



Establishment and Validation of Pre-Therapy Cervical Vertebrae Muscle Quantification as a Prognostic Marker of Sarcopenia in Patients With Head and Neck Cancer

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Background: Sarcopenia is prognostic for survival in patients with head and neck cancer (HNC). However, identification of this high-risk feature remains challenging without computed tomography (CT) imaging of the abdomen or thorax. Herein, we establish sarcopenia thresholds at the C3 level and determine if C3 sarcopenia is associated with survival in patients with HNC.

Methods: This retrospective cohort study was conducted in consecutive patients with a squamous cell carcinoma of the head and neck with cross-sectional abdominal or neck imaging within 60 days prior to treatment. Measurement of cross-sectional muscle area at L3 and C3 levels was performed from CT imaging. Primary study outcome was overall survival.

Results: Skeletal muscle area at C3 was strongly correlated with the L3 level in both men ($n = 188$; $r = 0.77$; $p < 0.001$) and women ($n = 65$; $r = 0.80$; $p < 0.001$), and C3 sarcopenia thresholds of $14.0 \text{ cm}^2/\text{m}^2$ (men) and $11.1 \text{ cm}^2/\text{m}^2$ (women) were best predictive of L3 sarcopenia thresholds. Applying these C3 thresholds to a cohort of patients with neck imaging alone revealed that C3 sarcopenia was independently associated with reduced overall survival in men (HR = 2.63; 95% CI, 1.79, 3.85) but not women (HR = 1.18, 95% CI, 0.76, 1.85).

Conclusions: This study identifies sarcopenia thresholds at the C3 level that best predict L3 sarcopenia in men and women. In HNC, C3-defined sarcopenia is associated with poor survival outcomes in men, but not women, suggesting sarcopenia may differentially affect men and women with HNC.

Keywords: head and neck cancer, squamous cell carcinoma, surgery, sarcopenia, cachexia, muscle wasting, body composition

INTRODUCTION

Patients with cancer frequently experience weight loss, including progressive lean and fat mass catabolism consistent with the paraneoplastic wasting syndrome of cachexia (1, 2). Excessive skeletal muscle wasting, or sarcopenia, is significantly associated with morbidity and mortality for patients with solid tumors (3–5). Sarcopenia can exist as an isolated finding as is often the case in the elderly or secondary to a disease process that activates catabolic programs—including cancer (1, 6). While sarcopenia is richly described as a negative prognostic marker for patients with primary tumors in the abdomen, only recently has its importance been identified in patients with head and neck cancer (HNC) (7–9). Indeed, sarcopenia is a significant predictor of survival and post-operative complications for patients with HNC and shows promise as a risk-stratification tool for patients with this disease (7–10). Furthermore, sarcopenia is significantly associated with the development of cancer-associated fatigue in patients with head and neck cancer, and improvement of muscle mass during disease progression through resistance training may be beneficial in mitigating fatigue and improve overall quality of life (11–13). Therefore, regular detection of sarcopenia in patients with head and neck cancer may allow for early intervention and risk-stratification, which could improve patients' quality of life and ultimate survival. Despite the clear utility in identifying sarcopenia in patients with HNC, clinical implementation of sarcopenia measures remains challenging due to the lack of established approaches that integrate with standard clinical workflow (14).

In terms of clinical detection, dual-energy x-ray absorptiometry was initially used in detecting sarcopenia, but the most widely utilized method today includes identification of cross-sectional skeletal muscle area from computed tomography (CT) scans (15). However, several alternative methods exist, including bioelectrical impedance analysis, ultrasound of the tibialis anterior, magnetic resonance imaging, and serum biomarker analysis (14, 16–18). Despite the advent of newer detection methods, CT-defined muscle wasting remains highly utilized for several reasons, including its relative ease of analysis compared to alternative methods, and its potential for automation and integration into the electronic health record (19, 20). Since imaging studies (CT or PET/CT) are routinely performed during the clinical workup of HNC, establishing cross-sectional skeletal muscle area thresholds utilizing these scans represent a low-cost, reliable, and reproducible method for determining sarcopenia in this patient population. Current skeletal muscle index (SMI, defined as cross-sectional skeletal muscle area normalized to patients' body height squared) values for defining sarcopenia are specific to abdominal or lower thoracic musculature (5, 21). As abdominal and lower thoracic imaging is not always performed as part of the HNC workup, only a subset of patients that have imaging studies capturing these regions are included in most previous reports, ultimately introducing selection bias. Therefore, defining and validating sarcopenia thresholds from routinely acquired head and neck images would greatly enhance clinical implementation while allowing better cross-study comparisons. Previous reports demonstrated a significant correlation between cervical and

abdominal vertebrae cross sectional muscle area in patients with HNC, suggesting that routine head and neck imaging may be used to identify sarcopenia (22–26). In the present study, we sought to expand upon these findings in a cohort of HNC patients treated with primary surgical resection by defining sex-specific sarcopenia thresholds, evaluating their prognostic value, and validating these associations in an independent patient cohort.

