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An explorative study on energy balance in patients with head and neck cancer

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ABSTRACT

Background: Involuntary body weight loss in head and neck cancer is common. Fundamental for weight loss is an energy imbalance where total energy expenditure exceeds energy intake.

Aim: To map energy intake and parameters of energy expenditure at the start of and after radiotherapy, and their relation to weight change, body mass index, and immune markers in patients with head and neck cancer.

Materials and Methods: Data from 20 patients on energy intake (24-hour dietary intake recalls), total energy expenditure (SenseWear Armband Pro3), resting energy expenditure (indirect calorimetry), body weight, body mass index, and immune markers in serum (C-reactive protein and Interleukin-6) were collected at the start of and after radiotherapy (median 8 mo, range 5–13).

Results: No statistical significance was shown between the two measurement points for energy intake or for the different parameters of energy expenditure. Median values for energy balance were 0.93 and 0.96 for the start of treatment and follow-up, respectively. Twelve and 13 patients had a negative energy balance at the start of radiotherapy and at follow-up, respectively.

Conclusion: A negative energy balance was seen for the majority of patients, which stresses the importance of nutritional treatment at the start of and after radiotherapy.

Introduction

Patients with head and neck cancer (HNC) often experience significant body weight loss during and after treatment (1–3). Fundamental for this weight loss is an energy imbalance where total energy expenditure exceeds energy intake (4).

There are many factors affecting energy intake in patients with HNC. Tumor site might cause insufficient food intake due to mechanical obstruction or pain (5), and treatment, i.e., radiotherapy (RT), surgery, and/or anticancer drugs might cause toxicities that affect food intake both during and after treatment (6,7).

The primary components of energy expenditure are basal energy expenditure and physical activity, both of which can be altered in patients with cancer (4). Reduced energy expenditure might be the result of reduced physical activity because of reduced physical function (8) and fatigue (9). Basal energy expenditure can be elevated, normal, or reduced (10,11), and this response might vary among different cancer types (12) as well as among individuals (13). More specifically, the inflammatory and metabolic response due to a tumor and/or treatment might increase basal energy expenditure (4,14,15).

Weight loss is a central criterion for diagnosing patients for malnutrition (16). Reduced fat-free mass has been correlated in studies on HNC to reduced hand grip strength (17) and impaired physical performance (8,17). Involuntary weight loss has important clinical implications because it is related to the development of malnutrition-related complications. Thus, for the surveillance of patients with HNC it would be useful to establish more knowledge on the relation between weight loss, body mass index (BMI), and energy balance.

Aim

The aim of the present study was to map energy intake and different parameters of energy expenditure at the start of and after radiotherapy and their relation...
to weight change, body mass index, and immune markers in patients with head and neck cancer.

**Materials and methods**

From 2010 to 2013, 20 patients were recruited from a tertiary care hospital in Sweden. Patients ≥18 years of age with a newly diagnosed HNC planned for curative RT were eligible and were consecutively asked to participate in the study by a research nurse. Exclusion criteria were dementia, physiological illness, or a social situation that would affect the possibility for the patient to complete the study. The patients received either RT (conventional fractionation or accelerated fractionation) as a single modality treatment or RT followed by surgery. Treatment details for each patient are shown in Table 1. Nutritional treatment according to the hospital regimes was given with the intent of keeping the patient in a steady energy state. None of the patients had tube feeding or parenteral nutrition at any of the measurement points.

**Study subjects**

All patients in the study cohort were men, and the median age was 54.5 years (range 43–71 years). Detailed tumor characteristics for each patient are shown in Table 1 (16 oropharyngeal, two oral cavity, and two unknown primary).

**Data collection**

Patients were measured at the start of RT (before the start or during the first week of RT) and with a median follow-up of 8 mo, (range 5–13 mo). The follow-up was chosen to capture the effect of late treatment toxicities rather than acute and occurred in a time when patients returned to the hospital for a medical checkup. One patient (no. 5) did not complete the second measurements because of a palliative situation. At both occasions, data on energy intake, energy expenditure, anthropometric measures, and immune markers were gathered.

