University of Groningen

CHANGES IN NUTRITIONAL STATUS AND DIETARY INTAKE DURING AND AFTER HEAD AND NECK CANCER TREATMENT

Jager-Wittenaar, Harriet; Dijkstra, Pieter U.; Vissink, Arjan; Langendijk, Johannes A.; van der Laan, Bernard F. A. M.; Pruim, Jan; Roodenburg, Jan L. N.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

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

[Link to publication in University of Groningen/UMCG research database](#)

CHANGES IN NUTRITIONAL STATUS AND DIETARY INTAKE DURING AND AFTER HEAD AND NECK CANCER TREATMENT

Harriët Jager-Wittenaar, RD,[1] Pieter U. Dijkstra, PT, MT, PhD,[1,2,3] Arjan Vissink, DDS, MD, PhD,[1]
Johannes A. Langendijk, MD, PhD,[4] Bernard F. A. M. van der Laan, MD, PhD,[5]
Jan Pruim, MD, PhD,[6] Jan L. N. Roodenburg, DDS, MD, PhD[1]

[1] Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen,
  Post Office Box 30001, 9700 RB Groningen, The Netherlands. E-mail: h.jager@onco.umcg.nl
[2] Department of Rehabilitation, University Medical Center Groningen, University of Groningen,
  Post Office Box 30001, 9700 RB Groningen, The Netherlands
[3] Graduate School for Health Research, University Medical Center Groningen, University of Groningen, Groningen,
  The Netherlands
[4] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen,
  Post Office Box 30001, 9700 RB Groningen, The Netherlands
[5] Department of Otorhinolaryngology/Head & Neck Surgery, University Medical Center Groningen,
  University of Groningen, Post Office Box 30001, 9700 RB Groningen, The Netherlands
[6] Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen,
  University of Groningen, Post Office Box 30001, 9700 RB Groningen, The Netherlands

Abstract: *Background.* The purpose of this study was to test whether nutritional status of patients with head and neck cancer changes during and after treatment.

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

Results. During treatment, body weight (-3.6 ± 5.3 kg; $p = .019$) and lean mass (-2.43 ± 2.81 kg; $p = .001$) significantly declined. Patients with sufficient intake (≥ 35 kcal and ≥ 1.5 grams protein/kg body weight) lost less body weight and lean mass than patients with insufficient intake (mean difference, -4.0 ± 1.9 kg; $p = 0.048$ and -2.1 ± 1.0 kg; $p = .054$, respectively). After treatment, only patients with sufficient intake gained body weight (2.3 ± 2.3 kg) and lean mass (1.2 ± 1.3 kg).

Conclusion. Patients with head and neck cancer fail to maintain or improve nutritional status during treatment, despite sufficient intake. © 2010 Wiley Periodicals, Inc. *Head Neck* **33:** 863–870, 2011

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

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

Little is known about changes in body composition in patients with head and neck cancer. Assessment of changes in body composition is of clinical importance.

In malnourished patients, lean mass depletion (ie, muscle mass depletion is responsible for the impaired immune function), which in turn results in a higher risk for postoperative complications and reduced response to cancer treatment.[11] Moreover, lean mass depletion is associated with reduced physical activity, reduced quality of life, and prolonged length of hospital stay.[1,12]

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

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

PATIENTS AND METHODS

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

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

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

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

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

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

Patients were asked for their body weight (without clothes and shoes) 6 months and 1 month before the start of treatment. The percentage of weight loss in the last month was calculated as

$$(\text{body weight 1 month ago} - \text{actual body weight}/ \text{body weight 1 month ago}) \times 100.$$

Percentage of weight loss in the last 6 months was calculated as

$$(\text{body weight 6 months ago} - \text{actual body weight}/ \text{body weight 6 months ago}) \times 100.$$

Malnutrition was defined as weight loss $\geq 10\%$ in the last 6 months or $\geq 5\%$ in the last month.[4,24–26] Body mass index (BMI kg/m^2) was calculated as actual body weight/height^2. BMI was classified as: underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5–25 kg/m^2), overweight (BMI > 25–30 kg/m^2) or obese (BMI > 30 kg/m^2).[27]

