Original Article

Masseter muscle parameters can function as an alternative for skeletal muscle mass assessments on cross-sectional imaging at lumbar or cervical vertebral levels

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Background: Patients with head and neck cancer are at increased risk of developing low skeletal muscle mass (SMM), which is associated with adverse treatment outcomes and prognosis. Low SMM is most commonly assessed by the skeletal muscle cross sectional area (CSA) at the third lumbar vertebra (L3) or more recently the third cervical vertebra (C3). L3 is not routinely imaged and C3 may be impacted by disease or treatment. As an alternative we analyzed masseter muscle characteristics and their relationship with L3 and C3 skeletal muscle CSA and overall survival (OS).

Methods: In this single-center retrospective study, 99 patients with head and neck cancer who underwent whole body FDG-PET/CT-scans were reviewed. Of these patients, L3 CSA, C3 CSA, masseter CSA, masseter thickness, masseter volume, masseter Hounsfield Unit values, lumbar skeletal muscle index (LSMI), cervical skeletal muscle index (CSMI), and masseter skeletal muscle index (MSMI) were recorded and correlated with each other and with OS.

Results: We included 72 male and 27 female patients. The masseter muscle parameters differed significantly between sexes. The Spearman correlation coefficients for C3 CSA–Masseter volume and L3 CSA–Masseter volume were 0.639 and 0.531 (P<0.001) respectively. In multivariate analysis low MSMI was a predictor of OS (HR 2.227, P=0.009).

Conclusions: There is a moderate to strong association between the masseter muscle volume (MV) and C3 CSA and L3 CSA. MSMI predicts OS. Further research should investigate the relationship between muscle function and masseter muscle parameters and impacting factors on masseter muscle dimensions.

Keywords: Sarcopenia; head and neck cancer; skeletal muscle mass (SMM); masseter muscle; computed tomography

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common type of cancer worldwide with 890,000 new cases and 450,000 deaths in 2018 (1). About two thirds of patients present with advanced stage disease. HNSCC at this stage is associated with a poor 5-year overall survival (OS) of less than 50%. There is a need for accurate prognostic factors to tailor treatment for HNSCC patients, and sarcopenia is emerging as a novel candidate in HNSCC (2-4).

Sarcopenia is defined as the loss of skeletal muscle mass (SMM) and muscle function (5), although measurements of only SMM are often used in literature. Sarcopenia is often the result of cancer cachexia (6,7).

Patients with HNSCC are at an increased risk for cancer related cachexia and sarcopenia. This is partly due to dysphagia caused by tumor localization or its treatment and side effects thereof. Moreover, patients with HNSCC might present with underlying malnutrition caused by poor diet, tobacco use or alcohol abuse (8,9). Low SMM cancer patients treated with surgery are at risk for complications and decreased survival (10). In HNSCC, low SMM has been associated with and increased risk of surgical complications and cisplatin dose limiting toxicity and with decreased survival (11-13). Low SMM can be considered as an emerging biomarker for the clinical setting in HNSCC patients (14).

While the gold standard for total SMM assessment is full body imaging, earlier research has shown that the muscle cross-sectional area (CSA) measured on a single abdominal cross-sectional slice at the level of the third lumbar vertebra (L3) on computed tomography (CT) imaging can provide accurate estimates of patient's total SMM (15). Unfortunately, patients treated for head and neck cancers do not usually have imaging performed at this level. Therefore, a method was developed to assess SMM on a single CT slide at the level of the third cervical vertebra (C3) in head and neck cancer patients (16). However, CSA assessment at this level may be impaired by extension of primary tumor and/or lymph nodes or previous treatment. Moreover, accurate assessment is time consuming (17,18). There is a need for a reliable index muscle that is consistently present on routine imaging, is rarely impacted by disease or treatment and is quick and easy to characterize using commonly used imaging software. For this purpose, we propose the masseter muscle. The masseter muscle has been shown to be adequate in determining SMM and predicting mortality in other fields of medicine (19-21).

The purpose of this study was firstly to investigate whether masseter muscle quantity measures correlate with the CSA at C3 and L3. Secondly, the study sought to investigate the association between these masseter muscle parameters and OS.

Methods

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 17-365/C) and individual consent for this retrospective analysis was waived.

Patient and study design

We reviewed patients with newly diagnosed, pathologically proven HNSCC who underwent a whole body FDG-PET/CT-scan between 2010 and 2018 at the University Medical Center Utrecht, the Netherlands (UMCU). Indications to perform a whole body FDG-PET/CT-scan in our institute were clinical suspicion of advanced (III/IV) stage at presentation, carcinoma of unknown primary tumor, recurrent disease and second primary tumor. Patients with previous HNSCC or second primary tumor were excluded. Patient scans who were incomplete, of insufficient quality or incompatible with current imaging software were excluded from further analysis.

