Mapping impact factors leading to the GLIM diagnosis of malnutrition in patients with head and neck cancer

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SUMMARY

Background & aims: In head and neck cancer, the combination of weight loss and elevated C-reactive protein levels means that patients have malnutrition as defined by the Global Leadership Initiative on Malnutrition (GLIM). This study aimed to identify impact factors for malnutrition as defined by the GLIM criteria among patients with head and neck cancer at the start of treatment and up to 12 months post-treatment.

Methods: In a prospective, observational study, patient, tumour, treatment, and nutritional data from 229 patients with head and neck cancer were collected at the start of treatment and at three follow-ups (7 weeks after the start of treatment and at 3 and 12 months after the termination of treatment). These clinical variables were statistically analysed in relation to malnutrition at each follow-up using univariate and multivariate analyses. Malnutrition was defined according to the two GLIM criteria of >5% body weight loss during the last 6 months and C-reactive protein >5 mg/L.

Results: The following factors were predictive for malnutrition in the multivariate analysis performed 7 weeks after the start of treatment: moderate or severe mucositis, chemoradiotherapy ± surgery, and the need for nutritional support (total or partial use of tube feeding/parenteral nutrition). Advanced tumour stage (III-IV) was significant for malnutrition at the start of treatment and at the 7 week and 3 month follow-ups, but not at 12 months.

Conclusions: Severe mucositis, chemoradiotherapy ± surgery, and advanced tumour stage were found to be impact factors for the diagnosis of malnutrition using GLIM at different follow-up times from the start of treatment up to 12 months after the end of treatment. Few patients with head and neck cancer are diagnosed with malnutrition according to the GLIM criteria in a long-term perspective after the termination of treatment. Research on the validity of the GLIM criteria is needed to build a comprehensive evidence base of impact factors for malnutrition in head and neck cancer.

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1. Introduction

Head and neck cancer (HNC) affects patients in a complex way because the head and neck contain several vital organs essential for functions such as breathing, intake of food and liquids, and communication [1]. Both the tumour and treatment may cause severe morbidity affecting one or several of these functions. Therefore, the treatment must be optimised, not only for curative intent, but also to preserve organ function when possible.

The main treatment modalities used are radiotherapy (RT) and surgery [1] and these can cause severe acute side-effects and late sequelae [2,3]. Acute reactions to RT are primarily related to lesions to adjacent healthy tissues in the radiation volume [2], and symptoms of these acute reactions include taste and smell alterations, mucositis, xerostomia, dysphagia, and pain in the mouth and throat [1–3]. Additionally, the tumour itself may add to poor oral intake by obstructing the bolus pathway or by inhibiting chewing and
swallowing, thereby increasing the risk of unintentional weight loss [4]. Thus, patients with HNC are a high-risk group for nutritional problems that might lead to malnutrition [2,5]. Potential consequences of nutritional impairment in HNC are increased risk of infections, postoperative complications, and higher hospital readmission rates [6-8] as well as decreased quality of life [9].

In recent years, efforts to clearly define malnutrition have been made by several international organisations, which have resulted in the Global Leadership Initiative on Malnutrition (GLIM) [10]. In this global consensus, malnutrition is diagnosed by any combination of at least one phenotypic criterion (weight loss, low body mass index [BMI], or reduced muscle mass) and one etiologic criterion (reduced food intake/assimilation or inflammation).

We found in an earlier study on the GLIM criteria [11] that the combination of the phenotypic criterion of >5% weight loss within the past 6 months and the etiologic criterion of C-reactive protein (CRP) > 5 mg/L diagnosed most patients with malnutrition. Hence, in the present study, the next step was to further examine this combination against clinical factors that might cause malnutrition to be able to define high-risk groups of patients with HNC who might need extra nutritional attention before, during, and after treatment.

1.1. Aim

The aim was to identify impact factors for malnutrition defined by one combination of the GLIM criteria among patients with head and neck cancer at the start of treatment and up to 12 months post-treatment.

2. Materials and methods

The present study derives from a larger Swedish prospective observational research study conducted at three tertiary referral hospitals. Inclusion criteria were newly diagnosed HNC with a curative treatment intent and a performance status of 0-2 according to the World Health Organization (WHO). Exclusion criteria were previous treatments for malignant neoplasms within the past 5 years, inability to understand the Swedish language, severe alcohol abuse, or cognitive diagnoses that inhibited participation. The main treatment modalities, in different combinations, were RT using intensity-modulated radiation therapy technique; surgery; chemotherapy mainly using cisplatin; other pharmacological treatments such as cetuximab; and brachytherapy. All patients had their nutritional status continuously monitored during treatment and were offered nutritional support according to local guidelines, i.e., patients with problems eating orally or experiencing >5% weight loss were given nutritional support.

