oral cavity and oropharyngeal carcinomas. *Cancer (American Cancer Society)* 2002;95:553-562.
7. Revasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Cancer: disease and nutrition are key determinants of patients quality of life. *Support Care Cancer* 2004;12:246-252.
8. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care* 1999;8:133-136.
9. Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. *Otolaryngol Head Neck Surg* 2001;125:645-648.
10. Regueiro CA, Aragon G, Millan I, Valcarcel FJ, de la Torre A, Magallon R. Prognostic factors for local control, regional control and survival in oropharyngeal squamous cell carcinoma. *Eur J Cancer* 1994;30A:2060-2067.
11. Bokhorst-van der Schueren MAE, Leeuwen van PAM, Sauerwijn HP, Kuik DJ, Snow GB, Quack JJ. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck* 1997;19:419-425.
12. Hammerlid E, Wirblad B, Sandin C, Mercke C, Edström S, Kaasa S, Sullivan M, Westin T. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck* 1998;20:540-548.
13. Vaughan TL, Davis S, Kristal A, Thomas D. Obesity, alcohol and tobacco as risk factors of oesophagus and gastric cardia. *Epidemiology, Biomarkers and Prevention* 1995;4:85-92.
14. UICC TNM Classification of malignant tumours. Sobin LH, Wittekind Ch. Fifth ed. Wiley-Liss tumor classification. Geneva 1997.
15. Feunekes GIJ, van Staveren WA, de Vries JHM, Burema H, Hautvast JGAJ. Relative and bio-marker based validity of food-frequency questionnaire estimating intake of fats and cholesterol. *Am J Clin Nutr* 1993;58:489-496.
16. Dutch Food Composition Table, Den Haag, the Netherlands 2001.
17. Tschudi D, Stoeckli S, Schmid S. Quality of life after different treatment modalities for carcinoma of the Oropharynx. *Laryngoscope* 2003;113:1949-1954
18. Kenway N, Leung SF, Johnson PJ, Woo J. Nutritional consequences of radiotherapy in nasopharynx cancer patients. *Nutr Cancer* 2004;49:156-161
19. Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. *Int J Cancer* 2001;93:380-383

3

A prospective study on malnutrition and quality of life in patients with head and neck cancer

M.G.A. van den Berg

E.L. Rasmussen-Conrad

L. van Nispen

J.J. van Binsbergen

M.A.W. Merkx

Oral Oncology. 2008;44:830-837



Summary

The objective of this observational prospective study in patients with squamous cell carcinoma (SCC) of the oral, oropharyngeal and hypopharyngeal cavity was to look into the relation between malnutrition ($\geq 10\%$ unintended weight loss within 6 months) and specific quality of life (QoL) parameters longitudinally.

Bodyweight and QoL were monitored in 47 patients with SCC at diagnosis, end of treatment and six months after treatment. EORTC QoLQ-C30 and H&N 35 questionnaires were used to assess QoL.

Significant lower scores on the global QoL during treatment ($p=0.01$) and revalidation ($p=0.02$) were found for patients who had lost $\geq 10\%$ compared to patients with $<10\%$ loss of weight within 6 month. Patients with radiotherapy and a treatment modality of radiotherapy with surgery or chemotherapy kept their unintended weight loss until the end of treatment.

Patients with head and neck cancer treated with radiotherapy are specifically susceptible to malnutrition during treatment with no improvement in body weight or QoL. Professional preventive nutritional support is therefore already required on diagnoses.

Introduction

Patients with squamous cell carcinoma (SCC) of the head and neck area are particularly at risk of developing malnutrition, due to the location of the tumour and their treatment. The incidence of malnutrition is high and affects 30-50% patients with a large tumour (T₂₋₄) located in the oropharynx and hypopharynx are particularly susceptible.¹⁻⁴ Unintended weight loss of more $\geq 10\%$ in six months or $\geq 5\%$ in one month is related to risk of malnutrition.³⁻⁵

In addition to the traditional clinical outcomes in tumour response and survival, health related quality of life (QoL) has been recognized to be important in clinical research and practice.⁶⁻¹⁷ Treatment of head and neck cancer patients should therefore not only aim at the improvement of clinical outcome but also maintain or improve QoL.¹⁸⁻¹⁹

The QoL depends on physical and psychological well-being and both may influence or be affected by nutritional status.¹⁷ The relation between unintended weight loss and QoL in cancer patients in general and patients with head and neck cancer in particular has been studied prospectively. These studies suggest a relation between unintended weight loss and impaired QoL from diagnoses until and/or during treatment/revalidation.^{8,10,12, 14, 16, 19, 20}

A logical conclusion would be that unintended weight loss and a subsequent decline in QoL may be prevented with adequate nutritional support.^{17, 21, 22}

QoL is an overall expression made up of various parameters. If the QoL score or a certain profile of parameters could show a relation with or predict the onset of unintended weight loss it would be beneficial to initiate adequate nutritional intervention. It is unknown which parameters in head and neck oncology patients are affected by unintended weight loss and a subsequent decline in overall QoL especially before diagnoses until the end of treatment and six months after treatment. Clarification of this subject is important to support guidelines for nutritional support in Head and Neck oncology patients. Therefore an observational, prospective study in patients with SCC of the oral, oropharyngeal and hypopharyngeal cavity to look into the relation between unintended weight loss and QoL at diagnosis, treatment and revalidation was set up. In addition, the relationship between other variables as age, gender, tumour stage, treatment, and QoL were evaluated.

Patients and Methods

Design

This observational, prospective non-randomized study was carried out between May 2002 and May 2004. Patients with primary untreated head and neck cancer and without other malignancies in their history were asked to take part.

Medical treatment i.e. surgery and/or radiotherapy and/or chemotherapy was in accordance with the guidelines of the Dutch Cooperative Working Group for Head and Neck Oncology.²³ Nutritional support during the study was in accordance with the common clinical practice at the RUNMC, which implies no structural professional nutritional support by a dietician to prevent weight loss was given. Prior to diagnoses (baseline) none of the patients had any professional nutritional advise from a dietician.²⁴ Advise by a dietician is individual tailored while nutritional advise by a trained nurse is concentrated on the use of energy enriched drink formulas.

Data collected during the first visit to the out-patient clinic (baseline), the end of treatment (treatment) and six months after the final treatment (revalidation) were used to assess the relation between unintended weight loss and QoL. At baseline patient characteristics such as demographic data (age, gender), tumour stage and location, treatment modality, usual healthy body weight (kg), actual body weight (kg) and height (m) were registered. Actual body weight was registered again during treatment and revalidation. The QoL questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC) EORTC QoLQ-C30 and EORTC QoLQ-H&N35 have been completed three times. All data were collected when patients visited the out-patient clinic and on admittance (Fig. 1). The study was approved by the Committee on Research Involving Human Subjects of the Radboud University Nijmegen Medical Centre (RUNMC).

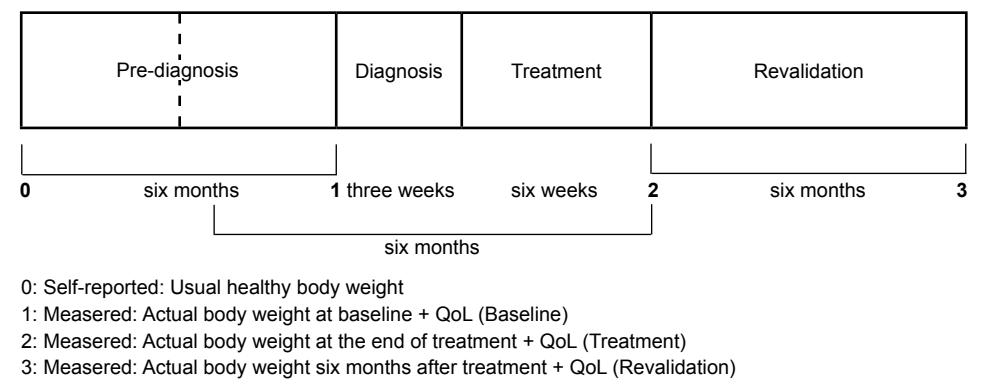


Figure 1 Study design: Weight in kg (0-3) and QoL (EORTC QoLQ-C30, QoLQ-H&N35) (1-3) measurements during pre-diagnosis, diagnosis, end of treatment and six months after treatment.

Patients

All incoming patients with SCC of the oral cavity, oropharynx, hypopharynx referred to the out patient clinic were considered eligible to enter the study. Inclusion criteria were age ≥18 years, treatment with curative intention and primary tumour stage II-IV (UICC TNM-tumour classification).²⁵ This group of patients is most at risk for malnutrition. Patients with major co-morbidity (ASA III-IV) or a history of other malignancies were excluded to prevent possible confounding. In all cases treatment was completed within three months after diagnosis. All participants gave their written informed consent. Patients were excluded if treatment was not carried out at the RUNMC or they were receiving treatment with palliative intent. This group serves as a specific model for patients with a high risk on unintended weight loss.

Unintended weight loss/Malnutrition

Unintended weight loss of 10% or more within the previous 6 months indicates malnutrition and correlates with clinical outcome.^{3,4,5} In this study the afore mentioned definition of malnutrition was used. Unintended weight loss was considered to be the outcome of the tumour or individual oncological treatment. The periods to establish unintended weight loss were defined as 6 months before diagnosis (baseline), 6 months before the end of treatment

(treatment) and 6 months after treatment (revalidation) (Fig.1). At baseline patients were asked about their usual body weight during the previous years when they were supposed to be free of disease and the possible weight change within 6 months prior to their first visit to the out-patient clinic. Weight was checked in the records of the general practitioner file.

Body weight during diagnosis, treatment and revalidation was assessed on a calibrated scale to one decimal point (Seca delta nr 707, Seca, Hamburg, Germany) without shoes, wearing lightweight clothes. Height (Seca scale) was measured at two decimal points.

Health related quality of life

Health related quality of life was assessed with the questionnaires EORTC QoLQ-C30 and EORTC QoLQ –H&N35. The general core questionnaire the EORTC QoLQ-C30 includes five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea), a global health QoL scale and six single items assessing additional items. The head and neck specific questionnaire EORTC QoLQ –H&N35 includes seven multiple item-scales such as pain, swallowing, senses, speech, social eating and eleven single items. The psychometric properties of these questionnaires in patients with cancer have been tested in several studies.^{7,26}

The QoL scores were calculated according the procedure in the EORTC QoLQ-C30 and EORTC QoLQ –H&N35 (version 3) scoring manual.²⁷ High scores on a functional scale represent a high/healthy level of functioning, while a high score on a symptom scale or item indicates a high level of problems.

Statistical analysis

Only data from patients responding to both questionnaires at baseline, throughout treatment were used to compare results over time. Data analyses were performed with the Statistical Package for Social Sciences (SPSS) version 12.0.1 (SPSS Inc., Chicago, IL, USA). For descriptive purposes two unintended weight loss groups were distinguished: unintended weight loss $\geq 10\%$ and $<10\%$ within 6 months. The Mann-Whitney U test was applied for comparisons between the two groups.

Stepwise linear regression analyses was used to select the predictors of unintended weight loss. A clinically relevant difference in QoL score was defined as a difference of 10 points or more over time or between groups.²⁸ All tests were two-tailed and a 5% significance level was used.

Results

Compliance

Sixty-eight patients who met the inclusion criteria signed the form of consent. Twenty-one patients were subsequently excluded either because they died during the study ($n=12$), were too ill to take part ($n=6$) or their data were incomplete ($n=3$). Finally 47 patients completed the study. Standard descriptive demographic information, tumour stage, location and medical treatment are presented in Table 1.

Table 1 Demographics and distribution of tumour location, tumour stage, treatment modality, body mass index and malnutrition ($\geq 10\%$ and $<10\%$ weight loss) at baseline, end of treatment and revalidation of 47 patients.

Characteristics	Total at Baseline	Weight loss within 6 month					
		Baseline		Treatment		Revalidation	
		$\geq 10\%$	$<10\%$	$\geq 10\%$	$<10\%$	$\geq 10\%$	$<10\%$
Number of patients	68	9	38	15	32	5	42
Mean age years (SD)	59 (10)	63 (9.5)	59 (9.5)	62 (9)	59 (9.5)	63 (7)	60 (10)
Gender							
Male	45	6	21	10	17	1	26
Female	23	3	17	5	15	4	16
Tumour location							
Oral cavity	36	2	21	4	20	1	23
Oropharynx	25	5	13	9	9	3	9
Hypopharynx	7	3	2	2	3	1	4
Tumour stage							
T ₂	36	3	26	5	24	2	27
T ₃	20	3	9	6	6	1	11
T ₄	12	3	3	4	2	2	4
Treatment							
Surgery	19	1	14	2	13	0	15
Radiotherapy	25	5	14	8	11	3	16
Surgery and radiotherapy	14	2	8	3	7	0	10
Chemotherapy and radiotherapy	10	1	2	2	1	2	1
Body mass index (kg/m ²)							
<18.5	9	2	4	6	3	4	5
18.5-25.0	39	2	25	6	27	0	29
>25.0	25	5	9	3	7	1	8

Values represent number of patients unless otherwise stated.

Data of the same patients ($n=47$) were analyzed during baseline, treatment and revalidation.

BMI (kg/m²): <18.5 = underweight; 18.5-25.0=normal range; >25 overweight.³³

Baseline: Weight (kg) at baseline minus weight 6 month before entering outpatient clinic

Treatment: Weight (kg) day of last treatment minus weight previous 6 month

Revalidation: Weight (kg) 6 month after last treatment.

Unintended weight loss

Correspondence was found between self reported weight at baseline and measured weight in the record of the general practitioner. Sixty eight percent of the patients were found to report their unintended weight loss within two kilograms.

Unintended weight loss of 10% or more was assessed in nine patients entering the study, while three patients remained malnourished during treatment and one patient continued to be malnourished until the end of revalidation. Thirteen out of 15 patients with radiotherapy or a treatment modality with radiotherapy were malnourished. Thirty two percent of the patients were malnourished at the end of the treatment (Table 1).

Severe unintended weight loss, 8.5% and 9%, was found in two more patients at the end of treatment, but not classified as malnourished since the cut-off point for malnutrition was set at over 10% unintended weight loss within 6 months.

During revalidation patients who had surgery gained weight within a range previous to diagnosis, while patients with radiotherapy and patients with a combined treatment kept their unintended weight loss until the end of treatment.

At baseline three patients had received professional nutritional support by a dietician. None of these patients had been assigned to the more than 10% unintended weight loss group. Five patients had professional nutritional support during treatment, while two patients had had professional nutritional support at the end of revalidation. Two patients who had received professional nutritional support had been classified in the $\geq 10\%$ unintended weight loss group at the end of treatment. At the end of revalidation one patient in the $\geq 10\%$ weight loss group had received professional nutritional support.

QoL and unintended weight loss

The longitudinal results for the EORTC QoLQ-C30 and –H&N35 scores for patients with $\geq 10\%$ of and $<10\%$ unintended weight loss within six months during baseline, treatment and revalidation are presented in Table 2.

Malnutrition in relation to QoL at baseline

Patients who had $\geq 10\%$ unintended weight loss in six months before baseline showed lower scores on the functional scales for global QoL, physical, role, and emotional functioning. On the symptom scales fatigue, pain, insomnia, appetite loss, swallowing, decreased sexuality, sticky saliva and coughing proved to be higher and therefore worse in the $\geq 10\%$ unintended weight loss group. The scores were significantly different for cognitive functioning ($p=0.05$), fatigue ($p=0.02$), dyspnoea ($p=0.01$) and loss of appetite ($p=0.02$). Eighteen scores deviated by more than 10 points and could be marked as clinically relevant (Table 2).

Malnutrition in relation to QoL at the end of treatment

During treatment the scores of patients who had lost $\geq 10\%$ weight had a tendency to decline on role and social functioning and were lower compared to the $<10\%$ unintended weight loss group. Scores on the QoL significantly differed for global QoL ($p=0.01$), fatigue ($p=0.03$), pain ($p=0.04$), senses problems ($p=0.05$), sticky saliva ($p=0.01$), coughing ($p=0.02$) and feeling ill ($p=0.01$) during treatment (Table 2).

Malnutrition in relation to QoL, six months after treatment

Six months after treatment the QoL scores of patients who had lost $\geq 10\%$ weight were lower on physical, role, emotional and cognitive functioning. Symptom scales also scored worse than in the $<10\%$ unintended weight loss group.

During revalidation the difference between the scores on global QoL ($p=0.02$), fatigue ($p=0.02$), nausea and vomiting ($p=0.02$), pain ($p=0.01$), social eating ($p=0.04$), dry mouth ($p=0.03$) and sticky saliva ($p=0.04$) proved to be significant.

The occurrence of malnutrition shows a decline in the global QoL score and is specifically prominent in patients treated with radiotherapy. Overall data show a tendency of severe weight loss and worse scores on QoL, although not significant for all items in QoL and throughout the time span from diagnosis until six month after treatment.

Table 2 EORTC QOLQ-C30 and QOLQ-H&H35 scores in 47 patients with $\geq 10\%$ and $<10\%$ weight loss within 6 month at baseline, during treatment and revalidation

Weight loss groups	Baseline			Treatment			Revalidation		
	$\geq 10\%$	$<10\%$		$\geq 10\%$	$<10\%$		$\geq 10\%$	$<10\%$	
Number of patients	9	38		15	32		5	42	
Score	Mean	<i>p</i>	Mean	Mean	<i>p</i>	Mean	Mean	<i>p</i>	mean
EORTC QOLQ-C30									
Global QOL	55		64	41	0.01 ^a	61	38	0.02 ^a	63
Physical functioning	65	^a	81	62		70	58	^a	77
Role functioning	58	^a	76	43	^a	55	58	^a	71
Emotional functioning	60	^a	72	66		73	52	^a	78
Cognitive functioning	77	0.05 ^a	87	77		82	70	^a	81
Social functioning	83		88	67	^a	80	80		80
Fatigue	44	0.02 ^a	29	63	0.03 ^a	45	69	0.02 ^a	34
Nausea and vomiting	19		13	22		16	42	0.02 ^a	5
Pain	46	^a	34	50	^a	35	54	0.01 ^a	26
Dyspnoea	24	0.01 ^a	11	24		16	17		15
Insomnia	54	^a	39	29		33	50	^a	30
Appetite loss	38	0.02 ^a	22	49	^a	38	58	^a	22
Constipation	8		10	13		20	25	^a	11
Diarrhoea	8		10	13		10	8		11
Financial difficulties	4		7	16		9	11		11
EORTC QOLQ-HN35									
Pain	47		42	56	0.04 ^a	41	60	^a	32
Swallowing	44	^a	30	60	^a	40	52	^a	30
Senses problems	6		15	53	0.05 ^a	33	37		33
Speech problems	26		20	51		43	28		25
Social eating	25		28	49	^a	17	61	0.04 ^a	23
Social contact	9		8	19	^a	41	18		11
Less sexuality	36	^a	22	44	^a	20	33		29
Teeth	24	^a	38	33	^a	46	67	^a	29
Opening mouth	29		38	53		55	67	^a	32
Dry mouth	38		36	71	^a	56	100	0.03 ^a	62
Sticky saliva	50	^a	31	89	0.01 ^a	26	75	0.04 ^a	50
Coughing	38	^a	27	47	0.02 ^a	29	42	^a	24
Felt ill	29		22	38	0.01	29	42	^a	17
Pain killers	100	^a	67	80	^a	61	67	^a	53
Nutritional supplement	63	^a	28	53		55	67	^a	26
Feeding tube	38	^a	8	67	^a	13	17		18
Weight loss	50	^a	39	87	^a	58	67	^a	21
Weight gain	13		19	13		19	0	^a	37

Values represent mean. *Note:* A high score on a functional scale represents a high/ healthy level of functioning, but a high score for a symptom scale or item indicates a high level of problems.

^a Clinically significant difference (10 point or more)

Table 3 Global QoL scores in 47 patients treated with surgery, radiotherapy, surgery with radiotherapy, chemotherapy and radiotherapy at baseline, during treatment and revalidation

Treatment modality	Surgery		Radiotherapy		Radiotherapy ^a	
Number of patients	15		19		13	
EORTC QOLQ-C30	Mean	(SD)	Mean	(SD)	Mean	(SD)
Global QOL score						
Baseline	60	(20)	61	(19)	60	(22)
Treatment	66	(20) ^b	45	(18) ^b	56	(22)
Revalidation	68	(20) ^b	54	(22) ^b	65	(12)

^a Radiotherapy = surgery and radiotherapy (n=10) and chemotherapy and radiotherapy (n=3).

^b Clinically significant difference (10 point or more).

QoL and treatment modalities

A clinically significant difference was found between the different treatment modalities. Surgery patients scored highest on QoL which indicate a better outcome where as patients treated with radiotherapy as single therapy modality score the lowest (Table 3).

Regression analysis

A stepwise linear regression analysis /ANOVA was performed to determine whether unintended weight loss could be predicted by patient characteristics (age, gender, tumour stage and treatment modality) and the QoL scores. The analysis was run with the data at baseline, end of treatment and six months later.

Tumour stage explained the variance (10%) of unintended weight loss during treatment. Tumour stage also accounts for 10% of the variance for emotional functioning, appetite loss and swallowing at baseline. The former applies for emotional functioning, social functioning and the symptom scales pain, swallowing, senses, social eating problems, teeth, opening mouth and dry mouth during treatment. Ten percent of the variance of emotional, cognitive and social functioning was explained by the tumour stage during revalidation, while treatment modality accounted for 10% of the variance for cognitive functioning and fatigue.

Discussion

In this prospective observational study the relation between malnutrition (unintended weight loss $\geq 10\%$ weight loss in 6 months) and QoL parameters in patients with SSC of the oral cavity, oropharynx and hypopharynx during diagnosis, treatment and revalidation was explored. Correlation between QoL scores and characteristics as unintended weight loss, age, gender, tumour stage and treatment modality was also evaluated.

Nineteen percent of the patients were considered to be malnourished at baseline, which corresponds with other studies.^{3,4,29} More patients (32%) were malnourished at the end of treatment. This result is in part similar to the percentage of malnourished patients found in studies of Hammerlid et al.¹² and Beaver et al.³⁰

Hammerlid et al. however defined malnutrition as 5% unintended weight loss and used anthropometrical criteria. Westin et al.³¹ found 38% of malnutrition but defines different (anthropometric) parameters for this condition than those applied in this study. In all other

nutritional studies unintended weight loss is mentioned as the most accepted criterion for malnutrition.^{3-5,9}

At diagnoses the group with more than 10% weight loss already scored significantly worse on cognitive functioning, fatigue, dyspnoea and appetite loss which implies that weight loss at diagnoses already has a major impact on important quality of life scores. Thereby, this group scored lower on global QoL during treatment and revalidation. The scores for fatigue were higher for the group with more than 10% unintended weight loss. This proved significant at baseline as well as during treatment and revalidation. Ravasco et al.²⁰ also found this in their study for the group with a declined nutritional status according to subjective global assessment (SGA).²⁰ Pain also seemed to be significantly worse in the more than 10% weight loss group during treatment and revalidation.

A relation between unintended weight loss and low QoL scores has been shown in several studies,^{9,13,16,21} but patients with less than 10% weight loss scored higher on QoL than the similar group in this study. In one study⁹ the group that lost less weight scored better between baseline and treatment on emotional and physical functioning and dyspnoea. During treatment and revalidation the better-nourished group had higher scores on global QoL, which is similar to the findings in this study. Which is also described in the study in Ravasco et al.²⁰ Contrary to a study of Hammerlid et al.¹² no correlations between QoL scores and severe unintended weight loss was found, however tumour locations were different and tumour stage I was included.

This shows that more than 10% of weight loss has a great impact on QoL scores already at diagnoses. No further deterioration of malnutrition in this stage is allowed especially when treatment has to be started. Also more than 10% weight loss seemed to be significantly worse for global quality of life, fatigue and pain. This confirms reducing weight loss from diagnoses till six months after treatment is needed.

Stepwise logistic regression analysis revealed that the tumour stage had a significant influence on QoL scores. The influence differed for each phase of treatment but was consequently significant for emotional functioning during the entire period (baseline-revalidation) Tumour stage was the most important variable in determining the value of cognitive and social functioning at the end of treatment and six months thereafter.

Treatment modality also appears to be a significant variable for cognitive functioning and fatigue. However, only a small part of the statistical variance in this model could be explained by the parameters applied. This suggests that other factors, not accounted for during and in this study, are relevant in determining the value of the global QoL score.

In prospective studies^{19,32} tumour stage was also found to have the most powerful impact on QoL scores. It seems that the development of the disease is most important for the global QoL of most patients. Tumour stage can be linked to duration of disease and the number and severity of problems that are more common with increased tumour size. The variables age and gender were found to have no significant influence in both QoL questionnaires. In the study of De Greaff et al.¹⁸ age and gender were also found to have minimal influence on the QoL scores. The variation in tumour stage explains a significant percentage in the variance of the global QoL score after treatment and revalidation, where factors such as coping, cognitive orientation and social support may also play a role in determining QoL scores.¹⁸ Since QoL is such a subjective measure, it is impossible to take all existing influencing factors into account.

No structural nutritional support by a dietician to prevent weight loss was given during this study.²⁴ As a result of this study the Head and Neck guidelines have been updated. Since the end of 2004 all Head and Neck cancer patients in the out-patient clinic and the clinical ward of the Radboud University Medical Centre have nutritional support by a dietician.

Malnutrition was defined as unintentional weight loss of 10% or more within the previous 6 months. To determine the percentage of unintended weight loss at diagnosis and after finishing treatment, the self-reported normal healthy body weight of the patients was used. The usual healthy body weight was defined as the stable body weight of the patients before the onset of the disease. The assumption was made and queried that this body weight had been stable for at least 6 months before diagnosis. To confirm this assumption weight has been checked in the records of the general practitioner.

A body mass index (BMI) ≤ 18.5 is a classification for underweight.³² If this classification had been taken into account in this study more patients would have been indicated as malnourished. Treatment modality largely depends on tumour stage and location. It appears that patients with radiotherapy as a single therapy or in combination with surgery or chemotherapy continuously scores worst. These patients are at risk of malnutrition during the entire treatment with no improvement in body weight or QoL after final revalidation. Data show a tendency of severe weight loss and worse scores on QoL. Although a significant correlation between weight loss and all items from diagnosis until six month after treatment could not be established in this study. It is possible to prevent severe weight loss¹⁷ or keep weight loss at a minimum with professional nutritional support and therefore positively influences the process of revalidation. A better score on QoL gives a better outlook on coping with possible side effects of treatment. Former implies that professional preventive nutritional support specifically for patients with radiotherapy is already required on diagnosis to prevent further unintended weight loss and should be maintained throughout the entire procedure at least until six months after treatment.

Conflict of interest statement

This study was supported by a grant from the College of Health Care Insurance (CVZ). Association of Academic Efficacy Programs (VAZ). Herewith all authors declare no financial or personal interest is involved that may bias or influence this study.

Acknowledgements

This study was supported by a grant from the College of Health Care Insurance (CVZ) Association of Academic Efficacy Programs (VAZ). We thank Nienke van der Veer, RN and Maurice van Dongen, RN and Marianne Arts, clinical nurse specialist of the Oral and Maxillofacial Surgery and Otorhinolaryngology Department RUNMC for their assistance in entering patients into the study. Thanks are also due to Jacqueline Arnts, RN and Heleen Lintz-Luidens nurse specialist of the Radiotherapy Department RUNMC for their excellent help in collecting data. We express our gratitude to Jeanne de Vries for the useful discussions on this subject and Caroline van Wayenburg for her suggestions on the text of this paper.