**Measures of energy intake**

Data for energy intake were collected during two weekdays and one weekend (only on weekdays for n = 2) using 24-hour dietary intake recalls. First, patients gave written information on the food and beverages consumed. Second, a dietitian gathered detailed information about food selection and portion sizes through a face-to-face (first measurement) or a telephone (second measurement) interview. Portion sizes were estimated using household measures and pictures for different portion sizes and food types from the Swedish National Food Administration (18). These were sent to the patients’ home before the telephone interview. Energy intake for each day was estimated using the software program Dietist XP version 3.2 (Kost och Näringsdata AB), and the mean value was used in the analyses.

**Measures of energy expenditure**

Total energy expenditure was collected using a device called the SenseWear Armband Pro3 (SWA, BodyMedia, Inc., Pittsburgh, PA, USA) (19). The armband is worn on the upper part of the right arm and uses sensors to
measure movement, heat flux, skin temperature, near
body temperature, and galvanic skin response. The soft-
ware program Interview Professional (version 6.1) es-
timates total energy expenditure from the SWA together
with information about the patient's age, sex, height,
weight, and whether the patient is a smoker or non-
smoker and is right or left handed. Patients used the
SWA during the same three days as the self-reported 24-
h dietary intake recalls, and the mean value was used in
the analyses. For six patients, data from the SWA were
available for two days, and for one patient the total
energy expenditure and energy intake were not meas-
ured on the same days. The armband was taken off dur-
ing RT or to avoid coming in contact with water.
During this time, the software program calculated an
estimation of energy expenditure corresponding to the
patients' basal energy expenditure. Only days in which
the armband was worn at least 20 h, were used in the
analyses (missing, \( n = 4 \) days).

Energy balance was calculated as the energy intake
divided by the total energy expenditure. For values
>1, patients were presumed to be in positive energy
balance, whereas for values <1 the patients were pre-
sumed to be in negative energy balance.

Resting energy expenditure was measured by indir-
ect calorimetry (Deltratrac\textsuperscript{TM} II MBM 200). Patients
had fasted for four hours, and the measurements took
place over 30 mins, with the patient in a supine posi-
tion (20). Physical activity level was calculated by
subtracting the resting energy expenditure from the
total energy expenditure.

**Anthropometric measures**

Height and weight were measured using a wall stadi-
ometer (to the nearest 0.1 cm) and an electronic scale
(to the nearest 0.1 kg). The patients wore light cloth-
ing and no shoes for the measurements. Weights at
start of RT and at follow-up were used to calculate
relative percentage weight loss. Weight loss of 5–10%
was classified as moderate and weight loss of >10%
was classified as severe (16), and a third group con-
sisted of patients with weight gain, no change in
weight, or little weight loss (<5%). Patients were also
divided into groups based on their BMI (weight in
kilograms divided by height in meters squared) as
underweight (BMI <20), normal weight (BMI 20–25),
and overweight or obese (BMI >25) (16). For patients
over 70 years, BMI <22 was considered underweight
and BMI between 22 and 27 was considered normal.
Malnutrition was defined using the Global Leadership
Initiative on Malnutrition (GLIM) criteria (16), which
is a consensus from the global clinical nutrition com-
unity on how to diagnose malnutrition. For the
diagnosis of malnutrition, at least one phenotypic cri-
terion and one etiologic criterion should be present,
i.e., weight loss, low BMI, or reduced fat-free mass
(phenotypic factors) and reduced food intake or inflam-
mation (etiologic factors).

**Blood samples**

Blood samples (four-hour fasting values) were gath-
ered for analyses of the immune markers C-reactive
protein (CRP, ref <10 mg/L) and Interleukin-6 (IL-6, ref <7 ng/L).

**Ethical approval**

The Regional Ethical Review Board in Umeå, Sweden
(Dnr 2010-24-31), approved the study, and all patients
signed written informed consent forms.

**Statistical analyses**

Non-parametric tests were used due to the limited
number of patients. For these statistical analyses, the
data software Statistical Package for the Social
Sciences (SPSS) version 25.0 was used. The Wilcoxon
signed rank test was used to analyze the change in
weight, BMI, total energy expenditure, resting energy
expenditure, energy intake, and physical activity level
between the two measured points. The Mann–Whitney U-test was used to analyze total
energy expenditure in patients with CRP and/or IL-6
above reference values compared to patients with CRP
and IL-6 in the normal range. The correlation
between energy balance and weight change percent or
BMI was carried out using the Spearman rank test.
All tests were two-sided, and a p-value \( \leq 0.05 \) was
considered statistically significant.