METHODS

Population Cohort and End Points

We performed a retrospective review by screening medical records of patients who underwent primary surgical resection of head and neck squamous cell carcinoma between January 1, 2005 and December 21, 2017 at Oregon Health and Science University in Portland, Oregon. Electronic health records were reviewed for data collection and included: patient demographics, body mass and height, comorbidities, tumor staging and subsite information, HPV/p16 status, smoking status, treatment information, evidence of recurrence, date and cause of death, and date of last follow up. Patients were classified as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) or obese (BMI >30). Smoking status was binned in 3 groups, including never smokers, <10 pack years, ≥10 pack years. Feeding tube classifications included patients never receiving a G-tube, those receiving a G-tube temporary, and those who had feeding tubes *in situ* at the time of last follow up. Tumor sites included: oropharynx, oral cavity, larynx, and other. Pathologic T staging was binned as either T0–2 or T3–4, while pathologic N staging was binned as either N0–1, N2–3, or NX. Charlson Comorbidity Index (CCI) score was calculated as previously described (27) and patients were subsequently stratified as either low risk (CCI <5) or high risk (CCI ≥5). After patient data were abstracted and coupled to their imaging information, all patient data were de-identified for subsequent analyses. This study was approved by the Institutional Review Board at Oregon Health and Science University. Requirement for informed consent was waived due to the retrospective nature of this study.

We utilized two separate cohorts of patients with HNC for analyses. The first cohort, defined as the training cohort, is utilized to establish C3 sarcopenia thresholds and contains patients that have CT imaging that captures both the L3 and C3 vertebral levels. The second cohort, defined as the validation cohort, consists of HNC patients with only neck imaging (skull base to lung apices) and is utilized for validation of these established C3 thresholds on mortality outcomes. Study inclusion for both training and validation cohorts was restricted to patients treated with primary surgical resection of head and neck squamous cell carcinoma at Oregon Health and Science University between January 2005 and December 2017 with PET/CT or CT scans within 60 days prior to surgical resection. Therefore, all patients' scans utilized in this study were capturing muscle area prior to surgery and/or adjuvant therapy. For the training cohort, patients were required to have a scan that captured both the C3 and L3 vertebral levels, while the validation cohort only required capture of the C3 level.

Computed Tomography Body Composition Analysis

Body composition analysis of skeletal muscle was performed as previously described in patients with HNC (9, 22). Briefly, the cross-sectional area of skeletal muscle at the center of the third lumbar (L3) and third cervical (C3) vertebrae was determined by segmentation of axial CT images (**Figure 1**). Segmentation analysis was performed using Slice-o-Matic Software (version 5.0; Tomovision; <https://www.tomovision.com>) to define muscle tissue cross-sectional area. Muscles delineated in the segmentation analysis included the rectus abdominus, abdominal wall, psoas, and the paraspinal muscle groups at the L3 level. Muscles measured at C3 included the paraspinal muscle group and the sternocleidomastoid (SCM). Muscle tissue was defined as -29 to 150 Hounsfield units as described previously (28). The resulting cross-sectional muscle area was then normalized to the square of the patient's height in meters and used to calculate skeletal muscle index (SMI). At the L3 level, sarcopenia is defined as an SMI of less than 52.4 cm²/m² for men and 38.5 cm²/m² for women (5). These thresholds are consistent with previous reports in head and neck cancer patients.

Statistical Analysis

To compare patient and clinical-disease characteristics at baseline, the Chi-square or Fisher's Exact tests were used for categorical variables; the Wilcoxon rank sum test was used for continuous variables. Data was presented as median (IQR) or frequency (%). Training cohort (n = 253) comparisons were stratified by L3-defined sarcopenia; validation cohort (n = 536) comparisons were stratified by C3-defined sarcopenia.

