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Scientific article

Sarcopenia as a Predictor of Feeding Tube Placement in Individuals with Oropharyngeal Cancer

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Purpose: In oropharyngeal squamous cell carcinoma (OPSCC), systemic loss of skeletal muscle mass (SMM), or sarcopenia, is a strong prognostic predictor of survival outcomes. However, the relationship between sarcopenia and nutrition-related outcomes is not well understood. This investigation evaluated the prognostic significance of sarcopenia for feeding tube (FT) placement in a cohort of OPSCC patients.

Methods and Materials: A retrospective cohort study was conducted with data collected from 194 OPSCC patients treated with definitive radiation therapy (RT) or chemoradiation therapy (CRT). Sarcopenia was assessed from computed tomography imaging at the level of the third cervical (C3) and fourth thoracic (T4) vertebrae. The prognostic nature of pretreatment sarcopenia and its relationship with FT placement was explored using logistic regression.

Results: The median age of patients included was 61.0 years, and the majority were male (83%). In this patient cohort, 87.6% underwent concurrent CRT, and 30.9% received a FT over the course of treatment. Sarcopenia was identified at baseline in 72.7% of patients based on C3 SMM measurements and in 41.7% based on measures at the level of T4. Based on measures at both C3 and T4, those with sarcopenia were significantly more likely to receive a FT and had significantly worse freedom from FT placement compared with patients without sarcopenia. Sarcopenia assessed at T4 was a significant predictor of FT placement.

Conclusions: SMM measured at T4 may represent a novel and practical biomarker for sarcopenia detection that is associated with the need for FT placement. These findings suggest that the detection of baseline sarcopenia could guide decision-making related to the need for nutritional support in OPSCC patients undergoing RT/CRT.

Introduction

Despite substantial improvements in the treatment of oropharyngeal squamous cell carcinoma (OPSCC), organ-sparing approaches such as radiation therapy (RT) or chemoradiation therapy (CRT) are associated with

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myriad toxicities, some of which can be severe.[1] Consequently, individuals treated for OPSCC generally have higher rates of dysphagia compared with other head and neck subsites[2] and often experience difficulty maintaining adequate levels of dietary intake and nutrition.[3,4] Consequently, patients undergoing treatment for OPSCC are also at high risk for significant weight loss[5] and malnutrition.[6] Because significant weight loss and malnutrition are well-established prognostic indicators for overall survival in this patient population,[7,8] efforts to mitigate such nutritional changes are of great importance to individual outcomes. To address these concerns, patients often receive enteral feeding to optimize caloric intake with the goal of preventing weight loss.[9] Prior studies indicate that feeding tube (FT) placement occurs in 33% to 62% of individuals undergoing treatment for OPSCC.[10,11] Moreover, a considerable proportion of these patients become dependent on FTs to sustain adequate levels of dietary intake and limit weight loss both during and after treatment.[12] Nevertheless, no universally accepted protocol currently exists to guide the decision-making process for recommending a FT.[13,14]

Despite the lack of consensus on guidelines for FT placement, baseline parameters that are easily ascertainable and have predictive value can facilitate informed decision-making. For example, significant pretreatment weight loss and low body mass index (BMI) are important factors to consider when determining the need for nutritional support.[15] One variable that has demonstrated potential prognostic utility is *sarcopenia*. Sarcopenia is defined as "a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality."[16] In head and neck cancer (HNC), sarcopenia assessed at baseline with computed tomography (CT) imaging is associated with an increased risk of prolonged hospital stay and FT dependency, poor locoregional disease control, and increased rates of postoperative complications.[17-19] The association between sarcopenia and survival is well-established; OPSCC patients with sarcopenia have significantly poorer survival,[20-22] highlighting the relevance of investigating sarcopenia as a prognostic factor in this population.

To date little research has investigated the prognostic significance of sarcopenia with respect to functional outcomes. An improved understanding of the potential association between pretreatment sarcopenia and functional outcomes, including FT placement, may facilitate improved risk stratification of OPSCC patients before treatment and result in provision of early, targeted interventions. Moreover, because investigation of sarcopenia in HNC is emerging, methods employed in sarcopenia measurement should be further explored and refined. Therefore, the objectives of the current study were to: (1) determine the prognostic significance of sarcopenia with respect to FT-placement and (2) explore varied measurement methods for the assessment of sarcopenia.

Methods and Materials

Participants

A retrospective chart review was conducted to identify patients who received diagnoses of OPSCC and were treated with definitive RT or CRT at a tertiary care center between January 2013 and October 2017. Adult patients who received diagnoses of primary OPSCC and underwent RT/CRT were included in this study. Patients were excluded based on the following conditions: (1) primary surgical treatment or surgery within 12 months after RT/CRT, (2) noncurative treatment intent or distant tumor metastasis leading to a change in treatment strategy, (3) FT in situ before multidisciplinary team (MDT) meeting, and/or (4) absence of CT imaging at the vertebral levels of interest.

Data collection

Patient demographics and treatment characteristics including age, sex, height, weight, tumor-node-metastasis (TNM) stage, treatment type (RT or CRT), OPSCC subsite, p16 status (as a surrogate biomarker of human papilloma virus [HPV] status), radiation dose, chemotherapeutic agents/regimen, comorbidities, date of death or last follow-up, and cause of death (if applicable) were collected from the electronic medical records of consecutive eligible patients. Data were collected for variables to be used as primary outcome measures, including FT placement (yes vs no), Performance Status Scale for Head and Neck Cancer (PSS-HN) normalcy of diet scores, and M.D. Anderson Dysphagia Inventory (MDADI) composite scores. Skeletal muscle mass (SMM) measurement was completed by the research team using baseline (ie, pretreatment) CT imaging. To investigate between-group differences at baseline with respect to demographic, treatment, and outcome variables, patients were classified based on FT placement: (1) OPSCC patients who received a FT associated with their treatment and/or condition (FT group) and (2) OPSCC patients who did not receive a FT within the first year of treatment (NFT group). Patients were also stratified based on sarcopenia status (present vs absent) using statistically derived optimal cut-off values.