Patient factors with known or expected relation to HNC outcome measures or development of sarcopenia were collected: age at diagnosis, gender, histological diagnosis, comorbidities scored using the Charlson Comorbidity Index (CCI) and the ACE-27 score, tumor site and tumor staging according to the 7th edition of the UICC TNM classification system, human papillomavirus (HPV) status for oropharyngeal carcinomas, weight loss 6 months before diagnosis and treatment regimens.

Radiological assessment

Segmentation of muscle tissue at the level of C3 and L3 was manually performed using the commercially available software package SliceO-matic (Tomovision, Canada). For analysis of the CSA at the level of C3, a standard method for slide selection was used, where the first slide to show

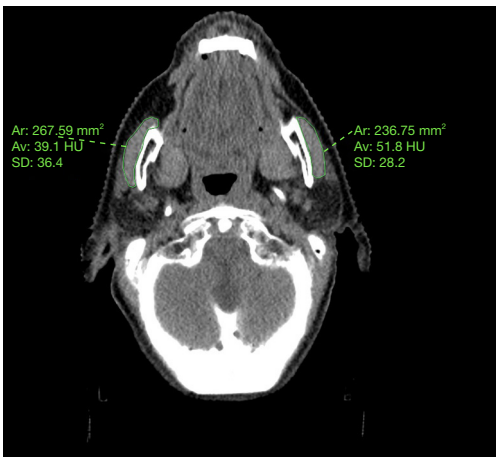

Figure 1 Example of masseter delineation using Intellispace.

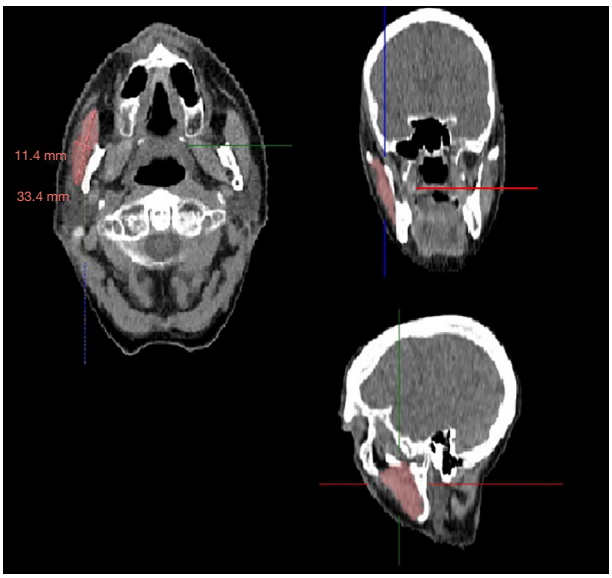

Figure 2 A 3D example of the measuring of masseter volume using the TumorTracking feature in Intellispace.

the entire vertebral arc and the transverse and spinous process when scrolling in a cephalad to caudad direction was selected. Skeletal muscle tissue was identified using Houndsfield Unit (HU) range settings from –29 to 150 HU and the outer contours of the sternocleidomastoid and paravertebral muscles were traced manually. The CSA at the level of C3 was determined as the sum of delineated areas of the paravertebral muscles and both sternocleidomastoid muscles within a HU range of –29 to 150 HU in cm^2.

For analysis of the CSA at level L3 the muscle groups analyzed were the psoas, paravertebral and the anterior abdominal wall.

For assessment of the masseter muscle, Intellispace (version 14, Phillips, Netherlands) was chosen for its ability to measure the volume of a selected structure (e.g., the masseter muscle) using the TumorTracking feature which allows for rapid tissue volume assessment. The following muscle parameters were chosen and measured: masseter cross-sectional area (MCSA), masseter muscle volume (MV), masseter muscle maximum thickness (MT). Furthermore, measurements of muscle quality defined by the Hounsfield unit (HU) and expressed as the average HU of all measured tissue (HU_{tot}) and in a region of interest (HU_{ROI}) were collected. MCSA was measured at the level of the dens of the second cervical vertebra (*Figure 1*).

Coronal tilt alignment was made according to a tangent running through the dens and hard palate. MCSA was measured by outlining the outer surface of masseter after which IntelliSpace automatically calculated the surface area (mm^2), a method independent of the HU value of the defined area. MV (cm^3) and HU_{tot} were automatically calculated after segmenting the entire muscle (*Figure 2*).

MT of the masseter was determined using the measuring-tool included in Intellispace (mm). HU_{ROI} was determined in a 1-centimeter diameter circle on the same level as MCSA.

Since the state of a patient's teeth may impact masseter function and size each patient was examined for the presence of dental elements (22). Dental status was scored as follows: [0] no missing dentition, [1] one or more missing teeth, [2] total absence of dentition.

Presence of scattering cause by (dental) implants was scored as follows: [0] no scattering present, [1] slight scattering present, [2] significant scattering present. Measurements were performed bilaterally for each patient and an average was calculated and used for further analysis.

