



Cut-off values for low skeletal muscle mass at the level of the third cervical vertebra (C3) in patients with head and neck cancer

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Background: Low skeletal muscle mass is associated with adverse outcomes in patients with cancer. For patients with head and neck cancer (HNC), skeletal muscle mass is often assessed at the third cervical vertebra on head and neck imaging. Due to the unavailability of standardized cut-off values for low skeletal muscle mass in patients with head and neck cancer, there is heterogeneity of cut-off values for low skeletal muscle mass described in literature. Therefore, we aim to provide standardized cut-off values for low skeletal muscle mass in HNC patients.

Methods: A retrospective cohort study was performed. Between 2008 and 2018, HNC patients with head and neck imaging were included. Skeletal muscle area (SMA) was manually delineated at the level of the third cervical vertebra and corrected for patients squared height to obtain the cervical skeletal muscle mass index. Gender and body-mass index specific cut-off values for low skeletal muscle mass were calculated based on mean cervical skeletal muscle mass index minus 2 standard deviations as suggested in literature.

Results: Of the 1,415 included patients, the majority was male (69.8%) and had a body mass index below 25 kg/m² (59.2%). A primary tumor localization in the oropharynx (35.3%) and a tumor, node, metastasis stage IV tumor (60.5%) were most frequently observed. Cervical skeletal muscle mass index was significantly correlated with gender ($r^2=0.4$, $P<0.01$) and body mass index ($r^2=0.4$, $P<0.01$). For male patients with a body mass index <25 and ≥ 25 kg/m², a cervical skeletal muscle mass index of respectively ≤ 6.8 and ≤ 8.5 cm²/m² was defined for low skeletal muscle mass. For female patients with a body mass index <25 and ≥ 25 kg/m², a cervical skeletal muscle mass index of respectively ≤ 5.3 and ≤ 6.4 cm²/m² was defined for low skeletal muscle mass.

Conclusions: This study is the first to provide standardized cut-off values for low skeletal muscle mass at the level of the third cervical vertebra in patients with HNC. This information may aid in the uniformity of low skeletal muscle mass definition in research.

Keywords: Skeletal muscle mass; head and neck cancer (HNC); sarcopenia; cut-off values; imaging biomarker

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Introduction

Research on body composition in cancer patients, and in particular on skeletal muscle mass (SMM), has increasingly gained interest over the past several decades. Low SMM is often referred to as sarcopenia, although a more comprehensive definition of sarcopenia is the combination of low SMM and low muscle function (1). Due to the unavailability of routinely performed muscle function tests, most research in oncological patients focusses on radiologically assessed SMM, measured on routinely performed computed tomography (CT) or magnetic resonance imaging (MRI). Radiologically assessed low SMM at diagnosis has shown to predict adverse outcomes in a variety of cancer types and treatments (2-6).

For head and neck cancer (HNC), low SMM has shown to be a significant predictive factor for cisplatin dose-limiting toxicity (7), the occurrence of a fistula after total laryngectomy (TLE) (8) and flap-related complications in microvascular free flap head and neck reconstructive surgery (9). It has also been shown that low SMM is prognostic for decreased survival in patients with HNC (10-14).

Several diagnostic imaging modalities can be used to quantify SMM such as MRI, CT, bioimpedance analysis (BIA) and dual energy X-ray absorptiometry (DEXA). BIA and DEXA are confounded by alterations in hydration, edema and food intake. Therefore, its use in assessing body composition of patients with cancer is not favored. First research on body composition was performed by measurement of skeletal muscle area (SMA) on a single axial-slice at the level of the third lumbar vertebra (L3) (15,16). The SMA at the level of L3 is then normalized for height to calculate the lumbar skeletal muscle index (lumbar SMI), which is used as a proxy of whole body skeletal muscle mass (17). Abdominal CT imaging is not routinely performed in patients with HNC and is often only available in patients with advanced disease and those at risk for distant metastasis.