2.1. Study subjects

The study included data from 229 patients who were diagnosed with HNC from October 2015 to June 2018 and who were followed up for up to 12 months after the end of treatment. Data from all patients were available at the start of treatment. The follow-ups had missing values due to missed appointments, palliative care, or that patients were deceased (7 weeks, n = 12 missing; 3 months, n = 20 missing; 12 months, n = 39 missing). During the study period, a total of 20 patients were deceased.

2.2. Data collection

Patients were included at the initiation of treatment at the tertiary referral hospital and were followed-up either at the tertiary referral hospital or at their local hospital. Research nurses collected the data and imported the data into a database specifically created for the research project in order to achieve reliable, safe, and easy collection of background data, primary data, and follow-up data.

Data at the start of treatment and at 7 weeks after the start of treatment with additional follow-ups at 3 and 12 months after the termination of treatment were analysed to identify factors related to malnutrition defined by one combination of the GLIM criteria [10]. The following factors were analysed: age using a nutritionally relevant cut-off (<70 years, ≥70 years) [10], gender (male, female), tumour site (opharynx, oral cavity, larynx, and other [hypopharynx, nasopharynx, salivary gland cancer, nasal and sinus cancer, cancer of the external auditory canal, ear cancer, and cancer of unknown primary]), tumour stage (I-II, III-IV) according to the Union for International Cancer Control (UICC 8), treatment modality (RT ± surgery, surgery, chemoradiotherapy [CRT] ± surgery, RT ± surgery + other pharmacological treatment, and brachytherapy), BMI (kg/m²) sorted into groups of underweight, normal weight, and overweight/obesity adjusted for age [10], oral intake or nutritional support (total or partial use of tube feeding/parenteral nutrition), and mucositis assessed according to the WHO [12] (none or mild: stage 0-I and moderate or severe: stage II-IV).

Patients were diagnosed with malnutrition when having inflammation defined by CRP >5 mg/L in combination with >5% body weight loss in the last 6 months [10]. This was the combination that diagnosed most patients with malnutrition in our previously published article [11] arising from the same original observational study. A blood sample for CRP was taken at the start of treatment and at the three follow-ups, and the analysis was carried out in certified laboratories. A lower limit for CRP of >5 mg/L, as suggested by the European Society for Clinical Nutrition and Metabolism (ESPEN), was used to indicate inflammation [13]. An 8-electrode bioelectrical impedance analysis (BIA) device (BC-418MA, Tanita Corporation, Tokyo, Japan) was used for the weight measurements. The patients did not wear outdoor clothing, socks, or shoes at the measurements. At some of the follow-ups, a body weight scale was used (instead of a BIA device) and the weight was either reported by a nurse or self-reported by the patient due to the long travel distance between the patient’s residence and the tertiary referral hospital. Weight was measured at the start of treatment, 7 weeks after the start of treatment, and at 3, 6, and 12 months after the termination of treatment. Weight at 6 months prior to treatment was self-reported by the patient. By using different follow-ups as the reference weight, the relative percentage body weight loss within the last 6 months was calculated at the start of treatment (reference weight 6 months prior to treatment), 7 weeks after the start of treatment (reference weight 6 months prior to treatment), 3 months after the termination of treatment (reference weight at the start of treatment), and 12 months after the termination of treatment (reference weight 6 months after the termination of treatment).

At 12 months after the termination of treatment, in addition to the combination of CRP >5 mg/L and >5% body weight loss in the last 6 months, the GLIM combination of CRP >5 mg/L and >10% body weight loss beyond 6 months (reference weight at the start of treatment) was used to define patients as malnourished.

2.3. Statistical considerations

The data were analysed using the statistical software IBM SPSS version 26.0. Descriptive data are presented for continuous variables as the mean ± standard deviation or range (min–max), and categorical variables are presented as numbers (%). Pearson's chi-squared test was used for the analyses of impact factors for malnutrition, and Fisher's exact test was used if the criteria for this test were not met. Logistic regression analysis was used to identify
independent impact factors for malnutrition, and only statistically significant variables from the univariate analysis were evaluated in the model. Results from the logistic regression analysis are presented as OR and 95% CI. All tests were two-sided, and the significance level was set to $p < 0.05$.