For those who received a FT over the course of treatment, information was collected about the type of enteral FT and timing of placement (ie, time from the first MDT consultation to FT placement). Our institution uses both proactive and reactive FT placement approaches, with a proactive FT recommendation at treatment outset for

patients deemed "at risk" for substantial weight loss. Patients without specific risk indicators are recommended to take nutrition by mouth as tolerated, with a reactive FT approach. In our clinic, the indication for a proactive FT is based on the overall judgment of the multidisciplinary team, weighing a number of different factors. More specifically, proactive FT placement was generally recommended to patients who initially presented with one or more of the following: significant weight loss (>5% in 1 month or >10% over 6 months),low BMI (< 18), undergoing concurrent CRT, or any symptoms that interfere with the ability to eat such as dysphagia, anorexia, dehydration, and/or pain.[23] Reactive FT placement occurred for patients demonstrating continued and excessive weight loss and declining oral intake throughout treatment, often with a threshold of 10% weight loss from baseline used to consider FT placement.

Measurement of skeletal muscle mass

The third cervical (C3) and fourth thoracic (T4) vertebral levels served as points of reference on head and neck CT scans for the quantification of SMM and assessment of sarcopenia. These 2 landmarks were selected due to strong correlations with full-body SMM[24,25] and documented prognostic value at these landmarks in HNC.[26] To determine a consistent anatomic location for measurement of SMM across patients at the level of C3, one investigator (NJ) reviewed axial CT scan slices in a caudal-to-cephalad direction through the C3 vertebra (as per methods described by Schwartz and colleagues[25]). The first caudal CT slice displaying the entire vertebral arc in addition to the transverse and spinous processes was selected for muscle contouring.

Measurement of SMM first required manual delineation of the right sternocleidomastoid muscle, left sternocleidomastoid muscle, and paravertebral muscles (Fig. 1). Second, the cross-sectional area of the delineated musculature at C3 was automatically retrieved as the total sum of pixels of the 3 muscles within the standard HU ranges from -29 to +150, corresponding with skeletal muscle density.[27] Finally, cross-sectional area measurements were mathematically adjusted for the squared height of each patient (m^2), resulting in a measure known as skeletal muscle index (SMI) (cm^2/m^2). These procedures were performed using delineation software MIM (MIM Software Incorporated, version 7.0.5, Beachwood, Ohio).

The process used for measuring SMM on an axial CT slice at the T4 vertebral level was similar to the procedure for C3 slice selection, albeit with contouring of different musculature. The musculature delineated at T4 included the right pectoralis minor and major muscles, the left pectoralis minor and major muscles, and the 'back muscles' (ie, the combined bilateral muscles of the erector spinae, levator scapulae, rhomboideus minor and major, and transversospinalis groups) (Fig. 1). One main observer (NJ) completed all skeletal muscle analyses. To evaluate interobserver and intraobserver reliability, 20 patients were randomly selected, and both C3 SMI and T4 SMI were derived again by the main observer (approximately 3 months from initial assessment) and a second experienced observer (SM) using explicit predefined procedural guidelines.

Statistical analysis

Descriptive statistics were generated to provide measures of central tendency for all outcome variables. Bivariate associations were compared using the Pearson's χ^2 test, Fisher's exact test, independent 2-sample *t* test, or Wilcoxon rank sum test, as appropriate. Outcome variables were analyzed to determine normality of distribution and to guide the selection of appropriate statistical tests. Statistical analyses were performed using 2-tailed testing at the a priori probability level of 0.05 to reflect a 95% confidence interval (CI). All statistical analyses were completed using SAS Analytics Software (SAS Institute, Version 9.4, Cary, North Carolina).

For reliability analyses, agreement between measurements was analyzed by calculating intraclass correlation coefficients (ICCs) using a 2-way mixed single measures model with absolute agreement. ICC estimates were rated as poor (< 0.5), moderate (0.5 − 0.75), good (0.75 − 0.9), and excellent (>0.9).[28] A logistic regression analysis was performed separately for both C3 SMI and T4 SMI to determine whether SMM could predict FT placement in OPSCC patients undergoing RT/CRT. Univariable logistic regression analyses were performed with FT placement as the dependent variable and age, sex, treatment, BMI, and SMI (for both C3 and T4) as independent/predictor variables for both analyses. Variables that yielded statistically significant results in the univariable regression ($P < .25$) were included in the multivariable regression model.[29] Assumptions of regression modeling including multicollinearity, homoscedasticity, and distribution of residuals were confirmed before analysis.