References

1. Brookes GB. Nutritional status-a prognostic indicator in head and neck cancer. *Otolaryngol Head Neck Surg* 1985;93:69-74.
2. Berg, MG van den, Rasmussen-Conrad EL, Gwasara GM, Krabbe PF, Naber AH, Merx MA. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. *Clin Nutr* 2006;25:765-72.
3. Van Bokhorst-de van der Schueren MAE, van Leeuwen PAM, Sauerwein HP, Kuik DJ, Snow GB, Quak JJ. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck* 1997;19:419-425.
4. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol* 2003;15:443-450.
5. Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. *Crit Rev Oncol Hematol* 2000;34:137-168.
6. Aaronson NK, Ahmed-zai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QoLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-376.
7. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the EORTC H&N35. *J Clin Oncol* 1999;17:1008-1019.
8. Bjordal K, Ahlner-Elmqvist M, Hammerlid E et al. A prospective study of quality of life in head and neck cancer patients. Part II: Longitudinal data. *Laryngoscope* 2001;111:1440-52.
9. Van Bokhorst-de van der Schueren MAE, Langendoen SI, Vondeling H, Kuik DJ, Quak JJ, van Leeuwen PAM. Perioperative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial. *Clin Nutr* 2000;19:437-444.
10. De Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. A prospective study on quality of life of patients with cancer of the oral cavity or oropharynx treated with surgery with or without radiotherapy. *Oral Oncol* 1999;35:27-32.
11. De Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Socio-demographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur J Cancer* 2001;37:332-339.
12. Hammerlid E, Wirblad B, Sandin C et al. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck* 1998;20:540-548.
13. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. *Br J Cancer* 2001;84:149-156.
14. Hammerlid E, Silander E, Horneham L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer; a longitudinal study. *Head Neck* 2001;23:113-125.
15. Ohrn KEO, Sjoden PO, Wahlin YB, Elf M. Oral health and quality of life among patients with head and neck cancer or haematological malignancies. *Support Care Cancer* 2001;9:528-538.
16. Petruson KM, Silander EM, Hammerlid EB. Quality of life as predictor of weight loss in patients with head and neck cancer. *Head Neck* 2005;27:302-310.

17. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol* 2005;23(7):1431-1438.
18. De Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head Neck* 2000a; 22:398-340.
19. De Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Long-term quality of life of patients with head and neck cancer. *Laryngoscope* 2000;110:98-106.
20. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomised controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck*. 2005;27:659-668.
21. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91:447-452.
22. Ravasco P, Monteiro-Grillo I, Camilo ME. Does nutrition influence quality of life in cancer patients undergoing radiotherapy? *Radiother Oncol* 2003a;67(2):213-220.
23. Guideline for the treatment of Mouth and Oropharynx Carcinome;(Richtlijn Mondholte-en Orofarynccarcinoom), Nederlandse Werkgroep voor Hoofd-Halstumoren, Alphen a/d Rijn, Van Zuiden Communications B.V. 2004.
24. Ouwers M, Marres H, Hermens R, et al. Quality of integrated care for patients with head and neck cancer: development and measurement of clinical indicators. *Head and Neck*. 2007;29: 378-386.
25. McKee PH, CN Chinyama, WF Whimster, WV Bogomoletz, GS delides, CJM de Wolf. *Comprehensive Tumour Terminology Handbook*. New York, John Wiley & sons, 2001, 384 p.
26. Bjordal K, De Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QoLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QoLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000; 36:1796-807.
27. Fayers PM, Aaronson NK, Bjordal K, Sullivan M. EORTC QoLQ-C30 scoring manual. Brussels: EORTC, 1995.
28. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in helaht related quality-of-life scores. *J Clin Oncol* 1998;16:139-144.
29. Nguyen TV, Yueh B. Weight loss predicts mortality after recurrent oral cavity and oropharyngel carcinomas. *Cancer* 2002;95:553-562.
30. Beaver MES, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. *Otolaryngol Head Neck Surg* 2001;125:645-648.
31. Westin T, Jansson A, Zenckert C. Mental depression is associated with malnutrition in patients with head and neck cancer. *Arch ortolayngol Head Neck Surgery* 1988;114: 1449-1453.
32. Hammerlid E, Bjordal K, Ahlner-Elmqvist M et al. A prospective study of quality of life in head and neck cancer patients. Part I: at diagnosis. *Laryngoscope* 2001;111:669-680.
33. World Health Organization. http://www.who.int/bmi/index.jsp?introPage=intro_3.html, January 2002.

4

Supportive care in early rehabilitation for advanced-stage radiated head and neck cancer patients

J. de Leeuw

M.G.A. van den Berg

T. van Achterberg

M.A.W. Merkx

Otolaryngology – Head and Neck Surgery. 2013;148:625-632



Abstract

Objective

To investigate the health-related quality of life (HRQoL) and supportive follow-up care needs one month post-treatment for patients with advanced-stage (stage III or IV) radiated head and neck cancer (HNC) who were treated with curative intent.

Study design

An exploratory, descriptive analysis of HRQoL data obtained from three treatment groups: conventional radiotherapy (RT, $n=21$), surgery+radiotherapy (SRT, $n=10$), and chemoradiation (CRT, $n=21$).

Setting, subjects and methods

The head and neck oncology centre of an university hospital. Fifty-two patients completed the EORTC QLQ-C30 and EORTC QLQ-H&N35 self-report questionnaires one month post-treatment. Descriptive statistics and clinically relevant differences between the groups were analysed.

Results

HRQoL outcomes between groups differed. Clinically relevant difference was observed in the RT and CRT group with respect to dry mouth, coughing, feeling ill, use of pain killers, and the use of nutritional supplements. The RT group differed from the other groups with respect to pain and swallowing. The CRT group differed from the other groups regarding role functioning.

Conclusions

HRQoL differs between RT, SRT, and CRT patients one month post-treatment. The RT- and CRT-treated patients reported higher impairment than the patients who were treated with SRT. Nutritional intake and oral function emphasize the importance of providing supportive care to radiated advanced-stage HNC patients throughout the treatment trajectory and the need for continuation during the first few post-treatment months.

Introduction

Every current treatment for head and neck cancer (HNC) places a burden on the patient, and nearly all patients experience a progressive deterioration in health-related quality of life (HRQoL) towards the end of treatment.^{1,2} For most patients, these health-related complications largely disappear during the first post-treatment years.^{3,4} However, if complications remain after one year, little—if any—significant improvement can be expected through the 3-year follow-up period, particularly among patients who received conventional radiotherapy as part of their treatment.^{1,5}

The choice of treatment for HNC is determined by both the tumour size (stage) and location of the tumour, and these factors must be considered when interpreting HRQoL outcome.⁶ Although multimodal treatment can lead to an increased prevalence of HRQoL consequences compared to single-modality treatments, the literature contains contradictory reports, particularly with respect to long-term differences (i.e., 12 months and longer).^{4,7-11} HNC patients who are treated surgically can experience complications such as wound infection, microvascular flap complications, shoulder disability, swallowing and/or chewing difficulties, and aesthetic changes.^{4,12} Radiotherapy can lead to complications such as mucositis, dysphagia and xerostomia, trismus and fibrosis.^{5,13-15} In addition to the aforementioned radiotherapy-related complications, chemoradiation-specific complications can include infection, hematopoietic suppression, renal failure, pneumonia, the need for tube feeding, and fatigue.^{8,9,16,17}

To provide on high-quality care and enhance treatment outcomes, it is important to assess HRQoL routinely throughout the treatment trajectory, address problems and complications in an early stage and discuss the short- and long-term treatment-related health consequences with the patient.^{3,18} Although many studies have investigated HRQoL in HNC patients, relatively few studies provide data regarding the immediate post-treatment period; indeed, the 3- and 6-month periods are the most commonly reported short-term measurements. Therefore, we determined HRQoL at one month post-treatment to add to the short-term data and to gain insight into the problems experienced by radiated HNC patients which received different treatment. We also use these results to provide a direction for the type and intensity of supportive follow-up care within the first weeks to months in the post-treatment period.

Methods

A descriptive exploratory analysis was performed on a subset of data from HNC patients ($n=160$) who participated in a prospective non-randomized trial between November 2007 and February 2009 (ClinicalTrials.gov NCT01167179).¹⁹ This trial assessed the effects of nurse-led follow-up consultations on psychosocial adjustment to illness and on health related quality of life. A usual care group ($n=80$), that functioned as a historical control group, was compared with an intervention group ($n=80$) for which nursing consultations were added to the medically oriented follow-up schedule. All patients ($n=160$) had completed the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires at the baseline measurement set at 1 month post-treatment. Until that moment all patients had received usual care during treatment. As from one month, the intervention group started with the additional nursing follow-up consultations.

Remaining longitudinal measurements were at 6 and 12 months, respectively. Participating patients had all been treated at the Head and Neck Centre of the Radboud University Centre for Oncology in Nijmegen, the Netherlands. All patients provided a written informed consent, and the study was approved by the Medical Ethical Committee of the district Arnhem-Nijmegen, and was conducted in accordance with the Declaration of Helsinki (CMO-nr. 2007/113).^{20,21}

Sample

The patient demographic and disease characteristics are presented in Table 1. The sample consisted of 52 HNC patients with locoregionally advanced (stage III or IV) cancer who had been treated with curative intent using conventional radiotherapy (RT group, $n=21$), surgery followed by radiotherapy (SRT group, $n=10$), or chemoradiation (CRT group, $n=21$). The treatment that each HNC patient received was in accordance with to the guidelines of the national Head and Neck Society.²²

Table 1 Demographics and Disease Characteristics ($n=52$ patients)

	Total	Surgery + Radiotherapy	Radiotherapy	Chemo radiation	<i>p</i> Value ^a
Number	52	10	21	21	
Gender					0.27
Male	39	6	15	18	
Female	13	4	6	3	
Age, y					0.40
Mean (Median)	56 (57)	58 (60)	58 (57)	53 (53)	
Range	26 - 82	26 - 82	44 - 75	30 - 75	
Cancer site					0.06
Oral cavity	9	7	0	2	
Oropharynx	15	0	9	6	
Hypopharynx	6	0	2	4	
Nasopharynx	4	0	0	4	
Larynx	15	2	10	3	
Other	3	1	0	2	
Stage ^b					0.48
III	13	1	6	6	
IV	39	9	15	15	

^a Kruskal-Wallis test

^b Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours. 7th ed. Geneva, Switzerland:UICC; 2011.

Data collection

HRQoL was measured using the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire with the Head & Neck Module (EORTC QLQ-C30 and QLQ-H&N35).^{23,24} The EORTC QLQ-C30 and the EORTC QLQ-H&N35 are cancer-specific, patient-based self-report questionnaires, and the psychometric properties of both questionnaires have been tested by several studies.^{25,26} The core questionnaire is composed of five functional scales, a global health status/QoL scale, and nine symptom scales. The additional head and neck module (EORTC QLQ-H&N35) contains 18 disease-specific

symptom scales. A high score on the functional scales and the global health status/QoL scale represents a high functional level, whereas a high score on the symptom scale represents a high level of symptoms.²⁴

Analysis

The mean scores and standard deviations of the EORTC QLQ scales were calculated in accordance with the recommended procedures in the scoring manual using SPSS 18.0.²⁴ Due to the small sample size and non-normal distribution of the data, the differences between treatment groups with respect to demographic and disease variables were tested using the non-parametric Kruskal-Wallis test. Clinically relevant differences between the groups were also calculated, as this adds to the meaningful clinical interpretation of otherwise aggregated mean EORTC scores. A difference of >10 points in mean EORTC scores was viewed as being clinically relevant.²⁷⁻²⁹ An EORTC mean score of 50 was used as a threshold to detect HRQoL items that indicated worse or better functioning within the groups. A mean score of ≤50 on the function scales and global health status/QoL or and a score of ≥50 on the symptom scales was regarded as a sign of impaired function on a given scale. Because this study was exploratory in design and contained a relatively small sample size, multiple statistical testing was not considered appropriate and was therefore not performed.

Results

Our analyses revealed that the treatment groups did not differ significantly with respect to age, gender, or stage grouping (Table 1). The average of the patients (39 men and 13 women) was 56 years (range, 26-82 years). Seventy-five per cent of the patients had a stage IV tumour, and the oropharynx and larynx were the two most common tumour locations. Intensity-modulated radiation therapy (IMRT) was used in the treatment of 34 (65%) patients. Although they were not statistically significant ($p>0.05$), the differences in tumour site between the treatment groups can be explained by the fact that the treatment variables were determined using established guidelines.²²

Functional scales and global health status/QoL

None of the groups had a mean score of ≤50 on either the EORTC QLQ-C30 functional scales or the global health status/QoL scale. With respect to the functional scales, role functioning was impaired in all groups, with the CRT group having clinically relevant lower scores (i.e. worse functioning) relative to the SRT and RT groups, respectively. Details are presented in Table 2.

Symptom scales

With respect to the EORTC QLQ-C30 and H&N35 symptom scales, the SRT group had mean scores of 50 points or higher for sticky saliva and weight loss, and the RT and CRT groups had mean scores of 50 or higher for dry mouth, sticky saliva, the use of pain killers, the use of nutritional supplements, and weight loss. Analyses of the clinically relevant differences between the groups revealed that compared to the other groups, the SRT group had higher

Table 2 EORTC QLQ-C30 and EORTC QLQ-H&N35 scores and clinically relevant differences between the treatment groups at 1 month posttreatment

	Surgery+ Radiotherapy (n=10), Mean (SD)	Radiotherapy (n=21), Mean (SD)	Chemo radiation (n=21), Mean (SD)	SRT vs. RT, Δ^a	RT vs. CRT, Δ^a	CRT vs. SRT, Δ^a
EORTC QLQ-C30						
<i>Functional scales^b</i>						
Global health status/ QoL	71 (15)	72 (17)	66 (25)			
Physical functioning	80 (14)	83 (18)	74 (29)			
Role functioning	69 (22)	75 (28)	57 (36)		+18	-12
Emotional functioning	81 (25)	81 (20)	83 (21)			
Cognitive functioning	83 (15)	85 (19)	83 (17)			
Social functioning	83 (28)	84 (21)	79 (23)			
<i>Symptom scales^c</i>						
Fatigue	33 (30)	32 (26)	44 (30)		-12	+11
Nausea/vomiting	8 (9)	28 (36)	19 (31)	-20		+11
Pain	19 (20)	34 (34)	19 (18)	-15	+15	
Dyspnoea	17 (18)	6 (18)	15 (24)	+11		
Insomnia	17 (28)	27 (25)	20 (21)			
Appetite loss	22 (27)	29 (40)	44 (30)		-15	+22
Constipation	17 (28)	27 (25)	20 (31)			
Diarrhoea	6 (14)	8 (15)	6 (13)			
Financial difficulties	11 (17)	13 (27)	10 (20)			
EORTC H&N35 ^c						
Pain	21 (24)	38 (25)	31 (17)	-17		
Swallowing	25 (25)	45 (33)	28 (26)	-20	+17	
Senses	33 (24)	41 (32)	36 (20)			
Speech	19 (27)	28 (24)	24 (24)			
Social eating	33 (36)	34 (26)	32 (27)			
Social contact	3 (6)	8 (14)	7 (11)			
Sexuality	31 (27)	29 (32)	44 (37)		-15	+13
Teeth	28 (33)	17 (32)	12 (20)	+11		-16
Opening mouth	44 (50)	27 (33)	37 (38)	+17		
Dry mouth	39 (25)	63 (36)	63 (30)	-24		+24
Sticky saliva	50 (28)	54 (38)	67 (33)		-13	+17
Coughing	11 (17)	38 (36)	39 (31)	-27		+28
Feeling ill	11 (17)	27 (33)	22 (28)	-16		+11
Pain killers	33 (52)	69 (48)	56 (51)	-36	+13	+23
Nutritional supplements	33 (52)	50 (52)	83 (38)	-17	-33	+50
Feeding tube	0 (0)	0 (0)	33 (49)		-33	+33
Weight loss	50 (55)	56 (51)	50 (51)			
Weight gain	33 (52)	25 (45)	17 (38)			-16

Abbreviations: CRT, chemoradiation; QoL, quality of life; RT, radiotherapy; SRT, surgery + radiotherapy

^a Δ = clinically relevant difference of >10 points, indicated by bold figures.^bHigher score, better functioning (range 0-100). ^cHigher score, more symptoms (range 0-100).

(i.e., worse) scores for problems with teeth, but lower (i.e., better) scores for nausea/vomiting, dry mouth, coughing, feeling ill, the use of pain killers, and the use of nutritional supplements. The RT group had higher (i.e., worse) scores for pain and swallowing, but no lower (i.e., better) scores on any scale compared to the other groups. The CRT group had higher (i.e., worse) scores for fatigue, nausea/vomiting, appetite loss, problems with sexuality, sticky saliva, the use of pain killers, the use of nutritional supplements, and the use of a feeding tube.

Discussion

The goals of this study were to gain insight into the HRQoL of irradiated advanced-stage HNC patients one month post-treatment and to determine which items should be given particular consideration in future supportive care during early rehabilitation. In the published literature, few studies have provided data regarding the early post-treatment period; therefore, it is difficult to compare our findings directly with the findings of others. Overall, the SRT group seemed to experience less of a decrease in HRQoL than the RT and CRT groups.

Function scales and global health status/QoL

With the exception of role functioning, the groups exhibited no clinically relevant differences with respect to their functional scales and global health status/QoL. Role functioning was most impaired in the CRT group relative to the other two groups. Several other studies that compared different treatment protocols have reported this same finding.^{17,30,31} With respect to our CRT group, this finding could be a function of the severity of symptoms related to various aspects of nutritional intake and/or appetite loss and to the fact that one-third of the patients remained dependent on tube feeding one month post-treatment (and all but 4 of the patients used nutritional supplements). Dependency on tube feeding is known to have a negative effect on social activities and role functioning.³²

Symptom scales

The clinically relevant differences between the treatment groups regarding the symptom scales pointed predominantly toward the scales that are related to nutritional intake (i.e., appetite loss, nausea/vomiting, swallowing, tube feeding, the use of nutritional supplements, and weight loss) and oral function (i.e., dry mouth, opening mouth, sticky saliva, and problems with teeth). In addition, the groups exhibited clinically relevant differences with respect to pain, coughing, and fatigue.

Problems related to nutritional intake

Several studies have reported that problems with respect to nutritional intake, swallowing, senses and impaired oral function can persist for well over a year post-treatment.^{1,21,33-35} Therefore, the importance of assessing and monitoring these items early seems obvious.³⁶ Early supportive care—including intensive nutritional counseling by a dietician regarding maintaining body weight—led to improved nutritional status, better treatment tolerance, fewer hospital admissions, and, consequently improved treatment outcome.³⁷⁻⁴² Most nutritional guidance programs end within eight weeks of treatment; however, some studies have argued

that patients with advanced-stage tumours—particularly patients who are treated using RT and CRT—require a longer period of dietary counseling.^{38,43} This is particularly important for patients who remain dependent on tube feeding (one-third of the CRT group in our study). Indeed, prolonged tube insertion can be associated with, impaired swallowing and speech and, a decrease in overall quality of life.⁴⁴⁻⁴⁶

In our study, we found clinically relevant negative scores for swallowing in the RT group, with a difference of nearly 20 points compared with the other groups. This result has been well-described in irradiated patients with pharyngeal cancer, and this was the predominant tumour site in our RT group.⁴⁷ On the other hand, pharyngeal cancer was also predominant in the CRT group, although the scores in this group for swallowing were similar to the scores in the SRT group, which contained no pharyngeal cancer patients. We have no further explanation for this finding. However, dysphagia and the associated increased risks of aspiration and pneumonia are well-known problems in this patient group.⁸ Therefore, an assessment of dysphagia prior to treatment and subsequent rehabilitation in patients with advanced and/or pharyngeal cancer may be an important predictor of chronic dysfunction.⁴⁸

The health consequences of problematic nutritional intake in HNC patients have also been studied qualitatively, and reports indicate that nutritional symptoms and concerns and fatigue can have the greatest impact on the patient's attempt to achieve a normal life after treatment has ended.⁴⁹ Another study suggested that healthcare professionals who address nutritional problems in HNC patients should also talk with patients regarding their experience of the (changed) meaning of food following treatment in order to help support the patient's need to cope with changes or losses in this area.⁵⁰

Problems related to oral function

The SRT group had clinically different scores with respect to problems with their teeth and opening their mouths. In this group, in which oral cancer was the predominant tumour site, problems with the teeth are an expected outcome, as surgical treatment routinely includes the extraction of teeth and extensive dental rehabilitation, including implants.⁵¹ The scores are consistent with the postoperative discharge scores reported by Lee et al. for HNC patients who were treated with surgery alone.⁵² The inability to bite or chew properly is a potential risk factor for the (gradual) deterioration of nutritional status and oral function and can also impact both short- and long-term HRQoL.⁵³ The SRT group seemed to carry a high risk, particularly in combination with a clinically higher (i.e., worse) score for opening the mouth. Hence, nutritional intake and oral function are clear points of attention for this group, and this is also confirmed by their high mean scores for sticky saliva and weight loss.

With respect to oral function, the RT and CRT groups had clinically relevant higher (i.e., worse) scores for dry mouth and sticky saliva compared with the SRT group. The mean scores for these items in both the RT and CRT groups were 10-20 points higher (i.e., worse) than in studies that reported three-month data for these same treatment groups.^{5,17} Although these symptoms tend to improve over time, their impact on the patient cannot be neglected, as they are predictors of long-term weight loss.⁵⁴

Pain and fatigue

Pain scores were highest (i.e., worse) in the RT group compared to the other two groups. We currently have no specific explanation for this finding in this treatment group, as pain is a known symptom during treatment and during the first post-treatment months in all irradiated HNC patients.⁵⁵ Pain can range from neuropathic pain to mucositis-related pain and other treatment-related pain. However, pain has been reported to be an undermanaged item in HNC patients, thus having a negative impact on all other HRQoL items; therefore, pain deserves to receive adequate professional attention.⁵⁶ Fatigue was present in all treatment groups, but scores were highest (i.e., worse) in the CRT group. Fatigue is most severe during radiation treatment and then improves gradually after treatment has ended.⁵⁷ However, because fatigue is often viewed as a general treatment-related side effect, it is perhaps not always addressed effectively. Moreover, increased levels of fatigue are tightly correlated with decreased QoL.⁵⁸ In summary, these results support our clinical experience that prolonged intensive supportive care is warranted for irradiated advanced-stage HNC patients during the early stage of rehabilitation. In our setting, the medical routine follow-up schedule consists of twice-monthly control visits to a physician in the first year of follow-up. To provide adequate supportive care for all irradiated HNC patients during the first few post-treatment months, we recommend that patients have frequent contact with the supportive care providers within the multidisciplinary head and neck team. This care could well be organized and coordinated within the context of nurse-led clinics, encompassing specific counseling of dietitians, dental health care professionals, and other supportive care providers.^{19,43,59} These contacts could be planned and guided in accordance with the severity of existing symptoms and problems, together with high-intensity contact immediately following treatment. It would be worthwhile to investigate whether such an intensified approach guided by symptom assessment can influence the general treatment outcome of HNC cancer patients.

When interpreting the results of this study, it is important to acknowledge the study's limitations. The treatment groups in this study were extracted from the cohort of a non-randomized prospective trial that was conducted in one hospital only. Consequently, we were unable to control how the groups were composed. Therefore, our relatively small sample size warrants caution in the generalization of our findings. However, despite this limitation, these results provide insight into short-term supportive care issues and differences with respect to various modalities for treating irradiated patients with advanced-stage HNC and will be helpful in improving supportive care further.

Conclusions

Our results indicate that several HRQoL items necessitate intensive supportive care at one month post-treatment for irradiated advanced-stage HNC patients, and this necessity is primarily a reflection of aspects regarding nutritional intake and oral function. The CRT and RT groups appear to have the highest need for intensive supportive care in the early post-treatment months. We argue that supportive care of these advanced-stage patient groups should be included in all phases of treatment and—depending on the severity of the symptoms—should be extended into the rehabilitation phase. A multidisciplinary head and neck team comprised of dietitians, nurses, dental health professionals and physicians is essential for incorporating this care into the treatment trajectory.

References

1. Hammerlid E, Silander E, Horneham L, et al. Health-related quality of life three years after diagnosis of head and neck cancer--a longitudinal study. *Head and Neck* 2001;23:113-125.
2. Abendstein H, Nordgren M, Boysen M, et al. Quality of life and head and neck cancer: a 5 year prospective study. *Laryngoscope* 2005;115:2183-2192.
3. Shepherd KL, Fisher SE. Prospective evaluation of quality of life in patients with oral and oropharyngeal cancer: from diagnosis to three months post-treatment. *Oral Oncol* 2004;40:751-757.
4. El-Deiry M, Funk GF, Nalwa S, et al. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2005;131:879-885.
5. Fang FM, Chien CY, Tsai WL, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy-a longitudinal study. *Int J Radiat Oncol Biol Phys* 2008;72:356-364.
6. Wan Leung S, Lee TF, Chien CY, et al. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. *BMC Cancer* 2011;11:128.
7. Alicikus ZA, Akman F, Ataman OU, et al. Importance of patient, tumour and treatment related factors on quality of life in head and neck cancer patients after definitive treatment. *Eur Arch Otorhinolaryngol* 2009;266:1461-1468.
8. Bower WF, Vlantis AC, Chung TM, et al. Mode of treatment affects quality of life in head and neck cancer survivors: Implications for holistic care. *Acta Otolaryngol* 2010;130:1185-1192.
9. Francis DO, Weymuller EA, Jr., Parvathaneni U, et al. Dysphagia, stricture, and pneumonia in head and neck cancer patients: does treatment modality matter? *Ann Otol Rhinol Laryngol* 2010;119:391-397.
10. Mowry SE, Ho A, Lotempio MM, et al. Quality of life in advanced oropharyngeal carcinoma after chemoradiation versus surgery and radiation. *Laryngoscope* 2006;116:1589-1593.
11. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Arch Otolaryngol Head Neck Surg* 2004;130:875-879.
12. LoTempio MM, Wang KH, Sadeghi A, et al. Comparison of quality of life outcomes in laryngeal cancer patients following chemoradiation vs. total laryngectomy. *Otolaryngol Head Neck Surg* 2005;132:948-953.
13. Netscher DT, Meade RA, Goodman CM, et al. Quality of life and disease-specific functional status following microvascular reconstruction for advanced (T3 and T4) oropharyngeal cancers. *Plast Reconstr Surg* 2000;105:1628-1634.
14. Al-Mamgani A, Mehilal R, van Rooij PH, et al. Toxicity, quality of life, and functional outcomes of 176 hypopharyngeal cancer patients treated by (Chemo)radiation: The impact of treatment modality and radiation technique. *Laryngoscope* 2012;122:1789-1795.

15. Rutten H, Pop LA, Janssens GO, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. *Int J Radiat Oncol Biol Phys* 2011;81:923-929.
16. Bucci MK, Bevan A, Roach M, 3rd. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. *CA Cancer J Clin* 2005;55:117-134.
17. Ackerstaff AH, Balm AJ, Rasch CR, et al. First-year quality of life assessment of an intra-arterial (RADPLAT) versus intravenous chemoradiation phase III trial. *Head Neck* 2009;31:77-84.
18. Pergolizzi S, Santacaterina A, Adamo B, et al. Induction chemotherapy with paclitaxel and cisplatin to concurrent radiotherapy and weekly paclitaxel in the treatment of loco-regionally advanced, stage IV (M0), head and neck squamous cell carcinoma. Mature results of a prospective study. *Radiat Oncol* 2011;6:162.
19. de Leeuw J, Prins JB, Teerenstra S, et al. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. *Support Care Cancer* 2013;21(2):537-547.
20. Medical Ethical Committee Region Arnhem-Nijmegen. Available at: www.cmoregio-a-n.nl. Accessed January 15, 2012.
21. World Medical Association. Available at: <http://www.wma.net>. Accessed January 15, 2012, 2011.
22. Oncoline. Dutch Guidelines Head and Neck Cancer. Available at: www.oncoline.nl. Accessed June 23, 2012.
23. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-376.
24. Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
25. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000;36:1796-1807.
26. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol* 1999;17:1008-1019.
27. Hammerlid E, Bjordal K, Ahlner-Elmqvist M, et al. Prospective, longitudinal quality-of-life study of patients with head and neck cancer: a feasibility study including the EORTC QLQ-C30. *Otolaryngol Head Neck Surg* 1997;116:666-673.
28. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996;5:555-567.
29. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139-144.
30. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:981-991.

