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ABSTRACT

Background: Low skeletal muscle mass (SMM) is associated with adverse outcomes. SMM is often assessed at the third lumbar vertebra (L3) on abdominal imaging. Abdominal imaging is not routinely performed in patients with head and neck cancer (HNC). We aim to validate SMM measurement at the level of the third cervical vertebra (C3) on head and neck imaging.
Material and methods: Patients with pre-treatment whole-body computed tomography (CT) between 2010 and 2018 were included. Cross-sectional muscle area (CSMA) was manually delineated at the level of C3 and L3. Correlation coefficients and intraclass correlation coefficients (ICCs) were calculated. Cohen's kappa was used to assess the reliability of identifying a patient with low SMM.
Results: Two hundred patients were included. Correlation between CSMA at the level of C3 and L3 was good ($r = 0.75$, $p < 0.01$). Using a multivariate formula to estimate CSMA at L3, including gender, age, and weight, correlation improved ($r = 0.82$, $p < 0.01$). The agreement between estimated and actual CSMA at L3 was good (ICC 0.78, $p < 0.01$). There was moderate agreement in the identification of patients with low SMM based on the estimated lumbar skeletal muscle mass index (LSMI) and actual LSMI (Cohen's κ: 0.57, 95%CI 0.45–0.69).
Conclusions: CSMA at C3 correlates well with CSMA at L3. There is moderate agreement in the identification of patients with low SMM based on the estimated lumbar SMI (based on measurement at C3) and actual LSMI.

Introduction

Over the last decade, research into the specific body composition of cancer patients and its relationship with clinical outcomes has tremendously increased due to the use of diagnostically performed imaging for quantification of different body compartments, including skeletal muscle mass (SMM) and adipose tissue mass [1,2]. Specifically a state of low SMM, sometimes termed sarcopenia, has gained interest as a novel risk factor for negative short- and long-term outcomes. In breast, gastrointestinal, hepato-pancreatic-biliary and respiratory cancer, amongst others, low SMM is associated with increased incidence of postoperative complications, chemotherapy-related toxicity, prolonged hospital stay and shorter disease-free and overall survival [3,4].

SMM is most commonly assessed on a single CT slice at the level of the third lumbar vertebra (L3), which has shown to have excellent correlation with whole body skeletal muscle volumes as measured using whole body MRI [5,6]. The cross-sectional skeletal muscle area (CSMA) at the level of L3 is then most commonly normalized for stature, to calculate the lumbar skeletal muscle index (lumbar SMI) [5]. The lumbar SMI is used as a proxy for SMM as a whole, and several cut-offs have

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been published to identify patients with low SMM [4].

In head and neck cancer (HNC), abdominal CT imaging is not commonly performed as part of the routine diagnostic work-up. Therefore, abdominal CT imaging to quantify SMM is not routinely applicable in HNC patients. To overcome this, a measurement method for SMM at the level of the third cervical vertebra (C3), which is featured on standard CT imaging of the head and neck area, was published by Swartz et al. [7]. A multivariate formula to calculate CSMA at the level of L3 from CSMA at the level of C3 was also published, to allow for comparison to other oncological research [7]. Wendrich et al. published a cut-off value for low SMM in HNC patients based on this method [8].

The measurement method for SMM at the level of C3 was used in several studies in HNC patients. The incidence of low SMM was high in several studies; typically 50% of patients and sometimes up to 77% of patients had low SMM prior to start of treatment [8–11]. In HNC patients, low SMM was associated with negative short- and long-term outcome such as chemotherapy dose-limiting toxicity, postoperative complications and decreased survival [8,9,12,13]. Only one previous study by Ufuk et al. has investigated the correlation between CSMA measurement at the level of C3 and L3. They showed that CSMA at the level of C3 was best associated with CSMA at the level of L3, and that the correlation between CSMA at the level of C3 and CSMA at the level of L3 was excellent [14]. Ufuk et al. segmented the sternocleidomastoideus (SCM) and paravertebral muscles (PVM) separately, Swartz et al. recommends using the CSMA at C3 of both the SCM and PVM. Ufuk et al. also used cut-off values for low SMM based on the study of Prado et al. which did not include HNC patients and did not validate the formula proposed by Swartz et al.