Earlier research has shown that there is excellent agreeability between image scoring software programs used for measuring CSA (23). Therefore, we found it acceptable to use the two programs independently and compare the data.

Body composition measurements

Weight and height were recorded during a patient's first consultation at our out-patient clinic and used to calculate body mass index (BMI) and body surface area (BSA) using the Mosteller formula (24). Lumbar skeletal muscle index (LSMI), cervical skeletal muscle index (CSMI) and masseter

skeletal muscle index (MSMI) were calculated by dividing the corresponding patient's CSA values by patient's squared height. There is, to our knowledge, no scientific consensus on a cut-off point for MSMI. We therefore designated patients present in the lowest quartile of MCSA for their specific gender as "low MSMI".

Overall survival

The status of the patient (alive/deceased) was acquired from the UMCU electronic patient data system on date of last follow-up. OS was defined as the time between the date of histologic diagnosis and death, or date of last follow-up. UMCU patient system is linked to the provincial government register and is updated continuously for patients living in the Utrecht province. Patients were considered alive if no date of death was available on date of last follow-up or if there was no physician note reporting on their death. Cause of date was determined by physician's notes.

Statistical analysis

SPSS 26 for Windows (IBM, Armonk, NY, USA) was used for analysis. Descriptive statistics were calculated with the continuous variables presented as mean (standard deviation) or median (interquartile range). Discrete variables were displayed as counts (percentages). Normality was investigated by using the Kolmogorov-Smirnov test. Characteristics and muscle measurements were analyzed using independent-samples *t*-test for normally distributed variables, independent-samples test for skewed variables and Fisher's exact test or Pearson's chi-squared test for categorical variables. Spearman correlation coefficients were calculated to establish the relationship between L3 measurements, C3 measurements and masseter measurements. A correlation coefficient of (–)0.8 to (–)1 was interpreted as a very strong correlation, (–)0.6–0.8 as strong, (–)0.4 to (–)0.6 as moderate, and (–)0.2 to (–)0.4 as a low correlation (25). Radiological measurements and patient characteristics were analyzed using Cox regression proportional hazards first as univariate analysis. Variables with a P value lower than 0.05 alongside lumbar and cervical muscle cross sectional area (CSA) were included for multivariate analysis. The backward step-method was chosen for multivariate analysis. The influence of MSMI classification and low LSMI using the cut-off established by Wendrich *et al.* (11) on OS was evaluated using Kaplan-Meier curves and associated Log-Rank tests.

Results

Search and inclusion

In total 139 patients who had undergone a CT-scan were screened for study viability. Of these patients 15.2% (n=21) had (partially) missing imaging and were subsequently excluded. Furthermore, in 3.6% (n=5) of included patients the available imaging was of insufficient quality for analysis either due to low resolution or poor image quality. In total, 113 whole body FDG-PET/CT-scans were included for further image analysis.

Patient, tumor and treatment characteristics

In total 99 patients were included, with a median age of 61.69 (IQR, 56.0–68.40) years. Of the included patients, 81 (71.7) were male. A minority of patients had no history of alcohol consumption (n=32, 28.3%) or smoking (n=13, 13.1%). Forty patients (40.4%) were categorized as having normal weight based on BMI score. Most patients presented tumorous disease localized in the oropharynx (n=66, 66.7%) of which 16 (16.2%) were HPV-positive. Most patients presented with a clinical stage IV disease (n=64, 64.6%) and patients were most commonly treated with a combination of radiotherapy and systemic therapy (n=53, 46.9%).

Twenty-six patients were designated as "Low MSMI" and seventy-three as "Normal MSMI". There was a statistically significant difference between these groups for LSMI, C3 CSA, CSMI and BMI (P=0.015, 0.019 and 0.014, respectively).

See *Tables 1,2* for patient, tumor and treatment characteristics and the comparison of these characteristics between the low MSMI and normal MSMI groups.

Body composition measurement

Table 3 shows a significant difference based on sex for HU_{tot} and HU_{ROI} (both P=0.049), BSA, L3 CSA, C3 CSA, MCSA, MV, MT, L3 SMI and MSMI (all P<0.001). There was no significant difference based on sex for BMI at time of diagnosis (*Table 3*).

Masseter left-right deviations, the effect of scattering on deviations and the impact of dental status on masseter parameters

Generally, there was some amount of left-right difference present. The deviations are shown as median (percentage

Table 1 Baseline characteristics of included patients and differences between low and normal masseter muscle index

