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Original Article

The impact of sarcopenia on tolerance of radiation and outcome in patients with head and neck cancer receiving chemoradiation

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ABSTRACT

Background and purpose: Sarcopenia is a predictor of poor prognosis in cancer patients. One potential mechanism for worse outcomes in sarcopenic patients is worse tolerance to treatment; this has not been investigated with regard to radiation treatment. We reviewed our institutional experience of head and neck cancer patients receiving concurrent chemoradiation and assessed outcomes with respect to sarcopenia.

Materials and methods: Patients treated between 2012 and 2016 were reviewed. Sarcopenia was assessed from radiation planning computed tomography (CT) scans using muscles at the C3 vertebral body using previously published methods. Survival was calculated using the Kaplan–Meier method. Association between patient factors and outcome was calculated in univariate and multivariate analyses.

Results: Two hundred and forty-six patients were included. Fifty-eight percent met criteria for sarcopenia. Thirty-seven percent experienced chemotherapy delays of >1 week and 14% had radiation treatment breaks >1 week. On multivariate analysis, concurrent smoking (HR 3.85, $p < 0.01$) and sarcopenia (HR 2.15, $p = 0.01$) were associated with chemotherapy toxicity and age >65 years (HR 2.94, $p < 0.01$) and sarcopenia (HR 2.99, $p = 0.04$) were associated with prolonged radiation breaks. Sarcopenia was associated with worse overall survival (HR 1.83, $p = 0.03$) and progression-free survival (HR 1.65, $p = 0.03$) in the overall cohort. When analyzed separately, sarcopenia was not associated with outcomes in p16-positive oropharynx cancers.

Conclusion: Sarcopenic patients receiving concurrent chemoradiation are more likely to require radiation treatment breaks and suffer chemotherapy toxicity than their non-sarcopenic counterparts. This may contribute to worse survival outcomes in head and neck cancer, with the exception of p16-positive oropharyngeal cancer.

The general treatment paradigm for locally advanced head and neck cancer (HNC) is concurrent chemotherapy and radiation (CRT). The addition of chemotherapy improves survival outcomes [1–3] and is associated with significant toxicities, including mucositis, dysphagia, and nausea/vomiting. Maintenance of nutrition during treatment presents a challenge. Patients may present with anorexia and malnutrition prior to treatment as a result of their cancer [4]. Most patients then lose significant amounts of weight [5] during treatment.

In addition to weight loss, patients with HNC often experience the loss of skeletal muscle mass, known as sarcopenia. Even overweight or obese patients may be harboring occult muscle mass loss [6]. Sarcopenia is known to correlate with worse outcomes in multiple cancers [7], and was recently shown to predict for worse overall survival (OS) in HNC [8]. One proposed mechanism for worse oncologic outcomes in patients with sarcopenia is an inability to tolerate optimal cancer therapies. Increased rates of chemotherapy toxicity [9–11] and postoperative complications [12,13] have been observed in sarcopenic cancer patients, including in HNC [14,15]. There has been less investigation on the significance of these measures in patients receiving external beam radiation therapy (EBRT) and CRT.

Computed tomography (CT) is a frequently used, well-validated method of measuring body composition [16]. Traditionally, CT based assessment of sarcopenia is performed by measuring the skeletal muscle at the L3 vertebral body. Routine CT imaging for

Abbreviations: HNC, head and neck cancer; CRT, concurrent chemotherapy and radiation; EBRT, external beam radiation therapy; CT, computed tomography; IMRT, intensity modulated radiation therapy; BMI, body mass index; SMI, skeletal mass index; CSA, cross-sectional area; OS, overall survival; PFS, progression-free survival.

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HNC encompasses the neck and chest but does not extend to the abdomen, which limits the applicability of measuring at L3 in this population. Recently, a method to calculate sarcopenia using skeletal muscle at the C3 vertebral body was described [17]. We sought to characterize rates of sarcopenia using the C3 vertebral body in patients with locally advanced HNC receiving CRT. We hypothesized that sarcopenic patients would have poorer tolerance to chemotherapy and radiation treatments and resulting inferior outcomes.