### 2.4. Ethical statement

Oral and written information was given to each participant, and written informed consent was obtained. The Regional Ethical Review Board in Uppsala reviewed and approved the study (No. 2014/447), and the study is registered at ClinicalTrials.gov (NCT03343236).

### 3. Results

#### 3.1. Patient characteristics

Patient, tumour, and treatment characteristics are presented in Table 1. The mean age was 63.5 (±11.0) years (range 32–89 years) and most patients were male (72.5%). The most common tumour location was the oropharynx (43.7%), and around half (50.7%) of the patients were treated with RT alone or in combination with surgery. Patients with advanced tumour stage (III and IV) more often received multimodal treatment with CRT or RT + surgery compared to patients with stage I and II tumour ($p = 0.039$).

#### 3.2. Nutritional status and nutritional support

The start of treatment showed the lowest number of patients with underweight (8.7%) according to BMI (<20 kg/m² if <70 years and <22 kg/m² if ≥70 years), and most patients with underweight were seen at the 3 month follow-up (12.5%). Mean weight declined from its highest value of 83.1 kg (±17.3) at the start of treatment to its lowest of 77.6 kg (±15.1) at 6 months after the termination of treatment. At the start of treatment, 11.4% of the patients were malnourished, and the highest frequency of malnutrition was observed at 7 weeks (42.4%). The characteristics of these patients are shown in Table 1. Following this peak, the number of malnourished patients decreased, with 5.2% of the patients diagnosed as malnourished at 12 months after the termination of treatment when using the combination of >5% weight loss and CRP >5 mg/L (Table 2) and 7.0% being diagnosed as malnourished when using the combination of >10% weight loss and CRP >5 mg/L.

Ninety-five patients (41.5%) were diagnosed with malnutrition on at least one occasion (start of treatment or any of the follow-ups) as calculated from patients with complete data for the follow-ups. The frequency of malnutrition over time for that sub-group of patients is shown in Fig. 1. Seventy-four patients were diagnosed with malnutrition at only one of the time points, with 57 of those being at 7 weeks after the start of treatment.

The number of patients receiving nutritional support was the highest at 7 weeks after the start of treatment (30.2%). At 12 months after the end of treatment, that number had decreased to 6.9%. Patients with moderate or severe mucositis received nutritional support more frequently at the 7 week follow-up compared to patients with no or mild mucositis ($p = 0.017$).

#### 3.3. Impact factors for malnutrition at the start of treatment and the different follow-ups

At the start of treatment, patients with advanced tumour stage (III-IV) were more often malnourished than patients with stage I-II tumour ($p = 0.029$) (Table 2). Univariate analyses showed the highest number of impact factors for malnutrition at 7 weeks after the start of treatment (Table 2). Patients in the following subgroups were more often malnourished at the 7 week follow-up: patients treated with CRT + surgery or the combination of RT + surgery + other pharmacological treatment ($p < 0.001$), patients needing nutritional support ($p < 0.001$), patients <70 years ($p = 0.019$), and patients with moderate or severe mucositis ($p < 0.001$). Moreover, patients with tumour of the oropharynx or the oral cavity were more often malnourished than patients with other tumour locations ($p = 0.001$), and patients with advanced tumour stage (III-IV) were more often malnourished than patients with stage I-II tumour ($p = 0.001$).

The highest number of impact factors for malnutrition was found at 7 weeks after the start of treatment, and therefore a