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

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

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

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

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

Statistical Analysis. Statistical analyses were performed using SPSS 16.0 for Windows software (SPSS, Chicago, IL). Descriptive statistics were used to summarize baseline patient characteristics. Results are expressed as mean $\pm$ SD, unless stated otherwise. Changes in body weight, lean mass, lean mass index, fat mass, fat mass index, grip strength, and phase angle over time were analyzed by General Linear Model repeated measures, using type of treatment (surgery and radiotherapy/chemoradiation vs radiotherapy/chemoradiation) as within-subject factor. In case of deviation from sphericity, a Greenhouse Geisser correction for degrees of freedom was used. Changes in performance status over time were analyzed by the Wilcoxon rank sum test. Differences in continuous variables between the 2 groups were analyzed by independent sample t tests and 1-way analysis of variance between 3 groups. Pearson correlation coefficient r was used to analyze the relationship between 2 continuous variables. In all analyses, statistical significance was set at $p < .05$.

RESULTS

Thirty-five patients could be included in the study (59% participation rate). The main reason for not being willing to participate in the study was expected physical or mental burden of participation ($n = 16$). Other reasons for no participation were: too busy due to the disease itself ($n = 6$) and not interested ($n = 2$). No significant differences in body weight and BMI were found between participants and nonparticipants. However, significantly more nonparticipants were treated with radiotherapy/chemoradiation (71%; $n = 17$) than participants (31%; $n = 9$; $p = .004$).

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

Phase angle measurements were performed in 27 patients, because in 2 patients bioelectrical impedance analysis could not be performed due to the presence of metal prostheses. In all other measurements,

Table 1. Baseline patient characteristics at T_0.

Characteristic	No. of patients	%*
Age, mean (SD), y	60.6 (10.0)	
Sex		
Male	23	79
Female	6	21
Tumor localization		
Larynx	7	24
Hypopharynx	2	7
Oropharynx	10	35
Oral cavity	10	35
Tumor size		
T1	1	3
T2	7	24
T3	8	28
T4	13	45
Type of treatment		
Radiotherapy	3	10
Surgery + radiotherapy	16	55
Chemoradiation	6	21
Surgery + chemoradiation	4	14
WHO performance status		
0	20	69
1	7	24
2	1	3
3	1	3
Malnutrition		
Yes	5	17
No	24	83
BMI, kg/m²		
<18.5 (underweight)	5	17
18.5–25 (normal weight)	13	45
>25–30 (overweight)	6	21
>30 (obese)	5	17
BMI, mean (SD), kg/m²		
Male	24.7 (5.2)	
Female	21.8 (5.8)	
Lean mass index, mean (SD), kg		
Male	17.9 (2.5)	
Female	14.2 (2.4)	
Fat mass index, mean (SD), kg		
Male	6.2 (3.0)	
Female	7.2 (3.4)	

Abbreviations: WHO, World Health Organization; BMI, body mass index.
*Sum of percentages may be dissimilar to 100%, due to rounding.

data of 29 patients were used in the analysis. Baseline patient characteristics are shown in Table 1. Body weight of patients treated with surgery and radiotherapy/chemoradiation was significantly higher (79.5 ± 18.0 kg) than of patients treated with primary radiotherapy/chemoradiation (69.0 ± 20.2 kg).

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

Five patients (25%) treated with surgery and radiotherapy/chemoradiation and 6 patients treated with radiotherapy/chemoradiation (67%) had received dietary counseling before the start of treatment. In total, 13 patients (45%) were (partially) fed by tube

feeding during radiotherapy. Twelve patients (41%) had received a prophylactic gastrostomy prior to the start of their treatment, of which 3 patients were treated with surgery and radiotherapy, 5 patients with primary chemoradiation, and 4 patients with surgery and chemoradiation. Two patients (7%) who were treated with surgery and chemoradiation did not use their gastrostomy. One of these 2 patients did not want to use tube feeding and in the other patient the gastrostomy had to be removed early due to infection. One patient (3%) used tube feeding by a nasogastric tube during treatment with chemoradiation, because prophylactic placement of a gastrostomy was not possible. One patient (3%) received therapeutic tube feeding by a nasogastric tube during radiotherapy.