Our current study aimed to validate the association between skeletal muscle area at the level of C3 and the level of L3 in a larger, diverse cohort of treatment-naïve HNC patients. It also aimed to investigate the accuracy of identifying patients with low SMM using the previously published cut-off value. As this study includes a diverse cohort of HNC patients with different tumor localizations and stages of disease, a relationship with clinical outcomes will not be a subject of investigation in our current study.

Patients and methods

Ethical considerations

All data was retrieved retrospectively and processed in an anonymized fashion. The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 16/595C). Formal patient informed consent was waived by the Medical Ethical Research Committee due to the retrospective and anonymized fashion of this study. This research was conducted in accordance with the Declaration of Helsinki.

Study population

Patients who were diagnosed at the University Medical Center Utrecht, The Netherlands between 2010 and 2018 with a primary head and neck squamous cell carcinoma were evaluated for this study. Since the effect of previous treatments of the neck on CSMA measurement at the level of C3 is not known, patients previously treated with surgery or radiotherapy of the neck were excluded. As such, all patients included were treatment naïve. Patients were included if a pre-treatment whole body FDG-PET/CT scan in radiation mould (as part of radiotherapy treatment planning) was available. Other relevant parameters, including length and weight at the time of imaging, sex, age, tumor localization and clinical TNM stage as decided by the local multidisciplinary tumor board (7th and 8th edition) were retrospectively retrieved. Treatment characteristics and outcome parameters are not reported on in this study. In total, 200 patients were selected.

Assessment of cross-sectional muscle area

Pre-treatment FDG-PET/CT-imaging was performed in all patients according to a standardized protocol. All patients were imaged in radiation mould in standard radiation treatment position. Slice thickness was 2 mm with an interslice gap of 1 mm for the head and neck imaging. 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 lumbar vertebra (L3) and the third cervical vertebra (C3). The CSMA was defined as the pixel area within the delineated area with a radiodensity between −29 and +150 HU [15,16]. Delineation of muscle tissue was manually performed using the Volumetool v.1.6.5 Research Software Package, designed in our center as an image evaluation, registration and delineation system for radiotherapy planning [17].

For delineation of muscle tissue at the level of L3, the first slide when scrolling from caudal to cranial direction to show the entire vertebral arc and both transverse processes was selected. The contours of the abdominal wall and paraspinal muscles were manually traced. CSMA at the level of L3 was calculated by adding up the abdominal wall and paraspinal muscle area. For delineation of muscle tissue at the level of C3, the first slide when scrolling from caudal to cranial direction to show both transverse processes and the entire vertebral arc was selected. The contours of the paravertebral muscles and both sternocleidomastoid muscles were manually traced. The CSMA 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 CSMA of the contralateral sternocleidomastoid muscle was used as an estimation of the CSMA of the affected sternocleidomastoid muscle [7]. After delineation, CSMA was automatically retrieved from Volumetool. First, all head and neck CT scans (C3) were delineated, and afterwards all abdominal scans (L3). Fig. 1 shows muscle tissue delineation at the level of C3 and L3.

Cross-sectional muscle area at the level of L3

As well as the actually measured CSMA at the level of L3, the CSMA at the level of L3 was also estimated from the CSMA at the level of C3 using the prediction rule as described by Swartz et al, see Formula (1) [7].

$$CSMAatL3(cm2) = 27.304 + 1.363*CSMAatC3(cm2) + 0.640*Weight(kg) + 26.442*Gender(Gender = 1 for female, 2 for male) - 0.671*Age(years) \quad (1)$$

The lumbar SMI was then calculated using the formula published by Prado et al, see Formula (2) [5].

$$LumbarSMI(cm2/m2) = CMSAatL3/(height*height) \quad (2)$$

A cut-off for low SMM defined as a lumbar SMI $\leq$ 43.2 cm^2/m^2, as previously published by Wendrich et al, was used [8].