Freedom from FT placement was defined as the time from the first MDT consultation to FT placement or last follow-up, whichever occurred first, and was assessed using Kaplan-Meier estimates and compared by sarcopenia status (yes vs no) using the log-rank test. To identify patients with sarcopenia, an optimal SMI cut-off value based on FT placement was determined for both C3 SMI and T4 SMI using a Receiver Operator Characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, and specificity of the cut-off value were provided and an AUC of ≥ 0.70 was considered adequate for assessing the diagnostic capability of SMI.[30] Finally, the Youden index, also referred to as Youden's J statistic for

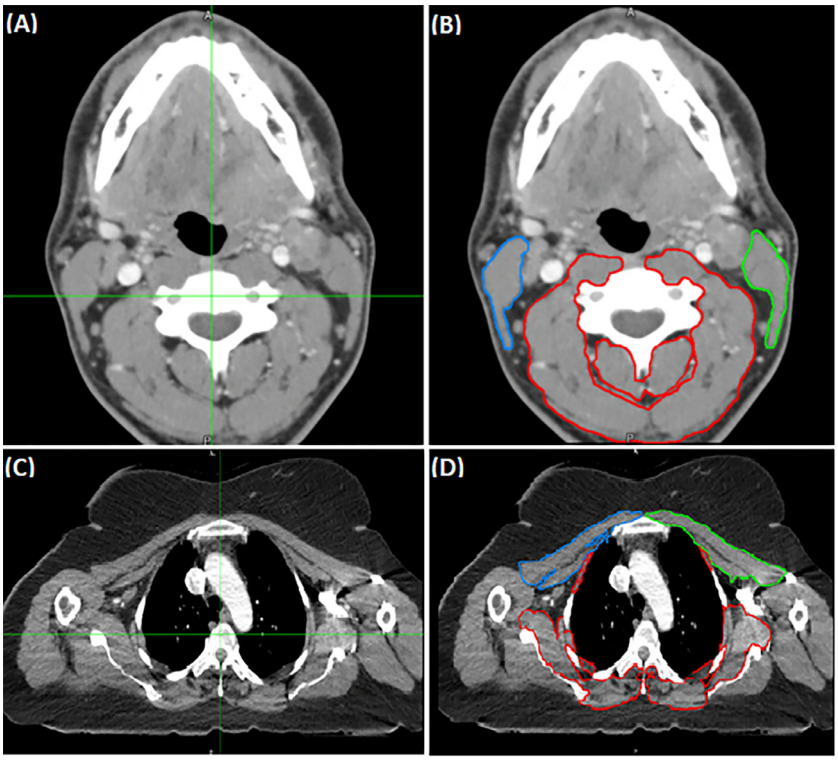

Figure 1 Axial CT-slice at the levels of C3 and T4. (A) standard CT-slice at the C3 level, (B) delineated/contoured CT-slice at the C3 level (red: paravertebral muscles; blue: right sternocleidomastoid muscle; green: left sternocleidomastoid muscle), (C) standard CT-slice at the T4 level, (D) delineated/contoured CT-slice at the T4 level (red: back muscles; blue: right pectoralis muscle; green: left pectoralis muscle).

dichotomous data, was used to determine the optimal C3 and T4 SMI cut-off value.[31]

Results

Baseline patient and treatment characteristics

Initial review of the medical records of 1729 consecutive patients who presented to the Head and Neck MDT between January 2013 and October 2017 identified 194 patients who met the inclusion/exclusion criteria. The median age of patients was 61.0 years (interquartile range [IQR]: 55 − 67), and the majority were male (n = 161; 83.0%). All patients received intensity modulated radiation therapy (IMRT) with 170 (87.6%) undergoing concurrent CRT treatment. Among all patients, T2 tumor staging was the most prevalent (n = 84; 43.3%). Comparing T-stage within the FT and NFT groups, most patients who required a FT had T4 tumor staging, whereas T2 tumor staging was most prevalent in the NFT group. The most common nodal stage was N2 (n = 133; 68.6%), both overall and within each group.

Within this patient cohort of 194 patients, 60 (30.9%) received an enteral FT [gastrojejunostomy (n = 48), gastrostomy (n = 9), or nasogastric (n = 3)]. The median timing of placement occurred at 47 days (range, 1-192) from the date of the first MDT consultation. Additional information on demographics, tumor characteristics, and treatment type is summarized in Table 1.

Reliability analysis

For interobserver reliability, ICCs for both C3 SMI (ICC: 0.987, 95% CI, 0.950-0.997, $P < .001$) and T4 SMI (ICC: 0.983, 95% CI, 0.935-0.996, $P < .001$) measurements demonstrated excellent reliability. ICCs for intraobserver reliability also were excellent for C3 SMI (ICC: 0.989, 95% CI, 0.967-0.995, $P < .001$) and T4 SMI (ICC: 0.980, 95% CI, 0.955-0.997, $P < .001$).

Baseline skeletal muscle mass

Patients who received a FT had significantly lower C3 SMI (mean ± standard deviation [SD]: 13.3 ± 2.3 vs 15.0 ± 3.3, $P < .001$), T4 SMI (mean ± SD: 45.1 ± 11.5 vs 53.8 ± 13.3, $P < .001$), BMI (mean ± SD: 25.0 ± 4.9 vs 27.9 ± 5.2, $P < .001$), PSS-HN normalcy of diet (mean ± SD: 71.8 ± 27.8 vs 82.0 ± 23.8, $P = .030$), and MDADI

Table 1 Pretreatment patient demographics and disease characteristics classified by FT status