Characteristics	All patients (n=99), N (%) or mean (± SD)	Normal MSMI (n=73), N (%) or mean (± SD)	Low MSMI (n=26), N (%) or mean (± SD)	P
Median age in years (IQR)	61.77 (55.95–67.42)	61.85 (54.84–68.40)	62.26 (57.18–65.14)	NS
Male sex	72 (72.7)	53 (72.6)	19 (73.1)	NS
Deceased	48 (48.5)	30 (41.1)	18 (69.2)	NS
Alcohol intake				NS
Never	26 (26.4)	18 (24.7)	8 (30.8)	
Light consumption (≤1 U/day)	24 (24.2)	15 (20.5)	9 (34.6)	
Moderate consumption (>1 and <4 U/day)	28 (28.3)	23 (31.5)	5 (19.2)	
Heavy consumption (>4 U/day)	21 (21.2)	17 (23.3)	4 (15.4)	
Smoking status				NS
Never	13 (13.1)	13 (17.8)	0 (0)	
Currently smoking	53 (53.5)	34 (46.6)	18 (69.2)	
Former smoker	30 (33.3)	26 (35.6)	3 (11.5)	
ACE-27 categories				NS
None	18 (18.2)	13 (17.8)	5 (19.2)	
Mild	33 (33.3)	25 (34.3)	8 (30.8)	
Moderate	33 (31.3)	24 (31.5)	8 (30.8)	
Severe	17 (17.2)	13 (16.5)	5 (19.2)	
Charlson Comorbidity Index score				NS
No risk [0]	2 (2.0)	2 (2.7)	0 (0.0)	
Low risk [1–2]	42 (42.4)	30 (41.1)	12 (46.2)	
Moderate risk [3–4]	36 (36.4)	26 (35.6)	10 (38.5)	
High risk (≥5)	19 (19.2)	15 (20.5)	4 (15.4)	
Body mass index				0.014
<20 (underweight)	18 (18.2)	9 (12.3)	9 (34.6)	
20–24.9 (normal weight)	40 (40.4)	28 (38.4)	12 (46.2)	
25–29.9 (overweight)	32 (32.3)	27 (37.0)	5 (19.2)	
>30 (obese)	9 (9.1)	9 (12.3)	0 (0.0)	
Body surface area	3.71 (±0.90)	3.82 (±0.93)	3.39 (±0.84)	0.043
C3 CSA	38.46 (±8.53)	39.74 (±7.83)	34.89 (±8.35)	0.019
L3 CSA	140.50 (±30.77)	143.84 (±30.45)	131.11 (±30.30)	NS
LSMI	45.18 (±8.21)	46.48 (±7.90)	41.51(±8.17)	0.015
CSMI	12.40 (±2.34)	12.86 (±2.13)	11.09 (±2.45)	0.001

Comparison of patient characteristics based on MSMI classification. P values >0.05 are shown as non-significant (NS). MSMI, masseter skeletal muscle index; ACE-27, adult co-morbidity evaluation 27; C3 CSA, cervical muscle cross sectional area; L3 CSA, lumbar muscle cross sectional area; LSMI, lumbar skeletal muscle index; CSMI, cervical skeletal muscle index.

Table 2 Tumor and treatment characteristics of included patients based on low and normal masseter muscle index

Tumor characteristics	All patients (n=99), N (%) or mean (±SD)	Normal MSMI (n=73), N (%) or mean (±SD)	Low MSMI (n=26), N (%) or mean (±SD)	P
Localisation				NS
Oral cavity	6 (6.1)	3 (4.1)	3 (11.5)	
Oropharynx	66 (66.7)	50 (68.5)	16 (61.5)	
Nasofarynx	3 (3.0)	2 (2.7)	1 (3.8)	
Hypopharynx	17 (17.2)	12 (16.4)	5 (19.2)	
Larynx	6 (6.1)	5 (6.8)	1 (3.8)	
Lymph node	1 (1.0)	1 (1.4)	1 (3.8)	
HPV-status				NS
Negative	60 (60.6)	43 (58.9)	17 (65.4)	
Positive (all oropharynx)	16 (16.2)	15 (20.5)	1 (3.8)	
Not recorded	23 (23.2)	15 (20.5)	8 (30.8)	
T-staging				NS
T0	1 (0.9)	1 (1.4)	0 (0.0)	
T1	18 (18.2)	14 (19.2)	4 (15.4)	
T2	32 (32.3)	25 (34.2)	7 (26.9)	
T3	22 (22.2)	15 (20.5)	7 (26.9)	
T4a,b	26 (26.2)	18 (24.7)	8 (30.8)	
N-staging				NS
N0	36 (36.4)	27 (37.0)	9 (34.6)	
N1	17 (17.2)	12 (16.4)	5 (19.2)	
N2a,b,c	45 (45.5)	33 (45.1)	12 (46.2)	
N3	1 (1.0)	1 (1.4)	0 (0.0)	
M-staging				
M0	92 (92.9)	69 (94.5)	23 (88.5)	NS
M1	2 (2.0)	2 (2.7)	0 (0.0)	
Mx	5 (5.1)	2 (2.7)	3 (11.5)	
Clinical staging				NS
Stage I	3 (3.0)	2 (2.7)	1 (3.48	
Stage II	14 (14.1)	15 (15.1)	3 (11.5)	
Stage III	18 (18.2)	14 (19.2)	4 (15.4)	
Stage IV	64 (64.6)	46 (63.0)	18 (69.2)	
Treatment characteristics				NS
Treatment modality				
Surgery with or without (chemo)radiotherapy	26 (26.2)	21 (28.8)	5 (19.2)	
Radiotherapy	25 (25.3)	18 (24.7)	7 (26.9)	
Radiotherapy with concurrent cisplatin, carboplatin or cetuximab	48 (48.5)	34 (46.6)	14 (53.2)	

Comparison of tumor and treatment characteristics based on MSMI classification. Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). MSMI, masseter skeletal muscle index; HPV, human papillomavirus.

