Sarcopenia, a strong determinant for prolonged feeding tube dependency after chemoradiotherapy for head and neck cancer

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Abstract
Background: Sarcopenia might be a relevant lead for optimization of the condition of patients with head and neck cancer (HNC) before chemoradiotherapy (CRT) to prevent long-term functional swallowing impairment, such as feeding tube dependency.

Methods: Regression analyses were performed to assess the association between skeletal muscle mass index (SMI), as a measure of sarcopenia, and prolonged (>90 days) feeding tube dependency in 128 patients with HNC treated with primary CRT.

Results: Sixty-one patients (48%) became prolonged feeding tube-dependent. Lower SMI increased the risk of prolonged feeding tube dependency in multivariable analysis (risk ratio 1.08; 95% confidence interval 1.02-1.14, \(P = .01\)) adjusted for body mass index, abnormal diet, and socioeconomic status.

Conclusions: Sarcopenia contributes to the risk of prolonged feeding tube dependency of patients with HNC treated with primary CRT. As sarcopenia might be a modifiable factor prior to treatment, it should be explored as a target for pre-treatment patients’ condition.

KEYWORDS
chemoradiotherapy, head and neck cancer, sarcopenia, skeletal muscle mass, tube feeding

1 | INTRODUCTION

Sarcopenia is a condition characterized by loss of skeletal muscle mass.1 It is mainly prevalent in the elderly but also occurs in younger patients with diseases that affect mobility and nutrition.2 Most retrospective studies on sarcopenia in patients with cancer consider CT-assessed skeletal muscle mass only, as muscle function tests are often not available.3 In several cancer types, pretreatment sarcopenia is associated with inferior treatment outcomes4 including postoperative complications5,6 and treatment-related toxicity.7,8 Recent studies confirm this association in head and neck cancer (HNC) with regard to treatment outcomes (ie, chemotherapy dose-limiting toxicity) and survival.
after concomitant chemoradiotherapy (CRT) and postoperative complications including pharyngocutaneous fistula after total laryngectomy.\textsuperscript{9,15} There is a paucity of information, however, on the influence of sarcopenia on functional outcomes.

One of the most important functional outcomes for patients with HNC is swallowing function, which is often compromised after CRT, due to an often multifactorial etiology.\textsuperscript{16} First, the extent of tumor and treatment disrupt normal swallowing physiology, and with more extensive tumor and treatment, the risk for developing swallowing problems is increased.\textsuperscript{17-24} Second, poor nutritional status can also contribute to swallowing dysfunction, due to loss of muscle mass and function.\textsuperscript{19-24} As a result of swallowing dysfunction, a substantial proportion (50%-70%) of patients become feeding tube-dependent during CRT.\textsuperscript{23} Due to the decline in swallowing muscle activity, nonuse atrophy of these muscles is inevitable, which is associated with further loss of swallowing muscle mass and function.\textsuperscript{23,25-28} Sarcopenia could be a factor worsening this vicious spiral by co-causing long-term swallowing dysfunction, as patients suffering from sarcopenia have limited reserves with regard to muscle mass and function. Consequently, these patients, nonuse atrophy of the swallowing muscles may even sooner lead to prolonged functional impairment.\textsuperscript{29,30}

Results from studies among patients with other cancer types suggest that pretreatment optimization of functional status, also known as prehabilitation, may improve functional outcomes.\textsuperscript{31,32} In patients with HNC, prehabilitation interventions prior to CRT could include exercise programs, targeting the swallowing muscles in combination with nutritional interventions. Especially focusing on high-risk patients for prehabilitation interventions to increase benefit has been suggested in the literature.\textsuperscript{33} A better understanding of the relationship between pretreatment sarcopenia and risk of long-term swallowing impairment and feeding tube dependency will help identify which patients might benefit from targeted interventions, as well as provide clues to the type of interventions to be used.