Changes in Nutritional Status and Performance Status. As shown in Table 2, body weight, BMI, and lean mass significantly declined during treatment ($p < .05$). In this period, patients lost 3.6 ± 5.3 kg of body weight, which was 4.7% of pretreatment body weight. Sixty-two percent of weight loss was loss of lean mass (2.4 ± 2.8 kg), which was 4.5% of pretreatment lean mass. Lean mass declined significantly in all body regions (arms, legs $p < .001$; and trunk $p < .05$). Prevalence of malnutrition shortly after treatment (at T_1) increased to 52% (15 of 29).

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

In men, lean mass tended to be depleted pretreatment and was depleted posttreatment (lean mass index <17.6 for men aged 35–74 years, Table 2).[28] In women, lean mass depletion (lean mass index <14.6–14.7 for women aged 35–74 years)[28] was observed both pretreatment and posttreatment. Neither in men nor women fat mass depletion was observed. A higher fat mass at T_0 was significantly related to loss of lean mass during treatment ($r = 0.51$; $p = .005$).

Loss of body weight and lean mass during and after treatment did not differ per age ($\geq$65 years vs <65 years), sex, tumor size (T1/T2 vs T3/T4), type of treatment (primary radiotherapy or chemoradiation vs surgery and radiotherapy, or surgery and chemoradiation), baseline nutritional status (malnutrition yes/no), and use of tube feeding (yes/no). However, a significant interaction between time and type of treatment was observed for changes in lean mass index over time ($p < .048$).

Grip strength significantly declined during treatment and significantly increased after treatment ($p < $

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

	T_0	T_1	T_2	p value
Body weight, mean (SD), kg	76.3 (19.0)	72.7 (16.5)	73.0 (15.0)	.019[*,†]
Body mass index, mean (SD), kg/m^2	24.1 (5.4)	23.0 (4.6)	23.1 (4.0)	.024[*,†]
Lean mass, mean (SD), kg	54.6 (11.4)	52.1 (10.7)	52.3 (10.3)	.001[†,‡]
Lean mass index, mean (SD), kg/m^2	17.2 (2.9)	16.5 (2.5)	16.6 (2.3)	.065[†,§]
Fat mass, mean (SD), kg	20.0 (9.8)	18.9 (8.1)	19.0 (7.0)	.298[†]
Fat mass index, mean (SD), kg/m^2	6.4 (3.1)	6.1 (2.5)	6.1 (2.2)	.502[†]
Grip strength, mean (SD), kg	39.8 (12.8)	35.3 (12.2)	37.0 (12.2)	<.001[†,‖]
Phase angle, mean (SD), °	6.3 (0.8)	5.8 (0.1)	6.0 (1.4)	.077[¶]

[*]$p < .05$ (T_0–T_1).
[†]Analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation vs radiotherapy/ chemoradiation) as within-subject factor. A Greenhouse Geisser correction for degrees of freedom was used because of deviation from sphericity.
[‡]$p < .05$ (T_0–T_1; T_0–T_2).
[§]Interaction between time and type of treatment (patients treated with surgery plus radiotherapy/chemoradiation versus patients treated with radiotherapy/chemoradiation) ($p < .05$).
[‖]$p < .05$ (T_0–T_1; T_1–T_2; T_0–T_2).
[¶]Analyzed by Wilcoxon rank sum test.

.001; Table 2). Decline in grip strength during treatment was significantly related to decline in body weight ($r = 0.42$; $p = .023$) and decline in lean mass ($r = 0.49$; $p = .007$) in this period. Such a relationship was not found after treatment (between T_1 and T_2).

Phase angle did not significantly change over time (Table 2). However, decrease in phase angle during treatment was significantly related to decrease in lean mass in this period ($r = 0.51$; $p = .007$).

Median performance status significantly decreased during treatment from 0 ("Fully active. Able to carry out all normal activity without restriction") to 1 ("Restricted in physically strenuous activity but ambulatory and able to carry out light work"; $p = .013$), and significantly recovered to 0 in the period after treatment ($p = .003$).

Dietary Intake. As shown in Table 3, energy and protein intake did not change over time. However, a significant interaction between time and type of treatment was observed for changes in energy intake over time ($p = .033$; Figure 1).

Patients with a sufficient intake during treatment lost significantly less body weight (mean difference 4.0 ± 1.9 kg; $p = .048$) and lean mass (mean difference 2.1 ± 1.0 kg; $p = .054$) than patients with an insufficient intake (Table 4). Furthermore, patients with a sufficient intake in the period after treatment gained body weight and lean mass, whereas patients with an insuf-

ficient intake lost body weight (mean difference 3.7 ± 0.9 kg; $p < .001$) and lean mass (2.0 ± 0.6 kg; $p = .001$) in this period.

