Pre- and post-treatment malnutrition in head and neck cancer patients
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Groningen: s.n.

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Chapter 5

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

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Head Neck: accepted for publication
ABSTRACT

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

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

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

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

INTRODUCTION

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

Malnutrition may have multiple causes in head and neck cancer patients. In the period before treatment, a major cause of malnutrition is insufficient food intake, related to mechanical obstruction of food or pain related to the tumor. In addition, cancer cachexia may contribute to malnutrition. Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. 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. Furthermore, cancer treatment may induce inflammation, either directly due to surgery, or indirectly due to (chemo)radiation induced mucositis. This inflammation may in turn result in (further) loss of muscle mass.

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

In previous prospective studies on malnutrition in head and neck cancer patients, various methods to assess nutritional status have been used. In some studies, nutritional status was assessed by means of changes in body weight or Patient Generated Subjective Global Assessment (PG-SGA). 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 and deterioration of nutritional status in patients not receiving dietary intervention. It is unknown, however, if and to what extent lean mass changed in these studies. Two other studies assessed body composition prospectively in head and neck cancer patients. In both studies, body weight and lean mass declined significantly during head and neck cancer treatment despite dietary counseling. 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. In that study, patients randomised to dietary counseling had significantly smaller deterioration of PG-SGA than patients not receiving dietary counseling, but they had no significant improvement in body weight and lean mass during treatment. 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. Currently, it remains unclear whether improvement of nutritional status or body weight in head and neck cancer patients is characterized by improvement of lean mass. The pitfall is that gain of body weight is characterized by mainly fat mass, whereas
improvement in lean mass is aimed for.

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

PATIENTS AND METHODS

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

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

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

All patients received individual dietary counseling during the study period, on admission for surgery and weekly during radiotherapy. Dietary counseling included advice on modification of food texture to alleviate treatment related oral symptoms like pain and dry mouth. To meet nutritional objectives of 35 kcal/kg body weight and 1.5 gram protein/kg body weight11,23, tube feeding or liquid dietary supplements were prescribed, either post-surgery or during radiotherapy or in post-treatment period.

Study measurements
Study assessments were carried out 3 times. First study measurement (T₀) was performed in the week before start of treatment. In this study measurement, body height, body weight, lean mass, fat mass, phase angle, grip strength, performance status and dietary intake were assessed. Second (T₁) and third (T₂) study measurement were performed 1 month and 4 months after end of treatment respectively. At these time points, assessment of all variables were repeated, except for body height.

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

Patients were asked for their body weight (without clothes and shoes) 6 months and 1 month before start of treatment. Percentage weight loss in the last month was calculated as (body weight 1 month ago – actual body weight / body weight 1 month ago) x 100. Percentage weight loss in last 6 months was calculated as (body weight 6 months ago – actual body weight / body weight 6 months ago) x 100. Malnutrition was defined as weight loss ≥10% in last 6 months or ≥5% in last month.4,24-26 Body Mass Index (BMI, kg/m²) was calculated as actual body weight / height². BMI was classified as: underweight (BMI <18.5 kg/m²), normal (BMI 18.5–25 kg/m²), overweight (BMI >25-30 kg/m²) or obese (BMI>30 kg/m²).27

Dual energy x-ray scans were performed to measure lean mass, fat mass and bone mineral content, with a Hologic Discovery A (Hologic Inc., Bedford, MA, USA). Changes in total lean mass, total fat mass, as well as changes in regional lean mass and fat mass (arms, legs and trunk) were analyzed. Lean mass index (kg/m²) was calculated as lean mass / (height)².12 Fat mass index (kg/m²) was calculated as fat mass / (height)².12 Change in body weight and lean mass of ≥0.5 kg were considered clinically relevant. Lean mass and fat mass depletion were defined as lean mass index and fat mass index <10th percentile.28 Lean mass index eliminates differences in lean mass associated with height.