31. Vergeer MR, Doornaert PA, Rietveld DH, et al. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. *Int J Radiat Oncol Biol Phys* 2009;74:1-8.
32. Rogers SN, Thomson R, O'Toole P, et al. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. *Oral Oncol* 2007;43:499-507.
33. Garcia-Peris P, Paron L, Velasco C, et al. Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: Impact on quality of life. *Clin Nutr* 2007;26:710-717.
34. van der Molen L, van Rossum MA, Burkhead LM, et al. Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. *Eur Arch Otorhinolaryngol* 2009;266:889-900.
35. Speksnijder CM, van der Glas HW, van der Bilt A, et al. Oral function after oncological intervention in the oral cavity: a retrospective study. *J Oral Maxillofac Surg* 2010;68:1231-1237.
36. Ganzer H, Touger-Decker R, Parrott JS, et al. Symptom burden in head and neck cancer: impact upon oral energy and protein intake. *Support Care Cancer* 2012;21:495-503.
37. Paccagnella A, Morello M, Da Mosto MC, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Support Care Cancer* 2010;18:837-845.
38. van den Berg MG, Rasmussen-Conrad EL, Wei KH, et al. Comparison of the effect of individual dietary counseling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *Br J Nutr* 2010;104:872-877.
39. Capuano G, Grosso A, Gentile PC, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck* 2008;30:503-508.
40. Ravasco P, Monteiro-Grillo I, Marques Vidal P, et al. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* 2005;27:659-668.
41. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91:447-452.
42. Kiss NK, Krishnasamy M, Loeliger J, et al. A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. *Support Care Cancer* 2012;20:2111-2120.
43. Larsson M, Hedelin B, Athlin E. A supportive nursing care clinic: conceptions of patients with head and neck cancer. *Eur J Oncol Nurs* 2007;11:49-59.
44. Morton RP, Crowder VL, Mawdsley R, et al. Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy. *ANZ J Surg* 2009;79:713-718.
45. Oozeer NB, Corsar K, Glore RJ, et al. The impact of enteral feeding route on patient-reported long term swallowing outcome after chemoradiation for head and neck cancer. *Oral Oncology* 2011;47:980-983.
46. Ehrsson YT, Langius-Eklöf A, Laurell G. Nutritional surveillance and weight loss in head and neck cancer patients. *Support Care Cancer* 2012;20:757-765.

47. Jaghagen EL, Bodin I, Isberg A. Pharyngeal swallowing dysfunction following treatment for oral and pharyngeal cancer--association with diminished intraoral sensation and discrimination ability. *Head Neck* 2008;30:1344-1351.
48. Patterson J, Wilson JA. The clinical value of dysphagia preassessment in the management of head and neck cancer patients. *Curr Opin Otolaryngol Head Neck Surg* 2011;19:177-181.
49. Molassiotis A, Rogers M. Symptom experience and regaining normality in the first year following a diagnosis of head and neck cancer: A qualitative longitudinal study. *Palliat Support Care* 2012;1-8.
50. McQuestion M, Fitch M, Howell D. The changed meaning of food: Physical, social and emotional loss for patients having received radiation treatment for head and neck cancer. *Eur J Oncol Nurs* 2011;15:145-151.
51. Pace-Balzan A, Rogers SN. Dental rehabilitation after surgery for oral cancer. *Curr Opin Otolaryngol Head Neck Surg* 2012;20:109-113.
52. Lee HF, Liu HE. Prospective changes of the quality of life for patients newly diagnosed with oral cancer during the acute stage. *Eur J Oncol Nurs* 2010;14:310-315.
53. Duke RL, Campbell BH, Indresano AT, et al. Dental status and quality of life in long-term head and neck cancer survivors. *Laryngoscope* 2005;115:678-683.
54. Petruson KM, Silander EM, Hammerlid EB. Quality of life as predictor of weight loss in patients with head and neck cancer. *Head Neck* 2005;27:302-310.
55. Epstein JB, Wilkie DJ, Fischer DJ, et al. Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. *Head Neck Oncol* 2009;1:26.
56. Whale Z, Lyne PA, Papanikolaou P. Pain experience following radical treatment for head and neck cancer. *Eur J Oncol Nurs* 2001;5:112-120.
57. Jereczek-Fossa BA, Santoro L, Alterio D, et al. Fatigue during head-and-neck radiotherapy: prospective study on 117 consecutive patients. *Int J Radiat Oncol Biol Phys* 2007;68:403-415.
58. Sawada NO, de Paula JM, Sonobe HM, et al. Depression, fatigue, and health-related quality of life in head and neck cancer patients: a prospective pilot study. *Support Care Cancer* 2012;20:2705-2711.
59. Wells M, Donnan PT, Sharp L, et al. A study to evaluate nurse-led on-treatment review for patients undergoing radiotherapy for head and neck cancer. *J Clin Nurs* 2008;17:1428-1439.

5

Comparison of the effect of individual dietary counseling and standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy

M.G.A. van den Berg

E.L. Rasmussen-Conrad

K.H. Wei

H. Lintz-Luidens

J.H.A.M. Kaanders

M.A.W. Merkx

British Journal of Nutrition. 2010;104:872-877



Abstract

Clinical research shows that nutritional intervention is necessary to prevent malnutrition in head and neck cancer patients undergoing radiotherapy. The objective of the present study was to assess the value of individually adjusted counseling by a dietician compared to standard nutritional care (SC). A prospective study, conducted between 2005 and 2007, compared individual dietary counseling (IDC, optimal energy and protein requirement) to SC by an oncology nurse (standard nutritional counseling). Endpoints were weight loss, BMI and malnutrition ($\geq 5\%$ weight loss/month) before, during and after the treatment. Thirty-eight patients were included evenly distributed over two groups. A significant decrease in weight loss was found 2 months after treatment ($p=0.03$) for IDC compared with SC. Malnutrition in patients with IDC decreased over time, while malnutrition increased in patients with SC ($p=0.02$). Therefore, early and intensive individualised dietary counseling by a dietician produces clinically relevant effects in terms of decreasing weight loss and malnutrition compared with SC in patients with head and neck cancer undergoing radiotherapy.

Introduction

Malnutrition is a substantial problem in Dutch health care. This applies for more than one in five patients.¹ In head and neck cancer patients malnutrition, specified as unintended weight loss of $\geq 5\%$ in one month and/or $\geq 10\%$ in six months, has been reported in 30-50%, particularly in those with squamous cell carcinomas in the oropharyngeal and hypopharyngeal areas.^{2,3} The most common treatments for these patients include surgery, radiotherapy, chemotherapy or a combination of these.^{4,5} The risk of nutritional deterioration is increased during actual treatment. Radiotherapy and/or chemoradiation induce morbidity; symptoms such as mucositis, impaired swallowing function, declined eating ability, xerostomia, dysgeusia, nausea, and vomiting may limit oral intake, and inevitably result in unintended weight loss during radiotherapy and for a prolonged period after the treatment.^{2,6-9}

Nutritional depletion in these patients reduces their tolerance to treatment. Malnutrition in head and neck cancer patients was significantly correlated with an increased risk of infections in patients undergoing surgery and the occurrence of major postoperative complications.^{3,10} In addition, higher mortality and morbidity rates, shorter failure-free survival,¹¹⁻¹⁴ and poorer quality of life in all therapies including radiotherapy have been reported.¹⁵⁻¹⁷ More specifically, unintended weight loss was found to be associated with a higher rate of recurrence and second primary tumours of the oral cavity and oropharynx after radiotherapy.¹³ Weight loss was found to be associated with reduced kidney function during cisplatin-containing chemoradiotherapy.¹⁴ Even though no cause effect relationships was established in this study of Lin et al., the findings emphasize the importance of intensive supportive measures beyond standard nutrition and hydration intervention.

It is therefore important to maintain an optimal nutritional status for patients through nutritional intervention during oncological treatment.

Several studies suggested that early and intensive nutritional intervention during radiotherapy may be beneficial in terms of decreasing the impact of side effects, decreasing unintended weight loss, and improving dietary intake, quality of life and treatment tolerance.^{6,18-21} According to published nutritional management guidelines for head and neck cancer patients, nutritional interventions must be initiated before and continued during and after cancer treatment and the implementation may be more successful if a dietician is involved.²²⁻²⁴

Although many studies demonstrate the benefits of full nutritional intervention program, including dietary counseling, there is little evidence for the potential added value of a professional dietician's support. In the current health care system there is a need to justify resources and to demonstrate the effects of individual dietary counseling.

The present study was designed to evaluate the effect of individual dietary counseling (IDC) by a dietician for patients with oral cavity, oropharyngeal or hypopharyngeal cancer, undergoing radiotherapy before, during and after treatment. The objective was to investigate whether individualised dietary counseling by a dietician would better maintain a patient's body weight, and thus prevent malnutrition compared to standard nutritional care (SC).

Experimental methods

Study design

A prospective clinical study on the impact of dietary counseling on unintended weight loss, BMI (kg/m²) and malnutrition in patients with head and neck carcinomas was carried out between January 2005 and February 2007 at the Radboud University Nijmegen Medical Centre. Patients with primary squamous cell carcinoma in the oral cavity, oropharynx or hypopharynx, age ≥18 years, stage II–IV (International Union Against Cancer TNM classification of malignant tumours) were included.²⁵ Patients were treated depending on stage, location of the tumour and general health conditions by radiotherapy, combined surgery, and radiotherapy or concomitant radio-chemotherapy in accordance with the guidelines of the Dutch Cooperative Head and Neck Oncology Group.^{4,5}

From 2005 till 2007, dietary counseling was given to all patients by a dietician before the start of radiotherapy.

Next, patients were assigned to one of the intervention groups based on their postal code. One group continued to receive individual dietary counseling by a dietician throughout the entire treatment and rehabilitation period (IDC). The other group was passed on to trained nurses for standard nutritional care during radiotherapy and thereafter (SC).

At baseline (the first visit to the outpatient clinic at the departments of Otorhinolaryngology or Oral and Maxillofacial Surgery) patients’ characteristics including age, sex, actual body weight (kg) and height (m) were registered. Parameters studied from baseline through to rehabilitation included body weight (kg), BMI (kg/m²; <18.5 = underweight; 18.5-25 = normal range; ≥25 = overweight; ≥30 = obese)²⁶ and malnutrition (unintended weight loss of ≥5% in 1 month and/or ≥10% in six months).^{3,27} Body weight was measured on a calibrated one decimal Seca scale (delta nr 707; Seca, Hamburg, Germany) wearing lightweight clothing under the same conditions.

Measurements were taken at five pre-determined time points for each treatment modality (Fig. 1).

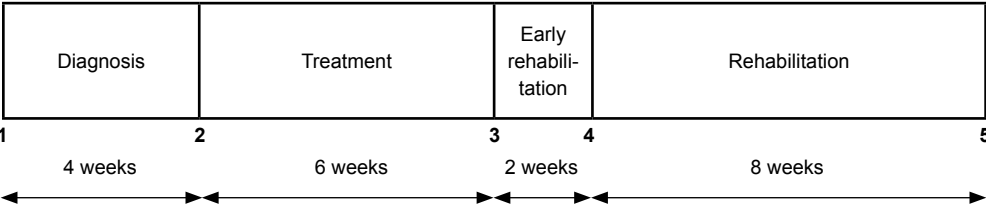


Figure 1. Data collection: Weight in kg (1-5) measured during diagnosis, treatment, early rehabilitation and rehabilitation.

Nutrition policy

Individual dietary counseling (IDC).

IDC in the present study is defined as individualised and intensive dietary counseling by dietitians focused on maintaining and/or improving a patient’s energy and protein intake. Counseling is based on four nutritional guidelines.^{4,5,28,29}

These guidelines describe treatment-related symptoms that influence dietary intake and offer advice on how to deal with these symptoms, including dietary counseling strategies, when

dietary counseling is necessary and when to start tube feeding (nasogastric/gastrostomy). To meet the specific nutritional goals for each patient, individual directions for dietary counseling were given. The patient's energy requirement was estimated at >125 KJ to a maximum of 167 KJ (>30–≤40 kcal) per kg of actual body weight depending on activities, metabolic stress, abnormal losses and treatment. The protein requirement was normally estimated at >1.0 to a maximum of 1.5 g of protein per kg ideal body weight depending on bedsores or other inflammatory disorders which require extra protein intake. Ideal body weight was estimated as follows: (1) if a patient was underweight ($BMI < 20 \text{ kg/m}^2$): ideal weight (kg) = $20 \text{ kg/m}^2 \times \text{height (m)}^2$; (2) if a patient was overweight ($BMI > 25 \text{ kg/m}^2$): ideal weight (kg) = $25 \text{ kg/m}^2 \times \text{height (m)}^2$; a patient having a BMI of 20–25 kg/m^2 was considered to be of ideal weight. IDC involved the prescription of a therapeutic diet with regular food which was adjusted to the individual's usual diet, thereby recognising personal eating patterns, feasible consistency and preferences. The dietitian would also take other relevant factors into consideration, namely the need for alleviation or arrest of local symptoms, as well as psychological factors and digestive and absorptive capacity. The prescription included the type, amount and frequency of feeding, and specified the energetic/protein level that had to be attained. If a patient's oral intake continued to diminish, energy- and protein-rich oral nutrition supplements were supplied separately or together with normal meals. Supplements (high energetic drinks) were offered to patients in their preferred flavours, and they were instructed to use them as drinks to be consumed between meals or in combination with snacks between meals. When all the above mentioned methods were insufficient to maintain the required energy and protein intake for patients, nutritional intake was achieved through tube feeding. Gastrostomy tubes were used in cases where tube feeding was expected to be necessary for a period longer than 6 weeks. From the start of radiotherapy until at least 2 months after treatment, patients were checked twice before and at least once a week during and after radiotherapy. The dietetic consultation consisted of twelve to fifteen visits, but could be arranged more frequently when requested. The dietitian was available to answer any queries or provide more information. When necessary, dietetic domiciliary care was arranged for the subsequent period.

Standard nutritional care by a nurse (SC)

Patients were seen twice by a dietitian before radiotherapy (IDC policy) and when radiotherapy started they were passed on to SC by a nurse. This is as follows: body weight of each patient was measured at least once a week on a calibrated scale wearing lightweight clothing.

Nutritional advice was based on a guideline specifically focused on treatment symptoms such as pain, nausea, xerostomia, mucositis, dysphagia, and how to deal with nutrition.²⁹

Interventions were mostly focused on evaluating pain due to radiation mucositis and adjusting pain medication. When nutritional intake seemed insufficient, advice on high energetic liquid nutrition and/or high energetic/protein supplements was given. If the above-mentioned methods failed to work, a nasogastric tube was used for patients who had lost more than 10% of their body weight. Gastrostomy tubes were used in cases where tube feeding was expected to be necessary for a period exceeding 6 weeks.

The frequency of nutritional advice was at least once a week, but this increased when more problems occurred (daily, if necessary, depending on the treatment phase and symptoms). Patients were seen at the outpatient clinic or contacted by phone up to a minimum of 3–4

four months after the treatment. Trained nurses offered patients support during and after the treatment in all areas concerning illness and side effects such as nutritional, psychological and skin problems, pain and constipation. This support was supervised by a radiation oncologist.

Statistical analysis

Data processing and statistical analysis were performed using Statistical Package for Social Sciences version 16.0 (SPSS, Inc., Chicago, IL, USA).

The percentage of unintended weight loss was calculated using baseline weight as a reference point.

A descriptive statistical analysis was performed for the two groups of patients. Differences in the distribution of patients' characteristics were evaluated by χ^2 test. Differences of the mean change in outcome between groups and within groups were tested by independent and dependent Student's *t* test, respectively. Fisher's exact probability test was performed to test the difference in malnutrition between the treatment groups. The level of statistical significance was set at $p < 0.05$, two-sided.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Committee on Research Involving Human Subjects of the Radboud University Nijmegen Medical Centre. Written informed consent was obtained from all subjects/patients.

Results

A total of thirty-eight patients met the inclusion criteria. The IDC group included twenty patients, and the SC group consisted of eighteen patients. Table 1 summarises baseline characteristics of the two groups. There were no significant differences between age, height, sex, weight, BMI, T stage, N stage, tumour site or treatment.

Percentage of unintended weight loss

The percentage weight changes for the two groups are shown in Fig. 2.

The IDC group had a maximum of 3% unintended weight loss 2 weeks after the treatment. This was approximately the same for the SC group. Two months after treatment, the IDC group started to gain weight (1% weight gain), while the SC group continued to lose 1.5% weight. Two months after treatment, weight loss was significantly different between SC and IDC ($p = 0.03$).

BMI

Most of the patients in IDC and SC groups had a normal BMI ($18.5 \text{ kg/m}^2 \leq \text{BMI} < 25 \text{ kg/m}^2$) throughout the study (Fig. 3). No patients were underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$). BMI for the IDC and SC did not differ significantly at any of the time points.

Table 1 Baseline characteristics of the patients (Mean values with their standard errors)

Variable	IDC (n=20)		SC (n=18)	
	Mean	SE	Mean	SE
Age (years)	63.8	1.9	61.6	2.1
Height (m)	1.70	0.00	1.71	0.02
Gender (male)	14.0		8.0	
Weight (kg)	69.3	3.4	71.0	3.8
BMI (kg/m ²)*	23.9	1.1	24.0	0.9
<18.5	3.0		1.0	
18.5 – 25.0	10.0		12.0	
>25.0	7.0		5.0	
T stage				
T ₂	6.0		11.0	
T ₃	7.0		4.0	
T ₄	7.0		3.0	
N stage				
N0	9.0		5.0	
N≥1	11.0		13.0	
Tumor site				
Oral Cavity	10.0		3.0	
Oropharynx	7.0		12.0	
Hypopharynx	3.0		3.0	
Treatment				
Radiotherapy	6.0		7.0	
Chemo/radiotherapy	6.0		5.0	
Surgery/radiotherapy	6.0		6.0	

IDC, individual dietary counseling; SC, standard nutritional care.

*BMI (kg/m²): <18.5, underweight; 18.5–25.0, healthy weight; >25.0, overweight (WHO).²⁶

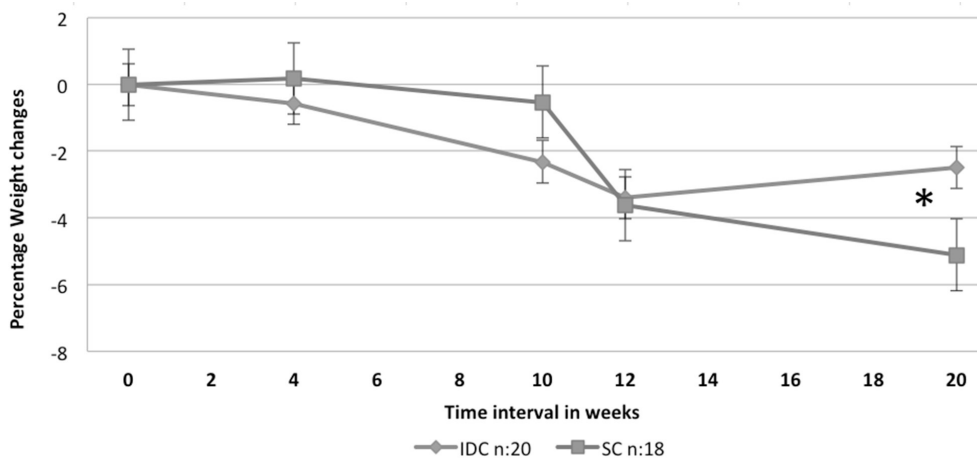


Figure 2. Percentage of unintended weight loss as a function of time (mean with their standard errors), with baseline as reference. IDC, individual dietary counseling; SC, standard nutritional care. *Mean values were significantly different between SC and IDC groups ($p=0.03$).

Malnutrition

Table 2 displays the prevalence of malnutrition from diagnosis until 2 months after treatment. Before the treatment, four of twenty patients in the IDC group and three of eighteen in the SC group were malnourished. During the treatment period, the IDC and SC groups remained stable. Two weeks after the treatment, there was a significant difference in malnutrition between IDC (0/20) and SC (5/18) groups ($p=0.02$).

Two months after the treatment, the highest prevalence of malnutrition was seen for SC group (3/18).

The prevalence of malnutrition by T stages is shown in Table 3. No significant differences were found between the T stages.

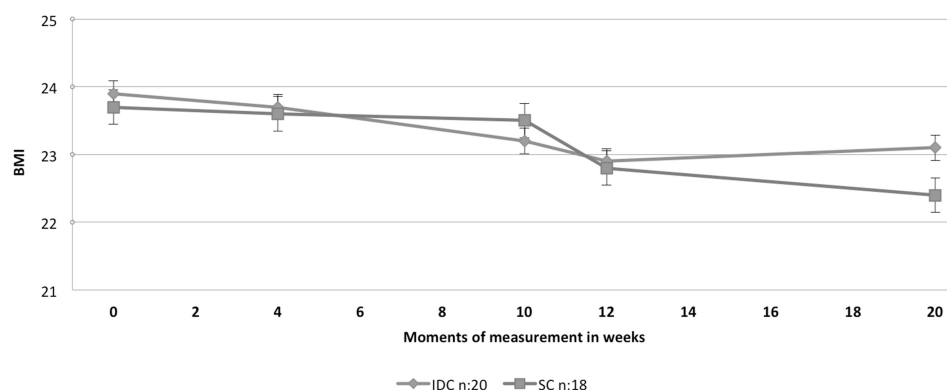


Figure 3. BMI as a function of time (means with their standard errors), with baseline as reference. BMI: <18.5 = underweight; 18.5–25 = healthy weight; >25 = overweight (WHO).²⁶ IDC, individual dietary counseling; SC: standard nutritional care.

Table 2 Prevalence of malnutrition* in individual dietary counseling (IDC) and standard nutritional care (SC) groups from diagnosis until rehabilitation.

Interval	Number of patients per nutrition intervention		Total (n=38)
	IDC (n=20)	SC (n=18)	
Diagnosis	4.0	3.0	7.0
Treatment	3.0	4.0	7.0
Early Rehabilitation	0.0 †	5.0 †	5.0
Rehabilitation	1.0	3.0	4.0

*Malnutrition was defined as 'unintended weight loss $\geq 5\%$ within one month'.

†Prevalence of malnutrition in IDC and SC groups was significantly different ($p<0.05$)

Table 3 Prevalence of malnutrition* per T stage from diagnosis until rehabilitation

Interval	Number of patients per T-stage			Total (n=38)
	T ₂ (n=17)	T ₃ (n=11)	T ₄ (n=10)	
Diagnosis	2.0	3.0	2.0	7.0
Treatment	3.0	3.0	1.0	7.0
Early Rehabilitation	5.0	0.0	0.0	5.0
Rehabilitation	3.0	1.0	0.0	4.0

*Malnutrition was defined as 'unintended weight loss $\geq 5\%$ within 1 month'.

Discussion

Malnutrition, defined as $\geq 5\%$ of unintended weight loss/month or $\geq 10\%$ unintended weight loss/6 months, is the most commonly used parameter in clinical practice for head and neck cancers.^{3,27} In the literature, the prevalence of malnutrition is associated with higher mortality and morbidity rates, shorter failure-free survival and poorer quality of life among radiotherapy patients¹¹⁻¹⁷ It is therefore essential to control unintended weight loss/malnutrition and maintain an efficient nutritional status for patients. The present study demonstrates the beneficial effect of IDC on weight change, BMI and malnutrition for patients with oral cavity, oropharyngeal and hypopharyngeal cancers treated with radiotherapy compared to SC.

Two different groups (IDC and SC) were compared in the current study. Patients' characteristics were evenly distributed. Treatment-induced side effects of patients receiving radiotherapy to the head and neck area peak at the end of the treatment course and continue for 2 or more weeks after the treatment.²⁰ This is reflected by a sharp weight reduction during this period, which continued until 2 months after the treatment, specifically in SC group, while the IDC group started gaining weight 2 weeks after the radiotherapy. There was a significant difference in unintended weight loss 2 months after treatment for the SC group compared to the IDC group.

The IDC group started with the same proportion of patients with malnutrition (4/20) v. SC (3/18) at diagnosis where malnutrition in the SC group increased over time. A significant difference in the prevalence of malnutrition for the early rehabilitation period was seen between the groups ($p=0.02$) which affirms that dietary counseling recovers malnutrition where SC increases malnutrition.

While looking at the overall results of this study, the most striking differences are observed in the (early) rehabilitation period. Two months after treatment, weight and BMI in the SC group were still declining. In future research, a longer follow-up is therefore required to determine the nadir of weight loss and the duration of full recovery. Also, more data about nutritional status should be included such as a comprehensive nutritional assessment tool (e.g. subjective global assessment or patient-generated subjective global assessment), anthropometric measurements (e.g. bio-impedance and/or handgrip) and food intake (e.g. dietary history or FFQ). Besides, it should be useful to include other endpoints such as quality of life, mortality, response to treatment and length of hospital stay.

These results indicate that IDC significantly contributes to maintaining and improving weight loss and malnutrition of head and neck cancer patients undergoing radiotherapy. This is an important clinically relevant finding which confirms the research objective of this study.

A randomised study performed by Ravasco et al.⁶ produced similar results. The study demonstrated that individualised dietary counseling (based on regular foods) for head and neck cancer patients' undergoing radiotherapy is the most effective way of improving a patient's nutritional intake, nutritional status and quality of life by the end of treatment until 3 months after treatment.

However, Ravasco used the Ottery's Subjective Global Assessment (unscored patient-generated subjective global assessment) to determine malnutrition. In this system, unintended weight loss is one of the deciding factors besides symptoms, metabolic stress and subcutaneous fat.

A randomised controlled trial by Isenring et al.^{20,21} showed that dietary counseling using the American Dietetic Association - Medical Nutrition Therapy radiation oncology protocol resulted in a significant reduction of unintended weight loss from the start of radiotherapy until 3 months after treatment compared with their standard practice (which consisted of general nutritional advice by a nurse and a booklet). Furthermore, the present study revealed an improvement in nutritional status (patient-generated subjective global assessment), dietary intake and quality of life in the dietary counseling group when compared to standard practice. This is the first prospective randomised controlled trial. A limitation of the present study is that two different tumour locations were involved (gastrointestinal and head and neck cancer).

Dawson et al.³⁰ reported a significant reduction in unintended weight loss in oral cancer patients undergoing combined modality treatment (surgery+radiotherapy) with increased dietary supervision compared to standard dietary counseling after revising their dietary protocol. However, this was not compared to nutritional standard care without dietary counseling. It is interesting to note that while there have only been a handful of studies in this area by different research teams, they have all demonstrated benefits of dietary counseling like our study.

To summarise, early and intensive IDC produces clinically relevant effects in terms of decreasing unintended weight loss and malnutrition compared with SC in patients with head and neck cancer undergoing radiotherapy. This is especially the case early after treatment and during the rehabilitation period.

The guidelines used by the Radboud University Nijmegen Medical Centre Department of Dietetics for head and neck cancer patients is a useful guide in supplying the level of dietary support required.^{4,5,28,29} In clinical practice, patients should receive regular and individualised dietary counseling from diagnosis until at least two months after radiotherapy and probably longer.

Acknowledgements

The present research received no specific grant from any funding agency in the public, commercial or non profit sector. All authors hereby declare that no financial or personal interest is involved which may bias or influence the present study.