Measurements of SMM at the level of the third cervical vertebra (C3) have shown to correlate well with SMM measurements at the level of L3 (18). Therefore, in order to avoid selection bias (i.e., only patients with abdominal CT included) in research on SMM in HNC, measurement of SMA at the level of C3 is the preferred method. Measurement of SMA at the level of C3 consists of segmentation of both sternocleidomastoid muscles and the

paravertebral muscles. If preferred, the SMA at the level of C3 can be converted to SMA at the level of L3 by using a previously published and validated prediction formula (18).

Accurate diagnosis of low SMM in clinical practice is impeded by heterogeneous cut-off values used to diagnose patients with low SMM. In oncological literature different cut-off values for low SMM are used. The most used cutoff values in the field of research on body composition are the ones defined by Prado *et al.* and Martin *et al.* (15,19). Prado *et al.* used optimum stratification analyses between muscle mass and mortality in a population of 250 obese [body mass index (BMI) ≥ 30 kg/m²] patients with respiratory or gastrointestinal malignancies and found cut-off values for low muscle mass to be 52.4 cm²/m² for men and 38.5 cm²/m² for women as the best predictor for mortality. Martin *et al.* also utilized optimum stratification analysis for low SMM as a predictor of mortality in a population of 1,473 patients with lung or gastrointestinal malignancies and incorporated both gender-specific and BMI-specific cutoffs: 41.0 cm²/m² for women and 43.0 cm²/m² for men with a BMI < 25 kg/m² and 53.0 cm²/m² for men with a BMI > 25 kg/m². These cut-off values are based on SMA at the level of L3 and are not applicable for patients with HNC in whom SMM segmentation at the level of C3 is performed.

The European Working Group of Sarcopenia in Older People (EWGSOP) recommends that low SMM should be defined as SMM less than 2 standard deviations (SD) below the mean SMM of typical healthy adults (20). It is unknown whether this recommendation also implies to patients with cancer, but reference values may provide a better direct comparison in between patients. Recently a study in a Dutch cohort of healthy persons revealed gender- and BMI-specific reference values for SMM at the level of L3 (21), which may be used to uniformly identify patients with a significantly lower SMM than a reference patient of the same gender and BMI.

The aim of this study is to provide gender- and BMI-specific cut-off values for low SMM as measured at the level of C3 in a large cohort of patients diagnosed with HNC. This information will contribute to the knowledge about the distribution of low SMM in HNC patients and will provide more uniformity in the definition of low SMM in HNC research. We present the following article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-911/rc>).

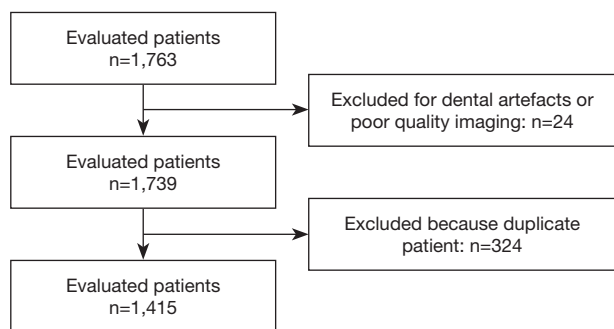


Figure 1 Flow diagram of inclusion in the study database.

Methods

Ethical considerations

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (No. 16/595 C and 17-365/C) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All data was retrieved retrospectively and used in an anonymized fashion. The requirement for informed consent from patients was waived because of its retrospective design.

Study population

Patient data collected in several earlier retrospective studies of our group that evaluated skeletal muscle mass in HNC patients were combined in a new database. Patients were diagnosed and treated with a curative intent at the University Medical Center Utrecht, The Netherlands between 2008 and 2018 with a primary HNC and include cohorts of patients planned for microvascular free-flap mandibular reconstruction (9), patients undergoing chemoradiotherapy (7) or bioradiotherapy (22), elderly patients with HNC (10) and patients with oropharyngeal cancer (11). Relevant parameters, including length and weight at the time of imaging, sex, age, tumor localization and clinical TNM stage (7th and 8th edition) were retrospectively retrieved. Patients were included only once in this study; for example, if a patient experienced recurrence of disease, only the body composition and CT data of the primary diagnosis was included. The CT imaging and body composition data concerning the recurrent HNC diagnoses were excluded. Other exclusion criteria include severe dental artefacts impeding accurate

delineation of skeletal muscle mass. After completion of the database, the database was checked for duplicates and all duplicate patients were removed. A flow diagram of all patients evaluated and included or excluded is shown in *Figure 1*.