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

Bioelectrical impedance analysis was used to measure resistance and reactance, using Bodystat® QuadScan 4000 (Bodystat Ltd.). Patients were in a supine position 15 minutes before measurement. Phase angle was calculated as arc-tangent (reactance / resistance) x 180° / π and expressed in degrees. A smaller phase angle, as observed in malnourished patients, suggests decreased cell integrity or cell death, whereas a larger phase angle suggest large quantities of intact cell membranes.21 Besides the function as nutritional indicator21,30,31, phase angle is a prognostic indicator as well.21,30,32 Phase angle is independent of regression equations and can be performed even in situations in which bioelectrical impedance analysis assumptions are not valid.30

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

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

Statistical analysis
Statistical analyses were performed using SPSS 16.0 for Windows software (SPPS Inc., Chicago, IL, USA).
Descriptive statistics were used to summarize baseline patient characteristics. Results are expressed as mean±SD, unless stated otherwise. Changes in body weight, lean mass, lean mass index, fat mass, fat mass index, grip strength, and phase angle over time were analyzed by General Linear Model repeated measures, using type of treatment (surgery and radiotherapy/chemoradiation versus radiotherapy/chemoradiation) as within-subject factor. In case of deviation from sphericity a Greenhouse Geisser correction for degrees of freedom was used. Changes in performance status over time were analyzed by Wilcoxon’s rank sum test. Differences in continuous variables between 2 groups were analyzed by independent sample t-tests and one-way ANOVA between 3 groups. Pearson’s correlation coefficient r was used to analyze the relationship between 2 continuous variables. In all analyses, statistical significance was set at p<0.05.

RESULTS

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

During the study period 1 patient was excluded because no indication for postoperative radiotherapy existed anymore. During the study period, 5 patients dropped out. Between T₀ and T₁, 1 malnourished patient died and 3 patients, of which 2 were malnourished, dropped out due to fatigue. Between T₁ and T₂, a well-nourished patient died. Twenty-nine patients completed all measurements.

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

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

Pretreatment prevalence of malnutrition was 17% (5/29). Malnourished patients had cancer in the supraglottic larynx (n=2), tongue (n=1) and hypopharynx (n=2). Four malnourished patients had received dietary intervention before T₀.

Five patients (25%) treated with surgery and radiotherapy/chemoradiation and 6 patients treated with primary radiotherapy/chemoradiation (67%) had received dietary counseling before start of treatment. In total, 13 patients (45%) were (partially) fed by tube feeding during radiotherapy. Twelve patients (41%) had received a prophylactic gastrostomy prior to start of treatment, of which 3 patients were treated with surgery and radiotherapy, 5 patients with primary chemoradiation and 4 patients with surgery and chemoradiation. Two patients (7%) that were treated with surgery and chemoradiation did not use their gastrostomy. One of these 2 patients did not want to use tube feeding and in the other patient the gastrostomy had to be removed.
Table 1. Baseline patient characteristics at T₀.

<table>
<thead>
<tr>
<th>Age (years), mean±SD</th>
<th>60.6±10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>n%</td>
<td></td>
</tr>
</tbody>
</table>

Gender
- Male 23 79
- Female 6 21

Tumor localization
- Larynx 7 24
- Hypopharynx 2 7
- Oropharynx 10 35
- Oral cavity 10 35

Tumor size
- T1 1 3
- T2 7 24
- T3 8 28
- T4 13 45

Type of treatment
- Radiotherapy 3 10
- Surgery + radiotherapy 16 55
- Chemoradiation 6 21
- Surgery + chemoradiation 4 14

WHO Performance status
- 0 20 69
- 1 7 24
- 2 1 3
- 3 1 3

Malnutrition
- Yes 5 17
- No 24 83

BMI (kg/m²)
- <18.5 (underweight) 5 17
- 18.5-25 (normal weight) 13 45
- >25-30 (overweight) 6 21
- >30 (obese) 5 17

<table>
<thead>
<tr>
<th>BMI, mean±SD (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
</tr>
<tr>
<td>24.7±5.2</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>21.8±5.8</td>
</tr>
</tbody>
</table>

Lean mass index, mean±SD (kg)
- Men 17.9±2.5
- Women 14.2±2.4

Fat mass index, mean±SD (kg)
- Men 6.2±3.0
- Women 7.2±3.4

a. Sum of percentages may be dissimilar to 100%, due to rounding.
early due to infection. One patient (3%) used tube feeding by a nasogastric tube during treatment with chemoradiation, because prophylactic placement of a gastrostomy was not possible. One patient (3%) received therapeutic tube feeding by a nasogastric tube during radiotherapy.