All authors contributed to the concept and design of the present study, acquisition, analysis and interpretation of data. All authors approved the final version of the present manuscript.

We are grateful to Jeanne de Vries (Department of Human Nutrition, Wageningen University, The Netherlands) for the useful discussions.

References

1. Meijers JMM, Schols JMGA, van Bokhorst-de van der Schueren MA, et al. Malnutrition prevalence in The Netherlands: results of the Annual Dutch National Prevalence Measurement of Care Problems. *Br J Nutr* 2009;101,417-423.
2. van den Berg MG, Rasmussen-Conrad EL, Gwasara GM, et al. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. *Clin Nutr* 2006;25,765-772.
3. van Bokhorst-de van der Schueren MA, van Leeuwen PA, Sauerwein HP, et al. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck* 1997;19,419-425.
4. CBO 2004 Richtlijn Mondholte-en Oropharynxcarcinoom. 1th ed. Alphen aan den Rijn: Van Zuiden Communications B.V.
5. Oncoline 2007 Richtlijn Hypopharynx carcinoom. Available at <http://www.oncoline.nl/index.php?language=en>.
6. Ravasco P, Monteiro-Grillo I, Marques VP, et al. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* 2005;27,659-668.
7. Newman LA, Vieira F, Schwiezer V, et al. Eating and weight changes following chemoradiation therapy for advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg* 1998;124,589-592.
8. Munshi A, Pandey MB, Durga T, et al. Weight loss during radiotherapy for head and neck malignancies: what factors impact it? *Nutr Cancer* 2003;47,136-140.
9. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care (Engl)* 1999;8,133-136.
10. Van Bokhorst-de Van der Schuer MA, von Blomberg-van der Flier BM, Riezebos RK, et al. Differences in immune status between well-nourished and malnourished head and neck cancer patients. *Clin Nutr* 1998;17,107-111.
11. Van Bokhorst-de van der Schuer, van Leeuwen PA, Kuik DJ, et al. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. *Cancer* 1999;86,519-527.
12. Liu SA, Tsai WC, Wong YK, et al. Nutritional factors and survival of patients with oral cancer. *Head Neck* 2006;28,998-1007.
13. Nguyen TV, Yueh B. Weight loss predicts mortality after recurrent oral cavity and oropharyngeal carcinomas. *Cancer* 2002;95,553-562.
14. Lin A, Jabbari S, Worden FP, et al. Metabolic abnormalities associated with weight loss during chemoradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2005;63,1413-1418.
15. Petruson KM, Silander EM, Hammerlid EB. Quality of life as predictor of weight loss in patients with head and neck cancer. *Head Neck* 2005;27,302-310.
16. Campbell BH, Spinelli K, Marbella AM, et al. Aspiration, weight loss, and quality of life in head and neck cancer survivors. *Arch Otolaryngol Head Neck Surg* 2004;130,1100-1103.
17. van den Berg MG, Rasmussen-Conrad EL, van Nispen L, et al. A prospective study on malnutrition and quality of life in patients with head and neck cancer. *Oral Oncol* 2008;44,830-837.

18. Rabinovitch R, Grant B, Berkey BA, et al. Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: a secondary analysis of RTOG trial 90-03. *Head Neck* 2006;28,287-296.
19. Goncalves Dias MC, de Fatima Nunes MM, Nadalin W, et al. Nutritional intervention improves the caloric and proteic ingestion of head and neck cancer patients under radiotherapy. *Nutr Hosp* 2005;20,320-325.
20. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91,447-452.
21. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. *J Am Diet Assoc* 2007;107,404-412.
22. Wood K. Audit of nutritional guidelines for head and neck cancer patients undergoing radiotherapy. *J Hum Nutr Diet* 2005;18,343-351.
23. Meuric J, Garabige V, Blanc-Vincent MP, et al. Good clinical practice in nutritional management of head and neck cancer patients. *Bull Cancer* 1999;86,843-854.
24. CBO 2004 Voeding en dieettherapie. Richtlijn Mondholte- en Oropharynxcarcinoom. 1th ed., pp. 187-190 Alphen aan den Rijn: Van Zuiden Communications B.V.
25. Mc Kee PH 2002 Wolf comprehensive tumour terminology handbook. 6th ed., pp 384 New York: John Wiley & Sons.
26. WHO 2004 BMI. Available at: http://www.who.int/bmi/index.jsp?introPage=intro_3.html
27. Ravasco P, Monteiro-Grillo I, Vidal PM, et al. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol* 2003;15,443-450.
28. Vogel-Boezeman J 2003 Elsevier gezondheidszorg, Dieet behandelingsrichtlijnen. Kanker. 1th ed., pp. 1-36 Maarssen: Elsevier.
29. Doornink N, Vogel J, Wipkink A, et al. 2006 Leidraad voor voedingskundigen bij kanker. Het hoofd-halscarcinoom. 4d ed., pp. 54-71 Haarlem: De Toorts.
30. Dawson ER, Morley SE, Robertson AG, et al. Increasing dietary supervision can reduce weight loss in oral cancer patients. *Nutr Cancer* 2001;41,70-74.

6

Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: A cross-sectional study

M.G.A. van den Berg

H. Rütten

E.L. Rasmussen-Conrad

S. Knuijt

R.P. Takes

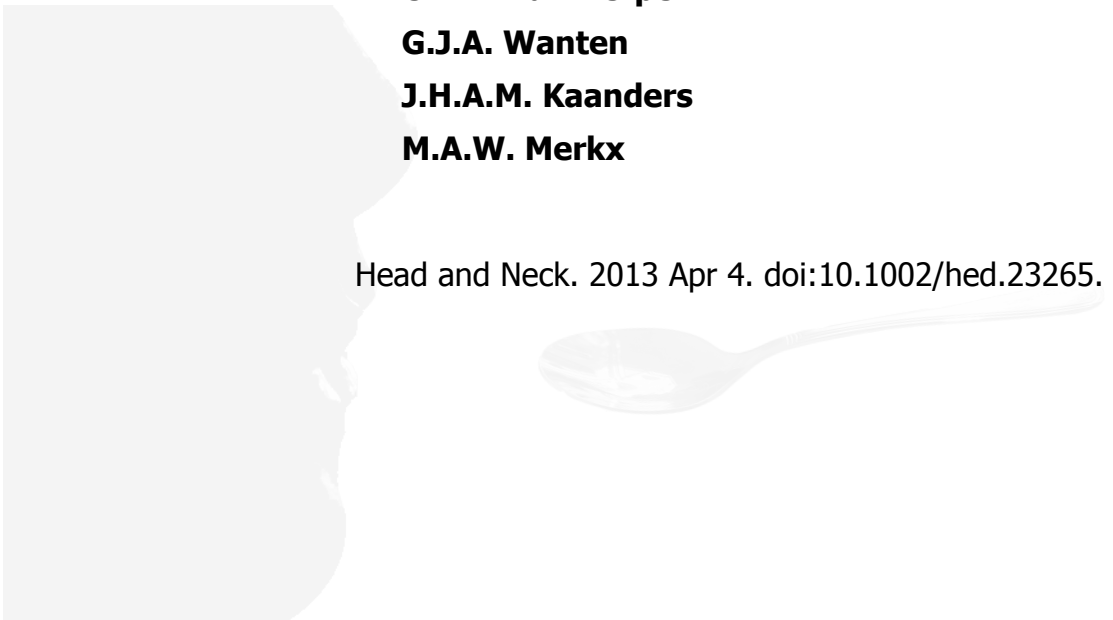
C.M.L. van Herpen

G.J.A. Wanten

J.H.A.M. Kaanders

M.A.W. Merkx

Head and Neck. 2013 Apr 4. doi:10.1002/hed.23265.



Abstract

Background

The aim of this study was to evaluate nutritional status, food intake and dysphagia in long term head and neck cancer survivors.

Methods

Thirty-two patients with stage III-IV head and neck cancer patients treated by chemoradiotherapy were invited to evaluate nutritional status (malnutrition, relative weight change), food intake (food modification; quality), and dysphagia.

Results

At a median follow up of 44 months, 6 of 32 patients were at risk for malnutrition. Female ($p=0.049$) and patients with high body mass index before treatment ($p=0.024$) showed more weight loss. None of the 32 patients could eat a “full diet”. Six patients used nutritional supplements/tube feeding. Low dysphagia-related quality of life scores were significantly correlated to increased food modification ($r=0.405$; $p=0.024$).

Conclusions

Nutritional advice in patients with head and neck cancer is still necessary years after chemoradiation and should focus on nutritional status, food modification, and quality, accord with recommended food groups.

Introduction

Side effects of (chemo)radiotherapy in patients with head and neck cancer patients are common during and immediately after completion of treatment. Acute symptoms such as mucositis, xerostomia, and distortion of taste and smell are frequently reported and may limit oral intake and lead to weight loss and dehydration during and directly after (chemo) radiotherapy.^{1,2}

Although chemoradiotherapy in locally advanced disease of the head and neck results in better locoregional control and survival than radiotherapy as single treatment modality, it is accompanied by increased toxicity.^{3,4}

Only reporting the acute side effects of a (chemo)radiation program will clearly be insufficient to understand the long term consequences.⁵ Most late side effects (>90 days after treatment) develop within the first 3 years after treatment and few appear or progress even after 3 years. Therefore to fully recognize long-term impact on treatment, patients with head and neck cancer must be followed for several years.^{6,7}

Dysphagia, xerostomia, osteoradionecrosis, trismus and oesophageal strictures are known late side effects in patients with head and neck cancer treated with (chemo)radiation.^{7,8} Swallowing dysfunction and aspiration are seen in a high proportion in these patients after combined chemoradiotherapy with prevalence estimates ranging from 30 to 100%.⁸⁻¹⁰ Dysphagia as a late side effect is stated to be a major concern in stage II-IV patients with head and neck cancer treated with chemoradiotherapy and was described as the most important adverse factor on quality of life (QOL).¹¹⁻¹³ Likewise, food intake seems to be highly affected by deterioration of swallowing function until 6 months after chemoradiotherapy.¹⁴ The impact on malnutrition risk and food intake in the long term (>90 days after treatment) has been reported only briefly by a few investigators.⁵ The purpose of this study was to comprehensively evaluate nutritional status, food intake and dysphagia in long-term head and neck cancer survivors treated by chemoradiation as we presume that these patients are at risk for malnutrition and decreased and/or altered food intake due to dysphagia. Within this framework we conducted a cross-sectional study.

Patients and methods

Study design:

Between May 2003 and December 2007, 77 patients with III–IV TNM stage head and neck cancer were treated with curative intent by means of accelerated chemoradiotherapy, comprising 68 Gy over 5.5 weeks with weekly cisplatin 40 mg/m², at the Department of Radiation Oncology of the Radboud University Nijmegen Medical Centre (RUNMC).

Between January and April 2009 a cross-sectional study was carried out. Forty of the 77 patients were alive without recurrences or second primary tumor. These 40 patients were invited to a multidisciplinary late morbidity clinic to evaluate nutritional status, food intake and dysphagia.

This study was approved by the research ethics committee of the RUNMC and was therefore performed in accord with the ethical standards laid down in the 1975 Declaration of Helsinki, as revised in 1983. All patients gave their informed consent prior to study (CMO: 2011/412).

Nutritional status: Malnutrition risk and “relative weight change”:

Malnutrition risk was assessed with the Malnutrition Universal Screening Tool (MUST), the first nutritional screening tool specifically designed to use in all healthcare settings for the entire range of adult patients.¹⁵

At the late morbidity clinic each patient's body weight was measured at 1 decimal with lightweight clothing on a calibrated scale (SECA-scale; model 770, Hamburg, Germany). Height was self-reported by the patient (cm). Data on body weight prior to chemoradiation was collected from each patient's medical or dietetic record (measured on the same scale under same conditions). Body Mass Index (BMI: kg/m²) was calculated.¹⁶ Subsequently, “relative weight change” was calculated as body weight at the late morbidity clinic minus body weight before chemoradiation divided by weight before treatment.

Food intake: food modification and food quality.

Food modification was measured in accord with “normalcy of diet” from the performance status scale for patients with head and neck cancer (PSS-HN). A rating scale in which the subscales “normalcy of diet”, “eating in public” and “understandability of speech” are rated from 0 to 100, with higher scores indicating a better performance. The PSS-HN has been shown to discriminate levels of functioning across a broad spectrum of head and neck cancer and has demonstrated good interrater reliability as well as sensitivity to differences in performance and change over time.¹⁷

Food intake over the previous month was evaluated by means of a dietary history by the dietician. This is a distinguished method to measure food intake¹⁸ Food consumption data were collected by a well-trained dietician, skilled in the identification of available foods, meals and food preparation techniques. During a face-to-face interview by means of a 24-hours record, previously written down by the patient, food intake and food pattern were checked. In-depth questionnaires about the quantity and quality of mean food intake over the last month were used.

The contents of household utensils were converted to “standard household portions sizes” to register the quantity of food intake.¹⁹ Food items were coded in accord with the Dutch food composition database, NeVo 2011, The Netherlands and calculated with “Vodisys” (medical software 1.3; Vodisys, Groningen, The Netherlands).²⁰ Subsequently, food intake was categorized following the labeling of the “recommended food groups” by the “Dutch food based dietary guideline” for qualitative food evaluation.²¹

The classification of “recommended food groups” categorized for sex and age was followed, which covers vitamins and mineral requirements. Intake of ≥75% of the recommended food group was determined to be in accord with requirements.

Dysphagia:

Swallowing assessment was carried out by a speech-language pathologist with additional video fluoroscopy at the Department of Radiology to assess the swallowing act. Also the MD Anderson Dysphagia Inventory (MDADI) questionnaire was filled in by patients. This is a validated and reliable self-administered questionnaire, designed specifically for evaluating the impact of dysphagia on the QoL (global; emotional, functional and physical) of patients with head and neck cancer rated from 0 to 100, with higher scores indicating a better performance.²²

Statistical analysis:

Normally distributed continuous variables were expressed as means and SD. Differences of the mean change in outcomes between 2 groups were tested with the independent Student's *t* test. Pearson chi-square and Fisher's exact test were used for ordinal data. The Pearson correlation coefficient and the Spearman correlation coefficient were used for correlation.

Data processing and statistical analysis were performed using the statistical software Statistical Package for the Social Sciences (SPSS 17.0; SPSS Inc., Chicago, IL, USA).

Results

Thirty-two of the 40 invited patients with head and neck cancer visited the late outpatient morbidity clinic at the Department of Radiation Oncology, RUNMC. Median follow-up after chemoradiation was 44 months (range 14-68). Table 1 represents patients and treatment characteristics of the 77 eligible patients compared to the 32 patients of our study population; no significant differences were found. Twenty patients had had dietetic counseling at some point in time during or after chemoradiotherapy but, not longer than 3 months after treatment. No structural dietetic counseling was given.

In accord with the MUST, 2 patients were at high risk and 4 patients had a medium risk of malnutrition. Five of these evaluations were based on a "BMI<18.5 or 18.5-20.0" and 1 patient due to "5 to 10% involuntary weight loss during the last 3-6 months".

Mean weight before chemoradiotherapy started was equal to the mean weight at the late morbidity clinic: 73 kg (SD 14.6) and 73.4 kg (SD 14.9), respectively. However, 16 patients had lost weight and 16 patients had been stable or gained weight since the start of chemoradiotherapy until the late morbidity clinic. The mean difference in relative weight loss (9%; SD 5%) and relative weight gain (10%; SD 9%) between the 2 groups was statistically significant ($p<0.001$). Patients were dichotomized in these 2 groups (Table 2²³). Differences between patients' characteristics for those 2 groups were tested and a significant difference for sex ($p=0.049$) and a higher BMI (>26.3) before chemoradiation were found in patients with weight loss ($p=0.024$).

Data from the late morbidity clinic were collected at different time intervals (14-68 months follow-up), but no significant correlation for relative weight change and time interval was found ($r=0.148$; $p=0.42$).

PSS-HN measurements are given in Table 3. They revealed that none of the patients could eat a "full diet" without restrictions. Six out of 32 patients (19%) could eat only soft foods (score 40-50). Twenty-four of the 32 patients (75%) could eat only with mild to moderate modifications. Difficulties with "eating in public" were present in 11 of 32 patients (34%) (PSS-HN ≤ 50).

Food quality has previously been categorized in accord with the Dutch food-based dietary guidelines for age groups (19-50 years, 51-70 years and ≥ 71 years) and sex.

In general greens, bread, potatoes/rice/pasta/legumes, milk products, cheese and low fat/diet margarine were far beneath recommended food intake (Table 4).

In 10 of 32 male patients a mean alcohol intake of 390 mL (SD 168; 1-4 alcohol units/day) was found. All of the consumers drank beer.

Table 1 Patient and treatment characteristics of all 77 patients and 32 patients at the late morbidity clinic.⁸

Characteristic	All 77 patients (%)	32 participants at the late morbidity clinic (%)
Sex		
Male	58 (75)	23 (72)
Female	19 (25)	9 (28)
Mean age, y (range)	55 (32-72)	55 (32-69)
Primary tumor site		
Oral cavity	12 (16)	2 (6)
Oropharynx	12 (53)	21 (66)
Hypopharynx	41 (30)	9 (28)
Larynx	23 (1)	0 (0)
T classification		
T ₁	2 (3)	0 (0)
T ₂	10 (13)	7 (22)
T ₃	33 (43)	14 (44)
T ₄	32 (42)	11 (34)
N classification		
N0	7 (9)	3 (9)
N1	10 (13)	3 (9)
N2a	3 (4)	1 (3)
N2b	20 (26)	9 (28)
N2c	30 (39)	14 (44)
N3	7 (9)	2 (6)
TNM Stage		
III	9 (12)	3 (9)
IV	68 (88)	29 (91)
Irradiation dose		
54 Gy	1 (1)	-
68 Gy	76 (99)	32 (100)
Irradiation technique		
IMRT	13 (17)	9 (28)
3D-conformal	54 (83)	23 (72)
Courses cisplatin		
<3	0 (0)	0 (0)
3-4	10 (13)	3 (9)
>4	67 (87)	29 (91)
Tube feeding*		
Before treatment	27 (35)	9 (28)
During treatment	37 (35)	16 (50)
Median duration in weeks (range)	10 (1-76)	10 (3-76)

Abbreviation: IMRT, intensity-modulated radiotherapy. *Indication tube feeding: more than 10% weight loss or patients who could only swallow liquids before the start of therapy.

Table 2 Patient characteristics for patient with and without relative weight loss

Characteristic	Total no. of patients (n=32)	No. of patients with weight loss (n=16)	No. of patients with stable weight/gained weight (n=16)	p value
Sex (n[%])				0.049*
Male	23 (72)	9 (39)	14 (61)	
Female	9 (28)	7 (77)	2 (23)	
Age (mean y, SD)	58 (9.1)	58 (10.7)	58 (7.4)	0.955
TNM stage (n[%]) 23				1.000
II	7 (22)	4 (25)	3 (19)	
III	14 (44)	7 (44)	7 (44)	
IV	11 (34)	5 (31)	6 (37)	
Tumor location (n[%])				0.170
Oral cavity	2 (6)	0 (0)	2 (13)	
Oropharynx	21 (66)	13 (81)	8 (50)	
Hypopharynx	9 (28)	3 (19)	6 (37)	
BMI before chemo radiation (mean [SD])	24.3 (5.2)	26.3 (5.1)	22.2 (4.6)	0.024*
Mean relative weight change (percentage [SD])	1 (12)	-9 (5)	10 (9)	<0.001*
Score MUST (n[%])				0.461
(mean [SD])Low risk (0)	26 (81)	12 (75)	14 (88)	
(mean [SD])Medium(1)	4 (13)	3 (19)	1 (6)	
(mean [SD])High risk (≥2)	2 (6)	1 (6)	1 (6)	
PSS-HN Normalcy of food intake ≤50 (n[%])	8 (25)	5 (31)	3 (19)	0.480
Tube feeding in history (n[%])	25 (78)	11 (69)	14 (88)	0.549
Dysphagia (n[%])†	24 (75)	13 (81)	11 (69)	0.683
Impaired video fluoroscopy (n[%]) ‡	17 (57)	9 (60)	8 (53)	0.808
MDADI (global) ≤50 (n[%])	9 (28)	6 (37)	3 (19)	0.317

Abbreviations: BMI, body mass index; MUST, malnutrition universal screening tool; PSS-HN, performance status scale for head and neck cancer patients; MDADI, MD Anderson Dysphagia Inventory.

* Significant ($p < 0.05$).

† Based on clinical research by a speech-language pathologist.

‡ Based on video fluoroscopy ($n = 30$).

Table 3 Performance Status Scale for all head and neck cancer survivors at the late morbidity clinic ($n=32$).

Characteristic	No. of patients (%)
Normalcy of diet	
100 full diet (no restrictions)	0 (0)
90 peanuts	7 (22)
80 all Meat	10 (31)
70 carrots, celery	3 (9)
60 dry bread and crackers	4 (13)
50 soft, chewable foods (eg, macroni, canned soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)	5 (16)
40 soft foods requiring no chewing (eg, mashed potatoes, apple sauce, pudding)	1 (3)
30 pureed foods (in blender)	0 (0)
20 warm liquids	0 (0)
10 cold liquids	0 (0)
0 non oral feeding (tube fed)	2 (6)
Understandability of speech	
100 understandable	18 (56)
75 understandable most of the time; occasional repetition necessary	9 (28)
50 usually understandable; face-to-face contact necessary	4 (13)
25 difficult to understand	1 (3)
0 never understandable; may use written communication	0 (0)
Eating in public	
100 no restriction of place, food, or companion (eats out opportunity)	21 (66)
75 no restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (such as liquids)	1 (3)
50 eats only in the presence of selected persons in selected places	6 (19)
25 eats only at home in the presence of selected persons	2 (6)
0 always eats alone	2 (6)

Note: The score a patient receives is the highest possible score for this patient.

Tube feeding from start of chemo radiotherapy until late morbidity clinic was used in 25 patients (78%), at some point with a median period of 10 weeks (mean 21, SD 23). At the late morbidity clinic, 6 out of 32 patients (19%) used nutritional supplements of which 2 used complete tube feeding, without any oral intake. One patient used tube feeding by a jejunum tube and 1 patient by a percutaneous radiologic gastrostomy. Four patients used 1 to 4 packages energy drinks a day. In 24 patients (75%), dysphagia was found based on clinical assessment by a speech-language pathologist. Videofluoroscopy, performed in 30 patients who were able to swallow, showed that 17 patients (57%) had impaired swallowing (Table 2). Mean MDADI global functioning was 73 (SD 29). No correlation was found for impaired swallowing malnutrition risk (MUST), "relative weight change" or food modification (PSS-HN). However, lower MDADI scores, global, showed a significant correlation with lower food modification scores (PSS-HN) ($r=0.405$; $p=0.024$).

Table 4 Qualitative food evaluation, mean values of food intake in food groups ($n=32$) and total patients with food intake in accord with $\geq 75\%$ of the recommended food groups.

Food groups	Mean values of food intake (mean [sd]) ($n=32$)	No. of patients with food intake ($\geq 75\%$) in accord with recommendation (n [%])*
Greens (g)	126 (72)	4 (13)
Fruit (g)	108 (269)	18 (56)
Bread (g)	116 (70)	12 (38)
Potatoes, rice, pasta, legumes (g)	123 (71)	14 (44)
Milk products (mL)	379 (276)	14 (44)
Cheese (g)	22 (24)	10 (31)
Meat/cold cuts, fish, chicken, eggs, meat, substitutes (g)	136 (84)	27 (84)
Low fat/diet margarine (g)	12 (11)	7 (22)
Fats and oils for baking/frying (g)	21 (20)	19 (59)
Liquids (mL)	1894 (745)	24 (75)
"Miscellaneous" (g) [†]	34 (33)	n.r.
Alcohol (mL) [‡]	122 (204)	n.r.
Nutritional supplements (mL) [‡]	144 (383)	n.r.

Abbreviation: n.r., no requirements.

* Based on individual patients in accord with 'Dutch food-based dietary guidelines- recommended food groups' for age groups and sex.

[†]All food items not belonging to 1 of these groups (eg, snacks, sugar, jams, chocolate sandwich spreads) were put under "miscellaneous". For these groups there are no requirements (n.r.).

[‡]Alcohol and nutritional supplements (tube feeding, diet formula and energy drinks) were added as separate groups. For these groups there are no requirements (n.r.).

Discussion

The purpose of this study was to comprehensively evaluate nutritional status, food intake and dysphagia in long-term head and neck cancer survivors treated by chemoradiation, given that we presume that these patients are at risk for malnutrition and decreased and/or altered food intake due to dysphagia.

The outcome of this study showed that 6 out of 32 (19%) patients were at risk for malnutrition (MUST); of these, 2 patients were at high risk. Five of these patients were at risk in accord with their low BMI; this probably occurred as a result of weight loss during and shortly after treatment, and for some reason they could not gain weight thereafter.

The patient group was dichotomized between those who had weight loss ($n=16$) and those with stable weight or weight gain ($n=16$) (Table 2). However, it is unknown whether weight loss was intentional/desirable for these patients. Patients with higher BMI before the start of chemoradiation 26.3 (SD 5) ($p=0.024$) and more females ($p=0.049$) were found in the group with weight loss. Weight loss in overweight/obese patients may not necessarily be desirable, particularly in older patients who may experience a disproportionate loss of lean muscle mass, leading to sarcopenic obesity and concomitant frailty.²⁴ In patients with head and neck cancer

treated with radiotherapy, either alone or combined with chemotherapy or surgery, Jager-Wittenaar et al²⁵ found that a higher fat mass at baseline is significantly related to loss of lean mass during treatment ($r=0.51$, $p=0.005$). This can indicate that extra support is needed for patients, especially woman, with a high BMI at the start of treatment. Due to the cross-sectional study design median follow-up after chemoradiation was 44 months with a range of 14 to 68 months. It should be mentioned that this was a highly heterogeneous time interval after the treatment period. However, there seemed no significant correlation with time interval and relative weight loss.

Food modification varying from mild to serious was necessary for all 32 patients. Six patients still used nutritional supplements or tube feeding (19%), 2 of them had no oral intake at all. This is in line with a study of Beeken en Calman,²⁶ who reported that 72% of patients required modifications of dietary consistency in oropharyngeal cancer treated with curative intent at a mean follow up of 3.5 years. Rademaker et al²⁷ described that 89% of the patients were able to eat orally and only 48% of patients (44/90) of patients could eat all foods (without modifications) until 12 months after (chemo)radiation (based on patients' reports). In contrast, a retrospective study carried out by Akst et al²⁸ found that, 24 months after chemoradiotherapy treatment, 7 of the 116 patients (6%) used tube feeding and 91% of patients (106/116) could eat a "normal diet". However, "normal diet" was not clarified.

In general, greens, bread, potatoes/rice/pasta/legumes, milk products, cheese, and low fat/diet margarine are far below the recommended food intake (Table 4). This is partially in line with the general Dutch population, in accord with the Dutch National Food Consumption Survey (2007-2010), where an insufficient intake of fruit, greens, fish and fiber is found.²⁹ So far no other literature has been found on the intake of food groups in patients with head and neck cancer after (chemo)radiotherapy. Accord to the report of the World Cancer Research Fund, nonstarchy vegetables and fruit in general protect against cancers of the mouth, pharynx, and larynx ($R^2=0.72$, confidence interval [CI]=0.63-0.82 per 50 g/day). In addition, there is consistent evidence for a dose-response relationship, whereby alcoholic drinks are a cause of mouth, pharynx, and larynx cancers ($R^2=1.24$, CI=1.18-1.30); this applies to beer in particular ($R^2=1.06$, CI=1.03-1.08).³⁰ Advice on the recommended vegetable and fruit intake also after treatment should therefore be emphasized. This applies also to the explicit benefit of alcohol limitation to decrease the risk of a secondary tumor. All this should be taken into account in nutritional advice in the long term.