Table 3 Body composition measurements per sex

Characteristic	Total (n=99)	Male (n=72)	Female (n=27)	P
BMI at diagnosis*	24.38 (21.52–26.72) [14.9–40.1]	24.65 (22.08–26.86) [14.90–38.40]	22.05 (18.65–26.18) [15.8–40.1]	NS
BSA at diagnosis	3.71 (0.90) [2.01–6.54]	3.94 (0.82) [2.56–6.54]	3.10 (0.82) [2.01–5.77)	<0.001
L3 CSA (cm^2)	140.50 (30.77) [65.32–234.95]	149.71 (28.52) [81.84–234.95]	111.93 (22.02) [65.32–158.49]	<0.001
C3 CSA (cm^2)	38.46 (8.21) [19.02–58.82]	41.22 (7.31) [25.90–58.82]	31.11 (5.59) [19.02–44.72)	<0.001
MCSA (mm^2)	397.72 (85.28) [234.12–624.35]	418.71 (84.89) [243.02–624.35]	341.75 (57.09) [234.12–509.07]	<0.001
MV (cm^3)	18.39 (5.46) [9.03–36.07]	19.78 (5.21) [9.57–36.07]	14.71 (4.32) [9.03–28.69]	<0.001
MT (mm)	13.09 (2.71) [8.80–22.00]	14.39 (2.93) [8.80-22.00]	12.11 (1.89) [9.70–16.10]	<0.001
HU_{tot} *	110.20 (92.30–129.40) [59.50–474.0]	112.40 (96.53–132.18) [68.10–192.26]	99.00 (86.60–127.59) [59.50–474.0)	0.049
HU_{ROI} (HU)*	55.80 (47.40–64.70) [22.00–310.55]	57.05 (48.09–65.48) [58.10–192.26]	51.45 (45.90–58.70) [22.0–83.15]	0.049
LSMI (cm^2/m^2)	45.18 (8.23) [23.70–65.08]	46.94 (8.02) [27.42–65.08]	40.46 (6.92) [23.70–52.15)	<0.001
MSMI (mm^2/m^2)	128.27 (24.60) [75.43–189.27]	131.71 (26.52) [75.43–189.27]	119.10 (15.48) [80.07–145.65]	<0.001

Comparison of body composition measurements between sexes. P values >0.05 are shown as non-significant (NS). Variables noted by an asterix are displayed in the following format: median (IQR) [range]. Unnoted variables are displayed in the following format: mean (SD) [range]. BMI, body mass index; BSA, body surface area; L3 CSA, lumbar muscle cross sectional area; C3 CSA, cervical muscle cross sectional area; MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness, HU_{tot}, the total HU-value of the measured tissue; HU_{ROI}, the HU value of a 1 cm diameter circle in the measured tissue; LSMI, lumbar skeletal muscle index; MSMI, masseter skeletal muscle index.

Table 4 Masseter muscle parameters left-right deviation

Measurement	Total
MCSA (mm^2)	36.48 (9.17%)
MV (cm^3)	1.04 (5.76%)
MT (mm)	1.00 (7.26%)
HU_{tot}	4.80 (4.15%)
HU_{ROI}	9.40 (16.80%)

Illustration of the deviation between the left and right-sided masseter parameters in individual patients. All variables are shown as median values (% of average masseter parameter). MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness; HU_{tot}, the total HU-value of the measured tissue; $HU_{ROI,}$ the HU value of a 1cm diameter circle in the measured tissue.

of average masseter characteristic). The median left-right difference for MCSA, MV, MT, HU_{tot} and HU_{ROI} were 36.48 mm^2 (9.17%), 1.04 cm^3 (5.76%), 1.0 mm (7.26%), 4.80 HU (4.15%) and 9.40 HU (16.80%) respectively (*Table 4*). There was a significant difference in left-right deviation of median MV and HU_{tot} for different scattering scores (P<0.001; *Table 5*). MV and HU_{tot} had a significant negative relationship with dental score (P=0.011 and 0.001, respectively; *Table 6*).