Materials and methods

Patient selection

After obtaining institutional review board approval, the medical records of patients with histologically proven HNC treated with CRT from January 2012 to July 2016 were reviewed. All patients with Stage III, IVA, or IVB disease by the AJCC 7th edition were included; patients with Stage IVC disease were excluded. Patients with primary cancers of occult origin or cutaneous squamous cell carcinomas were excluded as well. All patients were presented at multidisciplinary head and neck tumor conference. Demographic, treatment, and outcomes data were collected from the electronic medical record. Patients treated with primary surgery had postoperative CRT delivered per established risk factors [18]. Radiation was delivered from 60 to 70 Gy using intensity modulated radiation therapy (IMRT) for all patients. Induction chemotherapy was offered to patients at the discretion of patient's medical oncologist, as was the agent used for concurrent chemotherapy.

Radiation toxicity was defined as treatment days missed due to toxicity. Days missed due to holidays, machine downtime, or travel issues were not recorded. Weekend days were not recorded as potential days missed. Toxicity for chemotherapy included delays greater than 1 week in chemotherapy administration or failure to complete all planned cycles of chemotherapy. Only toxicities that occurred during concurrent chemotherapy administration, rather than induction chemotherapy, were included. Follow-up and survival outcomes were recorded from the date of diagnosis.

Body composition measurement

Heights and weights recorded on the day of CT simulation (or the closest available date in the medical record) were used for muscle mass and body mass index (BMI) calculations. BMI was calculated using the patient's weight in kilograms divided by their height in meters squared. Patients <65 years were stratified as obese (BMI >30) and non-obese (BMI <30) as defined by the National Institutes of Health (NIH) criteria [19]. However, there is evidence that BMI cut-offs that correlate with mortality are different in elderly patients, and as such, BMI >31 kg/m^2 was used in patients $\geq$65 [20].

The presence of sarcopenia was assessed using skeletal muscle index (SMI), a validated method of using CT-based measurements to calculate skeletal muscle mass [21]. CT images were obtained at the time of EBRT simulation. SMI was calculated as previously described by Swartz et al. [17]. Image analysis was performed using ImageJ on a standard desktop computer by a single researcher (R.G.G) who was not aware of patient outcomes. A single axial CT slice at the C3 vertebral body defined as the point at which the entire vertebral arc was visible when scrolling from the caudal to the cephalad direction was selected. The outer perimeter of the sternocleidomastoid and paravertebral muscles were manually segmented; skeletal muscle was defined as −29 to +150 Hounsfield Units (HUs), and the total cross-sectional area (CSA) was computed automatically within the contoured perimeters. Skeletal muscle CSA at C3 was converted using the equation described by Swartz et al to estimate skeletal muscle at L3. This value was then normalized for patient height by dividing by the height squared (m^2), leading to the lumbar SMI (cm^2/m^2) value to define sarcopenia.

Sarcopenia thresholds were made consistent with thresholds that have been associated with increased mortality in a large cohort of cancer patients [22]. For female patients, sarcopenia was defined as a SMI <41 cm^2/m^2, regardless of BMI. For male patients, sarcopenia was defined as SMI <43 cm^2/m^2 if their BMI was <25, and <53 cm^2/m^2 if their BMI was >25. Fig. 1 depicts the contours of the sternocleidomastoid and paravertebral muscles along with differences in skeletal muscle appearance in sarcopenic and non-sarcopenic patients.

Statistical analysis

Demographics, treatment characteristics, treatment tolerance, and outcomes were compared between patients with and without sarcopenia using Student's *t*-test for continuous variables and Chi-square or Fisher's exact test for categorical variables. The primary endpoints were OS and progression-free survival (PFS). If no radiographic or clinical progression was identified, patients were analyzed as censored using time from surgery to last recorded contact. OS and PFS curves were estimated using the Kaplan–Meier (KM) method. Univariate (UVA) and multivariate analyses (MVA) were performed using regression models to identify factors associated with completion of planned chemotherapy, radiation treatment breaks, OS, and PFS. To fit the multivariable model, variables with a global P-value of <0.05 in the UVA were included. Statistical analyses were conducted using the Statistical Analysis System (SAS Institute, Cary, NC). KM curves were generated using GraphPad Prism Version 7.00 for Windows (GraphPad Software, La Jolla, CA). All tests were 2-sided and a p-value of 0.05 was considered significant.

