

Nutritional status and skeletal muscle status in patients with head and neck cancer: Impact on outcomes

Merran Findlay^{1,2,3,4*} , Kathryn White^{1,3,4} , Chris Brown⁵  & Judith D. Bauer⁶ 

¹Cancer Services, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; ²Chris O'Brien Lifehouse, New South Wales, Camperdown, NSW, Australia; ³Cancer Nursing Research Unit, Susan Wakil School of Nursing and Midwifery, Faculty of Medicine and Health, University of Sydney, Camperdown, NSW, Australia; ⁴The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council, NSW, Australia; ⁵National Health and Medical Research Council Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia; ⁶School of Human Movement and Nutrition Sciences, University of Queensland, St Lucia, QLD, Australia

Abstract

Background Computed tomography (CT)-defined skeletal muscle depletion and malnutrition are demonstrated as poor prognostic factors in patients with head and neck cancer (HNC), however to date, have only been explored in isolation. We aimed to describe body composition profile and examine the impact of nutritional status as well as independently and concurrently occurring body composition features on overall survival, treatment completion, unplanned admissions and length of stay (LOS) in patients undergoing radiotherapy (RT) or chemoradiotherapy (CRT) of curative intent for HNC.

Methods This work is a retrospective, observational study of patients who had completed treatment of curative intent for HNC. Scored Patient-Generated Subjective Global Assessment (PG-SGA) was used to determine nutritional status. Tissue-density data were derived at the third lumbar vertebra (L3) with sarcopenia and myosteatosis defined by published, sex-specific threshold values stratified by body mass index for skeletal muscle index (cm^2/m^2) and skeletal muscle radiodensity (SMR, Hounsfield Unit).

Results Pre-treatment data ($n = 277$: 78% male, mean (SD) age 60 (13) years) revealed the prevalence of malnutrition (24.9%), sarcopenia (52.3%), myosteatosis (82.3%), and concurrently occurring sarcopenia and myosteatosis (39.7%). Malnutrition was independently associated with reduced OS for patients with moderate [hazard ratio (HR) 2.57; 95% confidence interval (CI) 1.45–4.55, $P = 0.001$] and severe (HR 3.19; 95% CI 1.44–7.07, $P = 0.004$) malnutrition on multivariable analysis but not sarcopenia (HR 1.09; 95% CI 0.70–1.71), $P = 0.700$ or myosteatosis (HR 1.28; 95% CI 0.57–2.84), $P = 0.500$). Malnutrition was associated with treatment discontinuation ($P < 0.001$), not completing RT as planned ($P < 0.001$), unplanned hospital admission ($P = 0.021$), and greater LOS ($P < 0.001$). Skeletal muscle status features were associated with unplanned hospital admissions for those with no features (32%), with sarcopenia only (50%), myosteatosis only (25%), and concurrent sarcopenia and myosteatosis (50%), $P < 0.001$. Similarly, a clinically relevant greater median (Q1, Q3) LOS was observed for those with sarcopenia only [5 (3, 32)], myosteatosis only [10 (5, 30)], concurrent sarcopenia, and myosteatosis [14 (4, 33)] days vs. those with no features [3 (2, 11)] days, $P = 0.2$.

Conclusions Malnutrition was a more powerful prognostic indicator than CT-defined skeletal muscle depletion and was independently associated with reduced OS in patients undergoing RT or CRT of curative intent for HNC. CT-defined skeletal muscle depletion studies should recognize the multifaceted nature of human body composition and also measure nutritional status using validated methods in order to move towards developing a typology of high risk criteria for this complex patient group.

Keywords Head and neck cancer; Sarcopenia; Myosteatosis; Body composition; Muscle mass; Muscle radiodensity; Radiotherapy; Malnutrition; Computed tomography; Survival

Received: 8 March 2021; Revised: 5 September 2021; Accepted: 11 September 2021

*Correspondence to: Merran Findlay, Cancer Services, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. Tel: +61 (0)411779420, Fax: +61 2 86271500. Email: merran.findlay@health.nsw.gov.au

Introduction

Head and neck cancers (HNC) comprise tumours of the lip, oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and salivary glands accounting for more than 650 000 cases and 330 000 deaths annually.¹ The high prevalence of skeletal muscle depletion (6.6–70.9%)² and malnutrition (30–50%)^{3,4} in patients with HNC impacts negatively on clinical, cost, and patient-centred outcomes. The multifactorial syndrome of cancer-associated malnutrition is characterized by progressive skeletal muscle loss with or without adipose tissue loss arising from the combination of reduced food intake and metabolic derangements.^{5–7} The Global Leadership Initiative on Malnutrition (GLIM) recommends the diagnostic criteria for malnutrition includes at least one phenotypic [involuntary weight loss, low body mass index (BMI), or reduced muscle mass] and one etiologic (reduced food intake or assimilation, disease burden, or inflammatory condition) criterion.⁸ Sarcopenia⁹ and more recently, myosteatorsis¹⁰ have been recognized as independent poor prognostic factors in patients with cancer regardless of weight or nutritional status.