**Results**

**Energy intake and energy expenditure**

Data for energy intake and energy expenditure at start
and follow-up are shown in Table 2, and relative
change in percent is shown in Figure 1. No statistical
significance was seen between the start of RT and fol-
low-up for any of the variables: energy intake \( (z = 0.806, N – Ties = 18, p = 0.420) \), total energy
expenditure \( (z = −0.501, N – Ties = 18, p = 0.616) \),
resting energy expenditure \( (z = −1.605, N – Ties = 17, p = 0.109) \) and energy spent on physical activity (z
Table 2. Energy intake and energy expenditure at the start of radiotherapy and at follow-up (median 8 mo, range 5–13 mo) in the study cohort (n = 20).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Total energy expenditure (kcal/24 h)</th>
<th>Resting energy expenditure (kcal/24 h)</th>
<th>Energy intake (kcal/24 h)</th>
<th>Physical activity (kcal/24 h)</th>
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<td>20</td>
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<td>(1612.50, 1787.50)</td>
<td>(1465.00, 1750.00)</td>
</tr>
</tbody>
</table>

*aWilcoxon’s test, p = 0.616.
*bWilcoxon’s test, p = 0.109.
*cWilcoxon’s test, p = 0.420.
*dWilcoxon’s test, p = 0.326.

Figure 1. Relative percent change in total energy expenditure (TEE), resting energy expenditure (REE), energy intake (EI), physical activity (PA), weight, and body mass index (BMI) in patients with head and neck cancer from the start of radiotherapy (RT) to follow-up (median 8 mo, range 5–13 mo). *Wilcoxon’s test, p < 0.001.
= −0.982, N – Ties = 16, p = 0.326). At follow-up, eleven patients had increased and five patients had decreased their energy spent on physical activity (missing, n = 4).

Median values for total energy expenditure recalculated to kcal per kilo body weight per day were 32.0 (Q1 28.8, Q3 33.5) at the start of RT and 34.5 (Q1 30.9, Q3 40.5) at follow-up. Median values for energy balance, i.e., energy intake divided by total energy expenditure were 0.93 (Q1 0.73, Q3 1.05) and 0.96 (Q1 0.66, Q3 1.08) for the start of treatment and follow-up, respectively. Twelve patients had a negative energy balance, i.e., their values for energy intake were lower than the total energy expenditure at the start of RT (r = −0.011, N = 20, p = 0.965) or at the follow-up (r = −0.0.051, N = 18, p = 0.842), respectively.

**Nutritional status**

One patient was diagnosed as malnourished at the start of RT (no. 20), and the corresponding number at follow-up was three patients (no. 2, 13, 16). Relative change in percent for weight and BMI is shown in Figure 1. Weight changed significantly between the two measurements (z = −3.784, N – Ties = 19, p < 0.001). Median weights at the start of RT and at follow-up were 85.8 kg (Q1 78.0, Q3 90.7) and 81.5 (Q1 71.8, Q3 83.1), respectively, corresponding to a percentage weight loss of −8.1% (Q1 −11.6, Q3 −4.5). Six patients had severe weight loss (>10%), eight patients a moderate weight loss (5–10%), and four had little weight loss (<5%), and one patient gained weight (missing, n = 1). There was no correlation between weight change percent and energy balance assessed at the start of RT (r = −0.109, N = 19, p = 0.658) or at follow-up (r = −0.228, N = 18, p = 0.363).

There was a significant decrease in BMI between the two measurements (z = −3.783, N – Ties = 19, p < 0.001). Median BMI at the start of RT and at follow-up were 26.0 (Q1 24.2, Q3 27.3) and 24.5 (min 22.6, max 26.0), respectively. At the start of RT, one patient was underweight, five patients were normal weight, and 14 patients were overweight/obese. At follow-up, two patients were underweight, eleven patients were normal weight, and six patients were overweight/obese. There was no correlation between BMI and energy balance at the start of RT (r = −0.011, N = 20, p = 0.965) or at the follow-up (r = −0.0.051, N = 18, p = 0.842), respectively.