Variable	All patients	FT group	NFT group	*P* value*
No. of patients	194	60	134	
Age in years:				
Median (IQR)	61 (55-67)	63 (56-67)	60 (53-67)	0.284‖
Sex: male, n (%)	161 (83.0)	47 (78.3)	114 (85.1)	0.248†
T classification, n (%)				<0.001†
T1	33 (17.0)	8 (13.3)	25 (18.7)	
T2	84 (43.3)	19 (31.7)	65 (48.5)	
T3	40 (20.6)	10 (16.7)	30 (22.4)	
T4	37 (19.1)	23 (38.3)	14 (10.4)	
N classification, n (%)				0.861†
N0	22 (11.3)	6 (10.0)	16 (11.9)	
N1	24 (12.4)	7 (11.7)	17 (12.7)	
N2a, N2b, N2c	133 (68.6)	41 (68.3)	92 (68.7)	
N3	15 (7.7)	6 (10.0)	9 (6.7)	
Treatment, n (%)				0.048†
RT	23 (11.9)	3 (5.0)	20 (14.9)	
CRT	170 (87.6)	56 (93.3)	114 (85.1)	
Tumor subsite, n (%)				0.006‡
Tonsil	98 (50.5)	22 (36.7)	76 (56.7)	
BOT	78 (40.2)	29 (48.3)	49 (36.6)	
Soft palate	3 (1.5)	0 (0.0)	3 (2.2)	
Pharyngeal wall	1 (0.5)	1 (1.7)	0 (0.0)	
Unknown	14 (7.2)	8 (13.3)	6 (4.5)	
HPV status, n (%)				0.718†
Positive	137 (70.6)	40 (66.7)	97 (72.4)	
Negative	29 (15.0)	10 (16.7)	19 (14.2)	
Unknown	28 (14.4)	10 (16.7)	18 (13.4)	
Baseline variable, mean ± SD (n)				
C3 SMI (cm^2/m^2)	14.5 ± 3.1 (194)	13.3 ± 2.3 (60)	15.0 ± 3.3 (134)	<0.001‖
T4 SMI (cm^2/m^2)	51.1 ± 13.4 (187)	45.1 ± 11.5 (58)	53.8 ± 13.3 (129)	<0.001‖
BMI (kg/m^2)	27.0 ± 5.3 (194)	25.0 ± 4.9 (60)	27.9 ± 5.2 (134)	<0.001‖
PSS-HN normalcy of diet	79.0 ± 25.4 (172)	71.8 ± 27.8 (50)	82.0 ± 23.8 (122)	0.030§
MDADI composite	86.4 ± 15.6 (151)	82.5 ± 16.3 (43)	87.9 ± 15.2 (108)	0.026§

Abbreviations: BOT = base of tongue; C3 SMI = skeletal muscle index at the third cervical vertebra; CRT = chemoradiation therapy; FT = feeding tube; HPV = human papillomavirus; IQR = interquartile range; MDADI = M.D. Anderson Dysphagia Inventory; NFT = no feeding tube; PSS-HN = Performance Status Scale for Head and Neck Cancer; RT = radiation therapy; T =; T4 SMI = skeletal muscle index at the fourth thoracic vertebra.

*Probability (*P*) value reported from various tests

†Pearson's χ^2 test

‡Fisher's exact test

§Mann-Whitney U/Wilcoxon Rank Sum test

‖Independent 2-sample *t* test.

composite scores (mean ± SD: 82.5 ± 16.3 vs 87.9 ± 15.2, $P = .025$) at baseline.

Predicting FT placement

Based on the logistic regression analysis, significant predictors of FT placement on univariable analysis were C3 SMI ($P = .001$), T4 SMI ($P = .001$), CRT versus. RT ($P = .060$), and BMI ($P < .001$). The multivariable logistic regression model with C3 SMI indicated that BMI (OR per 1 unit increase: 0.660, 95% CI, 0.437-0.998, $P = .049$) was the only significant predictor of FT placement. Based on this assessment, the model explained 14.0% (Nagelkerke R^2) of the variance in FT placement and correctly classified 70.1% of cases (concordance = 0.701). Table 2 presents the results for both univariable and multivariable logistic regression analyses for the association between C3 SMI and FT placement.

For measurements obtained at the level of T4, the multivariable logistic regression model indicated that T4 SMI (OR per 1 unit increase: 0.948, 95% CI, 0.912-0.984, $P = .006$) and CRT versus RT (OR, 4.591, 95% CI, 1.202-17.529, $P = .026$) were the only factors to remain statistically significant in the multivariable analysis. This model explained 18.5% (Nagelkerke R^2) of the variance in FT placement and correctly classified 71.1% of cases (concordance = 0.701). The results associated with the logistic regression analysis based on the association between T4 SMI and FT placement are also presented in Table 2.

Optimal sarcopenia cut-off values for C3 SMI and T4 SMI

An optimal SMI threshold value was calculated to identify patients with sarcopenia (ie, low SMM) based on the outcome of FT placement for both C3 and T4 vertebral levels. Results from the ROC analysis of sensitivity, specificity, and AUC associated with the optimal cut-off values are presented in Table 3. For C3 SMI, the optimal cut-off value was determined to be 16.4 cm^2/m^2. The AUC was 0.634 but remained significantly better than chance (AUC = 0.5, $P < .001$). Based on T4 SMI, an optimal cut-off value of 48.4 $cm^2/m2$ was identified with an AUC of 0.638 ($P < .001$). A ROC curve displaying the diagnostic accuracy for C3 SMI and T4 SMI and the occurrence of FT placement is shown in Fig. 2. Information on patients stratified based on sarcopenia status is reported in Table 4 for C3 SMI and in Table 5 for T4 SMI.