Sarcopenia, defined as low muscle mass, and quantified from computed tomography (CT) images as low skeletal muscle index (SMI) is a demonstrated poor prognostic factor in patients with HNC in latest meta-analyses^{11–13} although consensus regarding sarcopenia assessment, definitions, and reporting is still warranted. The gold standard of body composition analysis at the tissue-organ level is at the level of the third lumbar vertebra (L3)^{14–16}; however, HNC studies have also reported findings from other, yet to be validated, anatomical landmarks. The availability of diagnostic positron emission tomography-computed tomography (PET-CT) images taken as routine care pre-treatment and post-treatment in some centres facilitate the evaluation of sarcopenia in patients with HNC at L3 where visceral and subcutaneous adiposity can also be visualized and annotated, an important consideration in an era of sarcopenic obesity. Our recent systematic review also demonstrated associations between sarcopenia and both radiotherapy (RT) treatment breaks and chemotherapy dose-limiting toxicities.²

Myosteatorsis, defined as low skeletal muscle radiodensity (SMR), is a further radiologically defined prognostic marker inversely related to muscle lipid infiltration.¹⁷ We have recently demonstrated that myosteatorsis may also hold prognostic value in patients with HNC¹⁸ which has yet to be reported elsewhere and therefore justifies further investigation. To date, studies exploring the impact of skeletal muscle depletion in patients with HNC have examined only low SMI in isolation without evaluation of concurrent low SMR. This has been suggested in other cancer populations as inadequate

for description of body composition status for any given individual and that comprehensive assessment of potential combinations of body composition features is needed.¹⁹

Low skeletal muscle mass is one potential phenotypic criterion for malnutrition; however, malnutrition itself is also a recognized poor prognostic factor,²⁰ but our recent systematic review determined this has not yet been explored in conjunction with skeletal muscle depletion in patients with HNC.² The Scored Patient-Generated Subjective Global Assessment (PG-SGA) is a comprehensive nutrition assessment tool validated for use in oncology populations²¹ and recommended for use in routine practice by evidence-based guidelines.²² The tool comprises both a scored component based on patient-generated details of weight history, food intake, nutrition-impact symptoms and evaluation of activities and function, and also a clinician-generated global assessment of fat stores, muscle status, and fluid status based on physical examination. This tool was not designed to detect sarcopenia or myosteatorsis; however, it is consistent with the GLIM criteria and remains a valid and widely used method to diagnose malnutrition.

We aimed to describe the body composition profile of patients and examine the association between (i) nutritional status and (ii) independently or concurrently occurring body composition features comprising sarcopenia and myosteatorsis on outcomes including overall survival (OS), treatment completion, unplanned admissions and length of stay (LOS) in patients undergoing adjuvant or definitive RT or chemoradiotherapy (CRT) of curative intent for HNC.

Materials and methods

Study population and study design

A retrospective, observational cohort study was undertaken in adults (≥ 18 years) with a primary diagnosis of HNC treated with adjuvant or definitive RT or CRT of curative intent within a 5 year period between January 2013 and December 2017. Data of consecutive patients who commenced treatment during the study period were extracted from the Department of Radiation Oncology electronic medical record (eMR) system of a single tertiary treatment centre for HNC. Eligibility criteria included the availability of pre-treatment PET-CT scans taken as routine care. Exclusion criteria were no PET-CT scans available or of suitable quality for analysis and diagnoses that may occur in the head and neck region but do not fall into the accepted diagnostic grouping for HNC, for example, sarcoma.

Outcome measures

The primary outcome was OS, defined as death from any cause, where primary analysis compared OS (years) between skeletal muscle depletion (either sarcopenia or myosteatosis) or no skeletal muscle depletion and also between malnourished and well-nourished groups. OS was calculated from the end of RT or the last known date alive. Secondary outcomes included treatment completion, RT and CRT prescribed versus delivered, unplanned hospital admissions, and LOS (days).

Nutritional status and intervention

Nutritional status was assessed using the PG-SGA²¹ in line with best practice in oncology populations, evidence-based guidelines for nutritional management of patients with HNC²² and consistent with GLIM malnutrition diagnostic criteria. The PG-SGA categorizes patients as well-nourished (A) or either moderately (B) or severely (C) malnourished. Patients received nutrition assessment and intervention according to standard care derived from evidence-based guidelines²² with improved uptake achieved through a prior implementation science approach.²³ In our centre, nutrition intervention commonly involves nutrition support delivered via prophylactic gastrostomy in patients receiving multimodal treatment, particularly for those requiring adjuvant or definitive CRT. Nasogastric tube feeding was commenced for patients without a gastrostomy who were unable to maintain adequate nutrition and hydration orally. Enteral or oral nutrition support was initiated when clinically indicated according to nutritional status, weight, percentage weight loss, and nutritional intake. Routine care for high nutrition-risk patients in the treating centre aims for dietetic assessment weekly during treatment and for as long as needed in the post-treatment recovery and rehabilitation phase until weight and nutritional intake are stabilized and tube feeding is no longer clinically indicated.

Data collection

Patient characteristics, diagnosis, and treatment demographics were collected from the eMR and paper-based hospital records with death data current to 23 June 2020 obtained from the New South Wales Registry of Births, Deaths and Marriages.²⁴ Ethnicity (self-reported) was captured from the eMR and classified according to the Australian Standard Classification of Cultural and Ethnic Groups.²⁵ All research data was maintained using Sydney Local Health District hosted Research Electronic Data Capture.²⁶