Therefore, the objective of this study was to assess the direct relationship of pretreatment sarcopenia with prolonged feeding tube dependency in patients treated with primary CRT for HNC.
<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>&lt;90 d feeding tube-dependent (n = 67)</td>
<td>&gt;90 d feeding tube-dependent (n = 61)</td>
<td>Total cohort (n = 128)</td>
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<tr>
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<td>Men</td>
<td>46 (69)</td>
<td>44 (72)</td>
<td>90 (70)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>21 (31)</td>
<td>17 (28)</td>
<td>38 (30)</td>
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<td>60 (44-71)</td>
<td>61 (42-73)</td>
<td>59 (7)</td>
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<tr>
<td>ACE-27</td>
<td>0</td>
<td>34 (51)</td>
<td>24 (39)</td>
<td>58 (45)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>22 (33)</td>
<td>23 (38)</td>
<td>45 (35)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7 (10)</td>
<td>12 (20)</td>
<td>19 (15)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4 (6)</td>
<td>2 (3)</td>
<td>6 (5)</td>
</tr>
<tr>
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<td>Oral cavity</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (1)</td>
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<tr>
<td></td>
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<td>44 (66)</td>
<td>34 (56)</td>
<td>78 (61)</td>
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<td>17 (25)</td>
<td>22 (36)</td>
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<td>Larynx</td>
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<td>5 (8)</td>
<td>13 (10)</td>
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<td></td>
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<td>16 (26)</td>
<td>39 (31)</td>
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<td>T4</td>
<td>13 (19)</td>
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<td>N2</td>
<td>45 (67)</td>
<td>46 (75)</td>
<td>91 (71)</td>
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<td>N3</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>5 (4)</td>
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<td>2 (3)</td>
<td>2 (2)</td>
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<td></td>
<td>Stage III</td>
<td>15 (22)</td>
<td>5 (8)</td>
<td>20 (16)</td>
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<td></td>
<td>Stage IV</td>
<td>52 (78)</td>
<td>54 (89)</td>
<td>106 (83)</td>
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<tr>
<td>BMI mean (SD)</td>
<td></td>
<td>25 (15-35)</td>
<td>23 (16-33)</td>
<td>24 (4)</td>
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<tr>
<td>Pretreatment weight loss</td>
<td>No</td>
<td>51 (76)</td>
<td>29 (48)</td>
<td>80 (63)</td>
</tr>
<tr>
<td></td>
<td>&lt;10%</td>
<td>16 (24)</td>
<td>22 (36)</td>
<td>38 (30)</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>0 (0)</td>
<td>10 (16)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Pretreatment FOIS</td>
<td>7 (normal diet)</td>
<td>59 (88)</td>
<td>36 (59)</td>
<td>95 (74)</td>
</tr>
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<td></td>
<td>&lt;7</td>
<td>8 (12)</td>
<td>25 (41)</td>
<td>33 (26)</td>
</tr>
<tr>
<td>Prolonged feeding tube-dependent</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>67 (52)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>61 (48)</td>
</tr>
<tr>
<td>Neck SMI median (min-max)</td>
<td></td>
<td>13 (9-22)</td>
<td>12 (8-16)</td>
<td>12 (8-22)</td>
</tr>
<tr>
<td>Low neck SMI &lt;12.7</td>
<td>No</td>
<td>38 (57)</td>
<td>17 (28)</td>
<td>55 (43)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>29 (43)</td>
<td>44 (72)</td>
<td>73 (57)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td>0.2 (1.1)</td>
<td>0.1 (1.2)</td>
<td>0.1 (1.1)</td>
</tr>
</tbody>
</table>

**Note:** Not all percentages sum up exactly to 100% due to rounding.

**Abbreviations:** ACE-27, Adult Comorbidity Evaluation-27; BMI, body mass index; FOIS, functional oral intake scale; NA, not applicable; SMI, skeletal muscle index.
with an addition of 30% for disease, up to a body mass index (BMI) of 30 kg/m².⁴³