### Table 1

Characteristics of the studied patients with head and neck cancer ($n = 229$) and a sub-group of patients diagnosed with malnutrition defined by the Global Leadership Initiative on Malnutrition (GLIM) at 7 weeks after the start of treatment ($n = 97$).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sub-groups</th>
<th>Total $n = 229$</th>
<th>Malnutrition $n = 97$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD)</td>
<td></td>
<td>63.5 (±11.0)</td>
<td>61.9 (±10.7)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;70 years</td>
<td>154 (67.2)</td>
<td>75 (77.3)</td>
</tr>
<tr>
<td></td>
<td>≥70 years</td>
<td>75 (32.8)</td>
<td>22 (22.7)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>63 (27.5)</td>
<td>23 (23.7)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>166 (72.5)</td>
<td>74 (76.3)</td>
</tr>
<tr>
<td>Tumour site</td>
<td>Oropharynx</td>
<td>100 (43.7)</td>
<td>52 (53.6)</td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>67 (29.3)</td>
<td>31 (32.0)</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>28 (12.2)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34 (14.8)</td>
<td>10 (10.2)</td>
</tr>
<tr>
<td>Tumour stage UICC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>I-II</td>
<td>133 (58.1)</td>
<td>45 (46.4)</td>
</tr>
<tr>
<td></td>
<td>III-IV</td>
<td>95 (41.5)</td>
<td>51 (52.6)</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>1 (0.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Treatment type</td>
<td>RT ± surgery</td>
<td>116 (50.7)</td>
<td>38 (39.2)</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>27 (11.8)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td></td>
<td>CRT&lt;sup&gt;c&lt;/sup&gt; ± surgery</td>
<td>59 (25.8)</td>
<td>39 (40.2)</td>
</tr>
<tr>
<td></td>
<td>RT ± surgery + other pharmacological treatment</td>
<td>18 (7.9)</td>
<td>12 (12.4)</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy</td>
<td>9 (3.9)</td>
<td>4 (4.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hypopharynx, nasopharynx, salivary gland cancer, nasal and sinus cancer, cancer of the external auditory canal, ear cancer, and cancer of unknown primary.

<sup>b</sup> The Union for International Cancer Control’s (UICC).

<sup>c</sup> Radiotherapy.

<sup>d</sup> Chemoradiotherapy.
Table 2
Impact factors for malnutrition defined by the Global Leadership Initiative on Malnutrition (GLIM) in patients with head and neck cancer (n = 229) at the start of treatment and at different follow-ups (7 weeks after the start of treatment and 3 and 12 months after the termination of treatment). The combination used to define malnutrition was >5% body weight loss in the last 6 months and C-reactive protein >5 mg/L.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Start of treatment</th>
<th>7 weeks after the start of treatment</th>
<th>3 months after the end of treatment</th>
<th>12 months after the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malnutrition p²</td>
<td>Missing</td>
<td>Malnutrition p²</td>
<td>Missing</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>No (88.6)</td>
<td>26 (11.4)</td>
<td>No (88.6)</td>
<td>26 (11.4)</td>
</tr>
<tr>
<td>Age &lt;70 years</td>
<td>135 (87.7)</td>
<td>0.001</td>
<td>125 (86.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>68 (90.7)</td>
<td>0.001</td>
<td>75 (52.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender Male</td>
<td>149 (89.8)</td>
<td>0.001</td>
<td>139 (88.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>54 (85.7)</td>
<td>0.001</td>
<td>40 (72.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tumour site</td>
<td>Oropharynx</td>
<td>87 (87.0)</td>
<td>81 (86.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>59 (88.1)</td>
<td>0.058</td>
<td>45 (76.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>Larynx</td>
<td>24 (85.7)</td>
<td>0.058</td>
<td>25 (96.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>Other</td>
<td>33 (97.1)</td>
<td>0.058</td>
<td>28 (93.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>Tumour stage</td>
<td>I–II</td>
<td>123 (92.5)</td>
<td>117 (92.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>III–IV</td>
<td>79 (83.2)</td>
<td>0.001</td>
<td>61 (74.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment type</td>
<td>RT ± surgery</td>
<td>103 (88.8)</td>
<td>92 (87.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>26 (96.3)</td>
<td>0.001</td>
<td>22 (100.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>CRT² + surgery</td>
<td>54 (91.5)</td>
<td>0.001</td>
<td>48 (82.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>RT ± surgery +</td>
<td>13 (72.2)</td>
<td>0.001</td>
<td>11 (73.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>7 (77.8)</td>
<td>0.001</td>
<td>6 (66.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Oral intake</td>
<td>2 (88.9)</td>
<td>100 (66.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nutritional support</td>
<td>2 (66.7)</td>
<td>0.001</td>
<td>20 (29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Stage 0-1</td>
<td>54 (75.0)</td>
<td>152 (86.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage II-IV</td>
<td>53 (41.7)</td>
<td>0.001</td>
<td>84 (92.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Underweight</td>
<td>17 (85.0)</td>
<td>13 (46.4)</td>
<td>0.058</td>
</tr>
<tr>
<td>Normal weight</td>
<td>60 (83.3)</td>
<td>0.058</td>
<td>48 (52.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>126 (92.0)</td>
<td>0.058</td>
<td>59 (90.8)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