Table 2 Logistic regression analysis of predictive factors for FT placement based on C3 SMI and T4 SMI

	Univariable Analysis		
Variable	**OR**	**95% CI**	***P* value**
Age (per 1 year)	1.016	0.984-1.050	0.336
Male vs. Female	0.634	0.292-1.379	0.251
Treatment: CRT vs. RT	3.333	0.951-11.684	0.060
BMI (kg/m^2, per 1 unit)	0.887	0.829-0.949	< 0.001*
C3 SMI (cm^2/m^2, per 1 unit)	0.828	0.740-0.927	0.001*
T4 SMI (cm^2/m^2, per 1 unit)	0.945	0.918-0.972	< 0.001*
	Multivariable Model #1 (C3 SMI)		
Age (per 1 year)	—	—	—
Male vs. Female	—	—	—
Treatment: CRT vs. RT	3.257	0.893-11.876	0.074
BMI (kg/m^2, per 1 unit)	0.660	0.437-0.998	0.049*
C3 SMI (cm^2/m^2, per 1 unit)	0.899	0.784-1.032	0.130
	Multivariable Model #2 (T4 SMI)		
Age (per 1 year)	—	—	—
Male vs. Female	—	—	—
Treatment: CRT vs. RT	4.591	1.202-17.529	0.026*
BMI (kg/m^2, per 1 unit)	0.962	0.878-1.053	0.397
T4 SMI (cm^2/m^2, per 1 unit)	0.948	0.912-0.984	0.006*

Abbreviations: C3 SMI = skeletal muscle index at the third cervical vertebra; CRT = chemoradiation therapy; FT = feeding tube; RT = radiation therapy; T4 SMI = skeletal muscle index at the fourth thoracic vertebra.
*Denotes significant *P* value

Table 3 ROC curve analysis for C3 SMI and T4 SMI cut-off values based on FT placement

Variable	Cut-off (cm^2/m^2)	Sensitivity	Specificity	AUC	95% CI	*P* value
C3 SMI	16.424	0.933	0.358	0.634	0.556-0.712	< 0.001
T4 SMI	48.385	0.638	0.682	0.693	0.615-0.722	< 0.001

Abbreviations: AUC = area under the curve; C3 SMI = skeletal muscle index at the third cervical vertebra; FT = feeding tube; ROC = receiver operator characteristic; T4 SMI = skeletal muscle index at the fourth thoracic vertebra.

Freedom from FT placement

Kaplan-Meier analysis of freedom from FT placement was performed for patients with and without sarcopenia based on the ROC analysis-derived cut-off values for both C3 SMI and T4 SMI. For sarcopenia assessed at C3 (Fig. 3), this translated into a significantly worse freedom from FT placement for patients with versus without sarcopenia (1-year 61.9% vs 90.6%, log-rank $P < .001$). The median number of days between the first MDT consultation and FT placement was 41.0 (IQR: 34-41) for those with sarcopenia and receiving a FT (54/141) and 48.0 (IQR: 27-64) for individuals without sarcopenia and receiving a FT (5/53); however, this was not found to be significantly different ($P = .549$). For sarcopenia assessed at the level of T4 (Fig. 3), patients with sarcopenia had significantly worse freedom from FT placement compared with patients without sarcopenia (1-year 53.9% vs 80.7%, log-rank $P < .001$). For patients who received a FT, the median number of days between the first MDT meeting and FT placement was 42.0 (IQR: 18-60) for those with sarcopenia versus 59.0 (IQR: 42-68) for individuals without sarcopenia. The time to FT placement based on sarcopenia status at T4 was significantly different ($P = .031$).

Discussion

This study examined the potential relationship between sarcopenia and FT placement in patients undergoing radiation-based treatment for OPSCC. Our results indicate that, in this patient cohort, SMI measured from routine, pretreatment CT imaging at the level of T4 was significantly associated with an increased risk for FT placement. Moreover, T4 SMI remained significant in multivariable modeling when adjusting for potential covariates, indicating this relationship was not confounded. On the contrary, SMI evaluated at the level of C3 was not significantly associated with an increased risk for FT placement.

Assessment of sarcopenia on CT imaging

Inconsistencies related to the definition, measurement, and identification (ie, cut-off value estimation) of sarcopenia[32] have made it challenging to assess and subsequently mitigate some of the harmful effects of SMM loss.[33] Abdominal CT imaging at the level of the third lumbar vertebra (L3) is considered to be the 'gold standard' for

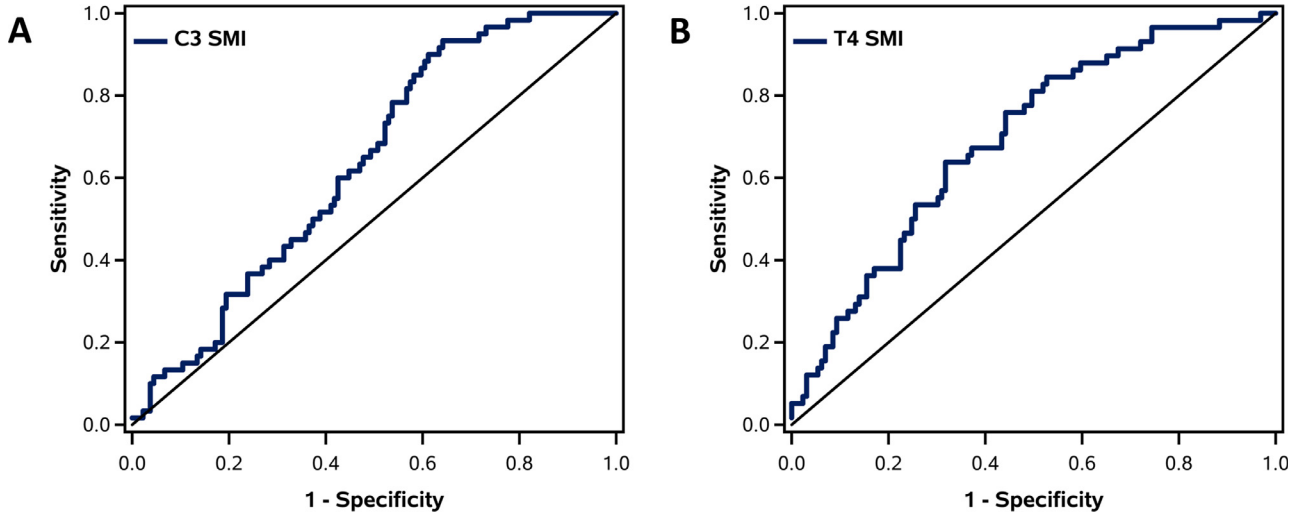

Figure 2 ROC curve based on FT placement. (A) C3 SMI, (B) T4 SMI.