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

Frequency of insufficient intake was significantly higher in overweight/obese patients (91%) than in normal weight (54%) or underweight patients (20%; $p = .021$).

DISCUSSION

Our study is 1 of the few studies that longitudinally performed advanced nutritional assessments in patients with head and neck cancer and related nutritional status to dietary intake. Patients in the current study were not able to maintain or improve lean mass during head and neck cancer treatment. Instead, patients lost about 5% of their pretreatment body weight, of which nearly two-thirds was loss of lean mass.

Generally, loss of body weight and lean mass are known to be the result of negative energy and protein balance.[9,11] The observed loss of body weight and lean mass during cancer treatment may point toward insufficient dietary intake. Whereas dietary intake of our patients was in line with the current recommendations of 30 to 35 kcal/kg and 1.2 to 2.0 gram

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

	T_0	T_1	T_2	p value[*]
Total energy, mean (SD), kcal	2448.7 (769.3)	2540.6 (745.5)	2652.8 (795.1)	.849
Energy/body weight, mean (SD), kcal/kg	34.2 (13.9)	36.2 (11.6)	37.9 (14.2)	.853
Energy/lean mass, mean (SD), kcal/kg	46.9 (17.6)	49.4 (14.5)	52.3 (17.7)	.749
Total protein, mean (SD), g	90.1 (29.0)	98.9 (30.2)	102.3 (31.5)	.596
Protein/body weight, mean (SD), g/kg	1.3 (0.5)	1.4 (0.5)	1.5 (0.5)	.416
Protein/kg lean mass, mean (SD), g/kg	1.7 (0.6)	1.9 (0.6)	2.0 (0.7)	.372

[*]Analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation vs radiotherapy/ chemoradiation) as within-subject factor.

FIGURE 1. Changes in dietary intake as expressed by energy end protein intake during and after treatment, per type of treatment. ■, Energy, surgery + RT/CRT*; □, Energy, RT/CRT; ▲, Protein, surgery + RT/CRT; △, Protein, RT/CRT; RT, radiotherapy; CRT, chemoradiation. *A significant interaction between time and type of treatment was found in changes in energy intake over time ($p = .033$), analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation vs radiotherapy/chemoradiation) as within-subject factor.
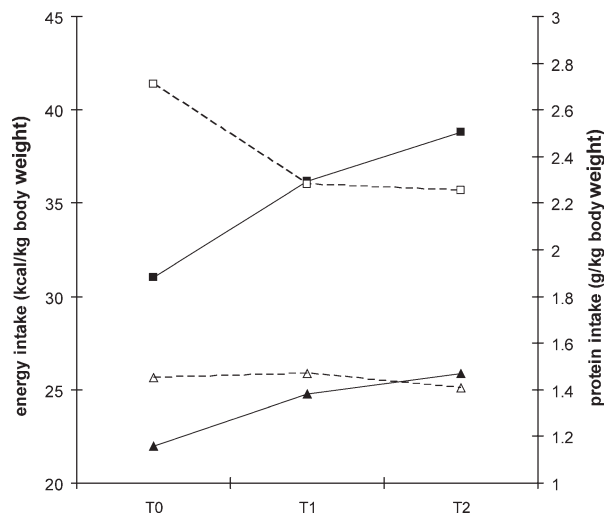
protein/kg body weight,[11] and whereas protein intake of 1.5 to 1.7 gram/kg body weight has generally been proposed as "optimal" to preserve lean mass in ambulant patients,[23] the optimal amount of energy and protein to preserve lean mass in patients with head and neck cancer is still unknown. In the current study, patients with an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg still had their lean mass declined (1.2 ± 3.3 kg). Post-hoc analysis revealed that if the cutoff score for sufficient protein intake was raised to 1.7 gram/kg body weight, the accompanied decline in body weight and lean mass were not significantly or clinically relevantly smaller than when using the cutoff score of 1.5 gram protein/body weight. Because the number of patients with an intake of >1.7 gram protein/kg body weight was rather small ($n = 8$), this finding should be validated, that the current recommendations for dietary intake proposed in the literature need reappraisal.