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

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg), mean±SD</td>
<td>76.3±19.0</td>
<td>72.7±16.5</td>
<td>73.0±15.0</td>
<td>0.019&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;), mean±SD</td>
<td>24.1±5.4</td>
<td>23.0±4.6</td>
<td>23.1±4.0</td>
<td>0.024&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lean mass (kg), mean±SD</td>
<td>54.6±11.4</td>
<td>52.1±10.7</td>
<td>52.3±10.3</td>
<td>0.001&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lean mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;), mean±SD</td>
<td>17.2±2.9</td>
<td>16.5±2.5</td>
<td>16.6±2.3</td>
<td>0.065&lt;sup&gt;a.d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fat mass (kg), mean±SD</td>
<td>20.0±9.8</td>
<td>18.9±8.1</td>
<td>19.0±7.0</td>
<td>0.298&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fat mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;), mean±SD</td>
<td>6.4±3.1</td>
<td>6.1±2.5</td>
<td>6.1±2.2</td>
<td>0.502&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grip strength (kg), mean±SD</td>
<td>39.8±12.8</td>
<td>35.3±12.2</td>
<td>37.0±12.2</td>
<td>0.001&lt;sup&gt;b,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phase angle (º), mean±SD</td>
<td>6.3±0.8</td>
<td>5.8±0.1</td>
<td>6.0±1.4</td>
<td>0.077&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a.  P<0.05 (T<sub>0</sub> - T<sub>1</sub>).  

b.  Analyzed by General Linear Model repeated measures, using type of treatment (surgery plus radiotherapy/chemoradiation versus radiotherapy/chemoradiation) as within-subject factor. A Greenhouse Geisser correction for degrees of freedom was used because of deviation from sphericity.  
c.  P<0.05 (T<sub>0</sub> - T<sub>1</sub>; T<sub>0</sub> - T<sub>2</sub>).  
d.  Interaction between time and type of treatment (patients treated with surgery plus radiotherapy/chemoradiation versus patients treated with radiotherapy/chemoradiation) (p<0.05).  
e.  P<0.05 (T<sub>0</sub> - T<sub>1</sub>; T<sub>1</sub> - T<sub>2</sub>; T<sub>0</sub> - T<sub>2</sub>).  
f.  Analyzed by Wilcoxon's rank sum test.

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

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy (kcal), mean±SD</td>
<td>2448.7±769.3</td>
<td>2540.6±745.5</td>
<td>2652.8±795.1</td>
<td>0.849</td>
</tr>
<tr>
<td>Energy/body weight (kcal/kg), mean±SD</td>
<td>34.2±13.9</td>
<td>36.2±11.6</td>
<td>37.9±14.2</td>
<td>0.853</td>
</tr>
<tr>
<td>Energy/lean mass (kcal/kg), mean±SD</td>
<td>46.9±17.6</td>
<td>49.4±14.5</td>
<td>52.3±17.7</td>
<td>0.749</td>
</tr>
<tr>
<td>Total protein (gram), mean±SD</td>
<td>90.1±29.0</td>
<td>98.9±30.2</td>
<td>102.3±31.5</td>
<td>0.596</td>
</tr>
<tr>
<td>Protein/body weight (gram/kg), mean±SD</td>
<td>1.3±0.5</td>
<td>1.4±0.5</td>
<td>1.5±0.5</td>
<td>0.416</td>
</tr>
<tr>
<td>Protein/lean mass (gram/kg), mean±SD</td>
<td>1.7±0.6</td>
<td>1.9±0.6</td>
<td>2.0±0.7</td>
<td>0.372</td>
</tr>
</tbody>
</table>