In our study, dysphagia was present in 75% of the patients of whom 57% had impaired swallowing based on videofluoroscopy. Impaired swallowing was not correlated with malnutrition risk, "relative weight loss" or food modification. However lower global MDADI scores (higher impact of dysphagia on QoL) were significantly correlated with lower food modification scores (PSS-HN) ($r=0.405$; $p=0.024$). Langendijk et al¹³ found that QOL (EORTC) was significantly affected by late radiation-induced adverse effects (RTOG_{swallowing}), grade 3 and 4 (fluids only and tube feeding, respectively). In spite of different questionnaires used, this almost shows the same results.

The current study indicates that malnutrition risk and weight loss still exist, especially in females and patients with high BMI before chemoradiation. A high degree of food modifications, use of nutritional supplements/tube feeding is still present in head and neck cancer survivors treated with chemoradiotherapy. Qualitative food intake based on food groups is far beneath the food

recommendations. A higher impact of dysphagia on QOL was correlated with lower normalcy of food intake.

Despite the small study population, this study gives unique information on nutritional status, food intake and dysphagia in head and neck cancer survivors in the long term, which is educational for dietitians/nutritionists and the awareness of the total multidisciplinary head and neck oncology team. We conclude that nutritional advice for the patients with head and neck cancer is still necessary for a long time after chemoradiation and should focus on malnutrition risk and weight loss, food intake with normal food consistency without nutritional supplements/tube feeding, and recommended food groups.

Acknowledgments

The authors thank M. Louwerse and P. Stekkinger for their interest and data collection and E. Bronkhorst for statistical analysis.

References

1. van den Berg MG, Rasmussen-Conrad EL, Gwasara GM, Krabbe PF, Naber AH, Merks MA. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. *Clin Nutr* 2006;25:765-72.
2. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;14:199-212.
3. Allen AM, Elshaikh M, Worden FP, et al. Acceleration of hyperfractionated chemo radiation regimen for advanced head and neck cancer. *Head Neck* 2007;29:137-142.
4. Blanchard P, Hill C, Guihenneuc-Jouyaux C, et al. Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. *J Clin Epidemiol* 2011;29(18):2590-2599.
5. Pauloski BR, Rademaker AW, Logemann JA, et al. Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. *Head Neck* 2006;28:1069-1076.
6. Trotti A. Toxicity in head and neck cancer: a review of trends and issues. *Int J Radiat Oncol Biol Phys* 2000;47:1-12.
7. Raber-Durlacher JE, Brennan MT, Verdonck-de Leeuw IM, et al. Swallowing dysfunction in cancer patients. *Support Care Cancer* 2012;20(3):433-443.
8. Rütten H, Pop LA, Janssens GO, et al. Long-Term Outcome and Morbidity After Treatment with Accelerated Radiotherapy and Weekly Cisplatin for Locally Advanced Head-and-Neck Cancer: Results of a Multidisciplinary Late Morbidity Clinic. *Int J Radiat Oncol Biol Phys* 2010;77:655-661.
9. Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemo radiation for locally advanced head and neck cancer. *Ann Oncol* 2004;15:383-388.
10. Frowen JJ, Perry AR. Swallowing outcomes after radiotherapy for head and neck cancer: a systematic review. *Head Neck* 2006;28:932-944.
11. Garcia-Peris P, Parón L, Velasco C, et al. Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: Impact on quality of life. *Clin Nutr* 2007;26:710-717.
12. Platteaux N, Dirix P, Dejaeger E, Nuyts S. Dysphagia in head and neck cancer patients treated with chemo radiotherapy. *Dysphagia* 2010;25:139-152.
13. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770-3776.
14. Agarwal J, Dutta D, Palwe V, et al. Prospective subjective evaluation of swallowing function and dietary pattern in head and neck cancers treated with concomitant chemo-radiation. *J Cancer Res Ther* 2010;6:15-21.
15. Scott A. Screening for malnutrition in the community: the MUST tool. *Br J Community Nurs* 2008;13:06,408,410-412.
16. World Health Organization. BMI Classification 2006. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed 5 April 2012.
17. List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. *Cancer* 1996;77:2294-2301.

18. Biró G, Hulshof KF, Ovesen L, Morim Cruz JA. Selection of methodology to assess food intake. *Eur J Clin Nutr* 2002;56 Suppl 2:S25-S32.
19. Donders-Engelen M, van der Heijden L, Hulshof K. Sizes, weights and code numbers. Wageningen University: Department of Human Nutrition, Wageningen; 2003.
20. National Institute for Public Health and Environment. Dutch food composition database Version 2011-3.0; 2011. <http://nevo-online.rivm.nl/>. Accessed 5 April 2012.
21. The Netherlands Nutrition Centre Foundation. Directives Food Choice;2011. <http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/12042011Richtlijnen%20voedselkeuze%20VC.pdf>. Accessed 5 April 2012.
22. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M.D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg* 2001;127:870-876.
23. TNM stage. Bobin LH, Wittekind C. TNM Classification of Malignant Tumours. 6th Edition. John Wiley & Sons, New York; 2002
24. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;9(7):629-635.
25. Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head Neck* 2011;33:863-870.
26. Beeken L, Calman F. A return to "normal eating" after curative treatment for oral cancer. What are the long-term prospects? *Eur J Cancer B Oral Oncol* 1994;30B:387-392.
27. Rademaker AW, Vonesh EF, Logemann JA, et al. Eating ability in head and neck cancer patients after treatment with chemo radiation: a 12-month follow-up study accounting for dropout. *Head Neck* 2003;25:1034-1041.
28. Akst LM, Chan J, Elson P, Saxton J, Strome M, Adelstein D. Functional outcomes following chemo radiotherapy for head and neck cancer. *Otolaryngol Head Neck Surg* 2004;131:950-957
29. Rossum CTM, Fransen HP, Verkaik-Kloosterman J, Buurma-Rethans EJM, Ocke MC. Dutch National Food Consumption Survey 2007-2010 : Diet of children and adults aged 7 to 69 years. National Institute for Public Health and the Environment; 2011. http://www.rivm.nl/Bibliotheek/Wetenschappelijk/Rapporten/2011/oktober/Dutch_National_Food_Consumption_Survey_2007_2010_Diet_of_children_and_adults_aged_7_to_69_years? Accessed 5 April 2012.
30. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective; 2010. http://www.dietandcancerreport.org/expert_report/report_contents/index.php. Accessed 5 April 2012.

7

Normalcy of food intake in head and neck cancer patients supported by combined dietary counseling and swallowing therapy: A Randomized clinical trial

M.G.A. van den Berg

J.G. Kalf

J.C.M. Hendriks

R.P. Takes

C.M.L. van Herpen

G.J.A. Wanten

J.P.H. Drenth

J.H.A.M. Kaanders

M.A.W. Merkx

Submitted



Abstract

Purpose

Dysphagia resulting in diminished or altered oral food intake requiring tube feeding is common among head and neck cancer patients. This randomized clinical trial investigated the effect of combined individual dietary counseling with individual swallowing therapy (intervention) compared to individual dietary counseling alone (control) on normalcy of food intake (NFI).

Patients and methods

Patients with stage II-IV head and neck cancer treated with primary or postoperative (chemo) radiation were randomly assigned to the intervention or control group. NFI was defined as food intake without tube feeding, dietary energy drinks/supplements or modified foods. Dysphagia severity, social eating, and nutritional status were also measured at the start of treatment and in weeks 6, 10, 18 and 30.

Results

Patients were recruited from March 2010 through April 2012. NFI was achieved at week 30 in 63% and 51% of patients in the intervention and control groups, respectively; the difference in NFI was 5.3 (95% CI: -4.2 to 14.9) in favor of the intervention group. The percentage of patients requiring tube feeding was low in the total study period in both the intervention (24%) and control (19%) group. No overall estimated difference was detected for dysphagia severity, social eating, or nutritional status. At week 10, the intervention group had improved recovery of dysphagia compared to the control group 0.6 (95% CI: 0.1 to 1.1), although this difference diminished by week 30.

Conclusion

This study demonstrates that adding individual swallowing therapy to individual dietary counseling does not improve normalcy of food intake but accelerated swallowing recovery.

Introduction

Patients with head and neck squamous cell carcinomas (HNSCC) often suffer from impaired oral food intake due to tumor symptoms and side effects of the treatment.¹⁻³ Dysphagia is one of the most prevalent and serious complications that can arise during and following radiation therapy and can severely restrict food intake.⁴⁻⁷ Temporary tube feeding, the use of oral nutritional supplements, and/or food modifications can be necessary to ensure adequate nutrient intake.⁸ However, resuming normal oral feeding after tube feeding can be difficult as a result of chronic dysphagia.^{4,9}

Any deviation from normal food intake can decrease quality of life. For example, increased eating time, considerable messiness with food, and reluctance to eat in public can have a negative impact on the patient's quality of life.^{4,10-12} Achieving normal food intake, which is defined as regular full oral intake without the need for tube feeding, energy drinks/supplements or modified foods, is therefore an important goal for patients with HNSCC.

Some prospective studies have suggested that preventive swallowing therapy can have a beneficial effect on swallowing function in patients with HNSCC who are treated with (chemo) radiation.^{13,14} Swallowing therapy can be effective at decreasing dysphagia severity, thereby reducing the need for tube feeding and improving oral food intake.^{15,16} We hypothesized that combining individual dietary counseling with individual swallowing therapy during and after (chemo)radiation can improve the patients' normalcy of food intake (NFI).

This randomized clinical trial evaluated whether concerted multidisciplinary treatment with individual dietary counseling and swallowing therapy improves NFI in patients with HNSCC treated with primary or postoperative (chemo)radiation compared to individual dietary counseling alone.

Patients and methods

Eligibility and Assignment

This study was performed at the Radboud University Nijmegen Medical Center and was approved by the university's research ethics committee (ABR: 28638.091.09). This study was registered at ClinicalTrials.gov (FOCISD: NCT01110980). Patient eligibility was assessed by the multidisciplinary head and neck oncology team.

Eligibility criteria: Patients ≥ 18 years of age with stage II-IV (UICC TNM-tumor classification) squamous cell carcinoma of the oral cavity, nasopharynx, oropharynx, hypopharynx or larynx and who received curative treatment with primary or postoperative (chemo)radiation were eligible.

Exclusion criteria: Patients with previous head and neck carcinoma treated by primary or postoperative (chemo)radiation or surgery, neurological or other non-tumor-related swallowing problems, an inability to comprehend and/or perform swallowing therapy and instructions and/or an inability to answer the study questionnaires.

Each patient provided written informed consent prior to randomization. Eligible patients were randomly assigned to either the intervention group or the control group at a 1:1 ratio using a computer-controlled randomization process with minimization of the following three potential

confounding variables: tumor location, tumor stage, and tumor treatment.

The patients, dietitians, and speech-language pathologists were aware of the treatment allocation. The patients were treated in accordance with the guidelines of the Dutch Head and Neck Society.

Control group: Individual dietary counseling (standard care)

The patients in the control group received standard care, defined as individualized intensive dietary counseling by a dietitian who focused on maintaining and/or improving the patient's energy and protein intake according to the patient's requirements.¹⁷ The patient's energy requirement was estimated as described by Harris and Benedict (1984) with an additional 30-50%.¹⁸ During treatment, each patient received dietary counseling each week and during the rehabilitation period at least every two months (or more frequently as needed) following protocol.¹⁷

Intervention group: Combined individual dietary counseling with individual swallowing therapy

Patients in the intervention group received the same individualized intensive dietary counseling as the patients in the control group. In addition, these patients received individual swallowing therapy by a speech-language pathologist to compensate for consequences of the tumor or (chemo)radiation on the efficacy and safety of oropharyngeal swallowing. The swallowing therapy consisted of the following interventions: (a) stretching exercises designed to maximize lip, tongue and jaw mobility; (b) compensations and swallowing maneuvers such as adapted head posture and supraglottic swallowing (e.g., to compensate for aspiration if needed)¹⁹; and (c) adaptations of food consistencies if needed. Patients who were at risk for aspiration or had substantial dysphagia and were (completely) dependent on tube feeding or modified food intake were supported by the speech-language pathologist to ensure safe oral intake with optimum food modification. Simultaneously, the dietitian provided advice regarding maintaining and/or improving the patient's energy and protein intake according to the patient's requirements, with tube feeding and energy drinks/supplements reduced as much as possible. The intervention sessions occurred from the first week of (chemo) radiation and lasted for 30 weeks. Patients were seen weekly during (chemo)radiation and were instructed to perform their exercises daily; after (chemo)radiation, patients were seen every two months and were monitored weekly through telephone sessions.

Data collection

Data were collected in week 0 (the first week of treatment), week 6 (the last week of treatment), week 10 (one month after treatment), week 18 (three months after treatment) and week 30 (six months after treatment).

Normalcy of food intake (NFI)

NFI was measured using the PSS-HN-normalcy of diet and NFIS-HN-F (Appendix 1).²⁰⁻²² PSS-HN is a validated clinician-rated instrument with the following three subscales: normalcy of diet, eating in public, and understandability of speech.²⁰ PSS-HN-normalcy of diet was used

to report food modification, with a score of 100 reflecting optimum NFI. The NFIS-HN-F score was calculated based on the mean values of a two-day food diary (one weekend day and one non-weekend day) that was reported by each patient. The amounts consumed were measured in milliliters or grams.²³ The food diary was “cross-checked” by the dietician. The food items were coded, and energy intake was calculated according to the Dutch Food Composition Database.²⁴ The optimum NFI according to the NFIS-HN-F was defined as a score of 6.

Dysphagia severity

Dysphagia severity was measured using the NFIS-HN-L, a clinician-rated oral intake scale specific for HNCP (Appendix 1).^{21,22} The M.D. Anderson Dysphagia Inventory (MDADI) a validated and self-administered questionnaire for patients with HNSCC, was used to assess the impact of dysphagia on the patient’s quality of life.²⁵ To measure swallowing capacity, the swallowing velocity and swallowing volume tests were performed.^{26,27}

Social eating

PSS-HN-eating in public was measured to identify quality of life issues with respect to the patient’s ability to share meals with others.²⁰

Nutritional status

Nutritional status was measured as check for good nutritional care. Each patient’s body weight was measured on a calibrated SECA scale (model 770, Hamburg, Germany), while wearing lightweight clothing. Height was measured with a SECA ruler (type DBGM, Hamburg, Germany). The patient’s body weight six months prior to the start of treatment was retrieved from the patient’s medical file, and “relative weight change” was calculated as the percent weight change relative to the weight at week 0. Body Mass Index (BMI) was calculated using the formula kg/m^2 .²⁸ Malnutrition was measured at week 0, week 18, and week 30 and was defined as the presence of at least one of the following criteria: a) unintentional weight loss of $\geq 5\%$ in one month and/or $\geq 10\%$ in six months; b) $\text{BMI} \leq 18.5$ in patients under the age of 65; and c) $\text{BMI} \leq 20$ in patients age 65 years or older.²⁹

Statistical methods

The Mann-Whitney U-test was used to test difference in the patient characteristics between the therapy groups for statistical significance in the case of continuous variables and the Pearson’s chi-squared test in case of two by two tables.

Prior to the analyses, the swallowing volume and the swallowing velocity was put to zero for those patients who were not able to swallow or did not dare to swallow.

A linear mixed model for repeated measurements was used to study the differences between the two treatment groups for each of the variables regarding “Normalcy of food intake”, “Dysphagia severity”, “Social eating” and “Weight change”, separately. The dependent variable was the specific variable. The independent class variables were the treatment group (two levels) and time point of measurement (four levels). The independent continuous variable was the baseline value of the specific variable. Also the interaction term between group and time point was included in the model. The intercept of each patient was treated as a random

variable to allow a different level for each patient. The estimated difference between the two groups with the 95% confidence interval is presented at 10 and at 30 weeks.

All patients with at least one follow-up measurement were included in the analysis (intention to treat).

Statistical analyses were performed using SPSS 20.0 for Windows (IBM, SPSS Inc., Chicago, IL, USA).

Sample size

Based on a difference of ten points on the PSS-HN normalcy of diet scale, two groups of 50 patients were required to achieve a power of 80% for performing an analysis of covariance with baseline as covariate (two-sided testing with $\alpha=0.05$). This result was based on a standard deviation of 25 and a test-retest correlation of 0.7.^{14,30} Thus, with an estimated withdrawal rate of 20%, 120 patients (60 patients per group) had to be enrolled in order to achieve this required sample size.

Results

Patients

One hundred and twenty patients were randomly assigned to either the intervention or control group from March 2010 through April 2012, with the last patient completing the measurements at week 30 in December 2012 (Fig. 1). Six patients (three from each group) withdrew their consent before the first measurement, stating that participation in the study during medical treatment would be too demanding. Thus, a total of 57 patients in each group were eligible for analysis (Fig. 1). One patient in the control group received swallowing therapy according standard care. The baseline characteristics by study groups showed no statistical differences (Table 1). The majority of the patients had relatively small T₂-stage tumors (68%) and received primary radiation (63%).

The percentage of patients who received tube feeding and energy drinks/supplements is presented in Table 2. At the start of treatment, two patients in the intervention group and one patient in the control group were already using tube feeding. Eleven patients in the intervention group were fed through a nasogastric tube, and three patients were fed through a percutaneous radiologic gastrostomy; 11 patients in the control group were fed through a nasogastric tube. In the first week of treatment, the prevalence of malnutrition was significantly higher in the intervention group ($p=0.03$); in weeks 18 and 30, the prevalence of malnutrition was similar between the two groups (Table 2).

Swallowing intervention

The intervention group received an average of nine (SD=3.6) swallowing therapy sessions, with a minimum of 4 and a maximum of 21 sessions; only five of the patients (8%) required 11 or more sessions. Except for the stretching exercises, the majority of the interventions (96%) were changes in head posture and food consistency. Nine of the patients (15%) needed to use a swallowing maneuver in order to achieve safe swallowing.

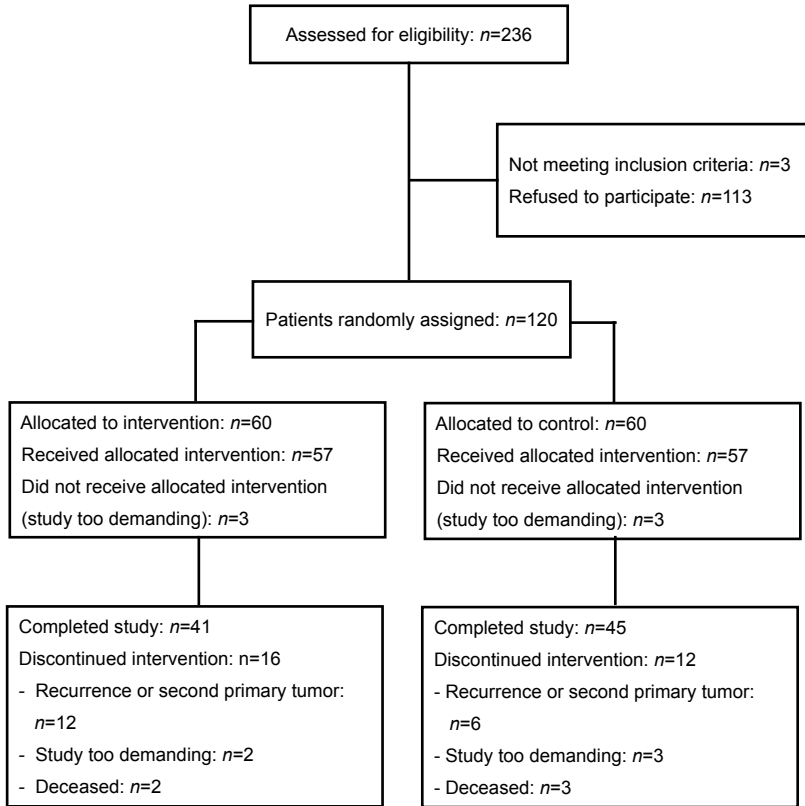


Figure 1. CONSORT diagram. Intervention: combined individual dietary counseling and individual swallowing therapy. Control: individual dietary counseling (standard care).

Normalcy of food intake

The observed mean (SD) values of the PSS-HN-normalcy of diet and NFIS-HN-F by point of measurements in each study group and the estimated differences between the study groups at week 10 and 30 are presented in Table 3. The estimated mean profiles of the PSS-HN-normalcy of diet and NFIS-HN-F were similar between the intervention and control groups (Fig. 2). Although the estimated mean difference in PSS-HN-normalcy of diet at week 30 was higher in the intervention group than in the control, a difference of 5.3 (95% CI: -4.2 to 14.9), this difference did not reach the level of statistical significance (Table 3). In addition, the percentages of patients with the optimum NFI score at week 30 were nearly identical to the percentages at week 0 (Table 4). The percentage of tube feeding was highest in week 10 for both groups (intervention: 17%, control: 12%) and then decreased to baseline values by week 30 (intervention: 3%, control: 0%).

Table 1 Baseline characteristics by study groups

	Intervention <i>n</i> =60 Median (range)/ <i>n</i> (%)	32 participants at the late morbidity clinic (%)
Demographic		
Age, years	63 (33-83)	60 (40-86)
Male	46 (77)	43 (72)
Disease		
T stage ^a		
T ₂	39 (65)	43 (72)
T ₃	8 (13)	7 (12)
T ₄	13 (22)	10 (16)
N stage ^a		
N ₀	30 (50)	25 (42)
N ₁	5 (8)	14 (23)
N ₂	23 (38)	20 (33)
N ₃	2 (4)	1 (2)
Stage grouping ^a		
II	22 (37)	20 (33)
III	9 (15)	14 (23)
IV	29 (48)	26 (44)
Tumor site		
Nasopharynx	3 (5)	3 (5)
Oral cavity	12 (20)	12 (20)
Oropharynx	20 (33)	16 (27)
Hypopharynx	5 (9)	10 (16)
Larynx	20 (33)	19 (32)
Treatment		
Radiotherapy	38 (63)	38 (63)
Postop. radiotherapy	9 (15)	9 (15)
Chemoradiation	9 (15)	10 (17)
Postop. chemoradiation	4 (7)	3 (5)
Treatment technique		
IMRT [*]	56 (93)	54 (90)
3D conformal [†]	4 (7)	6 (10)
Radiotherapy dosis, Gy	4 (6)	65 (5)
Anthropometric		
Weight, kg	70 (47-122)	72 (47-118)
Height, cm	175 (151-192)	175 (154-191)
Weight six months prior, kg	76 (45-131)	77 (47-122)
BMI, kg/m ² ^{††}	23 (17-40)	24 (16-44)

^aStage according to UICC TNM-tumor classification.

^{*}IMRT: intensity-modulated radiation therapy. [†]3D conformal: three-dimensional conformal radiotherapy. ^{††}BMI: Body Mass Index.

Table 2 Tube feeding, energy drinks/supplements, and malnutrition prevalence by study group

	Intervention <i>n</i> (%) / median (range)	Control <i>n</i> (%) / median (range)	<i>p</i> value
Tube feeding (yes)	14 (24%)	11 (19%)	0.39 ^a
Energy drinks/supplements (yes)	57 (100%)	54 (95%)	0.59 ^a
Time to onset tube feeding, days ^c	30 (0-43)	27 (18-131)	0.64 ^b
Duration of tube feeding, days ^d	33 (5-200)	28 (3-85)	0.37 ^b
Time to onset Energy drinks/supplements, days ^c	15 (0-143)	16 (0-115)	0.67 ^b
Duration of Energy drinks/ supplements, days ^d	64 (2-225)	76 (2-219)	0.59 ^b
Malnutrition (yes)			
week 0	15 (26%)	6 (10%)	0.03 ^a
week 18	16 (31%)	16 (33%)	0.83 ^a
week 30	10 (24%)	9 (20%)	0.24 ^a

^a Pearson's chi-squared test. ^b Mann-Whitney U-test.^c From week 0 until preparation use (tube feeding and energy drinks/supplements).^d Time between start and end of preparation use (tube feeding and energy drinks/supplements).

Dysphagia severity, social eating and nutritional status

The observed mean (SD) concerning dysphagia severity and social eating of the NFIS-HN-L, MDADI-E/F/P, swallowing volume (ml), swallowing velocity (ml/s), and PSS-HN-eating in public by point of measurements in each study group and the estimated differences between the study groups are presented in Table 3. With respect to NFIS-HN-L, the mean estimated NFIS-HN-L value at week 10 was statistically significantly higher in the intervention group than in the control group by 0.6 (95% CI: 0.1 to 1.1); however, this difference diminished by week 30 (Table 3 and Fig. 2).

Mean profiles of MDADI-E/F/P, swallowing volume, swallowing velocity, and PSS-HN-eating in public did not differ significantly between the intervention group and the control group (Table 3 and Fig. 2). Regarding swallowing velocity and swallowing volume 14% of the measurements was missing in the intervention group and 19% in the control group, because patients were not able to swallow or did not dare to swallow.

Additionally, in both groups the percentages of patients with optimum scores for dysphagia severity and social eating at week 30 were similar to their respective percentages at week 0 (Table 4).

Mean weight change profiles were nearly identical between the intervention group and the control group; however, at week 30 the intervention group had more weight gain compared to the control group 1.34% (95% CI: -0.45 to 3.14), although this difference did not reach the level of statistical significance (Table 3 and Fig. 2).

Table 3 The observed mean (SD) of the variables regarding “Normalcy of food intake”, “Dysphagia severity”, “Social eating” and “Weight change” by point of measurement in each study group and the estimated difference between the study groups at weeks 10 and 30, by using a linear mixed model for repeated measurements with adjustment to the baseline value.

	Observed					Difference in favor of the intervention	
	Week 0	Week 6	Week 10	Week 18	Week 30	Week 10	Week 30
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Normalcy of food intake							
PSS-HN-normalcy of diet*							
Intervention	78 (26)	50 (19)	59 (25)	72 (26)	85 (21)	-5.0 (-16.1 to 6.1)	5.3 (-4.2 to 14.9)
Control	75 (25)	50 (30)	60 (29)	76 (25)	79 (24)	0.0 (reference)	0.0 (reference)
NFIS-HN-F†							
Intervention	5.5 (0.9)	4.4 (1.1)	4.6 (1.3)	5.2 (0.9)	5.6 (0.7)	0.0 (-0.4 to 0.3)	0.2 (-0.2 to 0.7)
Control	5.6 (0.6)	4.5 (1.3)	4.6 (1.3)	5.2 (1.1)	5.3 (0.7)	0.0 (reference)	0.0 (reference)
Dysphagia severity							
NFIS-HN-L††							
Intervention	5.1 (1.2)	4.5 (1.1)	4.8 (1.1)	5.0 (1.0)	5.1 (1.0)	0.6 (0.1 to 1.1)	-0.1 (-5.2 to 0.3)
Control	5.0 (1.1)	4.2 (1.3)	4.3 (1.2)	4.8 (1.1)	5.1 (1.0)	0.0 (reference)	0.0 (reference)
MDADI-E							
Intervention	79 (12)	74 (12)	76 (12)	80 (12)	80 (12)	-0.4 (-5.0 to 4.2)	0.0 (-0.2 to 0.2)
Control	81 (10)	76 (11)	78 (11)	81 (11)	81 (11)	0.0 (reference)	0.0 (reference)
MDADI-F¶							
Intervention	78 (11)	73 (15)	76 (15)	76 (12)	79 (11)	-0.1 (-5.4 to 5.1)	0.1 (-0.1 to 0.3)
Control	80 (9)	75 (11)	77 (12)	78 (10)	79 (10)	0.0 (reference)	0.0 (reference)
MDADI-P#							
Intervention	76 (19)	58 (15)	65 (17)	73 (18)	74 (17)	-0.3 (-6.5 to 5.9)	0.0 (-0.3 to 0.3)
Control	78 (18)	60 (15)	68 (18)	72 (16)	77 (17)	0.0 (reference)	0.0 (reference)
Swallowing volume (ml)							
Intervention	42 (23)	32 (21)	40 (22)	44 (22)	48 (21)	-2.5 (-8.8 to 3.8)	5.9 (-1.1 to 12.9)
Control	48 (22)	35 (19)	40 (20)	42 (24)	46 (23)	0.0 (reference)	0.0 (reference)
Swallowing velocity (ml/s)							
Intervention	18 (10)	9 (8)	14 (10)	17 (10)	18 (9)	-0.0 (-4.0 to 3.8)	-2.0 (-5.3 to 1.3)
Control	17 (10)	11 (10)	15 (11)	18 (12)	19 (10)	0.0 (reference)	0.0 (reference)
Social eating							
PSS-HN-eating in public							
Intervention	78 (26)	45 (24)	58 (26)	72 (28)	82 (25)	-6.0 (-18.5 to 6.4)	2.3 (-8.6 to 13.1)
Control	79 (25)	51 (30)	63 (29)	79 (26)	80 (21)	0.0 (reference)	0.0 (reference)
Weight change							
Intervention	0 (0)	-2.6 (2.8)	-5.9 (5.1)	-5.5 (5.6)	-4.1 (6.7)	-1.54 (-3.41 to 3.14)	1.34 (-0.45 to 3.14)
Control	0 (0)	-2.7 (3.3)	-5.8 (4.8)	-6.0 (5.8)	-5.7 (6.0)	0.0 (reference)	0.0 (reference)

CI: Confidence interval.