Correlation was assessed using Pearson's rho, which assumes normal distribution and a linear relationship between the measurements. Rho greater than 0.8 is considered 'very strong' correlation; rho between 0.6-0.79 suggests 'strong' correlation. To test for linearity and homoscedasticity we plotted residuals versus fitted values, showing the loess (smoothing) curve in red. Receiver Operating Characteristic (ROC) curves were generated to show the general predictive ability of C3 to predict L3-defined sarcopenia; DeLong's test of correlated ROC curves was used to

discriminate between C3 measurement types (29). We used Youden's Index to determine the optimal C3 cut-off value for predicting sarcopenia.

Overall survival is the time from initial diagnosis until death by any cause, with participants censored at their last assessment date. Assumptions of proportionality in the survival models were verified graphically and using residual-based models. Univariate and multivariable Cox proportional hazard ratio models were used to assess the risk of death based on demographic and baseline clinical-disease characteristics. We used purposeful selection combined with Bayesian information criterion (BIC) to build the multivariable models, entering all variables from the univariate models with p-value < 0.2. Kaplan-Meier curves with log-rank test were used to display overall survival stratified by C3-defined sarcopenia. All analyses were conducted using R, version 3.5.3.

RESULTS

Determination of C3-Defined Sarcopenia Thresholds

The training cohort included patients with both abdominal and neck imaging in order to perform inpatient correlative analyses of L3 and C3 SMI values to identify appropriate C3 sarcopenia thresholds. Median age of this cohort is 61 (IQR 54, 68) years with 188/253 (74%) patients identifying as male. In this cohort, 6.0% of patients were underweight (BMI <18.5), 32% were normal weight (BMI 18.5-24.9), 38% were overweight (BMI 25-29.9), and 24% were obese (BMI >30). Eighty-nine patients were never smokers (35%), 51 (20%) patients smoked <10 pack years, and 113 (45%) patients had a ≥10 pack year history. Postoperatively, 130 (51%) patients received temporary feeding tubes while 47 (19%) patients still had feeding tubes *in situ* at the time of last follow up. The majority of this cohort had oropharynx disease (147 patients [58%]), while primary tumors in the oral cavity (55 [22%]) and larynx (19 [8%]) were less frequently observed (27). The majority of patients were classified as low-risk by the Charlson Comorbidity Index (CCI <5; 213 [84%]).

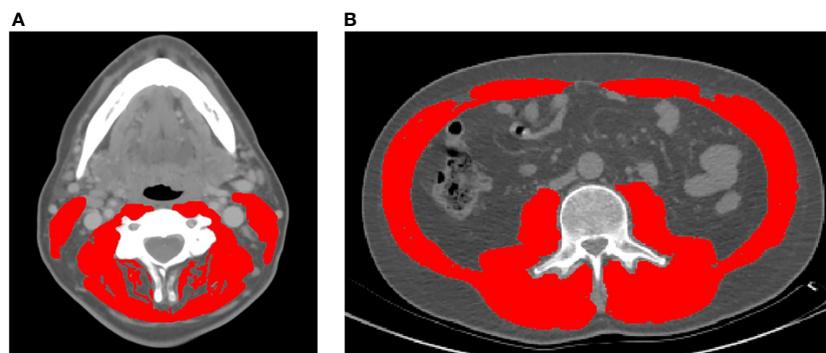


FIGURE 1 | Representative axial CT images of the third cervical (A) and third lumbar (B) vertebral levels used to quantify skeletal muscle index (highlighted in red).

One hundred three (41%) patients were treated by primary surgical resection alone, while 150 (59%) patients received adjuvant therapy (radiation and/or chemotherapy). Full characteristics and details of this cohort stratified by L3-defined sarcopenia are shown in **eTable 1 in the Supplement**.

Inpatient L3 and C3 levels were strongly correlated in both men ($n = 188$, $r = 0.77$; $p < 0.001$) and women ($n = 65$, $r = 0.80$; $p < 0.001$; **Figure 2; Supplementary Figure 1**). As it is possible for the borders of the SCM to be obscured by lymph node metastases, we performed comparative analyses amongst L3 and C3 SMI values, both inclusive and exclusive of the SCM, to examine whether inclusion of the SCM improves or worsens predictive capacity of L3-based sarcopenia. Including the SCM in C3 SMI measurements improved predictive capacity of L3-defined sarcopenia in women (AUC = 89.4% vs. 86.3%; $p = 0.03$), but not men (AUC = 85.9% vs. 85.0%; $p = 0.30$; **Supplementary Figure 2**). Therefore, we included the SCM in all subsequent analyses. The C3 SMI thresholds with the best model performance based on Youden's Index were $14.0 \text{ cm}^2/\text{m}^2$ for men and $11.1 \text{ cm}^2/\text{m}^2$ for women (**Figure 2**). Finally, we confirmed the utility of C3-defined sarcopenia in this training cohort through survival analysis which demonstrated an association between C3-defined sarcopenia in men (HR = 1.9; 95% CI, 1.2-5.5), but not women (HR = 0.84; 95% CI, 0.30-2.15), with HNC (**Supplementary Figure 3**).