Correlation between masseter parameters and muscle mass measured at C3 and L3

All masseter and muscle mass parameters had a highly significant correlation with each other (P=0.001 to P<0.001). The strongest correlation was between L3 CSA - C3 CSA (r=0.708), followed by C3 CSA–MV (r=0.639) and L3 CSA–MV (r=0.586). MT was moderately correlated to C3 CSA (r=0.509) and L3 CSA (r=0.431) and had low correlation with LSMI (r=0.361). MCSA had low to moderate correlation with L3 CSA and C3 CSA (r=0.451, 0.586). MSMI had a low correlation with LSMI and L3 CSA (r=0.278, r=0.215), but a moderate correlation with C3 CSA, r=0.415, *Table 7*).

Univariable Cox regression analysis of the effect of body composition indicators on OS

A selection of body composition indicators were tested using Cox univariate regression analysis. In univariate analysis, MCSA, low MSMI classification and CCI were all significantly associated with OS (*Table 8*). For variables that

Table 5 Effect of scattering on masseter left-right deviation

Measurement	Scatter score 0 (n=32)	Scatter score 1 (n=39)	Scatter score 2 (n=28)	P
MCSA (mm^2)	37.78 (17.07–37.78) [0.78–117.42]	37.32 (17.76–65.54) [0.00–158.55]	29.91 (15.00–54.79) [3.82–184.62]	NS
MV (cm^3)	1.45 (0.83–2.42) [0.02–5.31]	0.56 (0.24–1.73) [0.02–5.41]	1.51 (0.83–2.30) [0.05–4.25]	0.011
MT (mm)	0.85 (0.50–2.03) [0.00–8.00]	1.20 (0.50–2.00) [0.00–6.10]	1.00 (0.43–1.88) [0.10–3.20]	NS
HU_{tot}	2.85 (1.10–4.25) [0.0–25.50]	5.40 (2.40–8.80) [0.30–374.00]	8.85 (4.33–16.48) [0.50–26.60]	0.001
HU_{ROI}	8.65 (4.28–15.75) [0.10–38.98]	7.30 (4.40–17.00) [1.00–58.60]	13.00 (3.53–20.38) [0.30–548.90]	NS

Effect of scattering on deviations in masseter assessment. Scatter score is defined as follows: 0 = no scattering present, 1 = slight scattering present, 2 = significant scattering present. Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). All variables are shown as median (IQR) [range]. MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness; HU_{tot}, the total HU-value of the measured tissue; HU_{ROI}, the HU value of a 1 cm diameter circle in the measured tissue.

Table 6 Effect of dental status on masseter measurements

Measurement	Dental score, 0 (n=77)	Dental score, 1 (n=16)	Dental score, 2 (n=20)	P
MCSA* (mm^2)	403.71 (88.68)	380.04 (71.90)	375.30 (73.73)	NS
MV* (cm^3)	19.17 (5.90)	16.68 (4.90)	15.57 (2.84)	0.017
MT (mm)	12.75 (10.98–15.45)	13.05 (10.45–15.13)	12.10 (10.41–13.78)	NS
HU_{tot}	115.60 (98.15–133.15)	108.55 (96.3–116.35)	95.85 (83.78–112.08)	0.010
HU_{ROI}	56.85 (48.85–65.83)	56.05 (47.73–61.34)	53.03 (47.33–60.58)	NS

Effect of dental status on masseter parameters. Dental score is defined as follows: Dental status was scored as follows: 0= no missing dentition, 1= one or more missing teeth, 2= total absence of dentition. Variables noted by an asterisk are shown as mean (SD), unnoted variables are shown as median (IQR). Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness; HU_{tot}, the total HU-value of the measured tissue; HU_{ROI}, the HU value of a 1 cm diameter circle in the measured tissue.

were strongly correlated or dependent on each other (e.g., MSMI, low MSMI and MCSA) the variable with the lowest P value was included in the multivariate analysis. As to not exceed the >10 events per variable rule four variables were included (26). This left MSMI-classification, C3 CSA, LSMI and CCI as included variables. Low MSMI and CCI score remained as the only independent predictors of OS (HR 2.227, P=0.009 and HR 1.338, P<0.001, respectively; *Table 9*).

Overall survival

There was a significant difference in OS for patients with low MSMI compared to normal MSMI [17.92 months (IQR, 11.64–57.09) versus 34.10 months (IQR, 15.54–62.03) log rank P=0.015; *Figure 3*]. There was no significant difference in OS between patients with low and normal LSMI using the previously established cut-off value of LSMI <43.2 cm^2/m^2 (*Figure 4*) (11).