a p-value by Pearson's chi-squared test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.
b Hypopharynx, nasopharynx, salivary gland cancer, nasal and sinus cancer, cancer of the external auditory canal, ear cancer, and cancer of unknown primary.
c Radiotherapy.
d Chemoradiotherapy.
e Other pharmacological treatment.
logistic regression was performed for the impact factors that were statistically significant in the univariate analyses at this time point. In this model, malnutrition was used as the dependent variable (yes/no) alongside the following six independent variables: age (<70 and ≥70 years), tumour site (oropharynx, oral, larynx, and other), tumour stage (I + II and III + IV), treatment type (RT ± surgery, surgery, RT ± surgery, RT ± surgery + other pharmacological treatment, and brachytherapy), nutrition (oral intake or nutritional support), and mucositis (none or mild: stage 0-I and moderate or severe: stage II-IV). Of the independent variables in the model, moderate or severe mucositis, nutritional support, and treatment type were predictive for malnutrition at 7 weeks after the start of treatment. Patients with severe mucositis were more often diagnosed with malnutrition at 7 weeks (OR 3.34, 95% CI 1.53–7.28) compared to patients with no or mild mucositis. Patients needing nutritional support were more often malnourished at 7 weeks (OR 2.91, 95% CI 1.38–6.13) compared to patients with oral intake. Patients treated with CRT ± surgery were more often diagnosed with malnutrition (OR 2.71, 95% CI 1.19–6.22) compared to patients treated with RT ± surgery without chemotherapy.

At 3 months post-treatment, the following impact factors were found to be statistically significant for malnutrition (Table 2): advanced tumour stage (III-IV) (p < 0.001), moderate or severe mucositis (p = 0.001), and underweight according to BMI (p < 0.001). Patients treated with CRT ± surgery, RT ± surgery + other pharmacological treatment as well as brachytherapy were more often malnourished compared to the other treatment modalities (p = 0.035). Also, women were more often malnourished than men at this time point (p = 0.038).

At the last follow-up at 12 months after the termination of treatment, patients needing nutritional support were more often malnourished compared to patients with oral intake (p < 0.001), and patients with underweight were more often malnourished compared to patients with normal weight or overweight/obesity (p = 0.038) (Table 2). Using the GLIM combination of >10% weight loss and CRP >5 mg/L, patients needing nutritional support (p = 0.001) and patients with advanced tumour stage (p = 0.003) were more often malnourished at 12 months after the termination of treatment compared to the other groups.

4. Discussion

The present study shines a light on different impact factors for malnutrition using GLIM for the diagnosis of malnutrition in patients with HNC. Patients with advanced tumour stage (III-IV), patients treated with CRT ± surgery, and patients with moderate or severe mucositis were shown to be at high risk of the diagnosis of malnutrition using GLIM. In a review from 2013, Dechaphunkul et al. [14] highlighted the need for a clear definition of malnutrition because 24 different definitions for malnutrition had been used in previous research on patients with HNC. This study is, therefore, an important step towards building an evidence base for malnutrition in HNC diagnosed according to the GLIM criteria.

The decision to use the GLIM combination of weight loss >5% in the past 6 months (phenotypic) in combination with CRP >5 mg/L (etiologic) was based on our previous study originating from same study cohort [11]. In that study, we examined all combinations of GLIM and found this combination to be the one that diagnosed the most patients with malnutrition over time. The highest frequency of malnutrition was found at 7 weeks after the start of treatment, and a small portion (close to or under 10%) was diagnosed with malnutrition at the 3 and 12 month follow-ups. The present study further examined malnutrition over time in a sub-group of patients and found that the majority of patients were diagnosed with malnutrition at only one time point. Thus, few patients with HNC are diagnosed with malnutrition according to the GLIM criteria in a long-term perspective after the termination of treatment. However, it is important to recognise that many patients display clinically relevant weight loss after the termination of treatment, with a nadir of weight loss at approximately 6 months after the
termination of treatment as shown in the present and previous studies [15,16]. This highlights the importance of putting extra focus on the rather limited proportion of patients who suffer from long-term nutritional problems.