Assessment of cross-sectional muscle area at the level of C3

Muscle tissue was identified using Hounsfield Unit (HU) range settings from -29 to $+150$ HU, which is specific for muscle tissue. Muscle tissue was delineated at the level of the third cervical vertebra (C3). The SMA was defined as the pixel area within the delineated area with a radiodensity between -29 and $+150$ HU (23). Delineation of muscle tissue was manually performed using the Slice-O-matic software v 5.0. Muscle tissue delineation at the level of C3 was performed by selecting the first slide showing both transverse processes and the entire vertebral arc when scrolling from caudal to cranial direction. The contours of the paravertebral muscles and both sternocleidomastoid muscles were manually traced. The SMA at the level of C3 was calculated as the sum of the paravertebral muscle and both sternocleidomastoid muscles. If evident lymph node metastasis hindered accurate delineation of one sternocleidomastoid muscle, the SMA of the contralateral sternocleidomastoid muscle was used as an estimation of the SMA of the affected sternocleidomastoid muscle. After delineation, SMA was automatically retrieved from Slice-O-matic. For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. The overall intraclass correlation coefficient (ICC) for the muscle SMA obtained by CT and MRI has shown to be excellent (ICC 0.9, $P < 0.01$) (24), and can therefore be used interchangeably for measuring CSA at the level of C3. The cervical SMI (CSMI) was calculated by dividing the SMA at the level of C3 by the squared height of the patient. *Figure 2* shows muscle tissue delineation at the level of C3.

Statistical analysis

A test for normality (Kolmogorov-Smirnov) was performed to assess whether continuous variables were normally distributed. Continuous data are represented as mean \pm standard deviation (SD) if normally distributed, and median \pm range if skewed. Categorical data are represented as a number and percentage of total. The student's *t*-test, one-way ANOVA, Mann-Whitney U test were used where appropriate. Percentiles were used to describe the

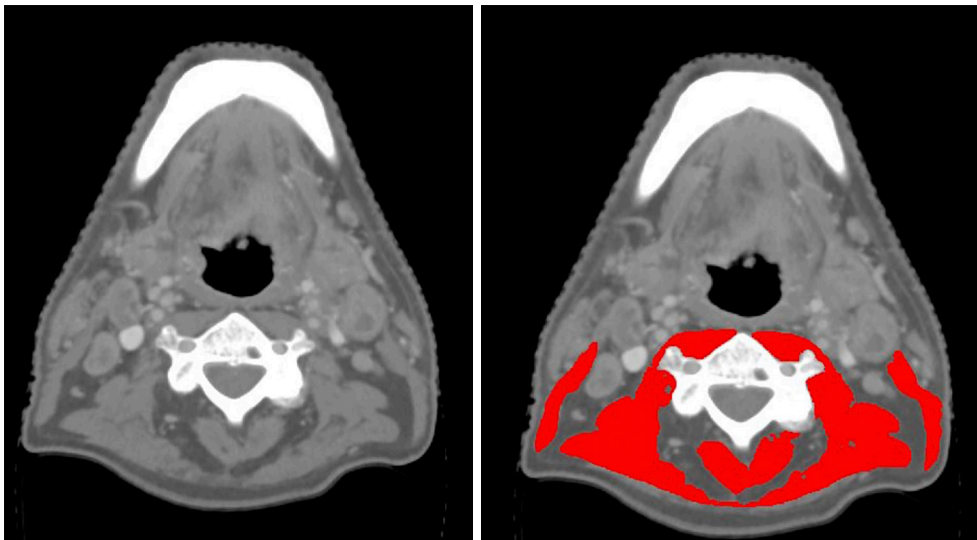


Figure 2 This figure displays two identical axial CT-slides at the level of C3; in the left axial slide muscle tissue is unsegmented. The right CT slide shows both sternocleidomastoid and paravertebral muscles segmented in red. CT, computed tomography.

distribution of SMA and CSMI. Chi-square test was used to investigate the association between gender and various clinical and demographic variables. Spearman correlation was used for correlation analysis of SMI and patients' characteristics such as BMI, age and gender. All statistical analyses were performed using the IBM SPSS Statistics version 25.0 software package (Chicago, Illinois, USA). A P value of <0.05 was considered statistically significant.