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics version 25.0 software package (Chicago, Illinois, USA). There were no missing data. A test for normality (Shapiro-Wilk test) was performed to assess whether continuous variables were normally distributed. For Table 1. continuous data are represented as mean ± standard deviation (SD) if normally distributed, and median ± 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. Depending on normality of variables, Pearson or Spearman Rank correlation coefficients were calculated to assess correlation between CSMA at the level of C3, at the level of L3 and predicted CSMA at the level of L3.

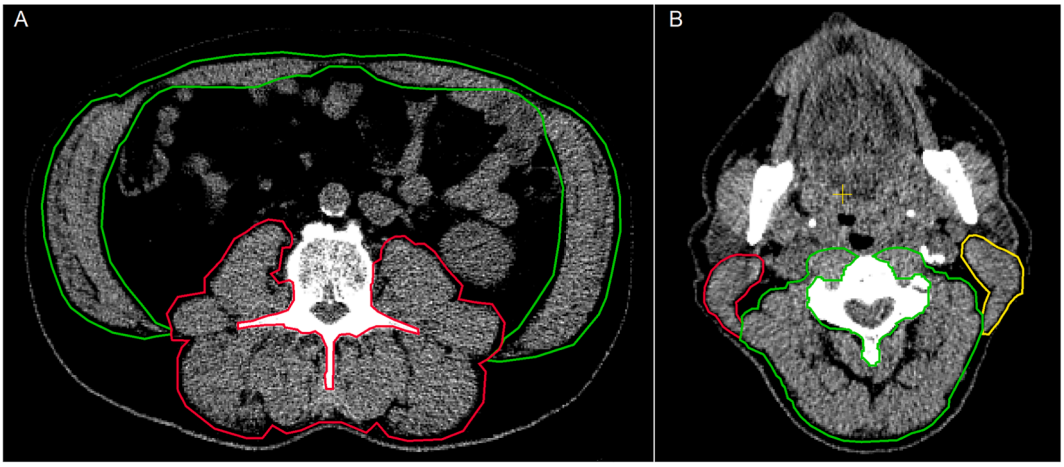

Fig. 1. Delineation of skeletal muscle tissue on transversal CT imaging at the level of L3 (1a) and at the level of C3 (1b). A Hounsfield Unit window of −29 to +150 was used to accentuate skeletal muscle tissue.

To assess the agreement between measurements, we calculated intraclass correlation coefficients (ICCs) using a two-way mixed single measures model with absolute agreement. The ICCs were rated as poor (0.00 – 0.49), fair to good (0.50 – 0.74), good (0.75–0.90) and excellent (>0.90) [18]. For agreement in classification of patients with low SMM, Cohen's κ was used. The agreement was rated as no agreement (<0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00) [19]. A two-tailed test of significance ($p = 0.05$) was used.

Results

Patient characteristics

For this study, 200 patients were included for analyses. Baseline patient characteristics are shown in Table 1. Patients were predominantly male and often presented with advanced disease (T3-4; N+). Weight and BMI at diagnosis were normally distributed. On average, patients had a normal BMI.

Image analysis

Delineation of muscle tissue at the level of C3 was successful in all patients. Six patients (8.6%) had evident growth of a lymph node metastasis into the SCM muscles. In these 6 patients, the CSMA of the affected SCM muscle was substituted by the CSMA of the unaffected, contralateral SCM muscle.

Correlation between CSMA at C3 and L3

Skeletal muscle area at the level of C3 was not normally distributed (Shapiro-Wilk test < 0.05). Spearman rank correlation analysis showed a good correlation between CSMA at C3 and CSMA at L3 (Spearman's $r_s = 0.75$; $p < 0.01$). Fig. 2 shows the direct correlation between CSMA measurements at the level of C3 and L3. Correlation between CSMA at C3 and CSMA at L3 was higher than the correlation between cross-sectional area of the paravertebral muscles only at C3 and CSMA at L3 (Spearman's $r_s = 0.75$ versus $r_s = 0.70$).