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

Changes in nutritional status and performance status

As shown in Table 2, body weight, BMI and lean mass significantly declined during treatment (p<0.05). In this period patients lost 3.6±5.3 kg body weight, which was 4.7% of pretreatment body weight. Sixty-two percent of weight loss was loss of lean mass (2.4±2.8 kg), which was 4.5% of pretreatment lean mass. Lean mass declined significantly in all body regions (arms, legs p<0.001; trunk p<0.05). Prevalence of malnutrition shortly after treatment (at T<sub>1</sub>) increased to 52% (15/29).
Overall, no significant changes in body weight, BMI and lean mass were found between first and second post-treatment assessment (between T1 and T2, Table 2). Ten patients (34%) lost body weight and lean mass both during and after treatment. At second post-treatment assessment, 11 patients (38%) had returned their body weight to pretreatment level. Prevalence of malnutrition at second post-treatment assessment declined to 24% (7/29).

In male, lean mass tended to be depleted pretreatment and was depleted post-treatment (lean mass index<17.6 for men aged 35-74 years, Table 2). In women, lean mass depletion (lean mass index<14.6-14.7 for women aged 35-74 years) was observed both pre- and post-treatment. Neither in male or female fat mass depletion was observed. A higher fat mass at T0 was significantly related to loss of lean mass during treatment ($r=0.51, p=0.005$).

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

Grip strength significantly declined during treatment and significantly increased after treatment ($p<0.001$, Table 2). Decline in grip strength during treatment was significantly related to decline in body weight ($r=0.42, p=0.023$) and decline in lean mass ($r=0.49, p=0.007$) in this period. Such a relationship was not found after treatment (between T1 and T2).

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

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

**Dietary intake**

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

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

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

Frequency of insufficient intake was significantly higher in overweight/obese patients (91%) than in normal weight (54%) or underweight patients (20%) ($p=0.021$).
Figure 1. Changes in dietary intake, as expressed by energy and protein intake during and after treatment, per type of treatment.

RT = radiotherapy.
CRT = chemoradiation.

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

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

<table>
<thead>
<tr>
<th>Energy intake</th>
<th>Protein intake</th>
<th>Energy intake</th>
<th>Energy intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35 kcal/kg BW</td>
<td>≥1.5 gram/kg BW</td>
<td>≤35 kcal/kg BW</td>
<td>≥1.5 gram/kg BW</td>
</tr>
<tr>
<td>ENERGY INTAKE</td>
<td>PROTEIN INTAKE</td>
<td>ENERGY INTAKE</td>
<td>ENERGY INTAKE</td>
</tr>
<tr>
<td>&lt;35 kcal/kg BW</td>
<td>&lt;1.5 gram/kg BW</td>
<td>≥35 kcal/kg BW</td>
<td>&lt;1.5 gram/kg BW</td>
</tr>
<tr>
<td>ENERGY INTAKE</td>
<td>ENERGY INTAKE</td>
<td>ENERGY INTAKE</td>
<td>ENERGY INTAKE</td>
</tr>
<tr>
<td>≥1.5 gram/kg BW</td>
<td>≥1.5 gram/kg BW</td>
<td>&lt;35 kcal/kg BW</td>
<td>&lt;1.5 gram/kg BW</td>
</tr>
</tbody>
</table>

**Change between T₀ and T₁**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>n=16</th>
<th>n=13</th>
<th>n=12</th>
<th>n=17</th>
<th>n=11</th>
<th>n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg), mean±SD</td>
<td>-1.1±4.8</td>
<td>-6.7±4.4 ( a )</td>
<td>-1.2±5.2</td>
<td>-5.3±4.8 ( b )</td>
<td>-1.1±5.5</td>
<td>-5.1±4.8 ( a )</td>
</tr>
<tr>
<td>Lean mass (kg), mean±SD</td>
<td>-1.4±2.8</td>
<td>-3.7±2.4 ( a )</td>
<td>-1.2±3.1</td>
<td>-3.3±2.3 ( b )</td>
<td>-1.2±3.3</td>
<td>-3.2±2.2</td>
</tr>
<tr>
<td>Fat mass (kg), mean±SD</td>
<td>0.3±2.4</td>
<td>-3.0±2.7 ( a )</td>
<td>0.1±2.5</td>
<td>-2.0±3.1</td>
<td>0.1±2.6</td>
<td>-1.9±3.0</td>
</tr>
</tbody>
</table>