2.5 Data collection

We collected the following variables retrospectively from the medical file: sex, age at diagnosis, comorbidity including the Adult Comorbidity Evaluation-27 (ACE-27) index, tumor site, T and N classification, general tumor (TNM) stage, pretreatment BMI, pretreatment weight loss (none, less, or more than 10% over the past 6 months compared with baseline), and pretreatment FOIS (scored retrospectively when not available). The FOIS reflects the functional oral intake on a seven-point ordinal scale with a score of 7 indicating a normal diet without restrictions.³⁶ Also, timing of feeding tube placement and duration of dependency were assessed. Prolonged dependency was defined as a tube in situ for more than 90 days after tube placement (nasogastric tube or percutaneous gastrostomy) at any time before or during CRT. This cutoff was chosen based on the consideration that after 90 days, acute local treatment-related toxicities have subsided and ongoing functional impairments can be considered chronic. Socioeconomic status (SES) was assessed by means of status scores according to postal codes with 0 being the mean status score in The Netherlands in 2017.³⁷ Negative and positive scores indicate SES below and above the mean, respectively.

2.6 Measurement of skeletal muscle mass

Skeletal muscle mass was measured on a routinely performed CT scan of the head and neck area using a previously described protocol (see Figure 1). A single CT slice at the level of C3 was selected for skeletal muscle mass measurement. First, the cross-sectional muscle areas (CSMA) of the paravertebral and sternocleidomastoid muscles at the level of the third cervical vertebra (C3) were segmented on the pretreatment head and neck CT scan.²⁸ The total skeletal muscle area at the level of C3 was defined as the CSMA of the paravertebral muscles and the left and right sternocleidomastoid muscles (total CSMA). The total CSMA was then normalized for height in meters, in a similar method compared with research in other cancer types, to calculate the neck skeletal muscle index.²⁹ Lower values of the neck SMI indicate lower skeletal muscle mass. All CT scans were segmented using Worldmatch, an in-house developed radiotherapy planning and image evaluation software tool.

2.7 Statistical analysis

Analyses were performed using IBM SPSS Statistics 23.0 and R 3.3.2.³⁰,³¹ P values <.05 were considered statistically significant. Univariable Poisson regression analysis with a log link was used to assess the crude and adjusted associations of neck SMI and prolonged feeding tube dependency in this sample, which we report as risk ratios (RR), with 95% confidence intervals (CI) and corresponding P values based on robust (sandwich) errors.⁴² In the multivariable analysis, the relationship was estimated adjusting for the most relevant confounders. During a consensus meeting, a directed acyclic graph (DAG) was constructed to identify potential confounders and mediators (see Figure 2). From the available data, potential confounders and mediators were chosen based on information from previous studies and expert opinion. The DAG indicated that, to estimate the direct effect of SMI on prolonged feeding tube dependency, the minimal set of adjustment covariables included BMI, FOIS, and SES. To assess the extent to which the effect of neck
SMI of prolonged feeding tube dependency was mediated by BMI, the relation was also estimated without adjusting for BMI.

2.8 | Cutoff for sarcopenia

As no normal values of the neck SMI exist, the optimal cutoff value of the neck SMI for predicting prolonged tube feeding was determined using the Youden point of the receiver operating characteristic (ROC) curve of neck SMI vs prolonged feeding tube dependency. To obtain an indication for clinical usefulness of pretreatment neck SMI measurements, the number of patients below this cutoff value (indicating sarcopenia) was assessed, stratified by their (predicted) probability on prolonged (>90 days) feeding tube dependency according to our previously published prediction model. This model included the clinical predictors FOIS, BMI, weight loss, and T classification and had the following formula: \[ Y = 0.617 + (0.145\cdot T2 + 0.382\cdot T3 + 0.727\cdot T4) + (-0.067\cdot BMI) + (0.543\cdot FOIS <7) + (0.356\cdot weight\ loss <10\% + 0.980\cdot weight\ loss >10\%). \]