CSMA at L3 was estimated from CSMA at C3 using the multivariate formula as described earlier (Formula (1)). Actual CSMA at L3 and estimated CSMA at L3 were normally distributed (Shapiro-Wilk test: $p > 0.05$). Fig. 3 shows the correlation between the estimated CSMA at L3 and the actual CSMA at L3. Pearson correlation analysis showed a high correlation between the estimated CSMA at L3 and the actual CSMA at L3 ($r = 0.82$; p < 0.01). The mean difference between the estimated CSMA at L3 and the actual CSMA at L3 was calculated (mean −9.4 cm^2, SD 17.8 cm^2; 7.0% of total CSMA at L3), meaning that the estimated CSMA at L3 was lower than the actual CSMA at L3. In 13 of 200 patients (7%) the estimated and actual CSMA at L3 differed more than 1.96 standard deviation from the average, suggesting a reasonably good agreement. The ICC between estimated CSMA at L3 and actual CSMA at L3 was good: 0.78 (95% CI: 0.61– 0.86, p < 0.01).

Table 1
Patient characteristics.

Characteristic	n (% or SD) total n = 200
Gender	
Male	147 (73.5)
Female	53 (26.5)
Age at diagnosis (years)	
Mean (SD)	63.5 (8.3)
Range	44.9 –85.6
Weight at diagnosis (kg)	
Mean (SD)	74.1 (16.4)
Range	40.0 – 122.0
BMI (weight/height^2)	
Mean (SD)	24.2 (4.6)
Range	14.0 –40.0
Localization	
Hypopharynx	57 (28.5)
Larynx	40 (20.0)
Oropharynx	83 (41.5)
Oral cavity	12 (6.0)
Nasopharynx	5 (2.5)
Unknown primary	3 (1.5)
T-status	
T1-2	92 (46.0)
T3-4	108 (54.0)
N-status	
N0	73 (36.5)
N1-2a	61 (30.5)
N2b-3b	66 (33.0)
M-status	
M0	183 (91.5)
M+	10 (5.0)
Mx	7 (3.5)

Agreement and accuracy in identification of patients with low skeletal muscle mass

Using Formula (2), the estimated lumbar SMI and actual lumbar SMI were calculated. The previously published cut-off value of ≤43.2 cm/m2 was used to determine low SMM. Using this cut-off, 96 patients were