Body composition analysis by computed tomography

Cross-sectional tissue-density data were derived from the CT component of PET-CT images taken for routine cancer staging at diagnosis. An individual, trained observer (MF) blind to patients' outcomes analysed single axial images at L3 using Slice-O-Matic, Version 5.0 (Tomovision, Magog, QC, Canada). All images were 3 mm thickness with a peak kilovoltage of 120. Recognized Hounsfield [Hounsfield unit (HU)] threshold values were applied for muscle (−29 to +150 HU), visceral adipose tissue (VAT, −50 to −150 HU), and subcutaneous adipose tissue (SAT, −30 to −190 HU). Adipose tissue external to the abdominal wall but within the muscle fascia was annotated as SAT with both SAT and VAT summed to yield total adipose tissue (TAT) as described by Mishra *et al.*²⁷ Mean surface area (cm²) for skeletal muscle, VAT, SAT and TAT and mean (HU) SMR were normalized for height (m²) and reported as SMI (cm²/m²), visceral adipose tissue index (VATI, cm²/m²), subcutaneous adipose tissue index (cm²/m²), and total adipose tissue index (cm²/m²). Sex-specific, BMI-stratified threshold values published by Martin *et al.* were applied for classifying patients with sarcopenia and myosteatosis.²⁸ Sarcopenia was defined as an SMI for female patients < 41 cm²/m² and for male patients < 43 cm²/m² (BMI < 25.0 kg/m²) and <53 cm²/m² (BMI ≥ 25 kg/m²). Myosteatosis was defined for both sexes as a mean SMR < 41 HU (BMI < 25.0 kg/m²) and 33 HU (BMI ≥ 25 kg/m²). The number and combination of body composition features exhibited by individuals was also captured to explore whether skeletal muscle depletion and obesity (defined as BMI ≥ 30 kg/m²) influence outcomes when occurring in isolation or concurrently.

Statistical analysis

Differences were analysed using paired *t*-tests and Pearson χ^2 test for continuous and categorical variables, respectively. Non-parametric variables were analysed using the Kruskal–Wallis test. Data are presented as mean (SD) and median (range or interquartile range) according to distribution normality. Survival curves were constructed using the Kaplan–Meier method with log-rank test reported. Unadjusted and adjusted Cox proportional hazard regression analyses were performed to determine hazard ratios (HR) that are reported with corresponding 95% confidence intervals (CIs). Covariates were investigated according to their prognostic value and included age, sex, ethnicity, disease stage, performance status, Charlson comorbidity index (CCI), BMI, human papilloma virus (HPV) status, alcohol use, and smoking history. Analysis was completed using R Version 1.2.5042 (Vienna, Austria).²⁹ Statistical significance was

considered at the level of $P < 0.05$ with all results also evaluated for clinical importance and implications for practice.

Ethics approval and reporting

The study was approved by the Human Research Ethics Committee at Royal Prince Alfred Hospital, Sydney, Australia (HREC/14/RPAH/524) with site-specific approval for this study to be conducted across Royal Prince Alfred Hospital (SSA/15/RPAH/148) and Chris O'Brien Lifehouse (LH15.017). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement to ensure comprehensive reporting.

Results

Within the study period, 359 patients underwent adjuvant or definitive RT or CRT for HNC. Of these, 277 patients had evaluable scans and met the inclusion criteria. Patients without evaluable scans were slightly older with mean (SD) age of 65 (13) vs. 60 years ($P = 0.003$), female (40% vs. 22%, $P = 0.002$) and more likely to have tumours of the oral cavity ($P < 0.001$). Scan availability can be dependent upon whether the staging investigations were undertaken in a centre elsewhere and also variation in clinician practices with regards to requesting PET-CT imaging for specific diagnoses.

Patient characteristics

Baseline demographics and clinical characteristics of included patients ($n = 277$) are presented in *Table 1*. The majority were male (78%), tumour type was predominantly squamous cell carcinoma (85%) with the three most common tumour sites oropharynx (41%), nasopharynx (15%), and larynx (13%). Most patients (79%) had advanced clinical stage (III/IV) according to American Joint Committee on Cancer 7th Edition³⁰ requiring multimodal treatment regimens (86%). Baseline nutrition and body composition characteristics are presented in *Table 2*. Body composition features differed by sex including SMI, SMR, VATI, SATI and TATI.

Skeletal muscle status, combination of body composition features, and nutritional status

The prevalence of the various combinations of body composition features in conjunction with nutritional status as determined by the PG-SGA Global Category is shown in *Figure 1*. Malnutrition was prevalent in 24.9% of patients, and while most frequently occurring in those with concurrent

sarcopenia and myosteatosi s (14.4%), it appeared to be present irrespective of body composition features. Sarcopenia prevalence overall was 52.3%; however, it was only present in isolation in a small proportion of patients (6.5%), more frequently occurring concurrently with myosteatosi s (39.7%) or with myosteatosi s and obesity combined (6.2%). Sarcopenic obesity was not present in any patients unless myosteatosi s was also present. Similarly, the overall prevalence of myosteatosi s was 82.3%, which was present in isolation (23.5%) but more so concurrently with sarcopenia (39.7%), concurrently with obesity (13.0%) and with sarcopenia and obesity combined (6.1%). Only 9.4% patients did not exhibit either a single or combination of body composition features, the majority of whom were well-nourished.