Results

Two hundred and forty-six patients met the above criteria for analysis. Median follow-up time was 35.1 months (range 1–83 months). The median age at diagnosis was 60 years old (range 19–88 years). A majority of patients had Stage IV disease (81%). The most common subsite was oropharyngeal cancer (63%); 117 patients (48%) were p16-positive oropharyngeal primaries. One hundred and forty-three (58%) patients met the established threshold for sarcopenia. The average SMI in female patients with sarcopenia was 33.7 cm^2/m^2 compared to 48.9 cm^2/m^2 in patients without. In male patients, the average SMI in patients with sarcopenia was 46.2 cm^2/m^2 compared to 53.6 cm^2/m^2 in patients without. Patients with sarcopenia were more likely to be greater than 65 years old ($p < 0.01$), female ($p = 0.03$), white ($p < 0.01$), and not be obese ($p < 0.01$). Table 1 demonstrates patient and treatment characteristics stratified by sarcopenia.

The most common chemotherapy regimen used concurrently with radiation therapy was cisplatin (70%) followed by cetuximab (17%). Thirty-seven percent of patients experienced chemotherapy toxicity. Forty-five percent of patients with sarcopenia had chemotherapy delays compared to only 26% of patients without ($p < 0.01$). The relationship between patient and treatment characteristics and the likelihood of chemotherapy toxicity and radiation breaks is seen in Table 2. On UVA, concurrent smoking ($p < 0.01$) and sarcopenia ($p < 0.01$) were associated with toxicity. On MVA, both concurrent smoking (HR 3.85, $p < 0.01$) and sarcopenia (HR 2.15, $p = 0.01$) remained significantly associated with toxicity.

Thirty-five percent of patients experienced at least one day of radiation delay due to toxicity. The median number of treatments

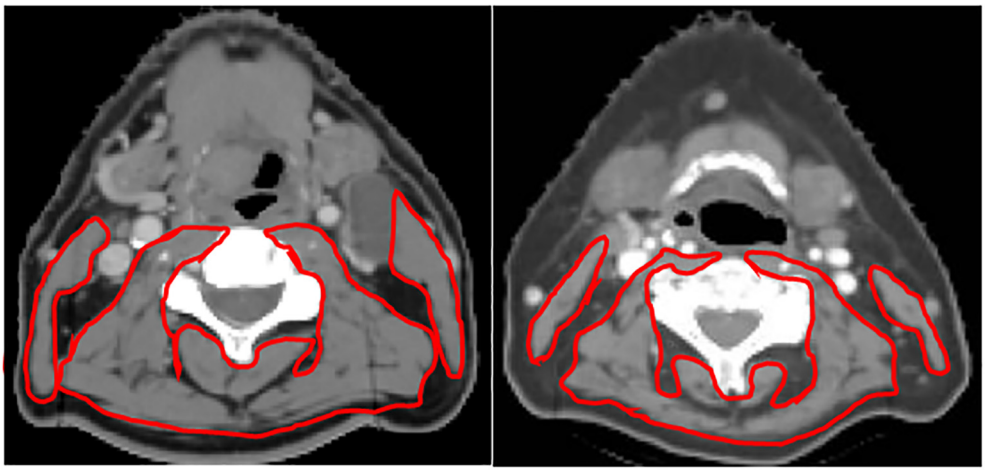

Fig. 1. Examples of skeletal muscle contours. Pictured are example contours of the sternocleidomastoid and paravertebral muscles on an axial slice at the C3 vertebral body in a patient without sarcopenia (left) and with sarcopenia (right).

Table 1
Characteristics and anthropometrics of patients with head and neck cancer stratified by skeletal muscle index.