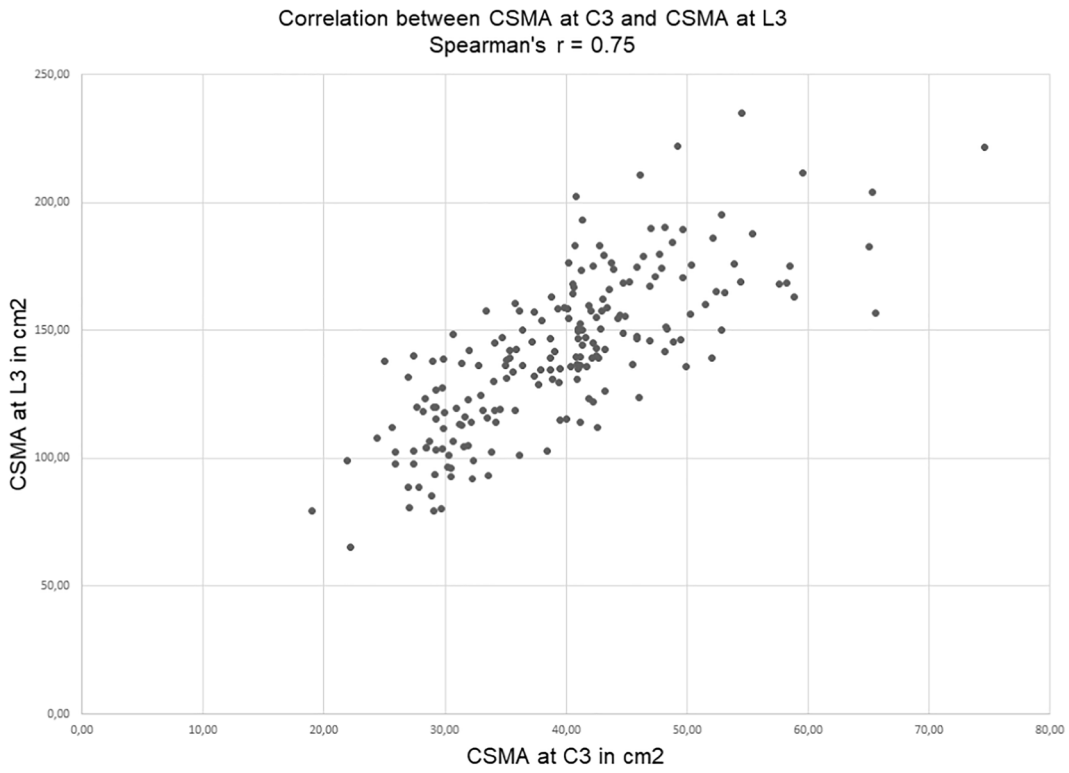

Fig. 2. Correlation between CSMA at the level of C3 and (actual) CSMA at the level of L3.

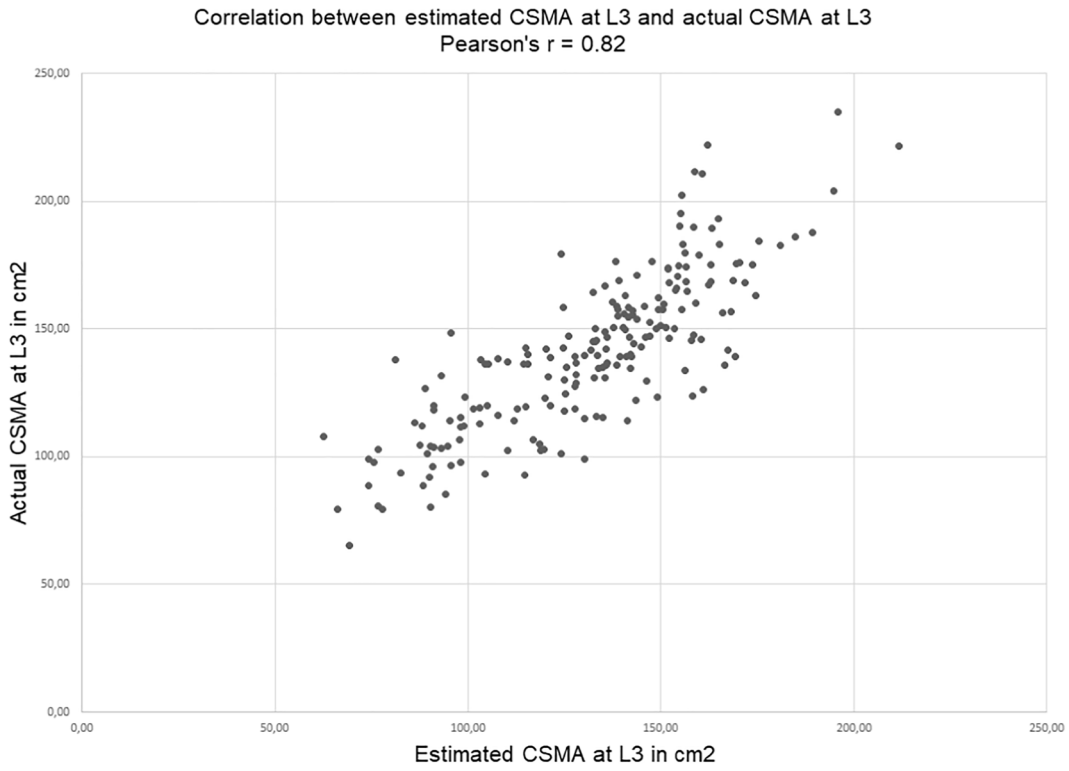

Fig. 3. Correlation between estimated CSMA at the level of L3 and actual CSMA at the level of L3.