**Change between T₁ and T₂**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>n=16</th>
<th>n=13</th>
<th>n=15</th>
<th>n=14</th>
<th>n=14</th>
<th>n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg), mean±SD</td>
<td>2.2±2.2</td>
<td>-1.9±2.1 ( c )</td>
<td>1.9±2.7</td>
<td>-1.3±2.4 ( a )</td>
<td>2.3±2.3</td>
<td>-1.5±2.3 ( c )</td>
</tr>
<tr>
<td>Lean mass (kg), mean±SD</td>
<td>1.1±1.3</td>
<td>-1.0±1.7 ( a )</td>
<td>1.0±1.6</td>
<td>-0.7±1.7 ( a )</td>
<td>1.2±1.3</td>
<td>-0.8±1.7 ( a )</td>
</tr>
<tr>
<td>Fat mass (kg), mean±SD</td>
<td>0.1±1.5</td>
<td>-1.1±2.3 ( a )</td>
<td>1.0±1.6</td>
<td>-0.8±2.3 ( a )</td>
<td>1.2±1.5</td>
<td>-0.8±2.3 ( a )</td>
</tr>
</tbody>
</table>

BW = body weight.

a. \( P<0.01 \), analyzed by independent samples t-test.
b. \( P<0.05 \), analyzed by independent samples t-test.
c. \( P<0.001 \), analyzed by independent samples t-test.
DISCUSSION

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

Generally, loss of body weight and lean mass are known to be the result of negative energy and protein balance.9,11 The observed loss of body weight and lean mass during cancer treatment may point towards insufficient dietary intake. Whereas dietary intake of our patients was in line with the current recommendations of 30-35 kcal/kg and 1.2–2.0 gram protein/kg body weight11, and whereas protein intake of 1.5-1.7 gram/kg body weight has generally been proposed as ‘optimal’ to preserve lean mass in ambulant patients23, the optimal amount of energy and protein to preserve lean mass in head and neck cancer patients is still unknown. In the current study, patients with an intake of ≥35 kcal/kg and ≥1.5 gram protein/kg still had their lean mass declined (1.2±3.3 kg). Post-hoc analysis revealed that if the cutoff score for sufficient protein intake was raised to 1.7 gram/kg body weight, the accompanied decline in body weight and lean mass were not significantly or clinically relevantly smaller than when using the cutoff score of 1.5 gram protein/body weight. As the number of patients with an intake of >1.7 gram protein/kg body weight was rather small (n=8), this finding should be validated, as well as that the current recommendations for dietary intake proposed in the literature need reappraisal.

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

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

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

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

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

Surprisingly, more than one-third of the patients using tube feeding did not meet the nutritional goals of ≥35 kcal/kg and ≥1.5 gram protein/kg body weight. The majority of the patients using tube feeding was treated with chemoradiation (77%). Insufficient intake in these patients may be related to nausea. Nausea is frequently present in patients treated with chemoradiation and is less frequently present in patients treated with radiotherapy alone. 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 and in patients with anorexia nervosa, during refeeding after a period of hypocaloric feeding. It has been suggested that nutrition exerts effects on muscle strength independently of muscle mass. Additionally, a negative association between grip strength and inflammatory activity has been reported. Therefore, the observed increase in grip strength in post-treatment period may reflect decreased inflammatory activity.

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

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

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

**ACKNOWLEDGEMENTS**

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

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

All authors have no conflict of interest.

**REFERENCES**

Chapter 5