	Normal SMI (n = 103, 41.9%)	Low SMI (n = 143, 58.1%)	P-value
Age			**<0.001**
<65 years	84 (50.3%)	19 (24.0%)	
>65 years	83 (47.7%)	60 (76.0%)	
Gender			
Male	90 (87.4%)	109 (76.2%)	**0.028**
Female	13 (12.6%)	34 (23.8%)	
Race			
White	84 (81.6%)	138 (96.5%)	**<0.001**
Non-white	19 (18.4%)	5 (3.5%)	
FIGO Stage			
III	30 (29.1%)	27 (18.9%)	0.060
IV	73 (70.9%)	116 (81.1%)	
Subtype			
Larynx/Hypopharynx	29 (28.2%)	30 (21.0%)	0.312
Oropharynx	63 (61.2%)	91 (63.6%)	
Other	11 (10.6%)	22 (15.4%)	
Smoking Status			
Never	34 (33.0%)	35 (25.5%)	0.303
Former	49 (47.6%)	73 (51.1%)	
Current	20 (19.4%)	35 (24.4%)	
P16-positive	54 (52.4%)	67 (46.9%)	0.388
Induction chemotherapy	9 (8.7%)	13 (9.2%)	0.910
Concurrent Cisplatin	75 (72.8%)	98 (68.5%)	0.468
Post-operative	17 (16.5%)	37 (25.9%)	0.080
†BMI			
Non-obese (<30 kg/m^2)	48 (28.6%)	55 (70.5%)	**<0.001**
Obese (>30 kg/m^2)	120 (71.4%)	23 (29.5%)	
Lumbar skeletal muscle index (cm^2/m^2)	53.0	43.3	**<0.001**

† Body mass index.

missed was 2 (range 1–30 days). Fourteen percent of patients required a treatment break of 1 week or greater. The most common reason for prolonged treatment break was poor oral intake due to esophagitis or mucositis, which occurred in 50% of patients. The next most common etiology was infection (19%). Sarcopenic patients were more likely to require a radiation treatment break of 1 week or greater (19% v 5%, $p < 0.01$). Among patients missing any days of treatment, there was no association with any patient or treatment factors, including sarcopenia. However, age >65 years ($p < 0.01$), BMI <30 ($p = 0.04$), and sarcopenia ($p < 0.01$) predicted for prolonged break from radiation on UVA. On MVA, SMI (HR 2.99, $p = 0.04$) and age >65 (HR 2.94, $p = 0.01$) remained significant.

KM curves for OS and PFS of the entire cohort stratified by sarcopenia are seen in Fig. 2. There was a significant difference in OS ($p = 0.01$) and PFS ($p = 0.02$) between patients with and without sarcopenia, with estimated OS at 3 years 79.9% versus 65.3% and estimated PFS at 3 years 81.3% versus 68.1% respectively. On multivariate regression models, non-p16-positive oropharynx status (HR 3.60, $p < 0.01$), non-cisplatin concurrent chemotherapy (HR 1.78, $p = 0.02$), concurrent smoking (2.15, $p = 0.04$), and sarcopenia (1.83, $p = 0.03$) were associated with worse OS and only non-p16-oropharynx negative status (HR 2.28, $p < 0.01$) and sarcopenia (HR 1.65, $p = 0.03$) were associated with worse PFS. UVA and MVA results for all patients can be found in Supplemental Table 1.

Survival analysis was then performed independently in patients with p16-positive oropharynx cancers and those without. Patient characteristics stratified into these groups can be seen in Supplemental Table 2. KM curves stratified by sarcopenia for p16-positive oropharynx patients can be seen in Fig. 3a, while those for all other patients are seen in Fig. 3b. In p16-positive oropharynx patients, there was no difference in either OS ($p = 0.82$) or PFS ($p = 0.38$) in sarcopenic compared to non-sarcopenic patients. In all other patients, the difference in OS ($p = 0.01$) and PFS ($p = 0.02$) remained significant, with the estimated OS at 3 years 71.2% and 53.2%, and estimated PFS at 3 years 78.1% and 56.3% in patients without and with sarcopenia, respectively. In multivariate regression models for OS for patients excluding p16-positive oropharynx patients, only sarcopenia was statistically significant (HR 1.94, $p = 0.04$), however there was a trend toward worse survival in patients with Stage IV disease (HR 1.95, $p = 0.054$). For PFS, both sarcopenia (HR 2.0, $p = 0.04$) and Stage IV disease (HR 2.07, $p = 0.046$) were significant on MVA. UVA and MVA results are shown in Table 3.

Discussion

This study examined the impact of sarcopenia, as measured by low skeletal muscle mass at the C3 vertebral body, on patients with HNC receiving CRT. The rate of sarcopenia in our study was 58%, within the range of other reports of sarcopenia in HNC ranging from 28% in patients with oropharyngeal cancer [23] to 77% in patients undergoing total laryngectomy [15]. This study is the largest to assess skeletal muscle mass using the C3 vertebral body and confirms that this method is effective in identifying patients in

Table 2
Univariate and multivariate predictors of chemotherapy toxicity and radiation breaks.