TABLE 2 | Results of multivariable Poisson regression analysis with no prolonged (>90 days) feeding tube dependency as outcome presented in RR and \( P \) values

<table>
<thead>
<tr>
<th>Multivariable analysis</th>
<th>RR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck SMI</td>
<td>1.08 (1.02-1.14)</td>
<td>.01</td>
</tr>
<tr>
<td>BMI</td>
<td>1.01 (0.97-1.06)</td>
<td>.63</td>
</tr>
<tr>
<td>SES</td>
<td>1.08 (0.91-1.27)</td>
<td>.38</td>
</tr>
<tr>
<td>FOIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;7 )</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>( \geq 7 )</td>
<td>0.44 (0.24-0.80)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence intervals; FOIS, functional oral intake scale; RR, risk ratios; SES, socioeconomic status; SMI, skeletal muscle index.

3 | RESULTS

The median neck SMI was 12 (range 8-22), and 61 patients (48%) became prolonged feeding tube-dependent (see Table 1).

3.1 | Sarcopenia and prolonged feeding tube dependency

Neck SMI was a significant prognostic factor for prolonged feeding tube dependency in univariable analysis, with lower SMI increasing the risk (RR 1.10; 95% CI 1.06-1.15, \( P < .001 \)). The RR after adjustment for BMI, FOIS, and SES was largely similar to a RR of 1.08 (95% CI 1.02-1.14, \( P = .01 \); see Table 2). This translates into a 26% relative risk increase for prolonged feeding tube dependency per interquartile range decrease in SMI (from 14 to 11). When not adjusting for the mediating effect of BMI, the adjusted RR was 1.09 (95% CI 1.04-1.14, \( P = .001 \)).

3.2 | Cutoff value for sarcopenia

The cutoff value of neck SMI in predicting prolonged feeding tube dependency with optimal sensitivity/specificity ratio was 12.7 (area under the ROC curve 0.64, sensitivity 72%, and specificity 57%). Seventy-three patients (57%) had a neck SMI below this cutoff, indicating sarcopenia with regard to this outcome. The number of patients with a low neck SMI stratified by predicted probability on prolonged (>90 days) feeding tube dependency according to our previously published prediction model are presented in Figure 3. The higher the predicted probability, the higher the proportion of patients with a low neck SMI. Of the 31 patients with a predicted probability below or equal to 30%, 8 (26%) had a neck SMI below the cutoff value (median SMI 13, range 9-22), compared with 49 of the 80 patients (61%) with a predicted probability between 30% and 60% (median SMI 12, range 9-21), and 16 of the 17 (94%) patients above 60% (median SMI 11, range 8-13). All the 16 patients who had a predicted probability above 60% and a neck SMI below the

FIGURE 3 | Number of patients with high and low neck SMI per predicted probability of prolonged feeding tube dependency according to the prediction model. SMI, skeletal muscle index
cutoff value became prolonged feeding tube-dependent and
all had their tubes placed either before (n = 9) or in the first
4 weeks of treatment (n = 7).

4 | DISCUSSION

To the best of our knowledge, this is the first study reporting
on the direct relation between sarcopenia and prolonged feed-
ing tube dependency during primary CRT for HNC. Our results
show that SMI measured at C3 level, as a measure of sar-
copenia, was significantly associated with an increased risk of
prolonged feeding tube dependency. Adjusting for BMI, FOIS,
and SES did not lead to substantial changes of the estimate of
the RR, suggesting the relationship was not confounded.

