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ORIGINAL ARTICLE

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 complications^{5,6} 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

van den Brekel and Stuiver are shared senior author.

Correction added on 14th October, after first online publication: Author degrees added.

after concomitant chemoradiotherapy (CRT) and postoperative complications including pharyngocutaneous fistula after total laryngectomy.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.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.¹⁷⁻²⁴ Second, poor nutritional status can also contribute to swallowing dysfunction, due to loss of muscle mass and function.¹⁹⁻²⁴ As a result of swallowing dysfunction, a substantial proportion (50%-70%) of patients become feeding tube-dependent during CRT.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.^{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, in these patients, nonuse atrophy of the swallowing muscles may even sooner lead to prolonged functional impairment.^{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.^{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.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.

2 | PATIENTS AND METHODS

2.1 | Ethical considerations

This retrospective cohort study was approved by the Institutional Review Board of the Netherlands Cancer Institute (IRB18.374/IRBd18105). As this was a retrospective study based on chart review, no (written) informed consent was necessary.

2.2 | Patient selection

A consecutive cohort of 128 patients treated with primary high-dose cisplatin-based CRT for a primary head and neck

squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx in the Netherlands Cancer Institute from February 2008 to December 2015 was used for the analysis. Patient characteristics are presented in Table 1. Of the cohort of 128 patients, 90 (70%) were men, the mean age was 59 years (SD 7, ranging from 42 to 73), and 58 patients (45%) had an Adult Comorbidity Evaluation-27 (ACE-27) of 0. Most patients (ie, 78, 61%) had an oropharyngeal carcinoma and 106 (83%) had stage IV disease. Ten patients (8%) lost more than 10% of their weight prior to CRT and 33 (26%) had an abnormal diet (functional oral intake scale [FOIS] <7) prior to CRT.

2.3 | CRT treatment

According to protocol, all patients were immobilized during radiotherapy planning and treatment in supine treatment position in a custom-made head-and-neck mask. For planning, contrast-enhanced CT-scan simulation was performed. All patients were treated with intensity-modulated radiotherapy or volumetric-modulated arc therapy. The radiation dose consists of 70 Gy to the primary tumor and the involved node(s) in N + disease, given in 2 Gy per fraction, five fractions a week. Elective irradiation of the neck was given to a dose of 46 Gy in 23 fractions in case of sequential boost and to 54.25 Gy in 35 fractions in case of concomitant boost. Concomitant cisplatin was added to the radiotherapy in case of locally advanced disease (T3/4, N2c/N3) or extracapsular extension as assessed by MRI. Patients were scheduled for a triweekly intravenous high-dose concomitant cisplatin (100 mg/m² on days 1, 22, and 43 of radiotherapy).

2.4 | Tube placement policy, nutritional policy, and swallowing exercises

None of the patients received prophylactic tube feeding.²³ Feeding tube placement was either advised to patients or deemed necessary for treatment completion in case of excessive weight loss (>5% of baseline body weight in 3 months or >10% in 6 months), insufficient oral intake (<50% of recommended daily calories and protein), dehydration, or proven aspiration based on videofluoroscopy at baseline or during the course of CRT. For patients who received a feeding tube, biweekly consultations were planned to evaluate weight, possible side effects of the enteral nutrition, and oral intake. According to Institution's protocol, all patients were seen by a speech language pathologist and dietitian for clinical checkup and counseling before CRT. All patients were enrolled in a prophylactic swallowing exercise program before treatment,³⁴ and all were advised to take 1.5 g/kg of protein per day and a caloric intake according to the Harris-Benedict 1984 equation

TABLE 1 Patient characteristics

		Number of patients (%)		Total cohort (n = 128)
		<90 d feeding tube-dependent (n = 67)	>90 d feeding tube-dependent (n = 61)	
Sex	Men	46 (69)	44 (72)	90 (70)
	Women	21 (31)	17 (28)	38 (30)
Age (y) Mean (SD)		60 (44-71)	61 (42-73)	59 (7)
ACE-27	0	34 (51)	24 (39)	58 (45)
	1	22 (33)	23 (38)	45 (35)
	2	7 (10)	12 (20)	19 (15)
	3	4 (6)	2 (3)	6 (5)
Tumor site	Oral cavity	0 (0)	1 (2)	1 (1)
	Oropharynx	44 (66)	34 (56)	78 (61)
	Hypopharynx	17 (25)	22 (36)	39 (31)
	Larynx	6 (9)	4 (7)	10 (8)
T classification	T1	8 (12)	5 (8)	13 (10)
	T2	23 (34)	15 (25)	38 (30)
	T3	23 (34)	16 (26)	39 (31)
	T4	13 (19)	25 (41)	38 (30)
N classification	N0	10 (15)	6 (10)	16 (13)
	N1	11 (16)	5 (8)	16 (13)
	N2	45 (67)	46 (75)	91 (71)
	N3	1 (2)	4 (7)	5 (4)
TNM stage	Stage II	0 (0)	2 (3)	2 (2)
	Stage III	15 (22)	5 (8)	20 (16)
	Stage IV	52 (78)	54 (89)	106 (83)
BMI mean (SD)		25 (15-35)	23 (16-33)	24 (4)
Pretreatment weight loss	No	51 (76)	29 (48)	80 (63)
	<10%	16 (24)	22 (36)	38 (30)
	>10%	0 (0)	10 (16)	10 (8)
Pretreatment FOIS	7 (normal diet)	59 (88)	36 (59)	95 (74)
	<7	8 (12)	25 (41)	33 (26)
Prolonged feeding tube-dependent	No	NA	NA	67 (52)
	Yes	NA	NA	61 (48)
Neck SMI median (min-max)		13 (9-22)	12 (8-16)	12 (8-22)
Low neck SMI <12.7	No	38 (57)	17 (28)	55 (43)
	Yes	29 (43)	44 (72)	73 (57)
Socioeconomic status mean status score (SD)		0.2 (1.1)	0.1 (1.2)	0.1 (1.1)