Results

Patients' characteristics

In total, the skeletal muscle mass data of 1,763 study subjects were entered in this study database. After deduplication, 1,415 unique patients were included for analysis in this study. A flow diagram of all patients evaluated and included or excluded is shown in *Figure 1*. Roughly two-third of patients was male, and one-third was female. Continuous variables were not normally distributed (Kolmogorov-Smirnov $P<0.05$). The median age of the included patients was 63.7 years at diagnosis, ranging between 19.6 and 97.6 years. The median BMI was 24.0 kg/m^2 (range, $13.3\text{--}48.2 \text{ kg/m}^2$); only a minority of patients were underweight at diagnosis with a BMI $\leq 18.5 \text{ kg/m}^2$: $n=129$, 9.1%. This study included tumors of all tumor head and neck sites and all tumor stages. The most common diagnosis was oropharyngeal carcinoma ($n=500$, 35.3%), and most patients were diagnosed with

a stage IV tumor ($n=800$, 59.4%). Significant differences between male and female patients were seen in age, height and TNM-stage. Female patients were more often older and smaller of stature and had lower of body weight and lower BMI. Male patients more often presented with stage IV disease, all $P<0.01$. Full patient and disease characteristics are shown in *Table 1*.

Correlation analysis

The SMA at the level of C3 and CSMI were not normally distributed (Kolmogorov-Smirnov $P<0.05$). SMM (CSMI) had a significantly low correlation with age at diagnosis (Spearman $r^2=0.1$, $P<0.05$) and a significantly moderate correlation with BMI (Spearman $r^2=0.4$, $P<0.01$) and gender (Spearman $r^2=0.4$, $P<0.01$). *Figure 3* shows the scatter plots of the association between CSMI and age and CSMI and BMI in females and males.

Distribution of SMM

The median SMA at the level of C3 was 39.0 cm^2 for men (IQR, $28.4\text{--}49.6 \text{ cm}^2$) and 27.8 cm^2 for women ($19.2\text{--}36.2 \text{ cm}^2$). The median CSMI was $12.3 \text{ cm}^2/\text{m}^2$ for men (IQR, $8.9\text{--}15.7 \text{ cm}^2/\text{m}^2$) and $10.0 \text{ cm}^2/\text{m}^2$ for women (IQR, $6.9\text{--}13.1 \text{ cm}^2/\text{m}^2$). The distribution of SMA at the level of C3 and from the 5th percentile up to the 95th percentile is shown in *Table 2*.

Table 1 Patient and tumor characteristics of the total study population (n=1,415)

Characteristics	All subjects (n=1,415)	Men (n=988)	Women (n=427)	P value
Age (years)	63.6 [57.0–69.8]	63.2 [56.6–69.6]	64.9 [58.0–70.0]	<0.01
Height (cm)	174 [168–180]	177 [172–182]	167 [162–172]	<0.01
Weight (kg)	73.9 [62.2–84.0]	77.2 [66.0–87.0]	66.5 [55.6–75.1]	<0.01
Body mass index (BMI) (kg/m ²)	24.0 [21.2–27.2]	24.5 [21.6–27.2]	23.9 [20.3–27.0]	<0.01
BMI categorical, n (%)				<0.01
Below 25	838 (59.2)	567 (57.4)	271 (63.5)	
25 or above	577 (40.8)	421 (42.6)	156 (36.5)	
Localization of tumor, n (%)				<0.01
Oropharynx	500 (35.3)	334 (33.8)	166 (38.9)	
Hypopharynx	207 (14.6)	174 (17.6)	33 (7.7)	
Larynx	267 (18.9)	209 (21.2)	58 (13.6)	
Oral cavity	319 (22.5)	188 (19.0)	131 (30.7)	
Nasopharynx	51 (3.6)	37 (3.7)	14 (3.3)	
Paranasal sinus	21 (1.5)	13 (1.3)	8 (1.9)	
Salivary gland	20 (1.4)	10 (1.0)	10 (2.3)	
Unknown primary	18 (1.3)	14 (1.4)	4 (0.9)	
Skin (lip, ear, face)	12 (0.8)	9 (0.9)	3 (0.7)	
AJCC stage, n (%)				<0.01
I	103 (7.3)	57 (5.8)	46 (10.8)	
II	165 (11.7)	118 (11.9)	47 (11.0)	
III	280 (19.8)	178 (18.0)	102 (23.9)	
IV	856 (60.5)	628 (63.6)	228 (53.4)	
X	11 (0.8)	7 (0.7)	4 (0.9)	