**Immune markers**

Data for immune markers are presented in Table 3. Median values for CRP were 5.0 mg/L (Q1 5.0, Q3 8.0) and 5.0 mg/L (Q1 5.0, Q3 5.0) at the start of RT and at follow-up, respectively. The corresponding values for IL-6 were 3.5 ng/L (Q1 2.0, Q3 5.0) and 3.0 ng/L (Q1 2.0, Q3 5.0), respectively. At the start of RT, five patients had elevated CRP and/or IL-6 above reference values. These patients had a significantly higher total energy expenditure at the start of RT (33.7 kcal/kg body weight/day, Q1 31.4, Q3 39.3) compared to patients with CRP and IL-6 in the normal range (median 29.9 kcal/kg body weight/day, Q1 28.4, Q3 33.1). At follow-up three patients had elevated levels of CRP and IL-6, but a significant increase in energy expenditure could not be found for these patients (U = 13, N1 = 3, N2 = 14, p = 0.313).

**Discussion**

The present study was undertaken to map the energy balance in patients with HNC at the start of and after RT. No statistical significance was shown between the
Data on energy intake in patients with HNC have shown a decrease in energy intake during RT and a subsequent increase during revalidation. Kenway et al. (21) and van den Berg et al. (22) studied energy intake in patients with nasopharyngeal cancer \( (n = 38) \) and patients with different tumors of the head and neck \( (n = 47) \) and found a decrease in energy intake during RT with a significant increase in energy intake at two months and six months post RT. In studies by Jager-Wittenaar et al. (17) and Silver et al. (8) on patients with different tumors of the head and neck \( (n = 29 \) and \( n = 17 \), respectively), no significant differences were found for energy intake over time (from the start of RT up to one and four months post RT). Additionally, the study by Kenway et al. (21) did not show significant differences in energy intake between the start of RT and revalidation at two and six months post RT. The current study adds important information to previous studies because it presents results on energy intake over a longer perspective after the termination of treatment. No significant difference in energy intake was shown between the start of RT and follow-up, and therefore the results from the present and previous studies indicate that patients with HNC in general can recover their energy intake and return to pre-RT energy intake in a long-term perspective after the termination of RT. However, how well this intake corresponds to the energy expenditure has not been previously well documented in HNC.

Though not significant, the relative change in percent for resting energy expenditure decreased from the start of RT to follow-up. Compared to the situation at the start of RT, previous studies have shown a significant decrease in resting energy expenditure during treatment (23) and up to three (24) and six months (21) after RT. Again, the present study adds important information on energy expenditure in HNC and implies lower values for resting energy expenditure after RT, probably due to reduced body weight (21). The current study also showed that the energy spent on physical activity increased from the start of RT to follow-up, which might be explained by improved physical function at the follow-up. The net effect for the decrease in resting energy expenditure and the increase in physical activity seen in this study was a relatively steady state on the group level in terms of total energy expenditure between the two measurement points.

Median values for energy balance were 0.93 and 0.96 at the start of RT and at follow-up, respectively. A previous study on patients with nasopharyngeal cancer showed data on total energy expenditure at the start of RT, end of RT, and at two and six months post RT by adding the resting energy expenditure measured by indirect calorimetry to energy spent on physical activity estimated by questionnaires (21). That study found a negative energy balance through all time points, with the largest difference between energy intake and energy expenditure at the start and end of RT. In the present study, twelve patients had a negative energy balance at the start of RT, corresponding to a median energy deficit of 760 kcal. The corresponding number at follow-up was 13 patients with a median energy deficit of 632 kcal. It is well known that patients with HNC might struggle with long-term treatment sequelae (7) that have an impact on many aspects related to food and eating (25). Xerostomia and mucosal sensitivity have, for example, been shown to significantly impact energy intake after RT (26). Along with the result from the present study, imposing a negative energy balance for the majority of patients both at the start of RT and at follow-up stresses the importance of nutritional treatment at the start of RT as well as for HNC patients who suffer from long-term treatment toxicities.