Survival Analyses in C3-Defined Sarcopenic Patients

We next applied these C3 SMI thresholds to an independent cohort of HNC patients with imaging studies (PET/CT or CT) that captured the head and neck, but not abdomen or lower thorax (**Table 1**). This validation cohort included patients with imaging of the head and neck, but not abdomen or lower thorax. Median age of patients in this cohort was 64 (IQR 56, 72) with 333 patients identifying as male (62%) and 203 identifying as female (38%; **Table 1**). Forty-one (7.7%) patients were underweight, 211 (40%) were normal weight, 164 (31%) were overweight, and 118 (22%) were classified as obese (BMI >30). This cohort included 162 (30%) never smokers, 68 (13%) patients with <10 pack years, and 306 (57%) patients with ≥ 10

pack years. Postoperatively, 174 (32%) patients received temporary feeding tubes and 105 (20%) patients still had feeding tubes at last follow up. In contrast to the training cohort, the preponderance of this cohort had oral cavity disease (306 patients [57%]), while primary tumors in the oropharynx (118 [22%]) and larynx (79 [15%]) were less frequently observed. Using CCI, 409 [76%] patients were classified as low risk and 127 were classified as [24%] high risk. In the validation cohort, 324 (60%) patients were treated by primary surgical resection alone, with 212 (40%) receiving adjuvant therapy (radiation and/or chemotherapy). Baseline patient characteristics stratified by C3-defined sarcopenia are shown in **Table 1**.

In this cohort, 53% (175/333) of men were classified as sarcopenic compared to just 38% (77/203) of women (**Table 1** and **eTable 2**). Univariate Cox proportional hazards analysis revealed advanced age at time of surgery, C3-defined sarcopenia, underweight BMI status, >10 pack-year smoking status, permanent feeding tube placement, negative HPV status, elevated CCI, pT3-4, pN2-3, group stage 4, angiolymphatic invasion (ALI), perineural invasion (PNI), and extranodal extension (ENE) as significant predictors of survival in men. Univariate cox modelling for variables associated with survival in women included permanent feeding tube placement, elevated CCI, T category (pT3-4), group stage 3 and 4, ALI, and PNI (**eTable 3**). Kaplan-Meier survival curves showed a significant difference in survival based on C3-defined sarcopenia for men but not women (**Figure 3**). On multivariable analyses, C3-defined sarcopenia (HR = 2.67; 95% CI, 1.72-4.15), ALI (HR = 2.00; 95% CI, 1.32-3.02), permanent feeding tube placement (HR = 2.33; 95% CI, 1.41-3.88), and age at time of surgery (HR = 1.04; 95% CI, 1.02-1.05) all remained significantly associated with overall survival for men (**Table 2**). In women, PNI (HR = 2.45; 95% CI, 1.48-4.06), ALI (HR = 2.13; 95% CI, 1.22-3.72), and pathologic T category (HR = 1.95; 95% CI, 1.20-3.16) were associated with reduced overall survival on multivariable analysis (**Table 2**). In the training cohort, advanced age was associated with sarcopenia in women, while advanced age was associated with sarcopenia in men in the validation cohort (**eTable 4**).

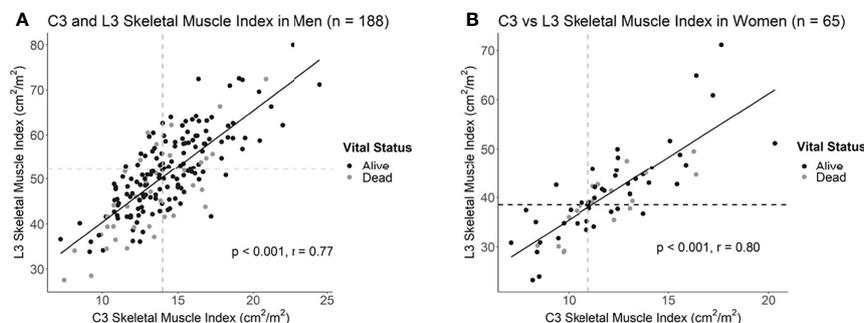


FIGURE 2 | Correlation plots of L3 and C3 skeletal muscle indices in (A) men and (B) women with head and neck cancer. Dotted lines delineate the intersection of previously established L3 sarcopenia thresholds with the estimated C3 sarcopenia thresholds.