Skeletal muscle status, nutritional status, and overall survival

Associations between skeletal muscle status and OS are presented in *Figure 2*. The number of body composition features was associated with reduced OS (log-rank $P = 0.017$) as was the combination of skeletal muscle features (log-rank $P = 0.0028$). Associations between nutritional status and OS are presented in *Figure 3*. Nutritional status as determined by PG-SGA Global Category was associated with reduced OS (log-rank $P < 0.0001$) as was malnutrition (moderately and severely malnourished combined) (log-rank $P < 0.0001$). Unadjusted and adjusted analyses are presented in *Table 3*. Covariates not associated with reduced OS in the cohort were excluded from the adjusted models. On adjusted analysis pre-treatment nutritional status remained an independent predictor of reduced OS for patients who were moderately malnourished (HR = 2.57; 95% CI 1.45–4.55), $P = 0.001$ or severely malnourished (HR = 3.19; 95% CI 1.44–7.07), $P = 0.004$ as did overall malnutrition (HR = 3.03; 95% CI 1.87–4.93), $P < 0.001$. Sarcopenia, myosteatosi s, number of body composition features, and combination of body composition features were also significant predictors of reduced OS on unadjusted analysis but did not remain so when adjusted for covariates that included malnutrition.

Treatment completion

Associations between nutritional status and skeletal muscle status vs. treatment completion are presented in *Table 4*. Nutritional status was associated with treatment discontinuation ($P < 0.001$) and whether RT was delivered as planned (<0.001). Treatment was discontinued for 10% of patients with concurrent sarcopenia and myosteatosi s vs. 0% for those with no skeletal muscle status features ($P = 0.14$). There was no association detected between

Table 1 Baseline demographics and clinical characteristics by skeletal muscle features of sarcopenia defined by low SMI and myosteatosis defined by low SMR

Characteristic	Overall, N (%) Total (N = 277)	SMI, N (%)			SMR, N (%)		
		Normal (N = 132 ^a)	Low (N = 145 ^a)	P value ^b	Normal (N = 49 ^a)	Low (N = 228 ^a)	P value ^b
Age at diagnosis, mean (SD), years	60 (13)	58 (13)	62 (13)	0.005	49 (12)	62 (12)	<0.001
Gender				0.65			0.10
Male	216 (78%)	105 (80%)	111 (77%)		43 (88%)	173 (76%)	
Female	61 (22%)	27 (20%)	34 (23%)		6 (12%)	55 (24%)	
Ethnicity				0.14			0.003
Asian	58 (21%)	22 (17%)	36 (25%)		19 (39%)	39 (17%)	
European	51 (18%)	23 (17%)	28 (19%)		3 (6.1%)	48 (21%)	
Oceanian	152 (55%)	76 (58%)	76 (52%)		24 (49%)	128 (56%)	
Other	16 (5.8%)	11 (8.3%)	5 (3.4%)		3 (6.1%)	13 (5.7%)	
Performance status				0.043			0.018
ECOG 0	149 (54%)	82 (62%)	67 (46%)		37 (76%)	112 (49%)	
ECOG 1	85 (31%)	38 (29%)	47 (32%)		11 (22%)	74 (32%)	
ECOG 2	19 (6.9%)	5 (3.8%)	14 (9.7%)		1 (2.0%)	18 (7.9%)	
ECOG 3	2 (0.7%)	0 (0%)	2 (1.4%)		0 (0%)	2 (0.9%)	
ECOG 4	1 (0.4%)	0 (0%)	1 (0.7%)		0 (0%)	1 (0.4%)	
Not documented	21 (7.6%)	7 (5.3%)	14 (9.7%)		0 (0%)	21 (9.2%)	
CCI, total, median (range)	5 (1–15)	4 (2–13)	5 (1–15)	0.021	3 (1–15)	5 (2–14)	<0.001
CCI				0.10			<0.001
≥6	116 (42%)	48 (36%)	68 (47%)		8 (16%)	108 (47%)	
<6	161 (58%)	84 (64%)	77 (53%)		41 (84%)	120 (53%)	
Disease stage (AJCC7)				0.86			0.41
I	10 (3.6%)	6 (4.5%)	4 (2.8%)		4 (8.2%)	6 (2.6%)	
II	25 (9.0%)	12 (9.1%)	13 (9.0%)		4 (8.2%)	21 (9.2%)	
III	50 (18%)	22 (17%)	28 (19%)		9 (18%)	41 (18%)	
IV	168 (61%)	79 (60%)	89 (61%)		27 (55%)	141 (62%)	
Other	24 (8.7%)	13 (9.8%)	11 (7.6%)		5 (10%)	19 (8.3%)	
Treatment modality				0.86			0.70
RT—definitive	38 (14%)	16 (12%)	22 (15%)		7 (14%)	31 (14%)	
CRT—definitive	132 (48%)	65 (49%)	67 (46%)		21 (43%)	111 (49%)	
Surgery + CRT—adjuvant	42 (15%)	21 (16%)	21 (14%)		10 (20%)	32 (14%)	
Surgery + RT—adjuvant	65 (23%)	30 (23%)	35 (24%)		11 (22%)	54 (24%)	
Tumour site				0.44			0.019
Oral cavity/lip	28 (10%)	13 (9.8%)	15 (10%)		5 (10%)	23 (10%)	
Oropharynx	113 (41%)	54 (41%)	59 (41%)		17 (35%)	96 (42%)	
Hypopharynx	14 (5.1%)	3 (2.3%)	11 (7.6%)		1 (2.0%)	13 (5.7%)	
Larynx	37 (13%)	22 (17%)	15 (10%)		2 (4.1%)	35 (15%)	
Nasopharynx	41 (15%)	20 (15%)	21 (14%)		15 (31%)	26 (11%)	
Salivary gland	20 (7.2%)	8 (6.1%)	12 (8.3%)		6 (12%)	14 (6.1%)	
Nasal cavity/Paranasal sinus	11 (4.0%)	6 (4.5%)	5 (3.4%)		1 (2.0%)	10 (4.4%)	
Other	12 (4.3%)	5 (3.8%)	7 (4.8%)		2 (4.1%)	10 (4.4%)	
Unknown primary	1 (0.4%)	1 (0.8%)	0 (0%)		0 (0%)	1 (0.4%)	
Tumour type				0.31			0.001
Squamous cell carcinoma	236 (85%)	108 (82%)	128 (88%)		34 (69%)	202 (89%)	
Other	38 (14%)	22 (17%)	16 (11%)		13 (27%)	25 (11%)	
Not documented	3 (1.1%)	2 (1.5%)	1 (0.7%)		2 (4.1%)	1 (0.4%)	
Smoking status				0.21			0.003
Never smoked	97 (35%)	51 (39%)	46 (32%)		25 (51%)	72 (32%)	
Current smoker	56 (20%)	20 (15%)	36 (25%)		5 (10%)	51 (22%)	
Previous smoker	112 (40%)	56 (42%)	56 (39%)		14 (29%)	98 (43%)	
Not documented	12 (4.3%)	5 (3.8%)	7 (4.8%)		5 (10%)	7 (3.1%)	
Alcohol use				0.36			0.16
None or social only	157 (57%)	82 (62%)	75 (52%)		33 (67%)	124 (54%)	
1–2 standard drinks/day	26 (9.4%)	11 (8.3%)	15 (10%)		4 (8.2%)	22 (9.6%)	
>2 standard drinks/day	67 (24%)	27 (20%)	40 (28%)		6 (12%)	61 (27%)	
Not documented	27 (9.7%)	12 (9.1%)	15 (10%)		6 (12%)	21 (9.2%)	
HPV status				0.70			0.28
Negative	27 (9.7%)	10 (7.6%)	17 (12%)		2 (4.1%)	25 (11%)	
Positive	84 (30%)	42 (32%)	42 (29%)		14 (29%)	70 (31%)	
Not applicable	164 (59%)	79 (60%)	85 (59%)		32 (65%)	132 (58%)	
Not documented	2 (0.7%)	1 (0.8%)	1 (0.7%)		1 (2.0%)	1 (0.4%)	