Discussion

Patients with head and neck cancers are at an increased risk of sarcopenia compared to patients with other types of cancer (8,9,27). Previous reports have established that measuring muscle mass at level L3 on CT-scans is a reliable method for assessing total body SMM. Unfortunately, scans at this lumbar level are rarely available in patients with HNSCC. Previously published findings by Swartz *et al.* (16) show that the CSA of skeletal muscles at level C3 strongly correlate with the CSA of skeletal muscle at level L3, indicating that this is a viable alternative method. However, determining the CSA at C3 is time consuming and can be impacted by either treatment (e.g., neck dissection) or disease (e.g., invading lymph node in the SCM). We therefore investigated to what degree masseter muscle parameters are associated with levels L3 and C3, and their relationship on OS. We found moderate to strong

Table 7 Spearman correlation coefficients of the different skeletal mass measurements

Relation	Correlation coefficient	P
LSMI-MSMI	0.278	<0.001
LSMI-MCSA	0.350	<0.001
LSMI-MV	0.446	<0.001
LSMI-MT	0.361	<0.001
L3 CSA-MSMI	0.215	<0.001
L3 CSA-MCSA	0.451	<0.001
L3 CSA-MV	0.531	<0.001
L3 CSA-MT	0.431	<0.001
C3 CSA-MSMI	0.415	<0.001
C3 CSA-MCSA	0.586	<0.001
C3 CSA-MV	0.639	<0.001
C3 CSA-MT	0.509	<0.001
L3 CSA-C3 CSA	0.708	<0.001

Correlation between different masseter parameters, lumbar skeletal muscle index, cross-sectional area at level L3 and cross-sectional area at level C3 are shown. Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). LSMI, lumbar skeletal muscle index; MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness; MSMI, masseter skeletal muscle index; HU_{tot}, the total HU-value of the measured tissue; HU_{ROI}, the HU value of a 1 cm diameter circle in the measured tissue; L3 CSA, lumbar muscle cross sectional area; C3 CSA, cervical muscle cross sectional area.

Table 8 Univariable Cox regression analysis of the effect of risk factors and different radiological muscle measurements on overall survival

Risk factor	HR	95 CI	P
MCSA	0.996	0.992–1.000	0.03
MV	0.953	0.900–1.008	NS
MT	0.945	0.855–1.045	NS
HU_{tot}	0.995	0.987–1.004	NS
HU_{ROI}	0.996	0.982–1.010	NS
Low MSMI classification	2.052	1.141–3.692	0.014
Low LSMI classification	0.971	0.937–1.007	NS
L3 CSA	0.993	0.983–1.002	NS
C3 CSA	0.975	0.939–1.013	NS
Body mass index	0.953	0.895–1.014	NS
Body surface area	0.789	0.559–1.113	NS
Charlson Comorbidity Index	1.260	1.147–1.426	<0.001

Univariate analysis of factors associated with overall survival. Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). LSMI, lumbar skeletal muscle index; CSMI, cervical skeletal muscle index; MCSA, masseter cross sectional area; MV, masseter volume; MT, masseter maximum thickness; MSMI, masseter skeletal muscle index; HU_{tot}, the total HU-value of the measured tissue; HU_{ROI}, HU value of a 1 cm diameter circle in the measured tissue; L3 CSA, lumbar muscle cross sectional area; C3 CSA, cervical muscle cross sectional area.

Table 9 Multivariable Cox regression analysis of the effect of risk factors and radiological muscle measurements on survival

Risk factor	HR	95% CI	P
Charlson Comorbidity Index	1.338	1.158–1.532	<0.001
Low MSMI classification	2.227	1.227–4.004	0.009
Low LSMI classification	0.89	0.994–1.003	NS
C3 CSA	1.002	0.955–1.052	NS

Multivariate analysis of factors associated with overall survival. Statistically significant relationships are highlighted in bold. P values >0.05 are shown as non-significant (NS). MCSA, masseter cross-sectional area, MSMI, masseter skeletal muscle index, LSMI, lumbar skeletal muscle index, C3 CSA, cervical muscle cross sectional area.

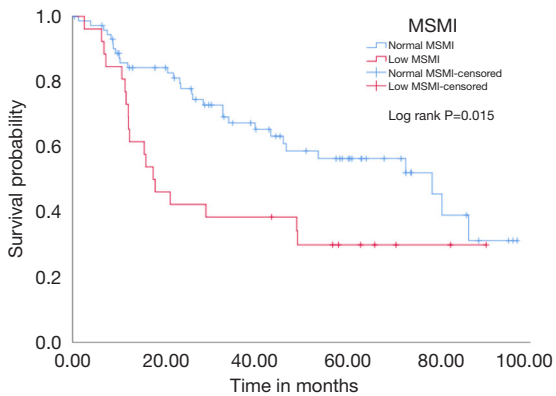

Figure 3 Kaplan-Meier curve displaying differences in survival probability based on MSMI classification. MSMI, masseter skeletal muscle index.