*PSS-HN -Normalcy of diet: Performance Status Scale-Head and Neck-normalcy of diet. Score 0 to 100; a higher score is better; †NFIS-HN-F (Appendix 1): Normalcy of Food Intake Scale-Head and Neck-Dietetic part. Score 1 to 6; a higher score is better; ††NFIS-HN-L (Appendix 1): Normalcy of Food Intake Scale-Head and Neck-Logopedic part. Score 1 to 6; a higher score is better; MDADI: M.D. Anderson Dysphagia Inventory - E/|| (emotional)F/¶ (functional)P/# (physical). Score 0 to 100; a higher score is better. PSS-HN –eating in public: Performance Status Scale-Head and Neck-eating in public. Score 0 to 100; a higher score is better

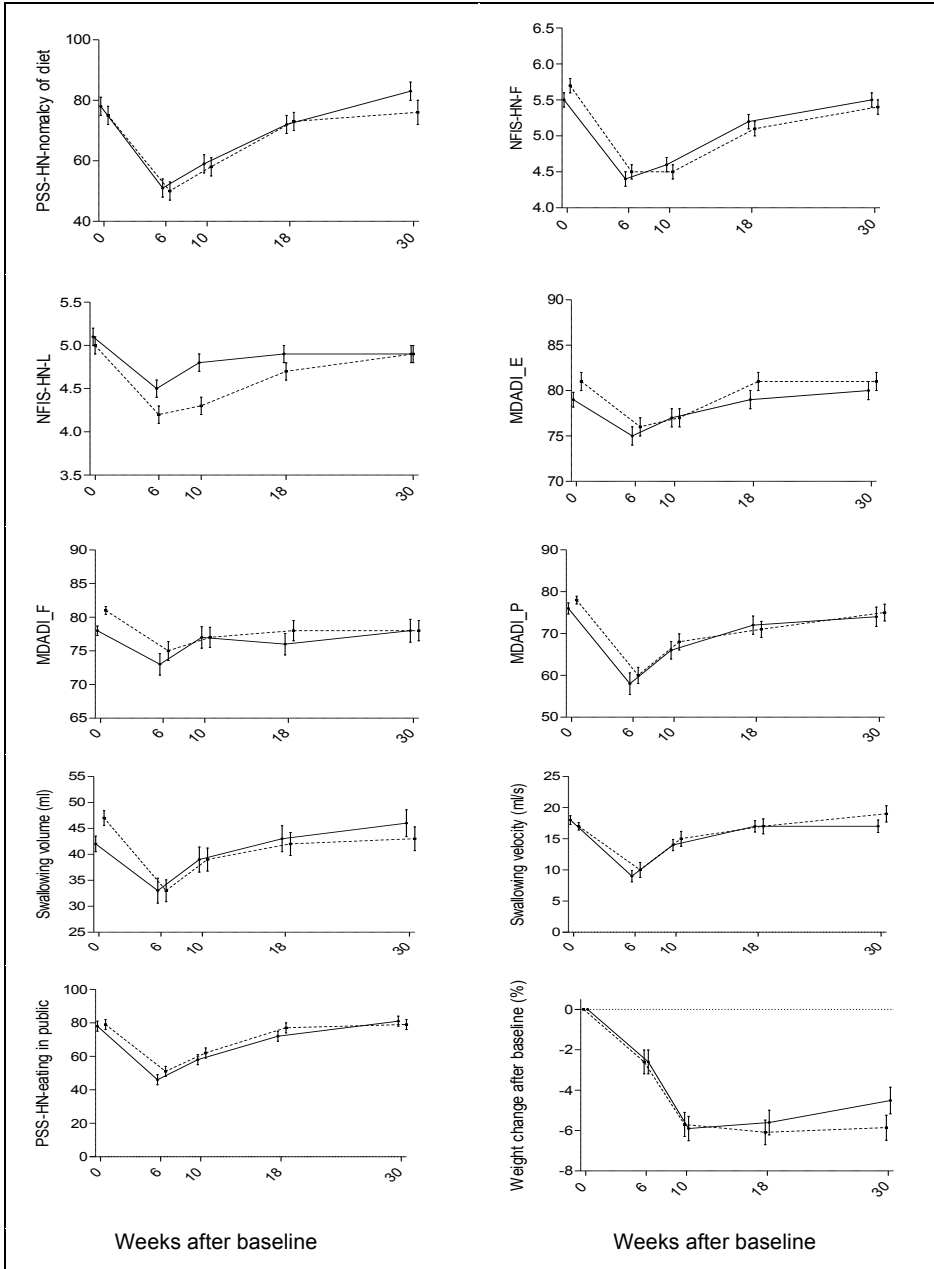


Figure 2. The estimated mean profiles from baseline up to 30 weeks of PSS-HN-normalcy of diet, NFIS-HN-F, NFIS-HN-L, MDADI_E/F/P, swallowing volume (ml), swallowing velocity (ml/s), PSS-HN-eating in public, weight change after baseline (%) for the intervention group (solid lines) and control group (dashed lines). The vertical bars indicate one standard error.

Table 4 The number (%) of the patients with an optimum score (i.e., normal) with respect to “Normalcy of food intake”, “Dysphagia severity” and “Social eating” by point of measurement, by study group.

	Week 0 <i>n</i> (%)	Week 6 <i>n</i> (%)	Week 10 <i>n</i> (%)	Week 18 <i>n</i> (%)	Week 30 <i>n</i> (%)
Normalcy of food intake					
PSS-HN-normalcy of diet					
Intervention	31 (54)	4 (7)	11 (20)	18 (35)	22 (63)
Control	26 (45)	8 (15)	12 (24)	19 (39)	21 (51)
NFIS-HN-F					
Intervention	39 (68)	9 (15)	18 (32)	27 (52)	30 (76)
Control	44 (77)	14 (25)	16 (30)	26 (56)	31 (68)
Dysphagia severity					
NFIS-HN-L					
Intervention	34 (59)	14 (25)	22 (40)	22 (43)	17 (42)
Control	28 (49)	14 (26)	10 (20)	17 (35)	22 (49)
Social eating					
PSS-HN-eating in public					
Intervention	30 (53)	4 (7)	10 (18)	20 (39)	25 (60)
Control	31 (54)	8 (15)	14 (28)	25 (52)	22 (48)

PSS-HN-normalcy of diet: Performance Status Scale-Head and Neck-Normalcy of diet (i.e. equal to 100); NFIS-HN-F (Appendix 1): Normalcy of Food Intake Scale- Head and Neck-Dietetic part (i.e. equal to 6); NFIS-HN-L (Appendix 1): Normalcy of Food Intake Scale- Head and Neck-Logopedic part (i.e. equal to 6); PSS-HN-eating in public: Performance Status Scale-Head and Neck-Eating in public (i.e. equal to 100).

Discussion

This randomized controlled trial of patients with a stage II-IV HNSCC treated with primary or postoperative (chemo)radiation revealed that the addition of individual swallowing therapy to individual dietary counseling did not significantly improve NFI. Moreover, the addition of individual swallowing therapy did not reduce the severity of dysphagia, nor did it improve social eating or nutritional status. However, the severity of dysphagia was decreased more in the intervention group at week 10, although this difference diminished by week 30.

A recent study compared the effect of prophylactic swallowing exercises during chemoradiation with post-treatment swallowing exercises and found that prophylactic swallowing exercises led to an improvement in PSS-HN-normalcy of diet and PSS-HN-eating in public that lasted up to six months after the end of treatment.³¹ Another trial compared active swallowing exercises from the start of treatment with either usual care or sham swallowing therapy in patients with head and neck cancer treated with chemoradiation.³² Swallowing musculature (measured using T₂-weighted MRI) was preserved better in the active swallowing exercise group than in the other treatment groups. However, functional oral intake scores did not differ significantly between the groups. These studies used rigid training regimes that included up to two daily exercises with a speech-language pathologist, irrespective of dysphagia severity.

One of the most important differences between studies that report a positive effect of prophylactic swallowing therapy and our current study is that we included lower staged HNSCC

patients who received primary or postoperative (chemo) radiation. Another possible reason for our lack of intervention effect may be the introduction of intensity-modulated radiation therapy (IMRT) in the course of our study. IMRT reduces irradiation of the swallowing musculature and salivary glands and has a positive effect on saliva production, including a reduction in the prevalence of complications such as xerostomia (dry mouth), less sticky saliva, and fewer restrictions in the type and amount of food intake until six months after treatment.³³ It is therefore possible that a beneficial effect of IMRT led to a bias against differences between the intervention group and the control group.

The patients in the control group may also have benefited from individual dietary counseling. This strategy may have prevented the need for changing the consistency of the food and/or the use of energy drinks/supplements or tube feeding by providing the most optimum alternative food to fulfill the patient's nutritional requirements. In addition, prophylactic gastrostomy placement is not included in our standard care. Reactive tube feeding was re-introduced in recent years based on published literature and expert opinion³⁴, and in our study this approach led to a transition from tube feeding to energy drinks/supplements in 95-100% of patients.

Another possible reason that we were unable to detect any positive effects of swallowing therapy is that the swallowing treatment regime used in other studies was more intense than in our study.^{31,32} However, it is very doubtful and unproven yet whether high-intensity treatment can be applied as a routine intervention, as the clinical condition of some of these patients during and immediately after radiation treatment precludes the use of such intensive treatments.

Evidence regarding the optimal timing and intensity of swallowing therapy is currently absent. It is therefore important to identify patients with severe dysphagia who may benefit from—and are able to undergo—intensive swallowing therapy during and/or after treatment. Maybe, extending swallowing therapy beyond radiation treatment will improve patient outcome, as patients will start to recover and will better be able—and more motivated—to perform training exercises in order to improve their NFI and decrease their dysphagia severity.

As with any clinical trial, our study has several inherent limitations. First, it was not possible to blind the dietician or speech-language pathologist with respect to the treatment allocation due to the combined treatment intervention, and this may have led to observation bias. In addition, we did not assess compliance in our study. However, a similar study has reported satisfactory compliance of preventive swallowing therapy.³⁵

In conclusion, adding individual swallowing therapy to individual dietary counseling during radiation treatment of patients with HNSCC did not significantly improve NFI, although it may slightly accelerate the recovery of dysphagia following radiation. Our data suggest that the use of IMRT and intensive individual dietary counseling with a reactive approach of tube feeding may have a positive effect on achieving NFI.

Acknowledgements

The authors would like to thank dietitians Monique Asseldonk, Mariska Louwerse and Mirjam van der Laan and speech-language pathologists Anne van Gerwen, Emmelien Kolvoort and Pauline Stekkinger for their dedicated treatment of the patients. Wim Lemmens is acknowledged for his statistical and data support.

Conflict of interest

This study was supported by a grant from Fresenius Kabi Nederland BV and Sorgente BV. Neither of these entities was involved in writing this report nor is responsible for the content of the report.

Appendix 1

Table 4 The number (%) of the patients with an optimum score (i.e., normal) with respect to “Normalcy of food intake”, “Dysphagia severity” and “Social eating” by point of measurement, by study group.

Score	Definition NFIS- HN score <i>Dietetic Part (F)</i>	<i>Logopedic Part (L)</i>
1	NPO*, withhold all oral food and fluids, except water (total tube feeding–parenteral nutrition)	Severe dysphagia, swallowing impossible and/or severe aspiration
2	Tube feeding in combination with oral intake (thick liquid/possibly incl. oral dietary supplements) with $\geq 50\%$ of nutritional intake ¹ provided by tube feeding	Dysphagia, great difficulty with food passage ² , swallowing impossible and/or severe aspiration
3	Soft and/or liquid oral intake (possibly incl. oral dietary supplements) with $< 50\%$ of nutritional intake ¹ provided by tube feeding	Moderate/severe dysphagia, difficulty with food passage, heavily needed compensation ³ and/or risk of aspiration
4	Soft and/or liquid oral intake with $\geq 50\%$ of nutritional intake ¹ provided by oral dietary supplementation (without tube feeding)	Mild dysphagia, difficulty with some food passage, some compensation ³ needed, and/or incidental aspiration
5	Oral intake of all food consistencies with $< 50\%$ of nutritional intake ¹ provided by oral dietary supplementation (without tube feeding)	Minimal dysphagia, difficulty with dry food only
6	Oral intake of all food consistencies without oral dietary supplementation or the need for tube feeding	Normal, can eat and drink everything as before

PSS-HN-normalcy of diet: Performance Status Scale-Head and Neck-Normalcy of diet (i.e. equal to 100);
 NFIS-HN-F (Appendix 1): Normalcy of Food Intake Scale- Head and Neck-Dietetic part (i.e. equal to 6);
 NFIS-HN-L (Appendix 1): Normalcy of Food Intake Scale- Head and Neck-Logopedic part (i.e. equal to 6);
 PSS-HN-eating in public: Performance Status Scale-Head and Neck-Eating in public (i.e. equal to 100).

References

1. Larsson M, Hedelin B, Johansson I, et al: Eating problems and weight loss for patients with head and neck cancer: a chart review from diagnosis until one year after treatment. *Cancer Nurs* 2005;28:425-435.
2. Mangar S, Slevin N, Mais K, et al: Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. *Radiother Oncol* 2006;78:152-158
3. Rademaker AW, Vonesh EF, Logemann JA, et al: Eating ability in head and neck cancer patients after treatment with chemoradiation: a 12-month follow-up study accounting for dropout. *Head Neck* 2003;25:1034-1041
4. Frowen JJ, Perry AR: Swallowing outcomes after radiotherapy for head and neck cancer: a systematic review. *Head Neck* 2006;28:932-944
5. Garcia-Peris P, Paron L, Velasco C, et al: Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: Impact on quality of life. *Clin Nutr* 2007;26:710-717
6. Manikantan K, Khode S, Sayed SI, et al: Dysphagia in head and neck cancer. *Cancer Treat Rev* 2009;35:724-732
7. Rutten H, Pop LA, Janssens GO, et al: Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. *International journal of radiation oncology, biology, physics* 2011;81:923-9
8. Arends J, Bodoky G, Bozzetti F, et al: ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clin Nutr* 2006;25:245-259
9. Agarwal J, Dutta D, Palwe V, et al: Prospective subjective evaluation of swallowing function and dietary pattern in head and neck cancers treated with concomitant chemoradiation. *J Cancer Res Ther* 2010;6:15-21
10. Nguyen NP, Frank C, Moltz CC, et al: Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2005;61:772-778
11. McQuestion M, Fitch M, Howell D: The changed meaning of food: Physical, social and emotional loss for patients having received radiation treatment for head and neck cancer. *Eur J Oncol Nurs* 2011;15:145-151
12. Terrell JE, Ronis DL, Fowler KE, et al: Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2004;130:401-408
13. Carroll WR, Locher JL, Canon CL, et al: Pretreatment swallowing exercises improve swallow function after chemoradiation. *The Laryngoscope* 2008;118:39-43
14. Kulbersh BD, Rosenthal EL, McGrew BM, et al: Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. *The Laryngoscope* 2006;116:883-6
15. Nguyen NP, Moltz CC, Frank C, et al: Impact of swallowing therapy on aspiration rate following treatment for locally advanced head and neck cancer. *Oral oncology* 2007;43:352-7
16. Crary MA, Carnaby Mann GD, Groher ME, et al: Functional benefits of dysphagia therapy using adjunctive sEMG biofeedback. *Dysphagia* 2004;19:160-164
17. van den Berg MG, Rasmussen-Conrad EL, Wei KH, et al: Comparison of the effect of individual dietary counseling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *The British journal of nutrition* 2010;104:872-7

18. Roza AM, Shizgal HM: The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *The American journal of clinical nutrition* 1984;40:168-82
19. Logemann JA: Evaluation and treatment of swallowing disorders. Austin/Texas, Pro-Ed, 1998
20. List MA, D'Antonio LL, Cella DF, et al: The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer* 1996;77:2294-301
21. Kalf JG van den Berg MGA, Kaanders JAHM, Merks MAW: Preliminary analysis of a 'normalcy of food intake' scale for head and neck oncology. *Dysphagia* 2011;26
22. van den Berg M, Kalf J, Kaanders J, et al: Psychometric analysis of a 'normalcy of food intake' scale for head-neck cancer oncology. *Clin Nutr* 2012;suppl7
23. Biro G, Hulshof KF, Ovesen L, et al: Selection of methodology to assess food intake. *European journal of clinical nutrition* 2002;56Suppl2:S25-32
24. 'RIVM' Dutch food composition database, Version 2011-3.0 http://www.rivm.nl/Onderwerpen/N/Nederlands_Voedingsstoffenbestand
25. Chen AY, Frankowski R, Bishop-Leone J, et al: The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Archives of otolaryngology--head & neck surgery* 2001;127:870-6
26. Nathadwarawala KM, Nicklin J, Wiles CM: A timed test of swallowing capacity for neurological patients. *Journal of neurology, neurosurgery, and psychiatry* 1992;55:822-5
27. Ertekin C, Aydogdu I, Yuceyar N: Piecemeal deglutition and dysphagia limit in normal subjects and in patients with swallowing disorders. *Journal of neurology, neurosurgery, and psychiatry* 1996;61:491-6
28. World Health Organization WHO: BMI Classification 2006 http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
29. 'Oncoline': Ondervoeding. Nation wide evidence based guideline, in LWDO (ed), 2012
30. Borm GF, Fransen J, Lemmens WA: A simple sample size formula for analysis of covariance in randomized clinical trials. *Journal of clinical epidemiology* 2007;60:1234-8,
31. Kotz T, Federman AD, Kao J, et al: Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. *Arch Otolaryngol Head Neck Surg* 2012;138:376-382
32. Carnaby-Mann G, Crary MA, Schmalfuss I, et al: "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *International journal of radiation oncology, biology, physics* 2012;83:210-9
33. Tribius S, Bergelt C: Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: is there a worthwhile quality of life gain? *Cancer treatment reviews* 2011;37:511-9
34. Paleri V, Patterson J. Use of gastrostomy in head and neck cancer: a systematic review to identify areas for future research. *Clin Otolaryngol* 2010;35:177-189
35. van der Molen L, van Rossum MA, Burkhead LM, et al: A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. *Dysphagia* 2011;26:155-170

8

Summary, general discussion and future perspectives

Summary and general discussion

Patients with head and neck carcinoma (HNC) have a particularly high risk for developing malnutrition due to the location of the tumor and complications that can arise from the treatment. This thesis describes six successive studies that focused on weight loss, quality of life (QoL), effect of individual dietary counseling, normal food intake, and dysphagia among HNC patients, with the goal of improving nutritional care.

Weight loss

Chapter 2 describes a prospective observational study regarding the time of onset as well as the extent of weight loss and energy intake in squamous cell HNC patients from diagnosis until six months after treatment; various treatment modalities were followed over time. Weight change was evaluated in 47 patients with squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx. During treatment, patients who received chemoradiation ($n=3$ patients; mean weight loss was 10.5 kg) or primary radiation ($n=19$ patients; mean weight loss was 3.3 kg) experienced more weight loss than patients who underwent surgery only ($n=15$ patients) or received postoperative radiation ($n=10$ patients). However, the chemoradiation results should be interpreted with caution, given the relatively low number of patients in this group. From the end of treatment until two months post-treatment, the patients who were treated with (postoperative) radiation had considerably more weight loss than patients who received surgery or chemoradiation. The HNC patients who underwent surgery alone experienced relatively little weight loss (a mean weight loss of 1.5 kg) between the time of diagnosis through the treatment, and they regained the lost weight soon after treatment.

Weight loss itself is a reflection of an energy imbalance that can be due to decreased energy intake, increased energy expenditure, and/or energy loss. Energy intake decreased from the time of diagnosis through the end of the treatment, particularly among the patients who were treated by (chemo)radiation. A similar pattern—in terms of decreased energy (and protein) intake during (chemo)radiation until one month following the treatment—was reported in a previous study.¹ In our study, a correlation was found between weight loss and decreased energy intake from baseline through the treatment period. However, mean energy intake did not decrease below the minimum energy requirements (30-35 kcal per kg body weight²) during the treatment (except for chemoradiation patients). Although this calculated energy requirement may not predict one's absolute energy requirements, similar findings were reported in other studies in which energy expenditure/kg free fatty mass (FFM) was measured at the start, during, and at the end of radiation therapy and followed a U-shaped (triphasic) pattern.³⁻⁶ Energy expenditure initially decreased during radiation therapy; at the end of treatment, energy expenditure increased, possibly due to hypermetabolism (e.g., mucositis, inflammation, and/or cancer cachexia). This might explain the observed drop in weight at the end of treatment despite optimal energy intake.

Overall, the treatment modalities that included radiation conferred the highest risk of weight loss from the start of treatment through two months post-treatment, and this is likely due to radiation-induced symptoms, which can include pain caused by mucositis, xerostomia, dysphagia, dysgeusia, and loss of appetite. HNC patients who receive radiation therapy should therefore receive additional attention with respect to nutritional care. These results

are consistent with previous reports in which radiation and concomitant chemoradiation were found to be independent factors for the development of weight loss, and chemoradiation was the primary risk factor for malnutrition.^{7,8} Other risk factors for severe weight loss during treatment that were identified in some studies include the site and stage of the tumor (**Chapter 3**), higher pre-treatment body weight, dysphagia, anorexia, and odynophagia.⁹⁻¹¹

Partly due to the findings in our study (**Chapter 2**) more intensely structured and expanded dietary counseling has now been implemented for patients with HNC at our hospital from the time of diagnosis through the rehabilitation period.

Quality of life

Chapter 3 describes a prospective observational study regarding the relation between malnutrition and quality of life for forty-seven patients with cancer of the oral cavity, oropharynx, or hypopharynx from the time of diagnosis, end of treatment and six months post-treatment. Malnutrition (defined as weight loss $\geq 10\%$ within 6 months) in this study was found in 19, 32, and 11% of the patients respectively at the time of diagnosis, end of treatment, and six months after treatment, respectively. Patients with malnutrition scored significantly worse on functional scales, including global QoL, cognitive functioning, and fatigue. Malnourished patients also performed worse (clinically relevant) in domains such as role functioning and physical, emotional, and social functioning. These findings are supported by previous studies in which fatigue, physical functioning, role functioning, and social functioning scores were significantly worse in malnourished (5% weight loss in three months) stage III-IV HNC patients at the time of diagnosis.¹² Similar results were reported in a cross-sectional study of post-treatment oral and oropharyngeal cancer patients, in which malnourished patients had significantly lower scores with respect to physical functioning and fatigue from one to three years after treatment (irrespective of the treatment modality).¹³ Another study of various HNC patients measured both weight loss and QoL at baseline and follow-up and found that 10% weight loss during and directly following treatment was associated with a significant negative impact on global QoL, social functioning, and social eating.¹⁴ These results emphasize the importance of minimizing weight loss in order to improve the patient's functional QoL outcome.¹⁵

The relationship between malnutrition and both fatigue and physical functioning is not surprising, given that malnutrition in HNC patients is characterized by decreased muscle mass and muscle function.^{5,13} Additional symptoms of depression (e.g., emotional functioning) and loneliness (e.g., role and social functioning) have also been correlated with weight loss.^{16,17} Impaired emotional, role, and/or social functioning may therefore have contributed to the weight loss that we observed in our study.

On the other hand, QoL is multifactorial and has a wide spectrum of predictive factors.¹⁸ Specifically, age, gender, tumor location, treatment modality, emotional state, smoking, and alcohol consumption-related toxicity can negatively affect the patient's quality of life.¹⁹ A similar effect was also found in the study presented in **Chapter 3** with respect to tumor stage and treatment modality.

In our study, symptom scores were significantly higher (i.e., patients had more symptoms and/or more severe symptoms) in the malnutrition group at the end of treatment and six months after treatment regarding pain, smell and taste alterations, stickiness of saliva, dry mouth, coughing, feeling ill and impaired social eating. These symptoms were the sequelae

of primary or postoperative (chemo)radiation that led to malnutrition, whereas impaired social eating (i.e., eating in public) was likely a consequence of these symptoms.²⁰

Chapter 4 describes an exploratory analysis of QoL issues in fifty-two HNC patients one month after treatment with three different treatment modalities: radiation, postoperative radiation, or chemoradiation. The location of the tumors in these patients ranged from the nasopharynx to the larynx, and the tumor stages ranged from stage III -IV.

Sticky saliva, weight loss, dry mouth, use of pain killers, and use of nutritional supplements were reported as the worst symptoms/outcome (score>50) one month after the end of treatment. These scores were partially supported by the QoL symptom scores (>50) at the end of treatment in **Chapter 3**. Patients in the radiation and chemoradiation group reported more serious impairments than the postoperative radiation group, an observation that has been confirmed by other studies.⁷

In general, the most striking differences between treatment groups revealed problems with nutritional intake (in case of appetite loss, swallowing difficulty, use of tube feeding or nutritional supplements, and/or weight loss) and impaired oral function (due to xerostomia, trismus, sticky saliva, and/or dental problems) which stresses out the need of further supportive care. Although the subpopulations in our study were relatively small, our results suggest which impairments can be expected to occur in a given treatment modality. One month after treatment was chosen for evaluation of QoL, as this is the period in which patients generally develop an interest in rehabilitation following an intensive treatment period and are willing to resume daily life with all of its obstacles. In some situations, these symptoms (including weight loss, dental problems, trismus, and dysphagia) can be ameliorated by the use of proper supportive care. On the other hand, some symptoms (such as sticky saliva, appetite loss, and xerostomia) are more difficult to manage. For some of these problems the dietician can be extremely beneficial.