Weight and BMI deteriorated significantly during the study period, which is in line with reports from earlier studies on patients with HNC (1-3). The largest weight loss has previously been seen during RT with a nadir at six months after the termination of treatment (1,3). The present study could not establish a direct correlation between weight change or BMI and energy balance, which previously has been described to be due to the fact that recovery in weight lags behind recovery in energy intake (21). Earlier studies on HNC have shown that 60–70% of the body weight loss is loss of fat-free mass (8,17). In the present study, only one patient at the start of RT and three patients at follow-up were malnourished according to the GLIM criteria (16). In these new criteria, at least one phenotypic criterion and one etiologic criterion should be present for the diagnosis of malnutrition, i.e., weight loss, low BMI, or reduced fat-free mass (phenotypic factors) and reduced food intake or inflammation (etiologic factors). Many of the patients in the present study had one etiologic factor (mainly reduced food intake), but few had a phenotypic factor despite the high prevalence of weight loss since few patients had a weight loss of >10% beyond six months. This indicates the importance of having
information on fat-free mass in order to be able to decipher the patients’ nutritional status further. Also, because fat-free mass is closely related to resting energy expenditure (24), assessment of fat-free mass would have added valuable information to the present study, enabling a more in-depth interpretation of the relationship between nutritional status and energy balance in HNC.

The present study also showed that patients with elevated immune markers, i.e., CRP and/or IL-6 above reference at the start of RT, had a significantly higher total energy expenditure compared to patients with values in the normal range. The contribution of disease-related inflammation to the development of malnutrition is reported to be the increase of resting energy expenditure and muscle catabolism (16), and cancer diseases have in general been stated to be associated with recurrent or chronic inflammation (15,16). Moreover, systemic inflammation might be induced in response to RT (14). To decipher if patients with HNC who present with elevated immune markers can be regarded as a risk group for malnutrition would therefore be an interesting approach for future studies.

The level of evidence for energy requirements in patients with cancer is low because few studies have measured total energy expenditure in patients with cancer, and all studies performed to date have all had small study samples (27–32). Existing guidelines on energy requirements for patients with cancer have been set to 25–30 kcal/kg body weight/day (33). From a clinical perspective, treatment centers in Sweden often use 30–35 kcal/kg body weight/day when calculating energy requirements in patients with HNC. A previous study on patients with HNC showed a loss of body weight and fat-free mass after RT with intakes <35 kcal/kg/day (17). The results from the present study showed that median values for total energy expenditure were 32.0 kcal/kg body weight/day at the start of RT and 34.5 kcal/kg body weight/day at follow-up. Hence, existing guidelines on energy requirements for patients with cancer might be correct on a group level at the start of RT but likely underestimate energy requirements after RT in patients with HNC. The results from the present study were generated from male patients exclusively. Women might have a lower energy expenditure than men, which can mainly be explained by differences in body composition between men and women (34), and this should be taken into account when considering how the results from the present study might be applied in clinical practice.

To our knowledge, only three previous studies have used SWA to measure energy expenditure in patients with malignant disorders, i.e., studies on acute myelogenous leukemia (n = 10 patients) (30), gastrointestinal cancer (n = 14 patients) (31), and gastrointestinal cancer (n = 6 patients) (32), thus making the present study the first to use SWA in patients with HNC. SWA measures have been shown to correlate well with energy expenditure in healthy individuals with low or moderate physical activity (19,35). Additionally, a small pilot study on patients with malignant disorders has also showed promising validity (30). In a study by Viggiani et al. (32), patients with gastrointestinal cancer received nutritional counseling according to their measured total energy expenditure. However, studies are needed to further establish the accuracy of the SWA armband in a clinical setting.

The present study includes data from a rather small number of patients, and the results should therefore be interpreted as hypothesis generating. Selection bias should also be considered because patients who accepted participation might be in a better disease and nutritional state than patients who refrained. One important strength of this study is the extensive data collection for each patient. The measure of total energy expenditure has only been measured in few earlier studies on patients with cancer (27–32). It is difficult to capture true day-to-day variation when collecting data on total energy expenditure and energy intake and the data from the present study consist of mean values from three subsequent days at the start of treatment and follow-up. Dietary intake methods have limitations of patient memory and that the results rest on what the patients want to convey about their eating.

In conclusion, the present study adds important knowledge about nutritional surveillance in patients with HNC because few studies have mapped energy intake and different parameters of energy expenditure in patients with cancer, especially including information on total energy expenditure. A negative energy balance was seen for the majority of patients both at the start of RT and at follow-up, which stresses the importance of nutritional treatment for patients with HNC both at the start of RT and for the patients who suffer from long-term treatment toxicities. Also, current recommendations on energy requirements in patients with cancer likely underestimate energy expenditure on the group level in HNC after RT,
however larger studies on a heterogeneous patient cohort need to be conducted to establish the applicability in clinical practice.

**Disclosure statement**

The authors report no conflict of interest.

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