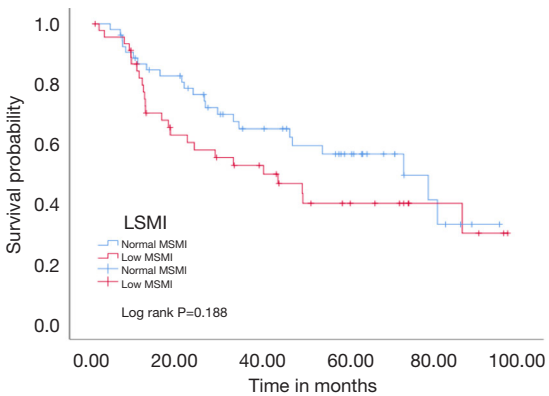

Figure 4 Kaplan-Meier curve displaying differences in survival probability based on LSMI classification using the pre-defined cut-off of 43.2 cm^2. LSMI, lumbar skeletal muscle index.

associations for most masseter parameters with muscle mass on level L3 and C3, with MV being the strongest followed by MCSA. Low MSMI was shown to be an independent predictor for OS in multivariate analysis.

We found that the scatter-score had a significant impact on MV and Masseter HU measurements. It stands to reason that scattering results in unreliable masseter HU-measurements, as scattering generally causes a larger spread of pixel values shown on imaging. The method we used to determine MV used the TumorTracking feature included in IntelliSpace which utilizes the pixel values recorded and inputs them into an algorithm to determine whether certain areas are related to each other. It follows that a larger spread in pixel-values decreases the reliability of the algorithm. Manual adjustment of the measured area was often required to fully include all masseter muscle tissue, although this too becomes unreliable when significant scattering is present. However, we found no significant relationship between scatter-score and MT, HU_{ROI} and MCSA (and subsequently MSMI) leaving these as viable options when significant scattering is present. Our included patient group had 3 (4.1%) patients with tumors in the oral cavity. These tumors were always unilateral with no significant ingrowth into the masseter muscle. Consequently, they did not significantly impact the masseter muscles. If significant impairment would be present, one solution could be that in the rare cases where the muscle is unilaterally significantly affected, a contralateral masseter measurement is counted twice.

Our findings are consistent with other studies which determine that MCSA predicts mortality in patients suffering from blunt trauma, traumatic brain injury or survival after carotid endarterectomy (19-21). However, differences between our study and earlier scientific reports should be noted. Oksala *et al.*, Wallace *et al.* and Hu *et al.* all used the MCSA measured at 2 cm below the arcus zygomaticus. In our study we chose the first slice showing the dens of the C2 vertebra as our landmark as this was easily identifiable when scrolling in cephalad-to-caudad

fashion. Secondly, whereas Wallace *et al.* and Hu *et al.* did not correct for head tilt, Oksala *et al.* adjusted their CT-scans for both sagittal and coronal head tilt. Based on a consensus discussion we chose to only adjust for coronal head tilt. Using our center's patient positioning protocol, we expected very little to no sagittal tilt in our imaging.

We corrected the observed MCSA by dividing by squared body height to determine a masseter muscle mass index (MSMI). The masseter muscle characteristics are dependent on various factors such as dental status and craniofacial structure (22,28). MCSA was adjusted by body height, as it has been established that muscle mass corrected by body height is an accurate adjustment method for other CSA measurements (29). We found a significant difference in muscle mass and body composition indicators for groups based on MSMI. Furthermore, we found a significant difference in OS between patients classified as normal or low MSMI classification (P=0.015). In multivariate analysis low MSMI classification significantly predicted OS.

Another limitation of our retrospective design is that patient frailty and sarcopenia as defined by the European Working Group on Sarcopenia in Older People (EWGSOP) could not be assessed. Sarcopenia is diagnosed by evaluating muscle mass, muscle quality, muscle strength and physical performance (6). Further prospective studies are needed that correlate masseter findings with muscle strength (e.g., by grip strength) and physical performance (e.g., by the Short Physical Performance Battery and the Timed Up and Go-test).

Finally, whole-body PET-CT-scans are only performed in patients with clinical suspicion of advanced (III/IV) stage at presentation. We reason that this does not cause any significant bias in our study as Swartz *et al.* found no significant difference in C3 or L3 CSA between patients with traumatic injury and head and neck cancer allowing for extrapolation to both healthy patients and patients with malignant disease (14).

Conclusions

We conclude that several masseter muscle parameters, namely MV, MCSA and MT, are significantly correlated (varying from moderate to strong) with cross-sectional muscle area at cervical and lumbar level. Additionally, MSMI, defined as MCSA divided by the squared patient's length in meters, proved to be an independent predictor for overall survival (HR 2.227), with other covariates for survival being: Low MSI-classification, C3 CSA, L3 CSA and CCI. Patients classified as having low MSMI had significantly decreased overall survival. In patients without cross-sectional imaging at level L3 or C3 or with impaired C3 measurements, masseter muscle parameters could serve as a (swifter assessable) alternative for SMM assessed by cross-sectional muscle area measurements at these vertebral levels. We recommend further studies to determine factors influencing masseter parameters as to formulate an improved method to correct for individual patient factors, e.g., dental status, previous dental disease, previous cancer treatment and facial morphologic features. Subsequently this research should correlate masseter parameters with muscle strength and physical performance.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-43). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 17-365/C) and individual consent for this retrospective analysis was waived.

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