Integrating an individualized prospective evaluation—including digital and/or pre-completed home QoL questionnaires—from the time of diagnosis until the start of rehabilitation can indicate the need for further dietary intervention based on the individual needs of the patient (**Chapters 3 and 4**).²¹

Effect of individual dietary counseling

Chapter 5 describes a prospective cohort study of 38 patients with T₂₋₄ tumors located in the oral cavity, oropharynx, or hypopharynx to investigate the added value of individual dietary counseling in addition to standard nutritional care by a nurse with respect to weight loss, BMI, and malnutrition. Individual dietary counseling provided by a specialized dietician was designed to achieve the patient's energy and protein requirements and led to a significant decrease in weight loss two months after treatment compared to providing standard nutritional care. However, because body composition was not assessed, it is unclear whether the weight gain that occurred in the individual dietary counseling group by two months post-treatment reflected an increase in fat mass, muscle mass, or both. A previous study conducted in the Netherlands reported that patients who received sufficient energy and protein intake as a result of individual dietary counseling had an increase in body weight that included a 50% increase in lean body mass between one month post-treatment and four months post-treatment.¹

The number of patients with malnutrition (i.e., weight loss $\geq 5\%$ within one month) decreased significantly from the start of treatment until two months after treatment when individual dietary counseling was provided, whereas the malnutrition rate increased in the group that received standard nutritional care. This finding is consistent with previous studies that found that individualized dietary counseling was also associated with decreased weight loss and improved intake of energy and protein.²² Two retrospective and three prospective studies of HNC patients who were treated with (chemo)radiation revealed that patients who received early dietician-led nutritional intervention had lower weight loss scores, fewer treatment interruptions, fewer unplanned hospitalizations, and had significant health-related cost savings.²³⁻²⁷ Maintaining body weight/nutritional status through intensive dietary counseling also resulted in smaller and fewer perturbations in overall QoL scores from the start of radiation treatment through three months following the start of treatment.²⁸ These findings are consistent with our finding that weight loss greater than 10% is associated with a significant decrease in QoL (**Chapter 3**).

Changes in total body weight can include changes in body components, FFM and/or fat mass (FM), and water content. Although we did not measure body composition in our study, such assessments might have supported our findings of malnutrition, as a drop in lean body mass can also indicate malnutrition and is associated with a loss of physical performance. Other studies have found that a drop in lean body mass accounts for 62-70% of weight loss in HNC patients both during and directly after primary or postoperative (chemo)radiation, possibly also in the context an elevated inflammatory state.^{1,5}

Our results suggest that at least some of the weight loss could not be prevented either by providing nutritional care or by achieving the required nutritional energy intake (**Chapters 2 and 5**), a finding that has been reported previously.²³⁻²⁷ This non-preventable weight loss might be the effect of decreased energy and/or protein intake, and/or it might be due to tumor-related inflammation. Abnormal metabolism resulting from tumor-related inflammation can prevent the patient from responding to conventional dietary counseling that is designed to achieve the patient's energy and protein requirements; this is reflected in the recent international definition of cancer cachexia: "Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."²⁹

‘Normal food intake’ and dysphagia

Chapter 6 reports the results of a cross-sectional cohort study to describe how nutritional status, food intake, and dysphagia were affected in 32 stage III-IV head and neck cancer survivors who were treated with chemoradiation with a median follow up of 44 months. According to the ‘Malnutrition Universal Screening Tool (MUST)’, 19% of these patients were at risk for malnutrition; in almost all cases, this risk was due to low BMI. Only one patient (3%) was malnourished based on recent weight loss acute malnutrition, similar to a previous report.¹⁰ These findings suggest that the rate of chronic malnutrition is higher than the rate of acute malnutrition. Surprisingly, according to the MUST findings, 50% of patients lost weight from the start of chemoradiation through the late morbidity clinic, but not within the last six months according to the MUST findings; it is possible that these patients were either unable or unwilling to gain weight.

Our findings show that none of the survivors could reach “normalcy of diet”; 94% of these patients ate mostly soft foods or at least reported minor adjustments in the consistency of their food, as measured using the validated Performance Status Scale for patients with HNC.³⁰ Nineteen percent (6/32) of patients still used nutritional supplements (energy drinks and/or tube feeding). When the same cohort was measured using the Functional Oral Intake Scale (FOIS), 15.6% had achieved “normalcy of diet”.³¹ However, the FOIS questionnaire is limited, as its use has only been validated in stroke patients, even though it measures valuable items such as tube feeding/oral diet in combination with food consistency. Because food consistency, the use of nutritional supplements (tube feeding and energy drinks/supplements), and dysphagia can reflect the patient’s limitations with respect to oral intake, we developed and validated our own tool to measure “normalcy of food intake” as a specific scale (the NFIS scale) for patients with HNC (**Chapter 7**).^{32,33}

Dysphagia was determined using a clinical assessment and was present in 75% of the 32 patients. Using videofluoroscopy, dysphagia was identified in 57% of the patients. This is consistent with another study of HNC survivors in which aspiration was measured in 44% of patients based on videofluoroscopy.³⁴ Furthermore, patients who experienced low dysphagia related quality of life (M.D. Anderson Dysphagia Inventory) had significantly less food modifications.

Based on the findings in this thesis and in previously published studies, dysphagia can be associated with both short-term and long-term decreased (oral) food intake, increased weight loss, and decreased quality of life (**Chapter 6**).^{9-11,34} Dysphagia is commonly reported among HNC patients before, during, and after their treatment (**Chapter 3 and 4**). Dysphagia decreases oral nutritional intake and therefore leads to weight loss. Weight loss can then further reduce swallowing function by decreasing the volume and strength of the swallowing musculature.³⁵ There are hints in the literature that treating dysphagia using preventive swallowing therapy is a promising strategy for improving oral intake and reducing the need for tube feeding, and this led to the randomized clinical trial that is described in **Chapter 7**.

Chapter 7 describes a randomized controlled trial with a multidisciplinary intervention of individual dietary counseling and individual swallowing therapy compared to individual dietary counseling only (‘usual care’); 120 patients with stage II-IV squamous cell HNC from nasopharynx till larynx, treated by (adjuvant) (chemo)radiation were evaluated for their ability

to achieve higher “normalcy of food intake” (NFI). No overall significant difference in NFI was found between the group that received both dietary counseling and swallowing therapy (hereafter referred to as the intervention group) and the group that received dietary counseling only (the control group). Six months after treatment, 63% of patients in the intervention group and 51% of patients in the control group achieved normal NFI (defined as regular full oral intake without energy drinks/supplements or tube feeding and no restrictions such as modified foods).

Overall, the incidence of tube feeding was low, only one-fifth of the total study population required tube feeding, and nearly all tube-fed patients (88%) used a nasogastric tube. The use of a nasogastric tube was primarily due to the reactive nature of tube feeding (i.e., a prophylactic tube was generally not placed prior to the start of treatment, as the tube feeding duration use expected to be shorter than six weeks). The low overall incidence of tube feeding could have contributed to the highly similar NFI score between the intervention and control group, as the added benefit of including swallowing therapy on NFI was expected to reduce the incidence of tube feeding in the intervention group.

Intensity-modulated radiation therapy (IMRT) is a commonly used advanced mode of delivering high-precision radiation. IMRT uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor—or specific areas within the tumor—while minimizing the radiation dose applied to unaffected, critical surrounding structures such as the salivary glands and swallowing musculature. Such high-precision delivery decreases the likelihood of developing post-radiation xerostomia or dysphagia, and IMRT reduces the need for tube feeding.³⁶ IMRT was used in 91% of our patients, and the aforementioned benefits may have contributed to reaching a higher NFI level. In addition, individual dietary counseling may have contributed to a lower incidence of tube feeding by encouraging patients to use oral intake as long as possible in order to ensure that their energy and protein requirements were met; this hypothesis was confirmed by a recent study.²⁷

Our study population was relatively heterogeneous with respect to treatment modality, which may have limited our ability to detect a difference between the intervention and control groups in terms of improved NFI and lower severity of dysphagia. As in some other studies that included only chemoradiation patients, significant differences in favor of including swallowing therapy were found in terms of NFI and dysphagia severity.^{37,38} A subgroup analysis regarding treatment modality was not possible, as the power calculation was not suitable for this purpose. Dysphagia severity, quality of life, and nutritional status were not estimated to differ between the intervention and control groups (**Chapter 7**). However, one month after treatment, the intervention group had improved recovery of dysphagia compared to the control group, although this difference dissappeared by six months after the treatment. Many HNC patients experience long-term dysphagia following non-surgical treatment.^{39,40} Therefore, one goal for further improvement in this area is to identify the specific patients who suffer from dysphagia following treatment and who might benefit from swallowing therapy; such patients could be identified by screening for dysphagia severity.

Implications for nutritional care in clinical practice

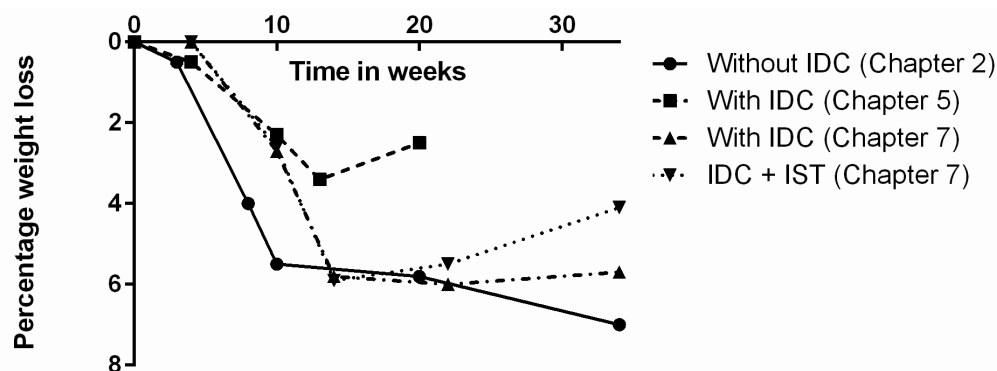


Figure 1. Mean percent weight change over time for HNC patients with or without individual dietary counseling with first out patient visit at week 0. IDC: Individual Dietary Counseling. Ch: Chapter. Proph. TF: Prophylactic tube feeding. Reac. TF: Reactive tube feeding.

Figure 1 shows mean percent weight loss over time for the HNC patients with or without individual dietary counseling. Among the various studies tumor stage were similar and tumor locations and tumor treatment were almost similar. However, some factors must be taken into consideration. For example, the results described in **Chapter 2** included patients who received surgical treatment, and only a few patients received chemoradiation; in contrast, the other two studies described in this thesis did not include surgical patients (who generally have a lower risk of weight loss). In addition, the studies took place in different years.

A clear difference in weight change following individual dietary counseling was found between the studies presented in **Chapters 5 and 7**; specifically, in favor of **chapter 5** were an earlier stabilization/reduction of weight loss was achieved. This finding may have been due to the more frequent use of feeding tubes in this study (50% of the patients used a feeding tube, 55% of which were via a gastrostomy), which was the policy of care in that earlier period. In contrast, in our study described in **Chapter 7**, only 20% of all patients used a tube feeding (88% of which were via a nasogastric tube). In general, tube feeding can ameliorate weight loss, and prophylactic gastrostomy tube feeding in particular can minimize weight loss more than reactive nasogastric tube feeding.⁴¹ This (reactive approach of) nasogastric tube feeding is associated with a lower incidence of (late) dysphagia due to more continued oral swallowing with more oral intake and in particular lower incidences of fibroses and late esophageal strictures compared to gastrostomy tubes.⁴² Moreover, reactive nasogastric tube feeding is generally initiated later and has a shorter duration due to the negative aesthetic inconvenience associated with a nasogastric tube.³⁶⁻⁴²

Aside from the reactive approach of nasogastric tube feeding in **Chapter 7**, a major issue is that out-patient contact in the early rehabilitation period (Fig. 1, beyond week 10) is less frequent, whereas post-treatment symptoms likely constitute a major restriction that results in a steep decline in body weight. Therefore, additional attention should be given to weight change in the initial post-treatment months and whenever tube feeding is deemed necessary (**chapter 4**). By implementing these simple strategies, excessive weight loss—and its associated adversities can likely be further prevented in individual patients.

Based on our findings, individual dietary counseling should be improved as follows:

During treatment, dietary counseling (based on reaching the patient's energy and protein requirements) cannot completely prevent weight loss, but it can minimize critical weight loss and should therefore be continued as described in the protocol (**Chapters 5 and 7**).⁴³ Dietary counseling in early rehabilitation period until two months thereafter results in a significant amelioration of weight loss and malnutrition, provided that the full intake of energy and proteins is ensured. Therefore, to prevent malnutrition, intensified dietary counseling in this post-treatment period (where the incidence of malnutrition is still relatively high) should be continued at the same level as during the treatment period (i.e., on a weekly basis to bi-monthly basis) until at least two months after treatment. Tube feeding should not be avoided, especially particularly during the post-treatment period. It is therefore important to instruct HNC patients at diagnosis regarding the fact that tube feeding is a logical—and occasionally necessary—treatment element. For most patients, reactive nasogastric tube feeding is preferable to prophylactic gastrostomy placement, as the expected period of tube feeding is six weeks or shorter. Moreover, nasogastric tubes are associated with higher oral food intake and a lower incidence of dysphagia (due to more swallowing) compared to gastrostomy tubes, and this allows patients to resume normal food intake sooner, which in turn improves their overall quality of life. To further improve the efficacy of individual dietary counseling, future research should attempt to further decrease weight loss in the post-treatment period and increase lean body mass. In addition, further improvements should be made to achieve near-normal food intake in order to improve the social aspects of food intake (particularly among chemoradiation patients), resulting in a lifelong focus of individual dietary counseling as well as other paramedical care aspects such as dysphagia (**Chapters 6 and 7**).³¹

Future perspectives

The results of the studies presented in this thesis answered our research questions, but they also raised new questions that must be addressed. In particular, future research should be aimed at further improving and customizing individualized dietary counseling for HNC patients. Three areas for future improvement can be identified and are described below.

Cancer cachexia

The first question that arose was, the extent to which weight loss in HNC patients is the result of decreased food intake due to symptoms such as mucositis, xerostomia, dysphagia, and decreased smell and taste based on starvation rather than inflammation/cancer cachexia. This question is particularly relevant to the treatment period and the first few weeks thereafter, when fulfilling energy requirements did not result in total weight stabilization (**Chapters 2, 5, and 7**).

The actual incidence of cancer cachexia in HNC patients is unknown. Indeed, the incidence likely depends on the definition used and on the tumor's characteristics. In recent years, efforts have been made to better categorize cancer cachexia, covering the spectrum from precachexia

through (refractory) cachexia; however, no clear consensus definition is currently available.^{2,29} After validating such a definition, sufficiently powered trials of HNC patients to investigate the actual incidence of cancer cachexia will be needed. In the meantime, interventions for cancer cachexia based on nutritional support, pharmacological treatment (for example, (hormonal) appetite stimulants such as ghrelin), and nutraceuticals (e.g., eicosapentaenoic acid) show some promise.⁴⁴⁻⁴⁸

Muscle mass

A second goal for further improving dietary counseling is to increase the patient's functional muscle mass. A multimodal treatment that combines physical exercise with adequate dietary intervention (e.g., energy and protein supplementation) can be supportive.⁴⁹ Compelling evidence suggests that physical exercise is well-tolerated and can be a safe adjunctive therapy to ameliorate cancer-related side effects.⁴⁹ Physical exercise can improve body composition (e.g., increased lean body mass), improve overall quality of life, decrease fatigue, and increase physical functioning in malnourished patients (**Chapter 3**).⁵⁰ Recently, a relatively small randomized study of 30 HNC patients found that progressive resistance training for three months following treatment led to an increase in lean body mass.⁵¹ Randomized controlled trials are needed to study the effect of combining physical exercise with adequate dietary intervention (to meet the patient's energy and protein requirements) in HNC patients; such studies can reveal the extent to which such a multimodal treatment will benefit this patient population before, during, and after treatment.

Normal food intake

Finally, in addition to maintaining and/or improving the patient's nutritional status, studies should focus on improving "normalcy of food intake" and therefore increase the pleasure of eating, social eating, and overall quality of life, particularly from early rehabilitation until six months after treatment, when many HNC patients lack normal food intake (**Chapter 7**), and even several years after treatment (**Chapter 6**). One month after treatment, 50-60% of patients still experience mild to severe dysphagia, and this condition can last for years after treatment (**Chapters 6 and 7**).

Further NFI improvement can be achieved by reducing the need for tube feeding, energy drinks/supplements and food modification, both improving quality of life and reducing costs. However, there is currently a knowledge gap with respect to effective interventions designed to prevent and/or solve problems associated with the social aspect of eating.^{52,53} We should establish whether other post-treatment factors can affect "normalcy of food intake". In addition to a physical approach, interventions that address the psychological and/or social aspects of eating should be developed and evaluated holistically in order to help patients cope with any lingering eating difficulties. These lifelong aspects merit further attention in future research and in programs for educating dietitians and other paramedical health care professionals who work with HNC patients.

Conclusion

Weight loss and malnutrition during and following treatment are highly prevalent among stage II-IV HNC patients, and these clinical features can become more severe during the end of treatment and the early rehabilitation period, particularly with treatment modalities that include (chemo)radiation. Malnutrition is associated with significantly poorer overall quality of life, fatigue, and impaired cognitive functioning. Individual dietary counseling is an effective approach for curtailing weight loss and malnutrition. Due to intensified treatment strategies, many HNC patients suffer from symptoms that can prevent normal oral food intake, which can lead to malnutrition and decreased quality of life; with severe dysphagia as one of the most prominent symptoms. Despite expectations, combined swallowing therapy to individual dietary counseling does not improve the patient's return to normal food intake.

References

1. Jager-Wittenaar H, Dijkstra PU, Vissink A, Langendijk JA, van der Laan BF, Pruim J, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head & neck*. 2011;33(6):863-70.
2. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clinical nutrition*. 2006;25(2):245-59.
3. Langius JA, Kruizenga HM, Uitdehaag BM, Langendijk JA, Doornaert P, Leemans CR, et al. Resting energy expenditure in head and neck cancer patients before and during radiotherapy. *Clinical nutrition*. 2012;31(4):549-54.
4. Garcia-Peris P, Lozano MA, Velasco C, de La Cuerda C, Iriondo T, Breton I, et al. Prospective study of resting energy expenditure changes in head and neck cancer patients treated with chemoradiotherapy measured by indirect calorimetry. *Nutrition*. 2005;21(11-12):1107-12.
5. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head & neck*. 2007;29(10):893-900.
6. Ng K, Leung SF, Johnson PJ, Woo J. Nutritional consequences of radiotherapy in nasopharynx cancer patients. *Nutrition and cancer*. 2004;49(2):156-61.
7. Palazzi M, Tomatis S, Orlandi E, Guzzo M, Sangalli C, Potepan P, et al. Effects of treatment intensification on acute local toxicity during radiotherapy for head and neck cancer: prospective observational study validating CTCAE, version 3.0, scoring system. *International journal of radiation oncology, biology, physics*. 2008;70(2):330-7.
8. Larsson M, Hedelin B, Johansson I, Athlin E. Eating problems and weight loss for patients with head and neck cancer: a chart review from diagnosis until one year after treatment. *Cancer nursing*. 2005;28(6):425-35.
9. Nourissat A, Bairati I, Samson E, Fortin A, Gelinat M, Nabid A, et al. Predictors of weight loss during radiotherapy in patients with stage I or II head and neck cancer. *Cancer*. 2010;116(9):2275-83.
10. Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan BF, Roodenburg JL. Malnutrition in patients treated for oral or oropharyngeal cancer--prevalence and relationship with oral symptoms: an explorative study. *Supportive care in cancer*. 2011;19(10):1675-83.
11. Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, et al. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head & neck*. 2010;32(3):290-300.
12. Capuano G, Gentile PC, Bianciardi F, Tosti M, Palladino A, Di Palma M. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. *Supportive care in cancer*. 2010;18(4):433-7.
13. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. *Head & neck*. 2011;33(4):490-6.

14. Langius JA, van Dijk AM, Doornaert P, Kruizenga HM, Langendijk JA, Leemans CR, et al. More than 10% weight loss in head and neck cancer patients during radiotherapy is independently associated with deterioration in quality of life. *Nutrition and cancer*. 2013;65(1):76-83.
15. Head BA, Heitz L, Keeney C, Myers J, Appana SN, Studts JL, et al. The relationship between weight loss and health-related quality of life in persons treated for head and neck cancer. *Supportive care in cancer*. 2011;19(10):1511-8.
16. Britton B, Clover K, Bateman L, Odelli C, Wenham K, Zeman A, et al. Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. *Supportive care in cancer*. 2012;20(2):335-42.
17. Schilp J, Wijnhoven HA, Deeg DJ, Visser M. Early determinants for the development of undernutrition in an older general population: Longitudinal Aging Study Amsterdam. *The British journal of nutrition*. 2011;106(5):708-17.
18. Rogers SN, Ahad SA, Murphy AP. A structured review and theme analysis of papers published on 'quality of life' in head and neck cancer: 2000-2005. *Oral oncology*. 2007;43(9):843-68.
19. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *Journal of clinical oncology*. 2008;26(22):3770-6.
20. McQuestion M, Fitch M, Howell D. The changed meaning of food: Physical, social and emotional loss for patients having received radiation treatment for head and neck cancer. *European journal of oncology nursing*. 2011;15(2):145-51.
21. Oates J, Clark JR, Read J, Reeves N, Gao K, O'Brien CJ. Integration of prospective quality of life and nutritional assessment as routine components of multidisciplinary care of patients with head and neck cancer. *ANZ journal of surgery*. 2008;78(1-2):34-41.
22. Garg S, Yoo J, Winquist E. Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. *Supportive care in cancer*. 2010;18(6):667-77.
23. Paccagnella A, Morello M, Da Mosto MC, Baruffi C, Marcon ML, Gava A, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Supportive care in cancer*. 2010;18(7):837-45.
24. Capuano G, Grosso A, Gentile PC, Battista M, Bianciardi F, Di Palma A, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head & neck*. 2008;30(4):503-8.
25. Valentini V, Marazzi F, Bossola M, Micciche F, Nardone L, Balducci M, et al. Nutritional counseling and oral nutritional supplements in head and neck cancer patients undergoing chemoradiotherapy. *Journal of human nutrition and dietetics*.
26. Jeffery E, Sherriff J, Langdon C. A clinical audit of the nutritional status and need for nutrition support amongst head and neck cancer patients treated with radiotherapy. *The Australasian medical journal*. 2012;5(1):8-13.
27. Kiss NK, Krishnasamy M, Loeliger J, Granados A, Dutu G, Corry J. A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. *Supportive care in cancer*. 2012;20(9):2111-20.

28. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *British journal of cancer*. 2004;91(3):447-52.
29. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *The lancet oncology*. 2011;12(5):489-95.
30. List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer*. 1996;77(11):2294-301.
31. Rutten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijackers AF, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. *International journal of radiation oncology, biology, physics*. 2011;81(4):923-9.
32. van den Berg MGA, Kalf JG, Kaanders JHAM, Merks MAW. Psychometric analysis of a 'normalcy of food intake' scale for head-neck cancer oncology. *Clin Nutr suppl*. 2012;7(1).
33. Kalf JG Van den Berg MGA, Kaanders JAHM, Merks MAW. Preliminary analysis of a 'normalcy of food intake' scale for head and neck oncology. *Dysphagia*. 2011;26.
34. Campbell BH, Spinelli K, Marbella AM, Myers KB, Kuhn JC, Layde PM. Aspiration, weight loss, and quality of life in head and neck cancer survivors. *Archives of otolaryngology--head & neck surgery*. 2004;130(9):1100-3.
35. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. *Nutrition journal*. 2012;11:27.
36. Koyfman SA, Adelstein DJ. Enteral feeding tubes in patients undergoing definitive chemoradiation therapy for head-and-neck cancer: a critical review. *International journal of radiation oncology, biology, physics*. 2012;84(3):581-9.
37. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. *Archives of otolaryngology--head & neck surgery*. 2012;138(4):376-82.
38. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *International journal of radiation oncology, biology, physics*. 2012;83(1):210-9.
39. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, Witte BI, de Bree R, Doornaert P, et al. Prospective evaluation of health-related quality of life in long-term oral and oropharyngeal cancer survivors and the perceived need for supportive care. *Oral oncology*. 2013;49(5):443-8.
40. Wilson JA, Carding PN, Patterson JM. Dysphagia after nonsurgical head and neck cancer treatment: patients' perspectives. *Otolaryngology--head and neck surgery*. 2011;145(5):767-71.
41. Paleri V, Patterson J. Use of gastrostomy in head and neck cancer: a systematic review to identify areas for future research. *Clinical otolaryngology*. 2010;35(3):177-89.

42. Paleri V, Roe JW, Strojan P, Corry J, Gregoire V, Hamoir M, et al. Strategies to reduce long-term postchemoradiation dysphagia in patients with head and neck cancer: An evidence-based review. *Head Neck*. 2013
43. van den Berg MG, Rasmussen-Conrad EL, Wei KH, Lintz-Luidens H, Kaanders JH, Merks MA. Comparison of the effect of individual dietary counseling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *The British journal of nutrition*. 2010;104(6):872-7.
44. Argiles JM, Olivan M, Busquets S, Lopez-Soriano FJ. Optimal management of cancer anorexia-cachexia syndrome. *Cancer management and research*. 2010;2:27-38.
45. Argiles JM, Stemmler B. The potential of ghrelin in the treatment of cancer cachexia. *Expert opinion on biological therapy*. 2013;13(1):67-76.
46. Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia-pathophysiology and management. *Journal of gastroenterology*. 2013.
47. Yeh KY, Wang HM, Chang JW, Huang JS, Lai CH, Lan YJ, et al. Omega-3 fatty acid-, micronutrient-, and probiotic-enriched nutrition helps body weight stabilization in head and neck cancer cachexia. *Oral surgery, oral medicine, oral pathology and oral radiology*. 2013.
48. Weed HG, Ferguson ML, Gaff RL, Hustead DS, Nelson JL, Voss AC. Lean body mass gain in patients with head and neck squamous cell cancer treated perioperatively with a protein- and energy-dense nutritional supplement containing eicosapentaenoic acid. *Head & neck*. 2011;33(7):1027-33.
49. Jones LW, Alfano CM. Exercise-oncology research: past, present, and future. *Acta oncologica*. 2013;52(2):195-215.
50. Hunter KU, Jolly S. Clinical review of physical activity and functional considerations in head and neck cancer patients. *Supportive care in cancer*. 2013;21(5):1475-9.
51. Lonbro S, Dalgas U, Primdahl H, Overgaard J, Overgaard K. Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients--the DAHANCA 25A study. *Acta oncologica*. 2013;52(2):310-8.
52. Ottosson S, Laurell G, Olsson C. The experience of food, eating and meals following radiotherapy for head and neck cancer: a qualitative study. *Journal of clinical nursing*. 2013;22(7-8):1034-43.
53. Cousins N, Macaulay F, Lang H, Macgillivray S, Wells M. A systematic review of interventions for eating and drinking problems following treatment for head and neck cancer suggests a need to look beyond swallowing and trismus. *Oral oncology*. 2013;49(5):387-400.

Samenvatting



Patiënten met tumoren in het hoofd-halsgebied (HHT) lopen een groot risico op ondervoeding vanwege de locatie van de tumor en de bijwerkingen die kunnen ontstaan tijdens of direct na de behandeling. Dit proefschrift beschrijft zes opeenvolgende studies naar gewichtsverlies, kwaliteit van leven, effect van individuele dieet counseling, normale voedselinname en dysfagie bij HHT-patiënten, met als doel de voedingszorg van patiënten met HHT te verbeteren.

Gewichtsverlies

Hoofdstuk 2 beschrijft een prospectieve observationele studie naar de aanvang en mate van gewichtsverlies en de energie-inname bij patiënten met HHT, vanaf de diagnose tot zes maanden na de behandeling. Verschillende behandelvormen werden gevolgd in de tijd. De gewichtsverandering werd onderzocht bij 47 patiënten met een plaveiselcelcarcinoom van de mondholte, orofarynx of hypofarynx. Tijdens de behandeling hadden patiënten die een gecombineerde behandeling met chemotherapie en radiotherapie (chemoradiatie) en patiënten die alleen radiotherapie ondergingen gemiddeld het meeste gewichtsverlies ten opzichte van patiënten die alleen chirurgie of postoperatieve radiotherapie ondergingen. Vanaf het einde van de behandeling tot twee maanden na de behandeling hadden de patiënten die werden behandeld met (postoperatieve) radiotherapie aanzienlijk meer gewichtsverlies dan patiënten behandeld met chirurgie of chemoradiatie. Patiënten die primaire chirurgie ondergingen, hadden relatief weinig gewichtsverlies in de periode vanaf de diagnose tot het einde van de behandeling; dit gewicht stabiliseerde weer snel na de behandeling. De energie-inname verminderde in de periode vanaf de diagnose tot het einde van de behandeling, in het bijzonder bij patiënten die werden behandeld met primaire (chemo) radiotherapie. Dit werd gevolgd door een toename tijdens de revalidatieperiode. In onze studie werd een correlatie gevonden tussen gewichtsverlies en verminderde energie-inname vanaf de diagnose tot de behandelperiode. Hoewel de gemiddelde inname tijdens de behandelperiode niet lager was dan de berekende energiebehoefte van 30-35 kcal per kg lichaamsgewicht (behalve bij chemoradiatie patiënten), was er toch sprake van gewichtsverlies.