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

Inflammatory activity related to disease or treatment may increase energy expenditure and protein

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

	Energy intake ≥35 kcal/kg body weight	Energy intake <35 kcal/kg body weight	Protein intake ≥1.5 gram/kg body weight	Protein intake <1.5 gram/kg body weight	Energy intake ≥35 kcal/kg body weight and protein intake ≥1.5 gram/kg body weight	Energy intake <35 kcal/kg body weight and/or protein intake <1.5 gram/kg body weight
No. of patients	$n = 16$	$n = 13$	$n = 12$	$n = 17$	$n = 11$	$n = 18$
Change between T_0 and T_1						
Body weight, mean (SD), kg	−1.1 (4.8)	−6.7 (4.4)*	−1.2 (5.2)	−5.3 (4.8)†	−1.1 (5.5)	−5.1 (4.8)†
Lean mass, mean (SD), kg	−1.4 (2.8)	−3.7 (2.4)*	−1.2 (3.1)	−3.3 (2.3)†	−1.2 (3.3)	−3.2 (2.2)
Fat mass, mean (SD), kg	0.3 (2.4)	−3.0 (2.7)*	0.1 (2.5)	−2.0 (3.1)	0.1 (2.6)	−1.9 (3.0)
	$n = 16$	$n = 13$	$n = 15$	$n = 14$	$n = 14$	$n = 15$
Change between T_1 and T_2						
Body weight, mean (SD), kg	2.2 (2.2)	−1.9 (2.1)‡	1.9 (2.7)	−1.3 (2.4)*	2.3 (2.3)	−1.5 (2.3)‡
Lean mass, mean (SD), kg	1.1 (1.3)	−1.0 (1.7)*	1.0 (1.6)	−0.7 (1.7)*	1.2 (1.3)	−0.8 (1.7)*
Fat mass, mean (SD), kg	0.1 (1.5)	−1.1 (2.3)*	1.0 (1.6)	−0.8 (2.3)†	1.2 (1.5)	−0.8 (2.3)*

*$p < .01$, analyzed by independent samples t test.
†$p < .05$, analyzed by independent samples t test.
‡$p < .001$, analyzed by independent samples t test.