The results support our hypothesis that the relationship
between sarcopenia and prolonged tube dependency is a
causal one.43 First, the effect of SMI on the risk of tube
dependency was substantial: the effect size (RR 1.08) trans-
lates into a relative risk increase of 26% for patients per
interquartile range decrease in SMI. Second, adjustment for
confounders resulted in a minimal change of the estimated
interquartile range decrease in SMI. This prediction model could be used to select
patients with the highest estimated risk (30%-60%) had a neck SMI below
12.7. Assessment of neck SMI in this risk category has added
clinical value, as it enables identification of a modifiable fac-
tor. This can aid targeted optimization of patients’ pre-
treatment condition to decrease the risk on swallowing
impairment and tube feeding dependency; if low neck SMI is
present and considered modifiable, proactive tube placement,
with its associated risk for nonuse atrophy of swallowing
musculature, may be postponed. Postponing placement of a
tube lowers the risk for prolonged dependency. Thus, even if
prehabilitation would not fully mitigate the risk, postponing
tube placement still might result in shorter dependency
durations.

Prehabilitation includes the improvement of patients’ base-
line outcomes between diagnosis and start of treatment in
order to prevent or minimalize post treatment impairments.45
Several studies on other cancer types have investigated this
strategy and found positive results on body mass and overall
physical strength and function.31,32 In patients with HNC
receiving CRT, studies have been performed on preventive
swallowing exercises before or during treatment to improve
swallowing function.46-48 These interventions showed posi-
tive effects on post-treatment swallowing function.

In order to optimize muscle mass and function prior to
treatment to prevent functional impairment, a multifactorial
approach to resolve the modifiable factor sarcopenia would be
most effective.49 First, increase in muscle strength and mass
should be provoked by means of exercises. These exercises
ideally include targeted swallowing exercises, preferably with
progressive load, to increase swallowing muscle function, as
well as overall physical exercises to increase overall muscle
strength and mass.50 One has to keep in mind, however, that
the time period between diagnosis and start of treatment is
short and may be too short to effectively build up muscle
mass—if possible, exercises should therefore be continues
during treatment. Second, patients should be encouraged to
adhere to a high protein diet to facilitate muscle growth.
Patients treated in our institute, independently of their muscle
mass, are advised to increase their protein intake to at least
1.5 g/kg a day. Therefore, as part of prehabilitation, patients
should be advised to alter their diet (eg, consuming protein in
portions of 25-30 g per meal) and prescribing high-protein
medical nutrition to supplement their regular meals should be
considered.51,52 Considering the high prevalence of dysphagia
in patients with HNC before treatment, altering the route of
administration using a (temporary) feeding tube could be con-
sidered and might be the only way to reach the minimal pro-
in intake of 1.5 g/kg a day to optimize nutritional status.
Eventually, the combination of high protein intake and
(targeted) exercises might break the vicious spiral of muscle
function loss and malnutrition and thus long-term functional
outcomes might be improved. However, percutaneous endo-
scopic gastrostomy probe placement as a back-up is not
Sarcopenia, as measured by SMI at C3 level on routine CT imaging of the head and neck area, contributes to the risk of prolonged feeding tube dependency in patients with HNC treated with primary CRT. Due to its noninvasive and time-efficient character, routine measurement of neck SMI could be a valuable addition to clinical practice. First, it could aid in the shared decision making regarding proactive tube placement, especially in the intermediate risk category based on our previously published prediction model on prolonged feeding tube dependency risks. Second, sarcopenia might be modifiable prior to treatment, and as such it may present a relevant lead for pretreatment optimization of patients’ condition. The results of this study therefore warrant further research on the feasibility and effectiveness of such interventions.

5 | CONCLUSION

Sarcopenia, as measured by SMI at C3 level on routine CT imaging of the head and neck area, contributes to the risk of prolonged feeding tube dependency in patients with HNC treated with primary CRT. Due to its noninvasive and time-efficient character, routine measurement of neck SMI could be a valuable addition to clinical practice. First, it could aid in the shared decision making regarding proactive tube placement, especially in the intermediate risk category based on our previously published prediction model on prolonged feeding tube dependency risks. Second, sarcopenia might be modifiable prior to treatment, and as such it may present a relevant lead for pretreatment optimization of patients’ condition. The results of this study therefore warrant further research on the feasibility and effectiveness of such interventions.

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