TABLE 1 | Clinical-demographic tables for validation set, stratified by C3-defined sarcopenia (Men: C3<14.0; Women: C3<11.1; n = 536).

Risk Factor	Overall, N = 536 ¹	Sarcopenic, N = 252 ¹	Not sarcopenic, N = 284 ¹	p-value ²
Age at time of surgery	64 (56, 72)	65 (58, 71)	62 (55, 72)	0.200
RT Fractions	33 (30, 35)	33 (30, 35)	32 (30, 35)	0.028
(Missing)	344	166	178	
RT dose	6,300 (6,000, 6,600)	6,300 (6,000, 6,650)	6,000 (6,000, 6,600)	0.140
(Missing)	338	163	175	
Days from Diagnosis to surgery	31 (21, 42)	34 (21, 44)	29 (20, 41)	0.090
(Missing)	10	6	4	
Vital Status				<0.001
Alive	332 (62%)	134 (53%)	198 (70%)	
Dead	204 (38%)	118 (47%)	86 (30%)	
Sex				0.001
Male	333 (62%)	175 (69%)	158 (56%)	
Female	203 (38%)	77 (31%)	126 (44%)	
BMI				<0.001
Underweight	41 (8%)	33 (13%)	8 (3%)	
Normal weight	211 (40%)	126 (50%)	85 (30%)	
Overweight	164 (31%)	71 (28%)	93 (33%)	
Obese	118 (22%)	21 (8%)	97 (34%)	
(Missing)	2	1	1	
Smoking Status				0.003
Never smoke	162 (30%)	59 (23%)	103 (36%)	
<10 pack years	68 (13%)	31 (12%)	37 (13%)	
>= 10 pack years	306 (57%)	162 (64%)	144 (51%)	
Feeding Tube				0.053
No G-tube	257 (48%)	107 (42%)	150 (53%)	
Temporary G-tube	174 (32%)	92 (37%)	82 (29%)	
Permanent G-tube	105 (20%)	53 (21%)	52 (18%)	
HPV				0.055
HPV-	99 (57%)	48 (66%)	51 (50%)	
HPV+	76 (43%)	25 (34%)	51 (50%)	
(Missing)	361	179	182	
Charlson Comorbidity Score				0.900
< 5	409 (76%)	191 (76%)	218 (77%)	
>= 5	127 (24%)	61 (24%)	66 (23%)	
Tumor site				0.130
Oral cavity	306 (57%)	146 (58%)	160 (56%)	
Oropharynx	118 (22%)	48 (19%)	70 (25%)	
Larynx	79 (15%)	37 (15%)	42 (15%)	
Other	33 (6%)	21 (8%)	12 (4%)	
Pathologic T category (pT)				0.002
T0-2	354 (68%)	149 (61%)	205 (74%)	
T3-4	170 (32%)	97 (39%)	73 (26%)	
(Missing)	12	6	6	
Pathologic N category (pN)				0.500
N0-1	348 (66%)	161 (65%)	187 (67%)	
N2-3	151 (29%)	71 (29%)	80 (29%)	
x	26 (5%)	15 (6%)	11 (4%)	
(Missing)	11	5	6	
Group stage				0.024
Stage 1	145 (28%)	60 (24%)	85 (31%)	
Stage 2	109 (21%)	42 (17%)	67 (24%)	
Stage 3	83 (16%)	43 (17%)	40 (14%)	
Stage 4	187 (36%)	101 (41%)	86 (31%)	
(Missing)	12	6	6	
Margins status				0.500
Margins-	424 (84%)	201 (86%)	223 (83%)	
Margins+	78 (16%)	33 (14%)	45 (17%)	
(Missing)	34	18	16	
ALI				0.800
Absent	324 (66%)	152 (66%)	172 (67%)	
Present	139 (28%)	65 (28%)	74 (29%)	
Indeterminate/Suspicious	26 (6%)	14 (6%)	12 (5%)	
(Missing)	47	21	26	

(Continued)