	Chemotherapy Toxicity				Prolonged Radiation Breaks			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age								
<65 years	*Ref*	0.07	*Ref*	0.08	*Ref*	**<0.001**	*Ref*	**0.007**
>65 years	1.66 (0.96–2.87)		1.71 (0.94–3.13)		3.75 (1.74–8.07)		2.94 (1.34–6.48)	
Gender								
Male	*Ref*	0.88			*Ref*	0.37		
Female	0.95 (0.50–1.84)				1.50 (0.63–3.58)			
Race								
White	*Ref*	0.9			8.37 (1.11–999.9)	0.15		
Non-white	2.45 (0.88–6.8)				*Ref*			
Stage								
III	*Ref*	0.68			*Ref*	0.28		
IV	0.88 (0.47–1.63)				1.73 (0.64–4.73)			
Subsite								
Larynx/Hypopharynx	*Ref*				*Ref*			
Oropharynx	1.10 (0.60–2.04)	0.48			1.45 (0.61–3.46)	0.22		
Other	1.83 (0.73–4.61)	0.19			0.81 (0.26–2.52)	0.43		
Smoking Status								
Never	*Ref*		*Ref*		*Ref*			
Former	0.60 (0.32–1.12)	0.75	2.07 (0.98–4.41)	0.86	1.93 (0.82–4.57)	0.16		
Current	3.34 (1.72–6.49)	**0.003**	3.85 (1.19–7.74)	**<0.001**	1.24 (0.47–3.28)	0.79		
P16-positive oropharynx								
Yes	Ref	0.95			*Ref*	0.22		
No	1.017 (0.61–1.71)				1.61 (0.75–3.45)			
Induction chemotherapy								
Yes	*Ref*	0.56			1.55 (0.35–6.99)	0.57		
No	1.76 (0.30–1.93)				*Ref*			
Concurrent Cisplatin								
Yes	*Ref*	0.51			0.66 (0.31–1.44)	0.30		
No	1.21 (0.69–2.15)				*Ref*			
Post-operative								
Yes	*Ref*	0.57			1.47 (0.64–3.40)	0.37		
No	1.20 (0.65–2.22)				*Ref*			
†BMI								
<30	1.29 (0.74–2.27)	0.37			2.80 (1.03–7.45)	**0.04**	1.71 (0.59–5.00)	0.32
>30	*Ref*				*Ref*		*Ref*	
Sarcopenia								
Yes	2.35 (1.36–4.06)	**0.002**	2.15 (1.19–3.8)	**0.01**	4.56 (1.69–12.30)	**0.003**	2.99 (1.04–8.64)	**0.04**
No	*Ref*		*Ref*		*Ref*		*Ref*	

† Body mass index.

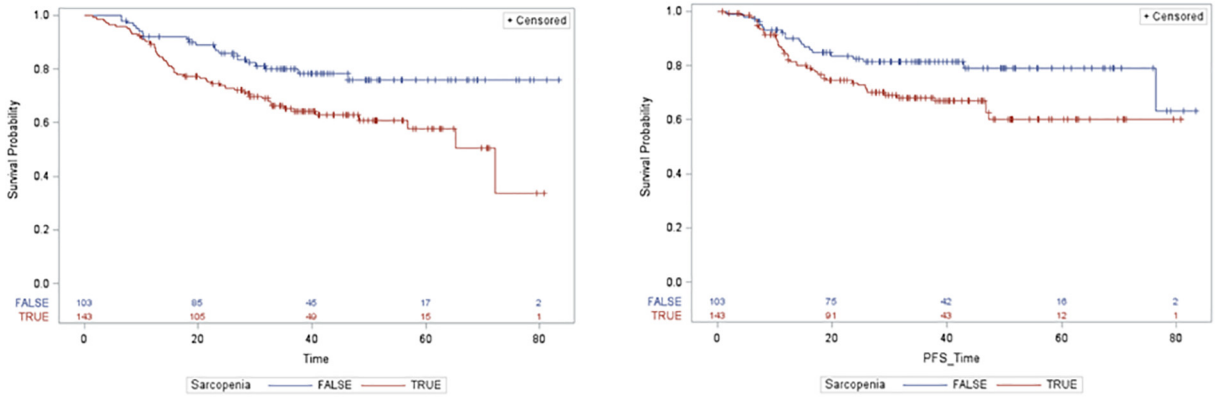

Fig. 2. Survival outcomes in the full cohort. Kaplan–Meier's curves of Overall Survival and Progression-Free Survival in all patients in the cohort stratified by the presence of sarcopenia as determined by pre-defined cut-offs.

whom sarcopenia is a poor prognostic factor. Our results suggest that established cut-offs for sarcopenia predict for poor tolerance to chemotherapy and radiation and poor survival outcomes in patients with HNC.