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/m².³⁵

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.³⁸ 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.³⁹ 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.^{40,41} *P* values <.05 were considered statistically significant. Univariable Poisson regression analysis with a log link was used to assess the crude and adjusted

FIGURE 1 Delineated CT-slide at C3 level [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Directed acyclic graph with confounders and mediators in the relation between sarcopenia and prolonged feeding tube dependency. Arrows indicate direction of effect. Dotted arrows indicate direction of effect for unavailable confounder (health literacy). BMI, body mass index; FOIS, functional oral intake scale; SES, socioeconomic status

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.²³ This model included the clinical predictors FOIS, BMI, weight loss, and T classification and had the following formula: $Y = 0.617 + (0.145 \cdot T2 + 0.382 \cdot T3 + 0.727 \cdot T4) + (-0.067 \cdot BMI) + (0.543 \cdot FOIS < 7) + (0.356 \cdot \text{weight loss} < 10\% + 0.980 \cdot \text{weight loss} > 10\%)$.

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

	Multivariable analysis	
	RR (95% CI)	<i>P</i> value
Neck SMI	1.08 (1.02-1.14)	.01
BMI	1.01 (0.97-1.06)	.63
SES	1.08 (0.91-1.27)	.38
FOIS		
7	1.00	
<7	0.44 (0.24-0.80)	.01

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 inter-quartile 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 feeding tube dependency during primary CRT for HNC. Our results show that SMI measured at C3 level, as a measure of sarcopenia, 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) translates 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 RR. Last, the relation between low muscle mass and functional impairment later on (ie, tube dependency) is biologically plausible, and analogous effects of low skeletal muscle mass have been observed for other clinical and functional outcomes of HNC treatment.^{12,44}

Our findings implicate that muscle mass and function may also modify patients' risk of feeding tube dependency. Thus, the presence of sarcopenia may be a relevant indication for optimization of patients' physical condition (through nutritional interventions and exercise programs targeting the [swallowing] muscles) prior to treatment, and routine assessment of neck SMI could be used to identify patients who will benefit most from prehabilitation. Future experimental studies are needed to assess the effect of such a policy.

Recently, we developed and published a clinical prediction model to estimate the risk of prolonged feeding tube dependency.²³ This prediction model could be used to select high-risk patients for proactive placement of a feeding tube to prevent unnecessary weight loss. In this cohort, 16 of the 17 patients (94%) with a high estimated risk (>60%) on prolonged feeding tube dependency—for whom clinicians might recommend proactive feeding tube placement—had a neck SMI below 12.7 (median SMI 11 [range 8-13]). Therefore, for these patients, the effort of assessing neck SMI can be saved as it is likely that all patients in this risk category will benefit from pretreatment supportive care focusing on optimizing muscle mass. We would recommend considering routine assessment of neck SMI for patients with an estimated risk below 60%, however, especially the intermediate risk category (30%-60%), as 49 of the 80 patients (61%) with an intermediate 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 factor. 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' baseline outcomes between diagnosis and start of treatment in order to prevent or minimize 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 positive 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 continued 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 considered and might be the only way to reach the minimal protein 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 endoscopic gastrostomy probe placement as a back-up is not

recommended as it is associated with substantial risks for patients who will eventually not need the tube. These risks can be avoided by close monitoring of the patient and placement of a tube when necessary.

A remaining uncertainty in this study, due to its retrospective nature, is that some variables that arguably could confound the association of sarcopenia with tube dependency were not available. In particular, health literacy, the degree to which someone is able to understand information to make health decisions, might be a confounding factor unaccounted for (see Figure 1). Also, analyses were performed on a subgroup of patients with HNC treated with CRT, and the conclusions may be generalizable to this specific population only. Future studies are needed to confirm the association in more heterogeneous HNC populations. Finally, we estimated sarcopenia using routinely performed CT imaging of the head and neck area, whereas the most common method for sarcopenia assessment in patients with cancer is based on abdominal CT imaging, for instance, using the psoas muscle or using total muscle area at the level of lumbar vertebra L3. However, abdominal imaging is not routinely available in patients with HNC, which limits its applicability in this population. Although the optimal measurement level, measurement method, or cutoff value for sarcopenia on CT imaging is still debated, a high correlation of C3 SMI with L3 SMI has been reported before.^{53,54} Thus, in patients with HNC, measurement on head and neck CT imaging currently appears to be the most applicable method.

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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