AJCC7, American Joint Committee on Cancer, 7th Edition; CCI, Charlson comorbidity index; CRT, chemoradiotherapy; HPV, human papilloma virus; RT, radiotherapy; SMI, skeletal muscle index; SMR, skeletal muscle radiodensity.

^aStatistics presented: median (minimum–maximum); mean (SD); n (%).

^bStatistical tests performed: *t*-test; χ^2 test of independence.

Table 2 Baseline nutrition and body composition characteristics by skeletal muscle features

Characteristic	Overall (N = 277; M:216; F:61)	SMI			SMR		
		Normal (N = 132 ^a ; M:105; F:27)	Low (N = 145 ^a ; M:111; F:34)	P value ^b	Normal (N = 49 ^a ; M:43; F:6)	Low (N = 228 ^a ; M:173; F:55)	P value ^b
Height (cm), mean (SD)	170 (9)	170 (9)	170 (9)	0.91	174 (7)	169 (9)	<0.001
Weight (kg), mean (SD)	75 (18)	80 (18)	70 (17)	<0.001	76 (15)	75 (19)	0.55
BMI (kg/m ²) mean, (SD)	25.8 (5.4)	27.6 (5.4)	24.1 (4.9)	<0.001	25.2 (4.4)	26.0 (5.6)	0.28
BMI category, (kg/m ²), N (%)				<0.001			<0.001
<20.0	37 (13%)	3 (2.3%)	34 (23%)		8 (16%)	29 (13%)	
20.0 to 24.9	94 (34%)	50 (38%)	44 (30%)		7 (14%)	87 (38%)	
25.0 to 29.9	88 (32%)	38 (29%)	50 (34%)		29 (59%)	59 (26%)	
≥30	58 (21%)	41 (31%)	17 (12%)		5 (10%)	53 (23%)	
SMA (cm ²), mean (SD)							
Males	146 (32)	166 (27)	128 (24)	<0.001	168 (29)	141 (31)	<0.001
Females	105 (22)	123 (18)	90 (11)	<0.001	100 (15)	105 (23)	0.47
SMI (cm ² /m ²), mean (SD)							
Males	49 (10)	56 (8)	43 (7)	<0.001	54 (8)	48 (9)	<0.001
Females	40 (8)	47 (5)	35 (4)	<0.001	39 (5)	40 (8)	0.50
SMR (HU), mean (SD)							
Males	30 (7)	32 (6)	28 (7)	<0.001	38 (4)	28 (6)	<0.001
Females	29 (8)	29 (7)	29 (9)	0.84	41 (5)	28 (7)	<0.001
VATI (cm ² /m ²), median (range)							
Males	48 (1–180)	50 (3–180)	46 (1–154)	0.57	38 (1–116)	50 (2–180)	<0.001
Females	31 (3–113)	33 (2–113)	31 (3–76)	0.038	5 (3–31)	34 (3–113)	0.002
SATI (cm ² /m ²), median (range)							
Males	48 (1–221)	51 (3–221)	45 (1–130)	0.011	46 (1–123)	48 (3–221)	0.15
Females	77 (14–221)	96 (18–221)	61 (14–193)	0.011	32 (14–125)	78 (18–221)	0.13
TATI (cm ² /m ²), median (range)							
Males	97 (2–353)	97 (10–353)	97 (2–242)	0.087	91 (2–228)	102 (6–353)	0.006
Females	116 (17–277)	141 (21–277)	94 (17–242)	0.007	35 (17–156)	117 (21–277)	0.050
Nutritional status, PG-SGA score, median (range)							
Overall	5 (1–42)	3 (1–25)	7 (1–42)	<0.001	4 (1–42)	5 (1–40)	0.45
Nutritional status, PG-SGA category, N (%)				0.004			0.053
A (well-nourished)	175 (63%)	97 (73%)	78 (54%)		39 (80%)	136 (60%)	
B (moderately malnourished)	50 (18%)	18 (14%)	32 (22%)		5 (10%)	45 (20%)	
C (severely malnourished)	19 (6.9%)	4 (3.0%)	15 (10%)		3 (6.1%)	16 (7.0%)	
Not documented	33 (12%)	13 (9.8%)	20 (14%)		2 (4.1%)	31 (14%)	
Nutrition support, N (%)				0.22			0.87
NGT	32 (18%)	10 (13%)	22 (23%)		5 (17%)	27 (19%)	
Gastrostomy—PEG	121 (70%)	58 (75%)	63 (65%)		22 (76%)	99 (68%)	
Gastrostomy—RIG	18 (10%)	8 (10%)	10 (10%)		2 (6.9%)	16 (11%)	
Gastrostomy—surgical	2 (1.1%)	0 (0%)	2 (2.1%)		0 (0%)	2 (1.4%)	
TPN	1 (0.6%)	1 (1.3%)	0 (0%)		0 (0%)	1 (0.7%)	