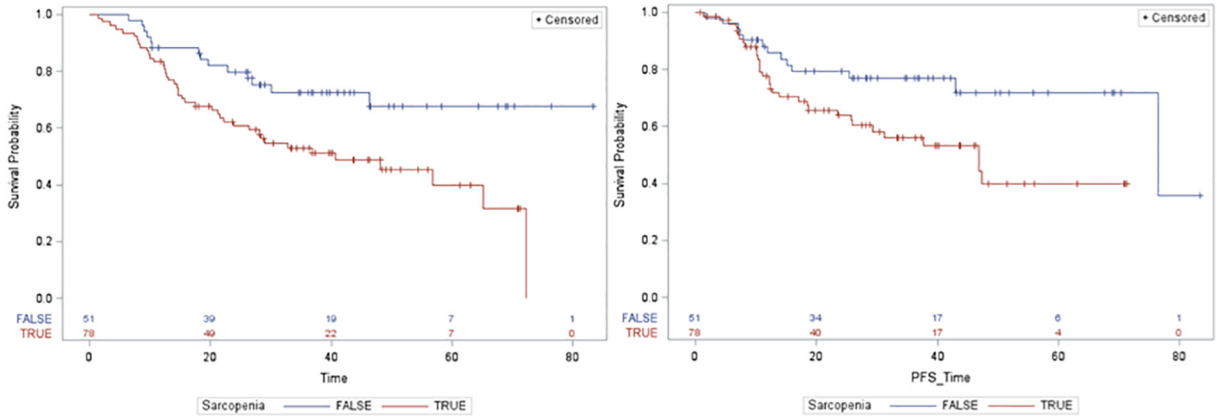

Fig. 3a. Survival outcomes in patients with p16-positive oropharynx cancer. Kaplan–Meier's curves of Overall Survival and Progression-Free Survival in p16-positive oropharyngeal patients stratified by the presence of sarcopenia as determined by pre-defined cut-offs.

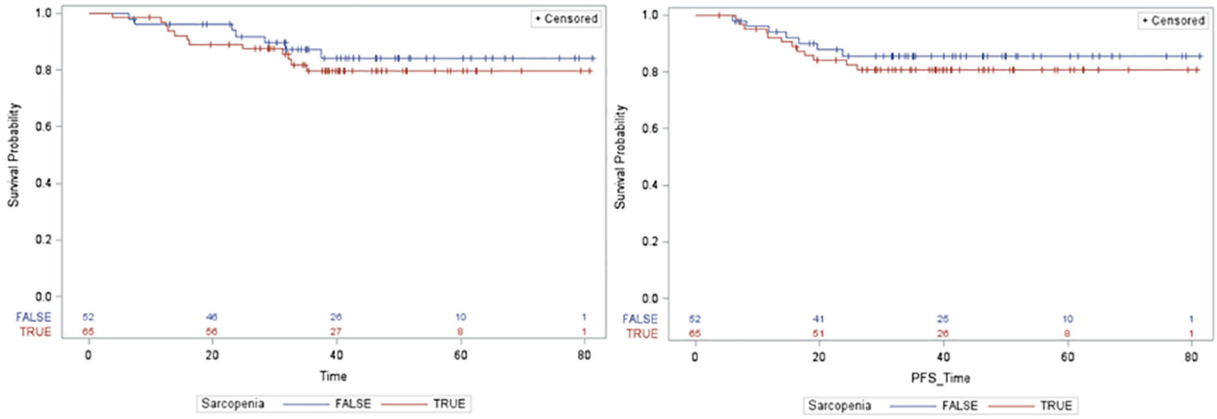

Fig. 3b. Survival outcomes in patients without p16-positive oropharynx cancer. Kaplan–Meier's curves of Overall Survival and Progression-Free Survival excluding patients with p16-positive oropharyngeal cancer stratified by the presence of sarcopenia as determined by pre-defined cut-offs.