determined to have low SMM using the estimated lumbar SMI, and 77 patients had low SMM using the actual lumbar SMI; see Table 2. The sensitivity of identifying patients with low SMM using the estimated lumbar SMI and a cut-off of $\leq$43.2 cm/m^2 was 84.4% and the specificity was 74.8%. The positive predictive value of the estimated lumbar SMI was 67.7% and the negative predictive value was 88.5%. The false positive value, indicating the number of patients that incorrectly were identified as having low SMM, was 25.2%. Cohen's kappa for agreement between low SMM using the estimated and the actual lumbar SMI was 0.57, indicating moderate agreement.

Table 2
Agreement between estimated and actual low skeletal muscle mass, defined as a lumbar SMI $\leq$ 43.2 cm^2/m^2.

		Low skeletal muscle mass: actual lumbar SMI $\leq$ 43.2 cm^2/m^2		Sum	
		Yes	No		
Low skeletal muscle mass: estimated lumbar SMI $\leq$ 43.2	Yes	65	31	96	PPV = 68%
	No	12	92	104	NPV = 88%
sum		77	123	200	
		Sens 84%	Spec 75%		Acc

Sens = sensitivity; spec = specificity; PPV = positive predictive value; NPV = negative predictive value.

Discussion

There is a need for a robust, easy and widely available SMM quantification tool specifically for HNC patients, to allow for routine assessment of SMM without the need for additional diagnostics. Swartz et al proposed a measurement of CSMA at the level of C3 as an alternative to measurement of CSMA at the level of L3, using standard head and neck CT imaging. Our current study shows that measurement of CSMA at the level of C3 provides a good estimation of CSMA at the level of L3 (r_s = 0.75). Total CSMA at the level of C3 had a higher correlation with CSMA at the level of L3 than cross-sectional area of paravertebral muscles only (r_s = 0.75 versus r_s = 0.70), which is in agreement with results of a previous study, albeit slightly lower [14]. Using the same multivariate formula as described earlier, in a different set of patients, we found a very good correlation (r = 0.82) between CSMA at the level of C3 and L3. The agreement in identification of patients with low SMM was moderate and the probability that a patient with low SMM according to C3 has a low SMM with the L3 method is 68%. A measurement of CSMA at the level of C3 provides a good estimation of CSMA at the level of L3 and subsequent analysis without the need for additional testing.

There was some variation in the identification of patients with low SMM based on the estimated lumbar SMI compared to the actual lumbar SMI. The estimated lumbar SMI however was on average −9.4 cm^2 (7.0%) lower than the actual lumbar SMI; classifying more patients as having low SMM than there actually are at L3. Because the cut-off value for low SMM (lumbar SMI $\leq$ 43.2 cm^2/m^2) is based on estimated lumbar SMI by use of segmented CSMA at the level of C3, other cut-off values for lumbar SMI may apply when segmentation of CSMA at the level of L3 is performed directly. This may explain the false positive rate of 25.2%. However, we acknowledge that an estimation of CSMA at the level of L3 based on CSMA at the level of C3 is not ideal and currently gives an overestimation of patients with low SMM. In the future this method is probably not sufficient as the most accurate estimation of a patient's total SMM. Indeed, Baracos published an article concluding that using single muscle as a sentinel muscle for whole body SMM is a flawed premise [20]. This problem probably also applies to CSMA on a single CT slice as a representation of whole body skeletal muscle volume. We do believe that at the current time, the CSMA at C3 can provide a good estimation of SMM of HNC patients without the need for additional diagnostics and at minimal effort, with considerable accuracy.