BMI, body mass index; HU, Hounsfield units; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; PG-SGA, Patient-Generated Subjective Global Assessment; RIG, radiologically inserted gastrostomy; SATI, subcutaneous adipose tissue index; SMA, skeletal muscle area; SMI, skeletal muscle index; SMR, skeletal muscle radiodensity; TATI, total adipose tissue index; TPN, total parenteral nutrition; VATI, visceral adipose tissue index.

^aStatistics presented: median (minimum–maximum); mean (SD); n (%).

^bStatistical tests performed: *t*-test; χ^2 test of independence.

skeletal muscle status and either RT or chemotherapy completion.

Unplanned admission and length of stay

Malnourished patients were more likely to require unplanned hospital admission with 58% of severely malnourished patients vs. 34% of well-nourished patients admitted ($P = 0.021$), (Table 4). Similarly, median (Q1, Q3) LOS was greater for severely malnourished [26 (9, 44)] and moderately

malnourished [12 (5, 37)] vs. well-nourished [7 (3, 20)] days, $P < 0.001$. Skeletal muscle status was associated with unplanned admissions for those with sarcopenia alone (50%), myosteatosis alone (25%), or concurrent sarcopenia and myosteatosis (50%) and those with no features (32%), $P < 0.001$. Clinically relevant differences in LOS was also associated with skeletal muscle status with median (Q1, Q3) LOS for those with sarcopenia alone [5 (3, 32)], myosteatosis alone [10 (5, 30)], and concurrent sarcopenia and myosteatosis [14 (4, 33)] vs. those with no skeletal muscle status features of 3 (2, 11)] days, $P = 0.2$.