While studies have examined the impact of sarcopenia on dose-limiting chemotherapy toxicity in multiple cancers, including HNC, little information exists regarding the impact on tolerance to radiation treatments. Radiation to the head and neck is marked by significant toxicities, which often require treatment breaks to allow for healing and recovery. However, these breaks allow for accelerated repopulation and increased radioresistance, and treatment breaks greater than 1 week are known to predict for worse treatment outcomes in patients receiving CRT [24]. In our study, nearly 20% of patients with sarcopenia required a treatment break greater than 1 week. Of these, a majority of breaks were due to mucositis, esophagitis, or dermatitis, all of which are direct results of radiation treatment as opposed to chemotherapy. These rates of radiation treatment breaks are similar to those seen in other frail populations in HNC. Daly et al. [25] found a rate of unplanned treatment breaks >3 days of 20% and unplanned hospitalizations of 33% among HNC patients receiving CRT. Huang et al. [26] reported their experience in treating patients over 75 and found rates of unplanned treatment breaks of 23% in those undergoing intensified radiation, though this did not differ significantly from younger patients.

Chemotherapy toxicity was also increased in sarcopenic patients compared to non-sarcopenic patients. Our findings closely parallel those of Wendrich et al. [14], who found rates of chemotherapy dose-limiting toxicity of 44% in sarcopenic patients compared to 14% in non-sarcopenic patients using a similar population of HNC patients. These are comparable to our rates of 45% and 26%, respectively. The mechanism for increased toxicity of cancer treatments in sarcopenic patients is yet unknown. For patients receiving chemotherapy, proposed mechanisms include changes in pharmacokinetics that are inadequately captured by dosing based on body surface area [27,28], increased frailty from inactivity and comorbidity captured by low skeletal muscle mass [29], or a pro-inflammatory state resulting from their disease of which sarcopenia is a sensitive marker [30].

The increased toxicity of radiation therapy in sarcopenic patients may be related to similar factors as well. For example, radiation-induced fatigue is known to be associated with increased levels of proinflammatory cytokines, including TNF-α and IL-6, both of which are increased in patients with sarcopenia [31]. These factors have also been shown to be associated with oral mucositis in animal models [32]. TGF-β is another factor elevated in sarcopenic patients [33] that has been shown to mediate radiation-induced injuries. Thus, a sarcopenic patient's underlying pro-inflammatory state may be exacerbated by radiation therapy. Alternatively, sarcopenia may be a marker of a clinically distinct "frailty syndrome" marked by declines in physiologic reserve and a resulting inability to manage acute stressors [34]. These patients may be less suited to tolerate the significant toxicities that accompany CRT in HNC.

Our study is the largest to examine sarcopenia using pre-established cut-offs in p16-positive oropharyngeal patients. While sarcopenic patients had worse survival outcomes overall, this was driven by patients without p16-positive oropharyngeal cancers.

Table 3
Univariate and multivariate predictors of OS and PFS excluding patients with p16-positive oropharynx cancer.

	Overall Survival				Progression-Free Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age								
<65 years	*Ref*	0.051	*Ref*	0.37	*Ref*	0.41		
>65 years	1.70 (0.99–2.89)		0.78 (0.45–1.35)		1.28 (0.71–2.31)			
Gender								
Male	*Ref*	0.59			*Ref*	0.15		
Female	0.84 (0.45–1.57)				0.59 (0.28–1.22)			
Race								
White	*Ref*	0.42			*Ref*	0.97		
Non-white	0.72 (0.33–1.59)				1.02 (0.57–2.19)			
Stage								
III	*Ref*	**0.01**	*Ref*	0.054	*Ref*	**0.03**	*Ref*	**0.046**
IV	2.3 (1.19–4.53)		1.95 (0.99–3.84)		2.25 (1.10–4.58)		2.07 (1.01–4.23)	
Subsite								
Larynx/Hypopharynx	*Ref*				*Ref*			
Oropharynx	1.50 (0.82–2.75)	0.19			1.75 (0.90–3.41)	0.10		
Other	0.97 (0.48–1.95)	0.97			1.13 (0.53–2.39)	0.75		
Smoking Status								
Never	*Ref*				*Ref*			
Former	1.40 (0.65–3.05)	0.39			1.80 (0.75–4.36)	0.19		
Current	1.23 (0.52–2.92)	0.63			1.35 (0.51–3.62)	0.55		
Induction chemotherapy								
Yes	*Ref*	0.55			*Ref*	0.69		
No	0.55 (0.22–1.38)				0.79 (0.24–2.54)			
Concurrent Cisplatin								
Yes	*Ref*	**0.03**	*Ref*	0.12	*Ref*	0.17		
No	1.81 (1.06–3.08)		1.54 (0.90–2.65)		1.51 (0.84–2.72)			
Post-operative								
Yes	*Ref*	0.89			*Ref*	0.29		
No	0.96 (0.53–1.73)				0.72 (0.39–1.32)			
†BMI								
<30	1.63 (0.84–3.16)	0.15			2.04 (0.95–4.40)	0.07		
>30	*Ref*				*Ref*			
Sarcopenia								
Yes	2.29 (1.25–4.21)	**0.01**	1.94 (1.03–3.67)	**0.04**	2.16 (1.11–4.18)	**0.02**	2.0 (1.03–3.88)	**0.04**
No	*Ref*		*Ref*		*Ref*		*Ref*	