TABLE 1 | Continued

PNI				0.400
Absent	344 (70%)	158 (68%)	186 (72%)	
Present	142 (29%)	72 (31%)	70 (27%)	
Suspicious (Missing)	4 (1%) 46	1 (0.4%) 21	3 (1%) 25	
ENE				0.300
Absent	402 (83%)	185 (81%)	217 (85%)	
Present (Missing)	80 (17%) 54	43 (19%) 24	37 (15%) 30	
Recurrence				0.130
No recurrence	402 (75%)	181 (72%)	221 (78%)	
Recurrence	134 (25%)	71 (28%)	63 (22%)	
RT				>0.9
No RT	325 (61%)	153 (61%)	172 (61%)	
RT	211 (39%)	99 (39%)	112 (39%)	
Chemotherapy				0.800
No Chemo	437 (82%)	207 (82%)	230 (81%)	
Chemo	99 (18%)	45 (18%)	54 (19%)	
Treatment Group				>0.9
Surgery	324 (60%)	152 (60%)	172 (61%)	
Surgery + Adjuvant	212 (40%)	100 (40%)	112 (39%)	

¹Statistics presented: Median (IQR); n (%).

²Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test.

Bold text indicates $p < .05$.

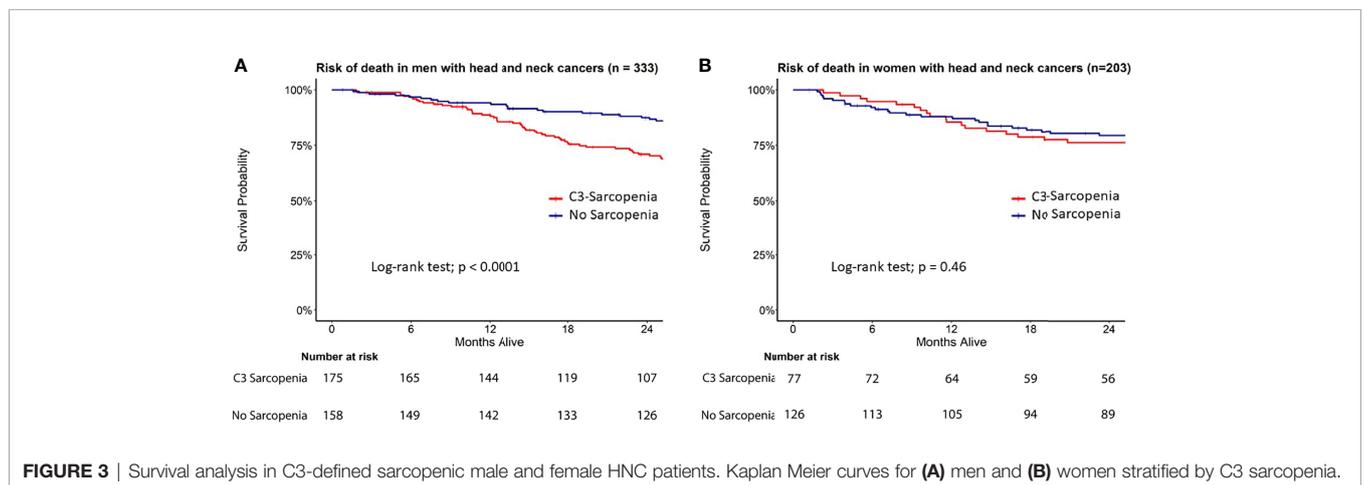


FIGURE 3 | Survival analysis in C3-defined sarcopenic male and female HNC patients. Kaplan Meier curves for (A) men and (B) women stratified by C3 sarcopenia.

DISCUSSION

Skeletal muscle depletion is a well-established prognostic marker in multiple clinical and disease settings, including cancer (7, 8), trauma (30), and drug dose scaling to minimize toxicities (31). Previous reports demonstrate the prognostic utility of sarcopenia is independent of patient body mass (5, 8, 32), and that height and weight formulae are not sufficient to capture sarcopenia (33). However, identification of this high-risk disease feature is challenging in HNC because imaging studies that capture the abdomen or lower thorax are infrequent in this population. Although previous studies demonstrate promise in utilizing neck imaging as a marker of sarcopenia (22, 25, 26, 34), we sought to expand upon these foundational studies by putting forth normalized sex-specific sarcopenia thresholds and testing their prognostic utility in an independent cohort of patients with

neck imaging alone. To our knowledge, our study is the first to establish normalized sex-specific C3 sarcopenia thresholds and validate their prognostic value in an independent cohort of HNC patients with imaging studies specific to the neck. We found that these C3 SMI thresholds were prognostic in men, but not women, with HNC.