Table 4 Pretreatment patient demographics and disease characteristics classified by sarcopenia status assessed at the level of third cervical vertebra (C3)

Variable	All Patients	Sarcopenia	Nonsarcopenia	*P* value*
No. of patients	194	141	53	
Age in years:				
Median (IQR)	61 (55-67)	61 (55-67)	59 (53-66)	0.098‖
Sex: male, n (%)	161 (83.0)	109 (77.3)	52 (98.1)	< 0.001†
T classification, n (%)				0.057†
T1	33 (17.0)	19 (13.5)	14 (26.4)	
T2	84 (43.3)	60 (42.6)	24 (45.3)	
T3	40 (20.6)	30 (21.3)	10 (18.9)	
T4	37 (19.1)	32 (22.7)	5 (9.4)	
N classification, n (%)				0.593†
N0	22 (11.3)	15 (10.6)	7 (13.2)	
N1	24 (12.4)	17 (12.1)	7 (13.2)	
N2a, N2b, N2c	133 (68.6)	100 (70.9)	33 (62.3)	
N3	15 (7.7)	9 (6.4)	6 (11.3)	
Treatment, n (%)				0.392†
RT	23 (11.9)	15 (10.6)	8 (15.1)	
CRT	171 (88.1)	126 (89.4)	45 (84.9)	
Tumor subsite, n (%)				0.689‡
Tonsil	98 (50.5)	67 (47.5)	31 (58.5)	
BOT	78 (40.2)	59 (41.8)	19 (35.8)	
Soft palate	3 (1.5)	3 (2.1)	0 (0.0)	
Pharyngeal wall	1 (0.5)	1 (0.7)	0 (0.0)	
Unknown	14 (7.2)	11 (7.8)	3 (5.7)	
HPV status, n (%)				0.206†
Positive	137 (70.6)	96 (68.1)	41 (77.4)	
Negative	29 (14.9)	25 (17.7)	4 (7.5)	
Unknown	28 (14.4)	20 (14.2)	8 (15.1)	
FT placement, n (%)				< 0.001†
Yes	60 (30.9)	55 (39.0)	5 (9.4)	
No	134 (69.1)	86 (61.0)	48 (90.6)	
Baseline variable, mean ± SD (n)				
BMI (kg/m^2)	14.5 ± 3.1 (194)	13.0 ± 2.0 (118)	18.4 ± 1.9 (76)	< 0.001‖
PSS-HN normalcy of diet	81.8 ± 18.4 (194)	77.4 ± 17.2 (118)	93.4 ± 16.5 (76)	< 0.001§
MDADI composite	79.0 ± 25.4 (172)	76.7 ± 26.3 (102)	84.7 ± 21.9 (70)	0.065§

Abbreviations: BOT = base of tongue; CRT = chemoradiation therapy; FT = feeding tube; HPV = human papillomavirus; IQR = interquartile range; MDADI = M.D. Anderson Dysphagia Inventory; PSS-HN = Performance Status Scale for Head and Neck Cancer; RT = radiation therapy.
*Probability (*P*) value reported from various tests
†Pearson's χ^2 test
‡Fisher's exact test
§Mann-Whitney U/Wilcoxon Rank Sum test
‖Independent 2-sample *t* test.

Table 5 Pretreatment patient demographics and disease characteristics classified by sarcopenia status assessed at the level of the fourth thoracic vertebra (T4)

Variable	All patients	Sarcopenia	Nonsarcopenia	*P* value*
No. of patients	187	78	109	
Age in years:				
Median (IQR)	61 (55-67)	63 (58-70)	59 (53-64)	<0.001‖
Sex: male, n (%)	154 (82.4)	52 (66.7)	102 (93.6)	<0.001†
T classification, n (%)				0.046†
T1	33 (17.6)	12 (15.4)	21 (19.3)	
T2	82 (43.9)	28 (35.9)	54 (49.5)	
T3	36 (19.3)	16 (20.5)	20 (18.3)	
T4	36 (19.3)	22 (28.2)	14 (12.8)	
N classification, n (%)				0.571†
N0	21 (11.2)	11 (14.1)	10 (9.2)	
N1	23 (12.3)	11 (14.1)	12 (11.0)	
N2a, N2b, N2c	130 (69.5)	50 (64.1)	80 (73.4)	
N3	13 (7.0)	6 (7.7)	7 (6.4)	
Treatment, n (%)				0.401†
RT	22 (11.8)	11 (14.1)	11 (10.1)	
CRT	165 (88.2)	67 (85.9)	98 (89.9)	
Tumor subsite, n (%)				0.052‡
Tonsil	94 (50.3)	37 (47.4)	57 (52.3)	
BOT	77 (41.2)	29 (37.2)	48 (44.0)	
Soft palate	3 (1.6)	3 (3.8)	0 (0.0)	
Pharyngeal wall	1 (0.5)	1 (1.3)	0 (0.0)	
Unknown	12 (6.4)	8 (10.3)	4 (3.7)	
HPV status, n (%)				<0.001†
Positive	134 (71.7)	42 (53.8)	92 (84.4)	
Negative	29 (15.5)	22 (28.2)	7 (6.4)	
Unknown	24 (12.8)	14 (17.9)	10 (9.2)	
FT placement, n (%)				<0.001†
Yes	58 (31.0)	37 (47.4)	21 (19.3)	
No	129 (69.0)	41 (52.6)	88 (80.7)	
Baseline variable, mean ± SD (n)				
BMI (kg/m^2)	26.9 ± 5.2 (187)	23.6 ± 4.1 (78)	29.2 ± 4.5 (109)	<0.001‖
PSS-HN normalcy of diet	79.2 ± 25.4 (166)	74.0 ± 27.1 (68)	82.9 ± 23.8 (98)	0.022§
MDADI composite	86.5 ± 15.8 (146)	81.3 ± 16.8 (55)	89.6 ± 14.4 (91)	0.002§