Continuous variables are shown as median [interquartile range] and categorical variables as number (percentage of total). The Mann-Whitney U test was used for continuous characteristics and the Chi-square test for categorical variables. AJCC stage: American Joint Committee on Cancer staging system, for describing the extent of disease progression P value of <0.05 was considered statistically significant.

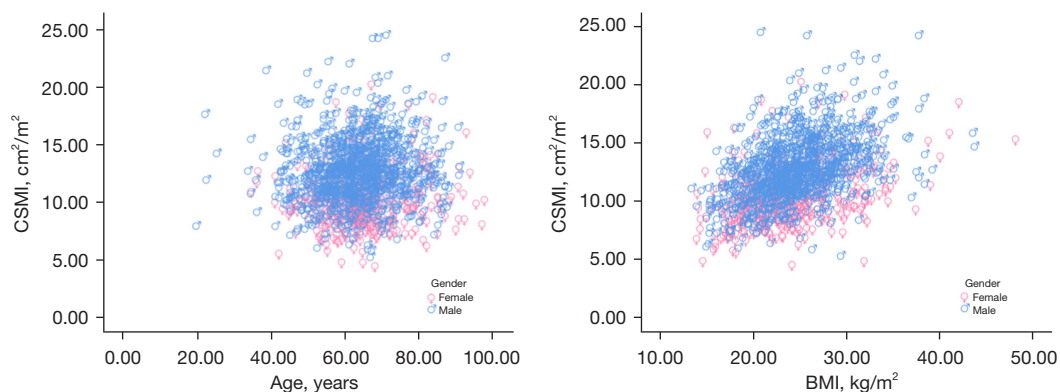


Figure 3 Scatterplots of the association between CSMI and age and CSMI and BMI. BMI, body mass index; CSMI, cervical skeletal muscle mass index.

Table 2 Distribution of SMM from the 5th until the 95th percentile

Mean/percentiles	SMA at the level of C3 (cm ²)		CSMI (cm ² /m ²)	
	Male, N=988	Female, N=427	Male, N=988	Female, N=427
Total mean ± SD	39.4 (8.3)	28.6 (6.8)	12.6 (2.7)	10.3 (2.4)
P5	26.9	19.1	8.4	7.0
P10	29.4	20.9	9.4	7.5
P25	33.6	24.0	10.8	8.6
P50	39.0	27.8	12.3	10.0
P75	44.2	32.4	14.2	11.7
P90	49.6	36.6	16.0	13.5
P95	53.7	40.1	17.2	14.8

SMM, skeletal muscle mass; SD, standard deviation; SMA, skeletal muscle mass area; CSMI, cervical skeletal muscle mass index; P, percentile; N, number of patients.

Table 3 Cut-off SMA values and gender- and BMI specific cut-off values for low SMA (cm²)

BMI categories	Male, N=988	Cut-off, mean – 2SD (cm ²)	Female, N=427	Cut-off, mean – 2SD (cm ²)
BMI <25 kg/m ²		≤22		≤15.1
N (%)	567 (57.4)		271 (63.5)	
M (SD)	36.6 (7.3)		26.9 (5.9)	
BMI ≥25 kg/m ²		≤26.9		≤16.9
N (%)	421 (42.6)		156 (36.5)	
M (SD)	43.1 (8.1)		31.5 (7.3)	

BMI, body mass index; N, number of patients; M, mean; SD, standard deviation; SMA, skeletal muscle mass area.