Several foundational studies demonstrated a strong correlation of C3 and L3 skeletal muscle area in patients with HNC consistent with our findings herein (22, 23, 25, 35–37). One report utilized a single SMI cut-off for both men and women, an approach that may not accurately account for intrinsic differences in body habitus between male and female sexes (36). A recent study by Ufuk and colleagues found that among the C2–C4 vertebral levels, the paraspinal muscles at C3 were the most predictive of L3 in males, while summative C2–C4 SCM measurements were the most discriminative in females (23).

TABLE 2 | Multivariable model for factors associated with risk of death with head and neck cancers in validation cohort, by sex (n = 536).

Variables:	Model selected for Men (n = 333)			Model selected for Women (n = 203)		
	HR ¹	95% CI ¹	p-value	HR ¹	95% CI ¹	p-value
C3-Sarcopenia			<0.001			
Not sarcopenic	—	—				
Sarcopenic	2.67	1.72, 4.15				
ALI			0.001			0.011
Absent	—	—		—	—	
Present	2.00	1.32, 3.02		2.13	1.22, 3.72	
Feeding Tube			0.002			
No G-tube	—	—				
Temporary G-tube	1.09	0.66, 1.81				
Permanent G-tube	2.33	1.41, 3.88				
Age at time of surgery	1.04	1.02, 1.05	<0.001			
PNI						<0.001
Absent	—	—		—	—	
Present				2.45	1.48, 4.06	
Pathologic T category (pT)						0.009
T0-2				—	—	
T3-4				1.95	1.20, 3.16	

¹HR, Hazard Ratio; CI, Confidence Interval.

Bold text indicates $p < .05$.

However, a combinatorial approach in which both paraspinal and SCM muscle groups was not utilized in this report, and it stands to reason that increasing the measurable skeletal muscle area at the cervical level would only serve to increase the predictive capacity for sarcopenia at the lumbar level, as our data herein suggest (**Supplementary Figure 2**). Another recent report investigating the predictive capacity of C3 SMI on L3 SMI in a Korean HNC population demonstrated significant correlation in non-sarcopenic patients, but no such correlation in sarcopenic patients (defined as a calculated L3 muscle index of $<55 \text{ cm}^2/\text{m}^2$ in men and $<39 \text{ cm}^2/\text{m}^2$ in women) (38). In the present study, we observe significant correlation for both non-sarcopenic and sarcopenic HNC patients. Possible explanations for these differences in results could be due to the population of study or techniques in measuring skeletal muscle area (38). Specifically, we included both paraspinal and SCM muscles when measuring C3 SMI due to its improved predictive capacity of L3 (**Supplementary Figure 2**); we also utilized previously published L3 sarcopenia thresholds of $<52.4 \text{ cm}^2/\text{m}^2$ for men and $<38.5 \text{ cm}^2/\text{m}^2$ for women (23, 38). Similarly, in another recent report utilizing cross-sectional muscle area at the C3 level to predict L3 cross-sectional area, the authors classified sarcopenia as the lowest quartile of predicted L3 muscle area, while the work herein sought to base C3 sarcopenia thresholds on L3 sarcopenia thresholds that are validated across multiple cancers and conditions (25). Accordingly, it is possible that these C3 sarcopenia thresholds extend to other diseases and clinical settings in which the abdomen or lower thorax are not routinely captured by CT imaging, such as neurologic cancers. However, identifying the most suitable sarcopenia thresholds appears to be multifactorial and dependent on sex and disease-specific conditions (39), further highlighting the need for validating sarcopenia thresholds in a context-specific manner.

In the context of this recent literature, we believe our work adds substantially to this area of research for several reasons:

(1) through the largest cohort study to date, we further evidence that muscle area at the C3 vertebral level is closely predictive of the L3 level in both sarcopenic and non-sarcopenic HNC patients; (2) we establish that measuring both paraspinal and SCM musculature is more predictive than paraspinal SMI calculations alone, as many previous studies utilize only paraspinal muscles for sarcopenia measurements; (3) we establish normalized sex-specific C3 thresholds that are best-predictive of widely published L3 sarcopenia thresholds, rather than utilizing *ad hoc* thresholds that are predictive of a single cohort; (4) we validate the prognostic utility of our proposed C3 sarcopenia thresholds in an independent cohort of patients with only neck CT imaging available; and (5) finally, we are the first to demonstrate a sexually-dimorphic survival outcome for HNC patients with sarcopenia, as sarcopenia was associated with reduced survival in men, but not women (25, 39). To our knowledge, this is the largest dataset of women with HNC stratified by sarcopenia, and the first to individually assess sex-specific survival outcomes during this disease.