This may be due to the population in which cut-offs for sarcopenia have been established. Martin et al. [22] used 1473 patients with lung and gastrointestinal cancer to establish body composition values that correlated with poorer outcomes; likewise, the study by Prado [35], which were the cut-offs used by Grossberg, also created cut-offs using lung and gastrointestinal cancers. While risk factors for other HNC patients mirror those of lung cancer, p16-positive oropharyngeal cancers occur in a distinct population who are more likely to be young, male, white, and without comorbidity [36]. As a result, there may be a need for distinct cut-offs in this population, or there may be an absence of a prognostic impact of sarcopenia due to different disease biology.

Limitations of our study include its retrospective nature, varied therapies received, and specific patient population. We obtained information about body composition at the time of simulation to allow for a more equal comparison of toxicity of CRT. However, patients that were post-operative or who received induction chemotherapy may have developed sarcopenia only after initial treatment, whereas patients receiving concurrent CRT only had sarcopenia before any treatment, which may bias our results. Additionally, despite limiting our study to patients receiving CRT, there was significant heterogeneity among patients in chemotherapy received, though type of chemotherapy was not significant on multivariate analysis. We included patients treated by a variety of radiation oncologists, so it is possible there was some variation in radiation planning that is not accounted for. Finally, obesity and physical activity rates vary widely across age, ethnicity, and geography, and this may limit the generalizability of our patient cohort.

Future directions would include study of a larger p16-positive cohort to see if body composition measures that correlate with outcomes in that specific population could be identified. Other avenues would be to examine the effects of other body composition measures in head and neck cancer. Studies in other malignancies have suggested that the skeletal muscle density (SMD), measured in mean HUs at the L3 vertebral body, may correlate more strongly with outcome than SMI [37]. Another measure of interest is skeletal muscle gauge (SMG), which incorporates both SMI and SMD into one variable [38]. However, there have not yet been studies correlating SMD at the C3 and L3 vertebral bodies, and it is unknown what the relationship between these two measurements would be.

Additionally, sarcopenia is potentially a modifiable risk factor, and identification of sarcopenic patients may allow for early interventions to minimize treatment delays and improve outcomes. These efforts may take a variety of forms. Early, intense nutritional interventions have been demonstrated to minimize weight loss and improve treatment tolerance [39]. A recent study from the Trans-Tasman Radiation Oncology Group (TROG) assessed the impact of psychological interventions on nutritional status and found patients in the treatment arm were more well-nourished,

lost a smaller percentage of weight, and a higher quality of life [40]. Alternatively, there are current trials assessing the impact of a supervised progressive resistance training program in HNC cancer patients both during and after CRT treatments and its impact on body composition, muscle strength, and functional performance [41]. Since sarcopenia was assessed at the time of CT simulation in our study, early referrals for patients with low SMI could be made prior to initiation of CRT treatments. A prospective trial examining the impact of these interventions specifically in patients with sarcopenia identified at the time of simulation would be illustrative.

In conclusion, our findings add to a growing literature that suggest that body composition plays a role in outcomes in head and neck cancer and identifies a potential cause, which is poorer tolerance of chemotherapy and radiation treatments. It remains to be seen whether interventions can reverse these changes and improve outcomes.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.023.

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