Table 4 Cut-off CSMI values and gender- and BMI-specific cut-off values for low CSMI (cm²/m²)

BMI categories	Male, N=988	Female, N=427
BMI <25 kg/m ²		
N (%)	567 (57.4)	271 (63.5)
M (SD)	11.8 (2.5)	9.7 (2.2)
Cut-off value, M – 2SD (cm ² /m ²)	≤6.8	≤5.3
BMI ≥25 kg/m ²		
N (%)	421 (42.6)	156 (36.5)
M (SD)	13.7 (2.6)	11.4 (2.5)
Cut-off value, M – 2SD (cm ² /m ²)	≤8.5	≤6.4

BMI, body mass index; N, number of patients; M, mean; SD, standard deviation; CSMI, skeletal muscle mass index.

Cut-off values for SMM

Tables 3,4 shows the mean with corresponding standard deviations (SD) of SMA and CSMI at the level of C3. Gender and BMI specific cut-off values were calculated based on mean – 2SD as suggested by the EWGSOP2 (20). For male patients with a BMI <25 kg/m², a CSMI ≤6.8 cm²/m² was defined and with a BMI ≥25 kg/m² a CSMI ≤8.5 cm²/m² was defined for low SMM. For female patients with a BMI <25 kg/m², a CSMI ≤5.3 cm²/m² was defined and with a BMI ≥25 kg/m² a CSMI ≤6.4 cm²/m² was defined for low SMM.

Discussion

This is the first study describing cut-off values for SMM measured on head and neck CT imaging or MRI at the level of C3 in patients with HNC. This study provided gender

and BMI-specific cut-off values of the mean (SD) quantity of SMM (SMA and skeletal muscle mass index). For male patients with a BMI <25 kg/m², a CSMI ≤6.8 cm²/m² was defined and with a BMI ≥25 kg/m² a CSMI ≤8.5 cm²/m² was defined for low SMM. For female patients with a BMI <25 kg/m², a CSMI ≤5.3 cm²/m² was defined and with a BMI ≥25 kg/m² a CSMI ≤6.4 cm²/m² was defined for low SMM.

A known risk factor for adverse outcomes in HNC is a low BMI, but BMI is an imprecise measurement of individual body composition and does not reflect variances in adipose tissue and lean body mass. Modern imaging techniques such as CT and MRI can add information on the body composition of a patient and can provide detailed information on skeletal muscle mass, adipose tissue mass and its ratio. In the management of HNC patients, CT and MRI of the head and neck are the most widely used imaging modalities for routine diagnostics and clinical decision making. MRI is considered one of the most accurate methods for analyzing quantitative and qualitative changes in body composition and is associated with an error in quantifying muscle that ranges between 1.1% and 4.4% (25).

CT, like MRI, is also considered as a highly precise imaging modality in investigating human body composition and has a reported precision error of about 1.4% for tissue areas (23). Both scanning methods are able to distinguish muscle mass from fat. CT imaging can reveal fat infiltration within muscle by identifying areas in the range of -190 to -30 HU (26). Currently, MRI and CT are considered to be accurate methods for quantifying muscle mass, due to their abilities to separate fat from other soft tissues. Therefore, this study included routinely performed CT and MRI imaging, which makes the results applicable to clinical practice. CT and MRI have already shown to have a significant agreement in measuring SMM and therefore can be used interchangeably in assessing SMM at the level of C3 (24). Using other software programs than the software program used in the current study (slice-O-matic) may give slightly different results, but these differences are not clinically relevant. A previous study showed that the measurement of SMA has an excellent inter-software agreement and therefore results of studies using different software programs may reliably be compared (27).

Reference values for SMM at the level of C3 for a healthy (non-HNC) Caucasian population are lacking, but reference values for SMM analysis at the level of L3 have been reported (21). Van der Werf *et al.* included 420 healthy Caucasian kidney donors (21). They found that SMI was

1.31-fold higher in men than in women. Previous studies also show that men have a significantly higher amount of skeletal muscle mass than women (28). In our study, we found a significant correlation between SMI and gender and between SMI and BMI. Therefore, gender and BMI-specific cut-off values were provided in this study.