Like many research areas, sarcopenia has largely been studied in males in both murine and clinical settings, while few studies evaluating sex as a biological variable exist (40, 41). Amongst experimental rodent models of colon- and HNC-associated cachexia, male mice lost a larger proportion of lean mass compared to female mice with similar disease burden (42, 43). Several studies also report a significantly lower prevalence of sarcopenia in women with various cancers, including non-small cell lung and gastrointestinal cancers (44, 45). In the present study, we observe 55% of men are sarcopenic at the time of diagnosis compared to just 39% of women ($p < 0.001$). In addition to reports that describe a decrease in the prevalence of sarcopenia in women at the time of cancer diagnosis, Kilgour and colleagues showed a strong association between muscle mass and cancer-associated fatigue in men, but not in women (46). Burkart and colleagues recently showed an association between

sarcopenia and overall survival in men with aggressive B-cell Non-Hodgkin Lymphoma, while women demonstrated no such association (47). Conversely, sarcopenia was associated with poorer survival outcomes in women with non-metastatic breast cancer (32). These studies and more suggest that sarcopenia may not only disproportionately appear between men and women during disease, but also differentially influence quality of life and mortality in a sex- and disease-specific manner (39).

It is plausible that the sarcopenia observed in this population is associated with cachexia, a disease-associated metabolic syndrome that significantly reduces patient's quality of life and ultimate survival (1). In the present study, it is possible that sarcopenia portends the development of cachexia more frequently in men than women, or that muscle loss is not associated with impaired resilience in women with HNC—future prospective investigations are needed to test these hypotheses. While this study demonstrates pre-therapy C3-defined sarcopenia is a useful prognostic marker in men, but not women, diagnosed with HNC, a recent report demonstrated that conversion to sarcopenia (detected by L3 muscle area) was associated with a reduction in overall survival in patients with HNC treated with definitive RT (7). Therefore, the sex-specific influence of post-therapy conversion to sarcopenia using the C3-sarcopenia thresholds established herein remains an area of active investigation. Collectively, our findings highlight the need for future studies to be deliberate in examining sex-specific effects and prevalence of sarcopenia.

Limitations

This study has several limitations that should be taken into consideration when interpreting these data. As with any retrospective review, this study is subjected to missing data and heterogeneous patient follow-up. This study was performed at a single tertiary care institution, resulting in a patient demographic that may not be reflective of other areas of the country. Finally, given the timeframe of this study that traverses the recognition of HPV/p16 as a prognostic factor, these patients are staged by the American Joint Committee on Cancer (AJCC) seventh edition, as opposed AJCC eighth edition staging criteria.

C3 thresholds were not developed against the 'gold standard' for sarcopenia, either volumetric full body cross sectional imaging or dual x-ray absorptiometry. A limitation of this study is that a surrogate marker of sarcopenia, normalized L3 skeletal muscle cross sectional area, is used to estimate the C3 threshold value and may imprecisely estimate sarcopenia. However, this measure is associated with survival endpoints in multiple disease states, supporting its use in the present study. We directly tested C3 measurements with risk of death using a partitioning approach (partDSA survival package in R) which generated a similar threshold value for men but provided no distinct C3 cut-off value for women.

CONCLUSIONS

Taken together, this study demonstrates that C3-sarcopenia thresholds are strongly associated with previously defined L3 sarcopenia thresholds, and C3-defined sarcopenia is

independently associated with reduced survival in men, but not women with HNC. We propose that the C3-defined sarcopenia thresholds herein represent a useful prognostic tool for men with HNC. Future research concerning these observations is warranted, including determining whether these thresholds and sex-specific survival associations extend to other pathologies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Institutional Review Board at Oregon Health and Science University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: BO, AG, and DC. Data curation: BO, JE, NS, MB, and JH. Formal analysis: CD and YC. Funding acquisition: BO and AG. Investigation: BO, CDF, MG, AG, and DC. Methodology: BO, JE, CD, and YC. Resources: BO, CD, CDF, MG, AG, and DC. Software: BO and AG. Supervision: CDF, MG, AG, and DC. Writing - original draft: BO, AG, and DC. Writing - review and editing: BO, JE, CD, NS, MB, JH, YC, CDF, MG, AG, and DC. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.812159/full#supplementary-material>

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Conflict of Interest: Author YC is currently employed by Seagen Inc, although this employment resulted after data and analyses were completed.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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