Mede op basis van de resultaten van deze studie (**hoofdstuk 2**), wordt in ons ziekenhuis nu intensieve gestructureerde dieet counseling gegeven aan HHT-patiënten vanaf de diagnose tot in de revalidatieperiode.

Kwaliteit van leven

Hoofdstuk 3 beschrijft een prospectieve observationele studie over de relatie tussen ondervoeding en kwaliteit van leven (EORTC QoLQ-C30 en H&N 35 vragenlijsten) van 47 patiënten met een tumor in de mondholte, orofarynx of hypofarynx op drie tijdstippen: het moment van de diagnose, het einde van de behandeling en zes maanden na de behandeling. Ondervoeding (gedefinieerd als gewichtsverlies $\geq 10\%$ binnen 6 maanden) kwam voor bij respectievelijk 19%, 32% en 11% van de patiënten op het moment van de diagnose, op het einde van behandeling en zes maanden na de behandeling. Patiënten met ondervoeding scoorden significant slechter op functionele schalen, waaronder algehele kwaliteit van leven, cognitief functioneren en vermoeidheid. Ondervoedepatiënten presteerden ook slechter (klinisch relevant) in de domeinen rol-functioneren en fysiek, emotioneel en sociaal functioneren. Ondervoede patiënten hadden aan het eind van de behandeling en/of 6 maanden na de behandeling

significant slechtere symptoomscores op het gebied van pijn, verminderde reuk- en smaak, droge mond, kleverig speeksel, hoesten, zich 'ziek' voelen en moeite met eten in het openbaar.

Hoofdstuk 4 omvat een cross-sectionele exploratieve analyse van de kwaliteit van leven (EORTC QLQ-C30 en H&N35 vragenlijsten) van 52 patiënten met hoofd-halstumoren een maand na de behandeling voor drie verschillende behandelmodaliteiten; radiotherapie, postoperatieve radiotherapie en chemoradiatie. De locatie van de tumor varieerde van nasofarynx tot larynx en het tumorstadium was III-IV. Het doel van deze studie was het in kaart brengen van de verschillende aspecten van kwaliteit van leven die om intensievere zorg en begeleiding vragen en de verschillen hierin tussen de drie behandelmodaliteiten. De resultaten lieten zien dat kleverig speeksel, gewichtsverlies, xerostomie, gebruik van pijnstillers en het gebruik van voedingssupplementen een maand na het einde van de behandeling gerapporteerd werden als de ergste symptomen c.q. het ergste resultaat van de behandeling (score > 50). Patiënten die radiotherapie en chemoradiatie ondergingen, rapporteerden meer ernstige beperkingen dan patiënten die met postoperatieve radiotherapie behandeld werden. In het algemeen werden de grootste verschillen tussen de behandelmodaliteiten gevonden bij problemen met voedselinname (verlies aan eetlust, dysfagie, sondevoeding of voedings-supplementen en/of gewichtsverlies) en verminderde orale functie (xerostomie, trismus, kleverig speeksel en/of tandproblemen). Dit benadrukt het belang van intensieve monitoring en continuering van ondersteunende zorg gedurende de eerste maanden van de follow-upfase voor deze specifieke groep HHT-patiënten.

Effect van individuele dieet counseling

Hoofdstuk 5 beschrijft een prospectieve cohort-studie van 38 patiënten met T₂₋₄ tumoren in de mondholte, orofarynx en hypofarynx. Het doel van deze studie was het onderzoeken van de toegevoegde waarde van individuele dieet counseling ten opzichte van de standaard voedingszorg door een verpleegkundige. De uitkomstmaten van deze studie waren gewichtsverlies, body mass index (BMI) en ondervoeding, gemeten vóór, tijdens en na de behandeling. De individuele dieet counseling door een gespecialiseerd diëtist was gericht op het voorzien in de energie- en eiwitbehoeften van de patiënt. In vergelijking met de standaard voedingszorg leidde dieet counseling tot een significante daling van gewichtsverlies twee maanden na de behandeling. Het aantal patiënten met ondervoeding (≥5% gewichtsverlies binnen een maand) was twee maanden na de behandeling significant lager voor de groep met individuele dieet counseling, terwijl het aantal patiënten met ondervoeding in de groep die de standaard voedingszorg ontving toenam.

Normale voedselinname en dysfagie

Hoofdstuk 6 beschrijft een cross-sectionele cohort-studie van de voedingsstatus, voedselinname en dysfagie bij 32 HHT-patiënten met stadium III-IV tumoren die behandeld waren met chemoradiatie na een mediane follow-up van 44 maanden. Op grond van de score op de Malnutrition Universal Screening Tool (MUST) had 19% van de patiënten een verhoogd risico op ondervoeding. In bijna alle gevallen was dit risico te wijten aan een lage BMI. Slechts één patiënt (3%) was ondervoed op basis van recent gewichtsverlies. De scores op de Eating

in Public-subschaal van de gevalideerde Performance Status Scale for Head and Neck Cancer Patients lieten zien dat geen van de overlevenden een “normaal dieet” kon gebruiken. Vierennegentig procent van de patiënten at zacht voedsel of voedsel met kleine aanpassingen in consistentie. Negentien procent (6/32) nam nog steeds energieverrijkte drinkvoeding tot zich en/of moest gebruik maken van sondevoeding. Dysfagie werd in 75% van de gevallen gediagnosticeerd aan de hand van de klinische beoordeling door de logopedist en in 57% aan de hand van videofluoroscopie. Bovendien hadden patiënten met een lage score op dysfagie (MD Anderson Dysphagia Inventory) significant minder aanpassingen in voedselconsistentie nodig.

Op basis van de bevindingen in dit proefschrift en eerder gepubliceerde studies, blijkt dat dysfagie wordt geassocieerd met zowel afgenomen (orale) voedselinname, toegenomen gewichtsverlies en verminderde kwaliteit van leven op de korte en lange termijn. Dysfagie wordt vaak gerapporteerd door patiënten met hoofd-halstumoren voor, tijdens en na de behandeling (**hoofdstukken 3 en 4**). Er zijn aanwijzingen in de literatuur dat de behandeling van dysfagie met preventieve sliktherapie een veelbelovende strategie is om de orale voedselinname te verbeteren en het gebruik van sondevoeding te verminderen. Vanuit deze achtergrond werd een gerandomiseerde klinische studie uitgevoerd die beschreven is in het volgende hoofdstuk.

Hoofdstuk 7 beschrijft een gerandomiseerde gecontroleerde studie waarin een multidisciplinaire interventie bestaande uit individuele dieet counseling gecombineerd met individuele sliktherapie vergeleken werd met primaire individuele dieet counseling (usual care). Honderdtwintig HHT-patiënten, 60 patiënten per groep, met een stadium II-IV plaveiselcelcarcinoom van nasofarynx tot larynx die behandeld werden met (postoperatieve) (chemo) radiotherapie werden beoordeeld op hun vermogen om een “normale voedselinname” tot zich te nemen. Normale voedselinname (NFI) werd gedefinieerd als een volledig orale voedselinname zonder energie- en/of eiwitverrijkte drinkvoedingen/supplementen of sondevoeding en zonder beperkingen in voedselconsistentie. Er werd geen significant verschil in NFI gevonden tussen de groep met dieet counseling en sliktherapie (interventiegroep) en de groep die alleen dieet counseling kreeg (controlegroep). Er was geen significant verschil in mate van dysfagie, kwaliteit van leven en voedingsstatus tussen de interventiegroep en de controlegroep. Wel bleek de interventiegroep een maand na de behandeling sneller te herstellen van dysfagie dan de controlegroep. Zes maanden na de behandeling werd NFI bereikt in 63% van de interventiegroep en 51% van de controlegroep. De incidentie van sondevoeding in de totale populatie was laag, slechts 20% van de patiënten had sondevoeding nodig; vrijwel alle patiënten met sondevoeding (88%) kregen een neusmaagsonde.

Op basis van onze bevindingen zou individuele dieet counseling als volgt verder kunnen worden verbeterd.

Tijdens de behandeling kan dieet counseling (gericht op het waarborgen van de energie- en eiwitbehoefte van de patiënt) gewichtsverlies niet volledig voorkomen, maar wel kritisch gewichtsverlies minimaliseren. Dieet counseling zoals beschreven in **hoofdstukken 5 en 7** zou daarom op dezelfde wijze moeten worden voortgezet. Dieet counseling direct na de behandeling tot twee maanden na de behandeling resulteert in een significante vermindering van gewichtsverlies en ondervoeding, mits wordt voorzien in de totale behoefte aan energie en eiwit. Om ondervoeding verder terug te dringen, moet dieet counseling worden

geïntensiveerd in de periode direct na de behandeling tot ten minste twee maanden na de behandeling, omdat de incidentie van ondervoeding dan nog relatief hoog is. Dit zou op hetzelfde niveau moeten worden voortgezet zoals gedurende de behandelingsperiode (dat wil zeggen, op een wekelijkse basis tot twee maal per maand) tot ten minste twee maanden na behandeling. Sondevoeding moet daarbij niet worden vermeden, met name in de periode direct na de behandeling. Het is daarbij belangrijk dat HHT-patiënten bij aanvang van de behandeling verteld wordt dat sondevoeding een logisch en soms noodzakelijk onderdeel van de behandeling is.

Voor de meeste patiënten heeft plaatsing van een neusmaagsonde, de voorkeur boven een profylactische gastrostomie, aangezien de gemiddelde verwachte periode van sondevoeding zes weken of korter is. Ten opzichte van patiënten met een gastrostomiesonde, hebben patiënten met een neusmaagsonde een betere orale voedselinname en een lagere incidentie van dysfagie doordat ze vaak langer zelf blijven eten/slikken. Hierdoor kunnen ze weer sneller op een normale wijze voedsel tot zich nemen, wat hun algemene kwaliteit van leven verbetert. Om de effectiviteit van individuele dieet counseling verder te verbeteren, zou toekomstig onderzoek gericht moeten zijn op het verder verminderen van gewichtsverlies in de periode na de behandeling met een stabilisatie danwel toename van de spiermassa. Daarnaast zou dieet counseling zich moeten richten op het bereiken van een vrijwel normale voedselinname, om zo de negatieve sociale aspecten van een niet-normale voedselinname te minimaliseren.

Aanbeveling voor toekomstig onderzoek

Kanker cachexie

De mate van gewichtsverlies bij HHT patiënten is vaak het resultaat van verminderde voedselinname, door symptomen zoals mucositis, xerostomie, dysfagie en verminderde geur en smaak, op basis van hongeren en/of door inflammatie/ kankercachexia. De werkelijke incidentie van kankercachexie bij HHT-patiënten is niet bekend. Interventies om kankercachexie te beperken of te voorkomen met voedingsinterventies, medicamenteuze behandelingen (bijvoorbeeld met hormonale of andere eetlustopwekkende middelen zoals ghreline) en nutraceuticals (bijv. eicosapentaeenzuur) zouden mogelijk enige verbetering kunnen geven.

Spiermassa

Een tweede doelstelling voor de verdere verbetering van dieet counseling is om het vergroten van de functionele spiermassa van de patiënt. Een gecombineerde behandeling van lichaamsbeweging en adequate voedingsinterventie zouden hierin ondersteunend kunnen zijn. Lichaamsbeweging kan de lichaamssamenstelling verbeteren (bijv. de vetvrije massa vergroten) en aldus de algehele kwaliteit van leven verhogen, vermoeidheid verminderen en het lichamelijk functioneren van ondervoede patiënten verbeteren. Gerandomiseerde gecontroleerde studies zijn nodig om het effect van een combinatie van lichaamsbeweging en adequate dieet counseling (volwaardige energie- en eiwitbehoefte) in HHT patiënten te evalueren tijdens en na de behandeling.

Normale voedselinname

Ten slotte zouden vervolgstudies zich niet alleen op het handhaven en/of verbeteren van de voedingstoestand van HHT-patiënten moeten richten, maar ook op het bevorderen van het herstel van de normale voedselinname om hiermee het genot en het sociale aspect van eten te verbeteren.

Een verdere verbetering van normale voedselinname kan worden bereikt door het verminderen van de behoefte aan drinkvoeding/ voedingssupplementen en voeding met een aangepaste consistentie met name in de revalidatiefase, met behoud van een goede voedingstoestand. Dit zou kunnen leiden tot een verbetering van de kwaliteit van leven en mogelijk ook tot kostenbesparingen. Om patiënten te helpen omgaan met alle overige problemen rondom het eten, zouden naast fysieke behandelmethoden (bijvoorbeeld sliktherapie) ook holistische interventies op het gebied van de psychische en/of sociale aspecten van het eten moeten worden ontwikkeld en onderzocht om patiënten te helpen omgaan met alle resterende problemen rondom eten. Deze levenslange aspecten verdienen nadere aandacht in verder onderzoek en opleidingen van diëtisten en andere paramedische beroepsbeoefenaren die werken met HHT-patiënten.

Conclusie

Gewichtsverlies en ondervoeding tijdens en na de behandeling komen vaak voor bij HHT-patiënten met tumorstadiëring II-IV. De mate van ondervoeding neemt toe aan het einde van de behandeling en in de vroege revalidatieperiode, met name bij patiënten die worden behandeld met (chemo)radiotherapie. Ondervoeding wordt geassocieerd met een significant slechtere algehele kwaliteit van leven, vermoeidheid en verminderd cognitief functioneren. Individuele dieet counseling is een effectieve therapie om gewichtsverlies en ondervoeding te beperken.

Door intensieve behandelingsstrategieën hebben veel HHT-patiënten symptomen die een normale voedselinname belemmeren. Dit kan leiden tot ondervoeding en verminderde kwaliteit van leven. Dysfagie is hierin een van de meest prominente symptomen. Ondanks verwachtingen, blijkt een combinatie van sliktherapie en individuele dieet counseling niet te leiden tot een sneller herstel van de normale voedselinname bij HHT-patiënten.

Dankwoord



Het onderzoek blijkt voor mij een hele goede keuze! Het was een heel nieuw gebied en een groot avontuur, ik heb hier de afgelopen jaren met veel plezier en voldoening aan gewerkt!! Mede door de fijne contacten met patiënten en de prettige samenwerking op de werkvloer met alle andere betrokken hulpverleners heeft dit onderzoek kunnen plaatsvinden. We zagen knelpunten in de voedingszorg en door de samenwerking en stimulans van de hoofd halsketen heeft dit onderzoek uiteindelijk geleid tot dit resultaat! Daar ben ik trots op!! Ik heb met eigen ogen gezien hoe we de voedingszorg voor deze patiëntenpopulatie op een hoog niveau hebben gebracht en wat we voor deze patiëntengroep kunnen betekenen.

Ik wil graag iedereen bedanken die mij in dit promotietraject hebben bijgestaan. Hierbij wil ik graag een aantal personen in het bijzonder noemen:

Beste patiënten, bedankt voor jullie bereidheid om deel te nemen aan mijn onderzoeken en de bijdrage die jullie doordoor zelf hebben geleverd aan alle ontwikkelingen.

Beste professor Merkx, Beste Thijs, na een aantal jaren patiëntenzorg was jij degene die mij het vertrouwen heeft gegeven om dit promotietraject in te gaan! Je bent altijd toegankelijk geweest en dat maakte de afgelopen jaren erg prettig. Je had steeds een oplossing voor hoe verder. Ons overleg was niet alleen inhoudelijk zinvol maar ook gezellig. Op vrijdag middag even een kop koffie om de voortgang te bespreken, ik zal het missen. Bedankt voor alle ondersteuning, enthousiasme, geduld en humor. Dank dat je mijn promotor bent geweest en ik hoop dat we nog lang mogen samenwerken.

Beste professor Kaanders, Beste Hans, bedankt voor al jouw kritische en waardevolle input. Jouw rustige overwogen benadering heeft me erg geholpen. Ik heb veel waardering voor jou als klinisch onderzoeker. Je hebt er mede voor gezorgd dat onze gerandomiseerde studie organisatorisch goed van de grond is gekomen. Teksten werden elke keer beter met jouw opmerkingen. Even een kort telefoontje en ik kon weer verder. Bedankt voor de samenwerking, hopelijk blijft deze zo bestaan.

Beste professor Drenth, Beste Joost, Je hebt me vanaf het begin af aan gesteund. Je stond steeds klaar ondanks jouw overvolle agenda. Van jouw wetenschappelijke ervaring heb ik veel geleerd, in de werkbesprekingen maar ook daarbuiten. Dank voor jouw positieve en kritische inbreng. Hoop dat we deze samenwerking verder kunnen uitbreiden en het voedingsonderzoek binnen de afdeling MDL verder op de kaart kunnen zetten.

Beste dr. Wanten, Beste Geert, ik ken jou al vanuit de periode van het voedingsteam. Je gaat slagvaardige te werk en staat altijd klaar bij vragen. Jouw snelle reacties op mails en vragen heb ik heel fijn gevonden. De frisse blik op teksten, alle tips en suggesties waren van harte welkom. Hoop dat we in de toekomst het voedingskundig onderzoek binnen de afdeling MDL verder kunnen uitbreiden.

Beste Ellen, jij hebt me kennis laten maken met het voedingsonderzoek; methodologie en de statistiek. Daar ben ik je heel dankbaar voor! De gesprekken met jou waren altijd heel verhelderend. Je hebt me steeds gesteund en gestimuleerd om verder te gaan. Bedankt daarvoor!

Mede auteurs, en in het bijzonder **Ton Naber, Jaap van Binsbergen, Heidi Rütten, Robert Takes, Carla van Herpen en Jan Hendriks** hartelijk dank voor jullie bijdrage aan de artikelen. Leden van de manuscriptcommissie, **Beste Prof. Dr. Theo van Achterberg, Prof. Dr. Ellen Kampman en Prof. Dr. Henri Marres**, graag wil ik jullie bedanken voor jullie tijd en de kritische beoordeling van dit manuscript.

Beste Marjo, bedankt voor jouw luisterend oor op de momenten dat ik het zwaar had en voor de flexibiliteit die je me geboden hebt tijdens dit promotietraject. Je bent altijd erg enthousiast geweest en door met me mee te denken is het gelukt om de werkzaamheden voor onderzoek en patiëntenzorg te combineren.

Lieve Monique en Hester, samen met jullie hebben we de basis gelegd voor voedingszorg van de hoofd halsoncologische patiënt. Daar ben ik trots op! **Hester** ik waardeer jouw creativiteit en enthousiasme. **Monique** jouw gedrevenheid en collegialiteit bewonder ik. Bedankt voor jullie geweldige ondersteuning en feedback tijdens het onderzoek. Wat leuk dat jullie mijn paranimfen willen zijn!

Mirjam, Heleen, Renée, Annemieke, Mariska, Sanne en Iris, bedankt voor jullie waardevolle inzet de afgelopen jaren. We hebben een gedreven en gezellig team! Van patiënten hoor ik vaak terug dat ze zo blij zijn met onze ondersteuning.

Natuurlijk ook alle andere collega's van de afdeling MDL- diëtetiek! Bedankt dat jullie zo'n fijne collega's zijn en voor de interesse die jullie hebben getoond voor het onderzoek waar ik mee bezig ben geweest.

Onderzoekers van de afdeling MDL, het is prettig om met jullie van gedachten te wisselen. Het doen van onderzoek ik natuurlijk heel leuk maar af en toe ook wel wat eenzaam. Dan is het fijn om jullie te spreken.

Beste Jacqueline, wat fijn dat ik jou tijdens mijn promotietraject heb leren kennen. Het was heel prettig om met jou samen te werken! Wat heb ik lol gehad met jou! Dat was een zeer welkome afwisseling in het serieuze werk waar ik steeds weer veel energie van kreeg.

Beste Hanneke, met jou samen is mede het slikonderzoek tot stand gekomen. We hebben een grote stap gezet! De discussie's en overwegingen met jou heb ik als zeer waardevol ervaren. Je hebt grootste ideeën en bent een echte onderzoeker met hart voor je werk!

Beste Anne, Emmelien, Pauline en Simone, wat zijn jullie een geweldig team logopedisten! Jullie inzet en flexibiliteit om onze FOCISD-studie tot het laatste puntje te volbrengen waardeer ik enorm. Bedankt daarvoor.

Studenten van de opleiding voeding en gezondheid van de WUR: **Gelagister, Lilian, Koko, Lowela, Anouk en Ilse** jullie hebben onvoorstelbaar veel werk verricht. Dank voor jullie tijd en de waardevolle opdrachten die jullie hebben uitgevoerd.

Beste **PWHHT**, wat een prettige en gezellige werkgroep hebben we! Het was een plezier om met jullie samen te werken. Wat leerzaam om de congressen mee te organiseren. Bedankt voor de fijne tijd!

Beste Marianne, Maurice, Wilma, Germa, Janneke, Lisette, Truus, Heidi, Nifja, Jaya, Jacqueline, Heleen, Annemieke, Edith, Lotte, Gidi, Fred, Marion en alle andere verpleegkundigen, voedingsassistenten, paramedici, secretaresses en specialisten van de hoofd-halsoncologische keten wat is het prettig om met jullie samen te werken. De flexibele inzet van jullie en de gezellige praatjes op zijn tijd maken het extra plezierig om hier te werken!

Lieve vriendinnen en vrienden, bedankt voor alle gezellige en ontspannen momenten en voor de interesse die jullie getoond hebben. Lieve **Marjon, Yvon en Brigit**, we hebben de afgelopen decennia al heel wat levenservaring gedeeld. Bedankt voor de leuke, gezellige, mooie en bijzondere momenten die ik met jullie mocht delen, ik hoop dat we in de toekomst nog veel mooie momenten zullen beleven.

Lieve schoonfamilie, Theo en Corrie bedankt voor jullie gezelligheid en voor het feit dat jullie zo'n lieve opa en oma zijn. Bedankt voor alle momenten dat jullie klaar staan. **Lieve Mirjam, Erik, Julie, Ruben, Ernie en Janick** wat fijn dat jullie familie zijn!

Lieve familie, lieve pap en mam, bedankt voor jullie onvoorwaardelijke steun en de fijne onbezorgde jeugd die ik heb gehad! Hierdoor heb ik me kunnen ontwikkelen tot de persoon die ik nu ben! Bedankt daarvoor. Ik vind het geweldig om te zien hoe jullie van Jada en Evan kunnen genieten. Ik hou van jullie! **Lieve Jan, Karina, Jan, Nienke, Lotte, Wouter, Sanne en Diede** wat fijn dat jullie familie zijn!

Lieve Archie, Wat hebben we het fijn samen! Wat genieten we samen en met de kinderen, wij zijn een hecht team. Je hebt me altijd gestimuleerd om deze uitdaging aan te gaan en te volbrengen. Bedankt voor alle steun, tijd en ruimte die je me tijdens dit promotietraject gegeven hebt. Ik hou van jou!

Lieve Jada en Evan, wat ben ik trots op jullie! Ik geniet van jullie vrolijkheid en enthousiasme. Wat is het gezellig om samen te spelen of er samen op uit te gaan. Ik vind het fantastisch om jullie op te zien groeien en om samen met jullie de wereld te ontdekken. Wat hou ik enorm veel van jullie!!

List of publications



1. A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. **van den Berg MGA**, Rasmussen-Conrad EL, Gwasara GM, Krabbe PF, Naber AH, Merkx MAW. Clin Nutr. 2006;25(5):765-72.
2. A prospective study on malnutrition and quality of life in patients with head and neck cancer. **van den Berg MGA**, Rasmussen-Conrad EL, van Nispen L, van Binsbergen JJ, Merkx MAW. Oral Oncol. 2008;44(9):830-7.
3. Improving nutritional management within high-risk groups. van Wayenburg CA, van Binsbergen JJ, **van den Berg MGA**, Merkx MAW, van Staveren WA, Rasmussen-Conrad E, van Weel C. Br J Gen Pract. 2009;59(565):595-6.
4. Weight loss in head and neck cancer patients little noticed in general practice. van Wayenburg CA, Rasmussen-Conrad EL, **van den Berg MGA**, Merkx MAW, van Staveren WA, van Weel C, van Binsbergen JJ. J Prim Health Care. 2010;2(1):16-21.
5. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. **van den Berg MGA**, Rasmussen-Conrad EL, Wei KH, Lintz-Luidens H, Kaanders JHAM, Merkx MAW. Br J Nutr. 2010;104(6):872-7.
6. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. Rütten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijackers AF, **van den Berg MGA**, Merkx MAW, van Herpen CML, Kaanders JHAM. Int J Radiat Oncol Biol Phys. 2011;81(4):923-9.
7. Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: A cross-sectional study. **van den Berg MGA**, Rütten H, Rasmussen-Conrad EL, Knuijt S, Takes RP, van Herpen CML, Wanten GJ, Kaanders JHAM, Merkx MAW. Head Neck. 2013 Apr 4.
8. Supportive care in early rehabilitation for advanced-stage radiated head and neck cancer patients. de Leeuw J, **van den Berg MGA**, van Achterberg T, Merkx MAW. Otolaryngol Head Neck Surg. 2013;148(4):625-32.
9. Normalcy of food intake in head and neck cancer patients supported by combined dietary counseling and swallowing therapy: A Randomized clinical trial. **van den Berg MGA**, Kalf JG, Hendriks JCM, Takes RP, van Herpen CML, Wanten GJA, Drenth JPH, Kaanders JHAM, Merkx MAW. Submitted.

Curriculum Vitae



Manon van den Berg werd geboren op 13 Juli 1976 te Nijmegen. In 1994 behaalde zij haar HAVO- diploma aan het Comenius College te Uden. Vervolgens behaalde zij in 1998 haar Bsc titel Voeding en Diëtetiek aan de Hogeschool van Arnhem en Nijmegen. Na haar stage binnen de afdeling Diëtetiek in het Universitair Medisch Centrum Rotterdam en haar werkzaamheden in het Mesos Medisch Centrum, locatie Overvecht te Utrecht, startte zij in 1999 als klinisch diëtist in het Radboud Universitair Medisch Centrum te Nijmegen. Hier was zij werkzaam op vele klinische afdelingen waaronder Chirurgie, Traumatologie, Hart- thoraxchirurgie, Urologie, KNO en Mond-, kaak-, en aangezichtschirurgie. Naast deze werkzaamheden was zij nauw betrokken bij het tot stand komen van het 'Beroepsprofiel Diëtist' in 2003 vanuit de Nederlandse Vereniging van Diëtisten. Van 2001-2006 was zij werkzaam binnen het voedingsteam van het Radboud Universitair Medisch Centrum. Vervolgens kwam de nadruk te liggen op de hoofdhals oncologie. Na de universitaire cursussen 'Methodologie', 'Systematisch literatuuronderzoek', 'First Certificate in English' en 'Statistiek', is zij in 2007 part-time gestart met haar promotie onderzoek waarvan de resultaten staan beschreven in dit proefschrift. Zij is actief bestuurslid van de Nederlandse en Nijmeegse Paramedische Werkgroep Hoofd Hals Tumoren. Naast de in dit proefschrift beschreven publicaties heeft zij vele nationale en internationale presentaties verzorgd op dit gebied. Manon woont samen met Archie Bongers en hun kinderen Jada (2008) en Evan (2006).