Van der Werf *et al.* determined cut-off values based on the 5th percentile of SMM in healthy individuals. These 5th percentile cut-off values for low SMM (at L3) corresponded with the cut-off values presented by Prado *et al.* for patients with solid tumors in which cut-off values of SMM (at L3) were defined by the use of the optimal stratification method for endpoint mortality (15). This suggests that the cut-off value for low SMM of 2SD below mean SMM in healthy individuals corresponds with the value of low SMM predictive for mortality in cancer patients.

SMM parameters may differ between ethnicities. Although, we do not collect data on ethnicity in our treatment center, majority of patients has a Caucasian ethnicity. Because the cut-off values in our study are therefore mostly representative for the Western-European population, these cut-off values could probably not be extrapolated to other ethnicities. More research is needed to define cut-off values in other ethnic groups and in respect to treatment outcomes in patients with HNC such as surgical complications and dose-limiting toxicities.

Pre-treatment low SMM is common in patients with HNC, with a pooled prevalence of 42.0% in a recent meta-analysis (29). Several retrospective studies and a meta-analysis showed an association between pre-treatment low SMM and increased postoperative complications in surgically treated patients (8,9,29). In patients treated with primary chemoradiotherapy with cisplatin, chemotherapy dose-limiting toxicity was more often observed in patients with low SMM (7,30). A recent meta-analysis on the prognostic impact of low SMM in HNC patients showed that sarcopenia is prognostic of decreased survival (13,31). Routine measurement of skeletal muscle mass in HNC patients may aid in the identification of patients at high risk of short term and long term adverse outcomes during and after treatment. It may help in informing patients and aid in shared decision making in terms of risk of adverse outcomes associated with treatment. Furthermore, research should point out whether low SMM is prognostic only or that by intensive physical therapy and nutritional support, risks of adverse outcomes associated with low SMM can be decreased.

Our study has some limitations. Firstly, EWGSOP recommended the retrieval of SMM reference values in a

healthy population. However, in order to avoid unwanted extra radiation exposure at the head and neck region SMM segmentation on MRI is preferred. MRI of the head and neck region in otherwise healthy people is not routinely performed in clinical practice. Secondly, due to heterogeneity of tumor site, tumor characteristics and tumor stages included in this cohort study, no reliable cut-off value of low SMM for mortality could be provided. Our previous study in patients with HNC treated with curative intent cisplatin-based chemoradiotherapy showed that low SMM at diagnosis is a significant prognostic for decreased survival, changes in SMM after treatment were however not prognostic (32). Further studies are needed to validate the prognostic impact of the cut-off values for low SMM provided in the present study. The coincidence of low SMM and markers for systemic inflammation such as increased levels of CRP, interleukins or a higher platelet or neutrophil to lymphocyte ratio may be a sign of the presence of cancer related cachexia. Two recent retrospective studies showed that the coincidence of low SMM and systemic inflammation was associated with especially poor overall survival; possibly indicating the presence of cancer related cachexia (33,34). Further research is needed to clarify this relationship and its prognostic effect.

Our study also has some strengths. Firstly, this is the first study providing cut-off values for SMM at the level of C3. Although previous studies provided cut-off values for L3, these cut-off values are usually not applied in HNC research due to the unavailability of abdominal imaging in non-advanced stage HNC. Secondly, we included a large sample size with a large proportion of both female and male patients which strengthens the robustness of the cut-off values that were found.

Conclusions

In this study, cut-off values for low SMM in patients with HNC were presented in order to provide investigators a tool to further explore the association of low SMM and treatment outcomes in HNC patients. In addition, this tool can also be used for trials investigating interventions to improve SMM in patients with HNC and thereby possibly improve cancer treatment outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-21-911/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-911/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (No. 16/595 C and 17-365/C) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All data was retrieved retrospectively and used in an anonymized fashion. The requirement for informed consent from patients was waived because of its retrospective design.

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