Abbreviations: BOT = base of tongue; CRT = chemoradiation therapy; FT = feeding tube; HPV = human papillomavirus; IQR = interquartile range; MDADI = M.D. Anderson Dysphagia Inventory; PSS-HN = Performance Status Scale for Head and Neck Cancer; RT = radiation therapy.
*Probability (*P*) value reported from various tests
†Pearson's χ^2 test
‡Fisher's exact test
§Mann-Whitney U/Wilcoxon Rank Sum test
‖Independent 2-sample *t* test.

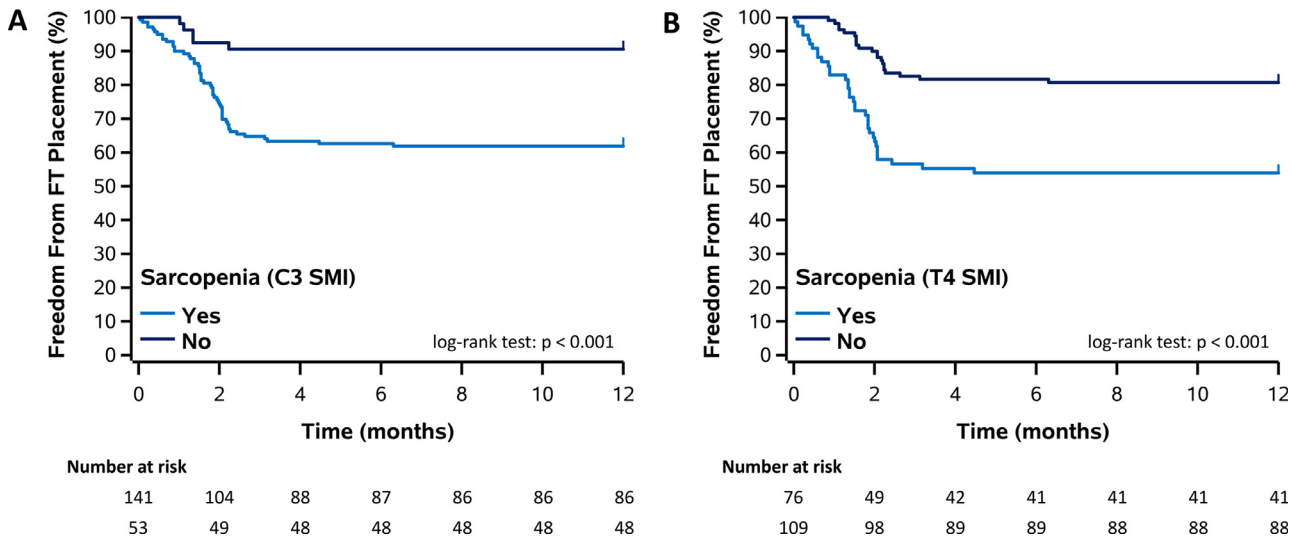

Figure 3 Kaplan-Meier survival analysis based on freedom from FT placement in patients with and without sarcopenia. (A) assessed at the level of C3, (B) assessed at the level of T4.

noninvasive evaluation of muscle quantity due to the strong correlation between L3-derived measurements and whole-body SMM.[34] However, acquisition of abdominal CT imaging is not standard practice in the context of OPSCC.[18] Consequently, the use of these methods to measure SMM may subject patients to additional imaging and associated burden (eg, the potential for increased radiation exposure in the acquisition of CT-derived lumbar measurements).[35]

In the context of HNC, the most feasible method to measure SMM may be at the level of C3 on head and neck CT imaging.[32] The detection of sarcopenia using this method has several advantages. First, measurements obtained at C3 are cost-effective and have a proven relationship with adverse outcomes and survival in HNC.[21,22] Such measurements also can be obtained directly from routine head and neck CT imaging.[36] The feasibility of C3 SMI was evident in the current study, as measurements were available for every patient. In contrast, baseline CT imaging at the thoracic level is not routinely performed in HNC patients and, consequently, this resulted in the exclusion of several patients (n = 7). SMM measured at the level of C3 also demonstrated excellent interrater and intrarater reliability, indicating that sarcopenia can be assessed reliably and that these measurements can be reproduced. These findings are consistent with previous research.[37] Importantly, when classified based on FT placement (yes vs no), patients who received a FT had significantly lower C3 SMI measurements at baseline and had significantly worse freedom from FT placement at 1-year posttreatment compared with patients without a FT.