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

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

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

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

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

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

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

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

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

REFERENCES

1. Soeters PB, Reijven PL, Van Bokhorst-de van der Schueren MA, et al. A rational approach to nutritional assessment. Clin Nutr 2008;27:706–716.
2. 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;15:1045–1050.
3. 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.
4. 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;19:419–425.
5. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. Clin Nutr 2008;27:793–799.
6. 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.
7. Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: surgery including organ transplantation. Clin Nutr 2006;25:224–244.
8. Ehrsson YT, Hellström PM, Brismar K, Sharp L, Langius-Eklöf A, Laurell G. Explorative study on the predictive value of systematic inflammatory and metabolic markers on weight loss in head and neck cancer patients undergoing radiotherapy. Support Care Cancer 2009. DOI: 10.1007/s00520-009-0758-4 [Epub ahead of print].
9. Guadagni M, Biolo G. Effects of inflammation and/or inactivity on the need for dietary protein. Curr Opin Clin Nutr Metab Care 2009;12:617–622.
10. Soeters PB, Grimble RF. Dangers, and benefits of the cytokine mediated response to injury and infection. Clin Nutr 2009;28:583–596.
11. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on Enteral Nutrition: non-surgical oncology. Clin Nutr 2006;25:245–259.
12. Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. Am J Clin Nutr 2004;79:613–618.
13. van den Berg MG, Rasmussen-Conrad EL, Gwasara GM, Krabbe PF, Naber AH, Merkx 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;25:765–772.
14. 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.
15. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. 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.
16. Ng K, Leung SF, Johnson PJ, Woo J. Nutritional consequences of radiotherapy in nasopharynx cancer patients. Nutr Cancer 2004;49:156–161.
17. 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; 29:893–900.
18. Isenring E, Bauer J, Capra S, Davies PS. Evaluation of foot-to-foot bioelectrical impedance analysis for the prediction of total body water in oncology outpatients receiving radiotherapy. Eur J Clin Nutr 2004;58:46–51.
19. Guo CB, Zhang W, Ma DQ, Zhang KH, Huang JQ. Hand grip strength: an indicator of nutritional state and the mix of postoperative complications in patients with oral and maxillofacial cancers. Br J Oral Maxillofac Surg 1996; 34:325–327.
20. Pham NV, Cox-Reijven PL, Wodzig WK, Greve JW, Soeters PB. SGA and measures for muscle mass and strength in surgical Vietnamese patients. Nutrition 2007;23:283–291.
21. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. Eur J Appl Physiol 2002;86:509–516.
22. Landi F, Russo A, Liperoti R, et al. Midarm muscle circumference, physical performance and mortality: results from the aging and longevity study in the Sirente geographic area (ilSIRENTE study). Clin Nutr 2010 [Epub ahead of print].
23. Sauerwein HP, Strack van Schijndel RJ. Perspective: how to evaluate studies on peri-operative nutrition? Considerations about the definition of optimal nutrition for patients and its key role in the comparison of the results of studies on nutritional intervention. Clin Nutr 2007;26:154–158.
24. Nguyen TV, Yueh B. Weight loss predicts mortality after recurrent oral cavity and oropharyngeal carcinomas. Cancer 2002;95:553–562.
25. Seltzer MH, Slocum BA, Cataldi-Betcher EL, Fileti C, Gerson N. Instant nutritional assessment: absolute weight loss and surgical mortality. JPEN J Parenter Enteral Nutr 1982;6:218–221.
26. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence based approach to treatment. Wallingford: CABI Publishing; 2003.
27. World Health Organization. Obesity. Preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland: World Health Organization, 1998.
28. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18–98 y. Int J Obes Relat Metab Disord 2002;26:953–960.
29. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 1985;66:69–74.
30. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2005;8:311–317.
31. Gupta D, Lis CG, Dahlk SL, et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. Nutr J 2008;7:19.
32. Gupta D, Lis CG, Dahlk SL, Vashi PG, Grutsch JF, Lammersfeld CA. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. Br J Nutr 2004;92:957–962.
33. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.
34. Burke BS. The dietary history as a tool in research. J Am Diet Assoc 1947;23:1041–1046.
35. Ki Y, Kim W, Nam J, Kim D, Park D, Kim D. C-reactive protein levels and radiation-induced mucositis in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;75:393–398.
36. Koc M, Taysi S, Sezen O, Bakan N. Levels of some acute-phase proteins in the serum of patients with cancer during radiotherapy. Biol Pharm Bull 2003;26:1494–1497.
37. Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. J Support Oncol 2007;5(9 Suppl 4):3–11.
38. Kyle UG, Morabia A, Slosman DO, Mensi N, Unger P, Pichard C. Contribution of body composition to nutritional assessment at hospital admission in 995 patients: a controlled population study. Br J Nutr 2001;86:725–731.
39. Hayes S, Davies PS, Parker T, Bashford J. Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone Marrow Transplant 2003;31:331–338.
40. Fountzilas G, Ciuleanu E, Dafni U, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. Med Oncol 2004;21:95–107.
41. Russell DM, Leiter LA, Whitwell J, Marliss EB, Jeejeebhoy KN. Skeletal muscle function during hypocaloric diets and fasting: a comparison with standard nutritional assessment parameters. Am J Clin Nutr 1983;37:133–138.
42. Rigaud D, Moukaddem M, Cohen B, Malon D, Reveillard V, Mignon M. Refeeding improves muscle performance without normalization of muscle mass and oxygen consumption in anorexia nervosa patients. Am J Clin Nutr 1997;65:1845–1851.
43. Stenholm S, Maggio M, Lauretani F, et al. Anabolic and catabolic biomarkers as predictors of muscle strength decline: the InCHIANTI study. Rejuvenation Res 2010; 13:3–11.
44. Barbosa-Silva MC, Barros AJ, Post CL, Waitzberg DL, Heymsfield SB. Can bioelectrical impedance analysis identify malnutrition in preoperative nutrition assessment? Nutrition 2003;19:422–426.
45. da Rocha EE, Alves VG, Silva MH, Chiesa CA, da Fonseca RB. Can measured resting energy expenditure be estimated by formulae in daily clinical nutrition practice? Curr Opin Clin Nutr Metab Care 2005;8:319–328.
46. Weijs PJ, Kruizenga HM, van Dijk AE, et al. Validation of predictive equations for resting energy expenditure in adult outpatients and inpatients. Clin Nutr 2008;27:150–157.