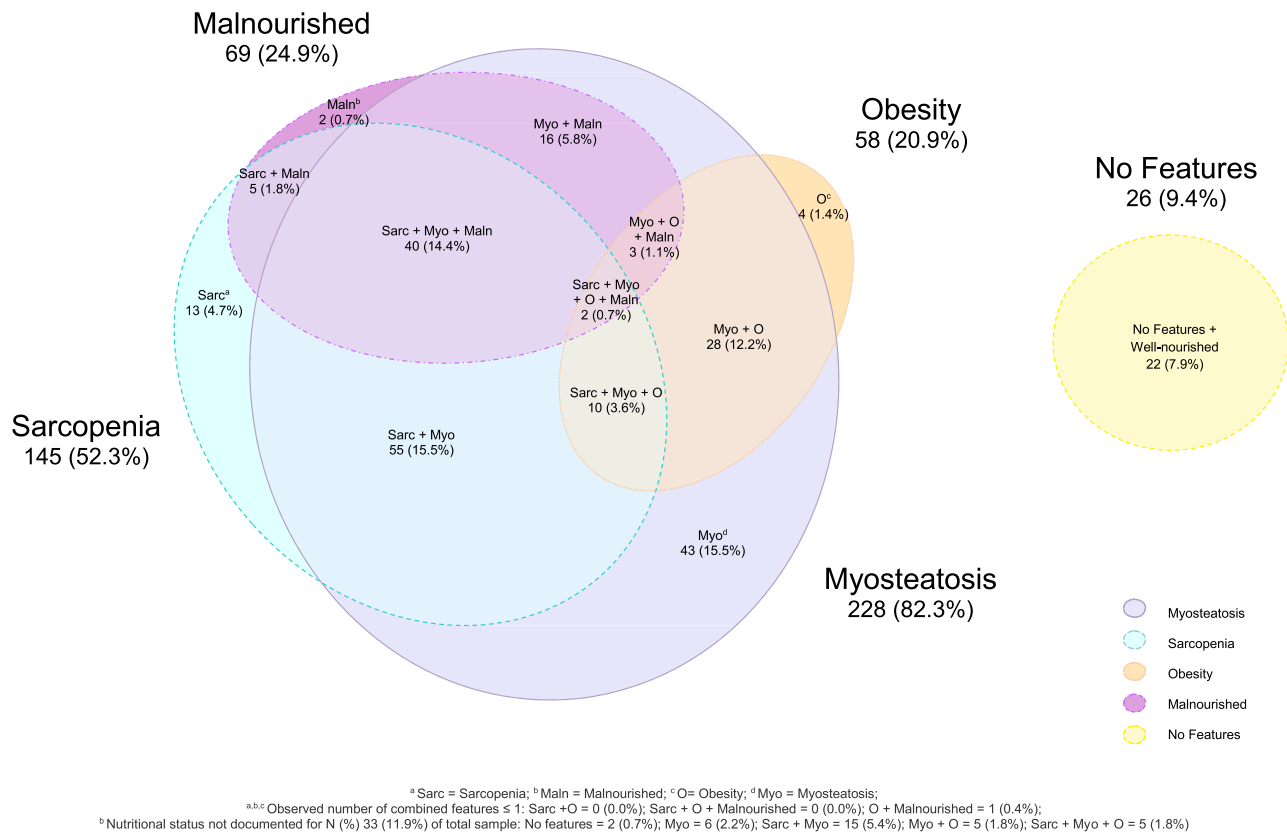


Figure 1 Euler diagram denoting pre-treatment combination of computed tomography-defined body composition features and baseline nutritional status as determined by Scored Patient-Generated Subjective Global Assessment ($n = 277$).

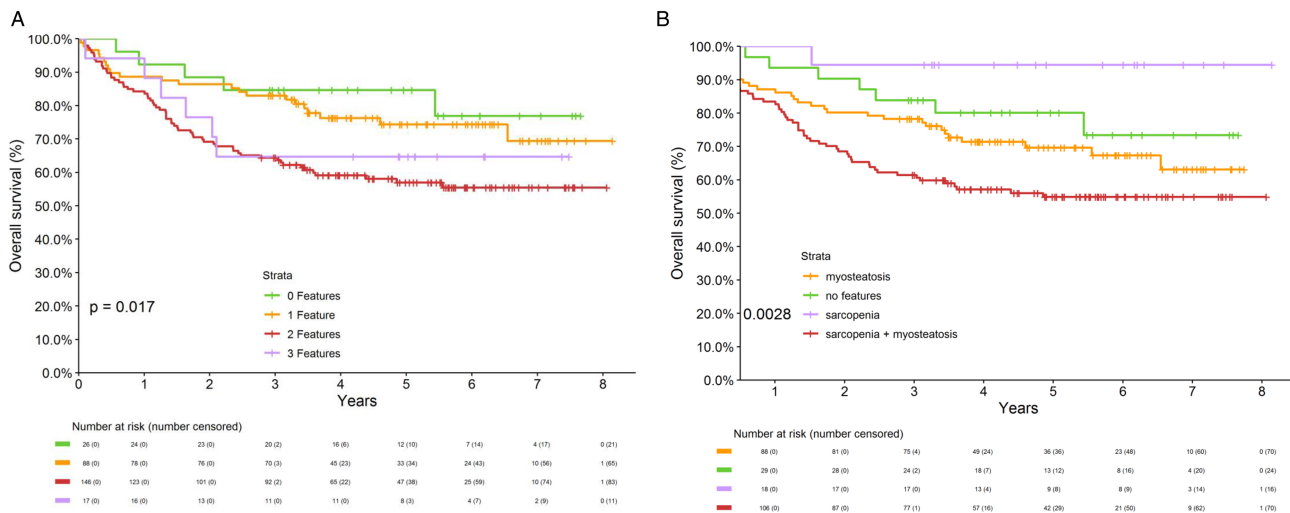


Figure 2 Kaplan–Meier survival estimates of overall survival with log-rank comparisons for: (A) number of body composition features; (B) combination of skeletal muscle status features.

Discussion

To the best of our knowledge, this is the first study to explore CT-defined body composition profiles, and in particular, the

association between (i) nutritional status and (ii) skeletal muscle status on outcomes for patients undergoing RT or CRT of curative intent for HNC. Key findings in our study were malnutrition is a more powerful prognostic factor than