Advanced tumour stage (III-IV) was a parameter shown to be relevant for malnutrition over time because it was significantly related to malnutrition at the start of treatment and at the subsequent three follow-ups. This parameter has also been shown to be of strong relevance for critical weight loss in HNC [16,17]. As shown in the present study, a more advanced tumour stage at the start of treatment often warrants a multifaceted treatment approach, and this has been shown to increase the risk of severe sequelae [1–3]. Tumours with advanced stage might also be more voluminous, resulting in mechanical obstruction of the bolus pathway [4]. Thus both tumour volume and treatment sequelae are likely reasons as to why tumour stage is a contributing factor to the frequency of malnutrition in HNC.

Approximately 26% of the patients in the present study received CRT ± surgery, and these patients demonstrated malnutrition more frequently both at the 7 week and 3 month follow-ups. The OR for this treatment modality was almost three times higher compared to RT ± surgery without chemotherapy in the multivariate analysis. It is well known that RT might produce both acute and late treatment toxicities; however, the risk for toxicities increases even more so when RT and chemotherapy are combined [3,5]. Earlier studies showed results in line with the present study, i.e. significant weight loss in patients treated with CRT [17–19]. Exposito et al. suggest, for example, that nutritional support should be started earlier in patients treated with CRT [20]. Hence, for clinical practice, patients planned for CRT should be considered to be a nutritionally vulnerable group. However, further research is needed to define the best way to deliver nutritional interventions to patients with HNC undergoing CRT [20,21].

Moderate to severe mucositis was the strongest predictive characteristic for malnutrition, and it was significant for malnutrition at the 7 week and the 3 month follow-ups, and the OR for mucositis was three times higher compared to no mucositis in the multivariate analysis. Mucositis is a common and severe sequela of both RT and chemotherapy, and it can lead to hospitalisation and nutritional impairment due to pain and discomfort [22,23]. Patients with mucositis therefore present with weight loss more frequently than patients without mucositis [24]. Hence, severe mucositis can have long-term effects on nutritional status and thus standardised follow-ups with repeated weight measurements for this sub-group should be strongly considered.

Nutritional support, i.e. the use of total or partial tube feeding/parenteral nutrition was one of the predictors of malnutrition in the multivariate analysis and was also shown to be of relevance for malnutrition at 12 months after the termination of treatment. Not surprisingly, this shows that nutritional problems leading to malnutrition were a prerequisite for nutritional support because patients in the present study received nutritional interventions when indicated, namely a ‘wait and see procedure’. In previous studies, the use of tube feeding has been correlated to weight loss, swallowing dysfunction, mucositis, and the use of opioid analgesics [15,16,25]. In the present study, patients with moderate or severe mucositis received nutritional support more frequently than patients with no or mild mucositis. This further supports the inverse relation between nutritional support and malnutrition.

The present study has several strengths. The data are extensive and include a large number of participants, which gives power to the analysis and increases transferability. The collection of data can easily be replicated because the methods used are well established in clinical practice, which gives the study strong communicative validity and good reliability. However, some limitations should be kept in mind when interpreting the results. It may be speculated that patients in the study had a better nutritional state because patients with a palliative intention and a performance status of >2 according to the WHO were excluded from the study. Also, missing values during the follow-ups might include patients with residual disease or death, i.e. patients with a presumed poorer nutritional state. The study also included a heterogeneous group of patients receiving different types of treatment modalities. Almost half of the patients had oropharyngeal cancer where the standard treatment consists of RT, sometimes in combination with chemotherapy. The present study used CRP as a marker for inflammation and a lower limit for CRP suggested by ESPEN [13]. However, what inflammatory marker and the appropriate limit to define inflammation should be addressed in future studies. It should also be acknowledged that the validity of the GLIM criteria has not yet been confirmed as the criteria are based solely on expert opinions [26].

In conclusion, the following impact factors were found to be of highest importance for identifying patients with malnutrition according to GLIM in HNC: advanced tumour stage (III-IV), treatment with CRT ± surgery, and moderate or severe mucositis. These patients might therefore benefit from extra nutritional attention before, during, and after treatment. Few patients with HNC were diagnosed with malnutrition according to the GLIM criteria in a long-term perspective after the termination of treatment. The validity of the GLIM criteria in HNC should be confirmed to be able to continue to build a comprehensive evidence base on high-risk groups for malnutrition among patients with HNC.

Statement of authorship

All authors contributed to the work, and the final version of the manuscript was approved by all authors. YTE designed the study and collected the data, SE and H-EK analysed and interpreted the data, SE and YTE drafted the manuscript, and YTE, SE, H-EK, and A-KH critically revised the manuscript.

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Declaration of Competing Interest

The authors report no conflict of interest.

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