Despite the advantages of performing sarcopenia assessment at C3 and the fact that C3 SMI has proven to be an excellent prognostic indicator in HNC,[38] the present findings indicate that pretreatment C3 SMI was not a significant predictor of FT placement in our patient cohort. One potential explanation for these results may be that measurements obtained at C3 may be more susceptible to the localized impact of the tumor and radiation and are, therefore, a poor biomarker of true sarcopenia. Moreover, given the close proximity of lymph node chains around musculature in the head and neck, muscle delineation at the C3 vertebral level may also be affected by the presence of nodal metastases.[25] It is also plausible that, because OPSCC patients commonly experience symptoms such as neck pain, their neck mobility may be reduced, which may consequently increase the potential for muscular atrophy in this region. Therefore, C3 SMI measures may not accurately reflect full-body SMM and may not be an ideal biomarker for predicting FT placement in patients with OPSCC.

Relationship between sarcopenia, body mass index, and feeding tube placement

Given that C3 SMI was significant in univariable analysis but not in the multivariable model, it is likely only predictive due to its association with other factors.[39] Our results indicate that the relationship between full-body SMM assessed at C3 and FT placement was confounded by factors such as BMI. Although these findings contradict the well-documented prognostic utility of sarcopenia in HNC,[32] research that does consider the potential confounding effect of BMI also has indicated that BMI may be a better prognostic indicator than sarcopenia for outcomes such as survival and locoregional control.[18] In addition, these results are expected when considering the risk-guided approach to FT placement in OPSCC at our

institution. The decision to place a FT is influenced by numerous factors, 2 of which are low BMI (≤18) and significant weight loss (≥5% in 1 month or ≥10% in 6 months). These factors in combination with a diagnosis of OPSCC predicate FT placement.[23] In addition, a low BMI is most likely to be highly correlated with significant weight loss. Consequently, C3 SMI may have more prognostic utility in a non-OPSCC patient cohort or in centers that employ a reactive FT placement philosophy.

In contrast, SMM measured at the T4 vertebral level may be more suitable for determining the need for FT placement given its significant association in multivariable logistic regression modeling. Measurements obtained at T4 could serve as a useful alternative considering that they are also accessible on routine head and neck imaging and are not directly impacted by the tumor, lymph node invasion, or radiation and/or surgery. Further, skeletal muscles at the level of T4 such as the trapezius and rhomboids are important stabilizer muscles for full-body, compound (ie, multijoint) movements[40] and total body strength.[41,42] For these reasons, the relationship between T4 SMI and FT placement may be less confounded by measures such as BMI. It is, therefore, plausible that T4 SMI is a more clinically relevant indicator for full body SMM and overall strength relative to C3 SMI. Nevertheless, only 2 studies reported in the literature have measured SMM using thoracic imaging.[32] This lack of exploration is not surprising given the relative novelty of sarcopenia assessment in HNC, especially at vertebral levels other than L3.[25]

Limitations

Although the current study reports important findings, we must acknowledge that our investigation has several limitations. First, because this study was conducted at a single tertiary care institution and for a homogeneous group of HNC patients (ie, those with OPSCC), these results may not be generalizable to all patients with HNC. The sample population for the current investigation was predominantly comprised of male patients, which limited our ability to determine sex-specific cut-off values for the detection of sarcopenia. However, considering that OPSCC is nearly twice as prevalent in males,[43] we believe our analyses and results are externally valid and representative of the OPSCC population as a whole. Second, risk-stratification for FT placement may also have biased the data considering that one of the covariates, BMI, was used in the decision-making process for the need for FT placement in this patient cohort. Because of the retrospective nature of the current study, it was difficult to ascertain which specific factors contributed to FT placement for individual patients. Consequently, there may have been some patients in the FT group who may not have required nutritional intervention.

In addition, several methodological considerations related to the measurement of SMM require discussion. For example, for some CT scans it was challenging to select an axial image that would satisfy both criteria in the image selection process (ie, both the entire vertebral arc and the transverse and spinous processes were displayed). Nevertheless, given that measurement of both C3 SMI and T4 SMI displayed excellent reliability, this technical challenge did not appear to influence SMM measurement in the present data set. One notable limitation for thoracic SMM measurements (ie, T4 SMI) is that there is no consensus on the procedure for selecting an axial slice for muscle contouring. However, to reduce the potential influence of this concern, we employed the method used by Van Heusden and colleagues.[24] This decision was made due to our belief that it appears to be the most transparent, replicable, and accurate strategy for image selection. In addition, because of the retrospective nature of the current investigation and the absence of routine lumbar CT imaging, we were unable to directly compare T4 measurements to "gold standard" L3 measurements. Future research should aim to correlate these measures to validate the significance of T4 SMI as a marker for sarcopenia and to ascertain its significance for clinical decision-making. Finally, although baseline measures of SMM have utility for determining the prognostic significance of sarcopenia and its association with important clinical outcomes, there should be a concentrated effort to assess posttreatment sarcopenia as well to understand which factors may contribute to poor SMM retention over the course of treatment.

Conclusions

Based on findings generated from this investigation, SMM measured from CT imaging at the level of C3 does not appear to be a strong prognostic factor for FT placement. Instead, the risk for FT placement may be more accurately determined according to SMM measurements obtained at the T4 level. Therefore, the results of the current study suggest that OPSCC patients with low BMI and T4 SMI should be closely monitored to facilitate pretreatment optimization of nutritional status and physical condition to limit or delay the need for FT placement.

The detection of sarcopenia at its earliest appearance (ie, baseline) in addition to other markers of malnutrition[44] could guide decision-making and allow for the communication of vital information regarding the necessity for FT placement. Ultimately, the findings of the present study provide insights into how an enhanced understanding of sarcopenia can facilitate the inclusion of accessible information and promote improved patient care in the context of OPSCC and its treatment. These findings also provide a rich resource for continued research into important questions related to sarcopenia

and FT recommendations, the result of which will have a direct impact on those treated for OPSCC.

Disclosures

None.

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