To facilitate implementation of SMM measurement in clinical practice, we believe the long-term focus should shift towards using artificial intelligence such as deep learning and machine learning to develop an automatic, whole muscle volume analysis based on routinely available CT imaging or MRI. Research into these methods are ongoing, and the expectation is that whole- or portion-of-body measurement of SMM will provide a much more accurate representation of a patients overall body composition and skeletal muscle status than the CSMA on a single CT slide or a single muscle, with no or very little manual work involved [21–23]. Indeed, the use of the CSMA at the level of L3 as an estimation of whole body skeletal muscle volume is based on studies using whole-body MRI for manual segmentation and calculation of whole-body skeletal muscle volume; in these studies, whole body MRI is referenced as the gold standard [6,24]. Manual segmentation of whole body MRI is time-consuming and therefore clinically not feasible. However, when software is available to perform automatic skeletal muscle volume analysis, a whole-body analysis approach seems preferred. In the short term, future studies may be aimed at developing gender-specific references values for CSMA at the level of C3, to allow for the use of CSMA at the level of C3 as a direct measure of SMM and to overcome the problem of several different cut-offs for low SMM that are currently available [25,26].

There are limitations to our study that need to be addressed. Most patients in our study presented with advanced stage disease; in our center, the indication for FDG-PET/CT is a suspected advanced stage disease. Inherently to the use of FDG-PET/CT, patients with limited disease are underrepresented in this study. We excluded patients who had received prior treatment for HNC for this validation study, because the effect of prior local treatment (e.g. radiotherapy or surgery) on the accuracy of delineation of CSMA at C3 is not known, and may cloud its relationship with CSMA at L3. It is well-known that patients with tobacco-related cancers of the upper aero-digestive tract have a substantial risk of developing a second primary malignancy in the same region. In another study by our group, also imaging of patients who had undergone prior treatment was also used, and found that low SMM as identified at the level of C3 was associated with adverse outcomes in patients with and without prior treatment [9]. Some patients with HNC will undergo MRI instead of CT imaging. In this study we only used CT imaging, according to the protocol described by Swartz et al. [7]. Two recent studies also showed excellent correspondence between CSMA on CT imaging and MRI, and concluded that CT and MRI can be used interchangeably [27,28]. The effect of different posture and different angles (e.g. in laryngeal cancer, CT scans are often angulated to better visualize the vocal cords) was not evaluated in this study, but may influence CSMA [29]. Future research should clarify this, but we expect that this problem will be overcome by using whole-body or portion-of-body skeletal muscle volumes using artificial intelligence. Finally, inter- and intraobserver variability was not investigated in this study. A previous study showed excellent interobserver agreement for skeletal muscle mass measurements at the level of C3 [30]. Inter- and intra-observer variability is well researched in skeletal muscle mass measurements both at the level of C3 and at the level of L3; studies show excellent agreement [31,32].

Our current study confirms the previously found strong correlation between CSMA at the level of C3 and CSMA at the level of L3. This method allows for research into the predictive and prognostic effect of low SMM in HNC patients, using routinely performed imaging of the head and neck region without any additional costs or burden for the patient. It may also be used to identify patients with low SMM at high risk of adverse clinical outcomes, who may benefit from treatment adaptation or additional supportive treatment. We acknowledge that there is some uncertainty in the identification of patients with low SMM, particularly an overestimation of patients with low SMM using the current method, of which the researcher and clinician should be aware. Future research should be aimed at optimalisation of SMM assessment methods using diagnostically performed CT imaging.

Conclusion

A measurement of CSMA at the level of C3 can be used to evaluate SMM in HNC patients and allows for investigating the predictive and prognostic value of low SMM in HNC patients using routinely performed CT imaging of the head and neck area. There is reasonable accuracy in the identification of patients with low SMM based on the estimated

lumbar SMI and the actual lumbar SMI. Future research should be aimed at optimizing methods to use routinely performed imaging for body composition analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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