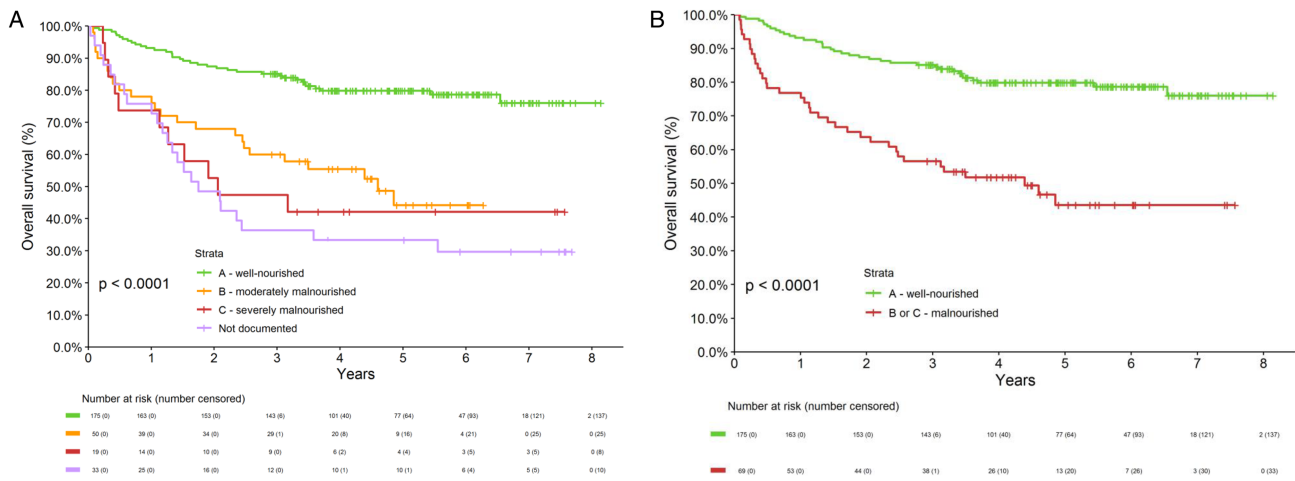


Figure 3 Kaplan–Meier survival estimates of overall survival with log-rank comparisons for: (A) nutritional status – Patient-Generated Subjective Global Assessment – global category; (B) nutritional status – well-nourished vs. malnourished.

Table 3 Regression models for associations between skeletal muscle status and nutritional status and overall survival

Variable	n	Pre-treatment			
		Unadjusted		Adjusted ^a	
		HR (95% CI)	P value	HR (95% CI)	P value
Nutritional status—PG-SGA category					
Well-nourished (A)	175	1.0 (ref) ^{M1}	<0.001	1.0 (ref) ^{A1}	<0.001 ^b
Moderately malnourished (B)	50	3.14 (1.88–5.24)		2.57 (1.45–4.55)	0.001 ^b
Severely malnourished (C)	19	3.97 (2.02–7.82)		3.19 (1.44–7.07)	0.004 ^b
Well-nourished (A)	175	1.0 (ref) ^{M2}	<0.001	1.0 (ref) ^{A2}	<0.001 ^b
Malnourished ^c (B and C combined)	69	3.82 (2.52–5.79)		3.03 (1.87–4.93)	
Skeletal muscle status					
No sarcopenia	132	1.0 (ref) ^{M3}	0.060	1.0 (ref) ^{A3}	0.700
Sarcopenia	145	1.48 (0.98–2.24)		1.09 (0.70–1.71)	
No myosteatosis	49	1.0 (ref) ^{M4}	0.006	1.0 (ref) ^{A2}	0.500
Myosteatosis	228	2.75 (1.33–5.68)		1.28 (0.57–2.84)	
Body composition features—number					
No features	26	1.0 (ref) ^{M5}	0.013	1.0 (ref) ^{A4}	0.8
1 Feature	88	1.36 (0.52–6.62)		0.83 (0.30–2.27)	
2 Features	146	2.61 (1.05–6.49)		0.96 (0.35–2.63)	
3 Features	17	2.02 (0.62–6.62)		0.92 (0.26–3.24)	
Body composition features—combination					
No features	26	1.0 (ref) ^{M6}	0.005	1.0 (ref) ^{A5}	<0.001
Sarcopenia only	18	0.27 (0.03–2.31)		0.26 (0.03–2.22)	0.200
Myosteatosis only	65	1.66 (0.62–4.44)		0.94 (0.33–2.63)	>0.900
Obesity only	5	2.09 (0.41–10.8)		1.29 (0.25–2.50)	0.800
Sarcopenia + Myosteatosis	110	2.88 (1.15–7.22)		1.07 (0.39–2.95)	0.900
Sarcopenia + Obesity	0	Not defined		Not defined	
Myosteatosis + Obesity	36	1.88 (0.66–5.34)		0.79 (0.27–3.39)	0.700
Sarcopenia + Myosteatosis + Obesity	17	2.02 (0.62–6.62)		0.96 (0.27–3.39)	>0.900

Models: Unadjusted (M1 to M6) and adjusted (A1 to A5).

CI, confidence interval; HR, hazard ratio; PG-SGA, Patient-Generated Subjective Global Assessment.

^aAdjusted for age, sex, ethnicity, performance status, disease stage, Charlson comorbidity index, and nutritional status (Malnourished).

^bAlso adjusted for low muscle attenuation but not for nutritional status.

^cMalnourished = PG-SGA B (moderate) or C (severe).

skeletal muscle status and is independently associated with reduced OS in patients with HNC. Importantly, malnutrition may be present, irrespective of body composition features and was also associated with treatment discontinuation, RT not completed as planned, unplanned admissions and greater

length of stay. Similarly, concurrently occurring sarcopenia and myosteatosis were also associated with unplanned admission and greater length of stay. This aligns with our previous work regarding the association between sarcopenia and myosteatosis on reduced OS¹⁸ and also broadens the existing

Table 4 Associations between skeletal muscle status and nutritional status vs. treatment and hospital admission outcomes

Variable	Outcome														
	Treatment discontinued			Radiotherapy delivered as planned			Systemic therapy delivered as planned ^a			Unplanned admission			Length of stay (days)		
	n	n (%) ^b	P value ^c	n (%) ^b	P value ^c	n (%) ^b	P value ^c	n (%) ^b	P value ^c	n (%) ^b	P value ^c	Median ^b	(Q1, Q3)	P value ^d	
Nutritional status—PG-SGA category															
Well-nourished (A)	175	5 (2.9%)	<0.001	168 (96%)	<0.001	90 (73%)	0.6	59 (34%)	0.021	7	(3, 20)	<0.001			
Moderately malnourished (B)	50	7 (14%)		44 (88%)		24 (83%)		19 (38%)		12	(5, 37)				
Severely malnourished (C)	19	1 (5.3%)		18 (95%)		7 (88%)		11 (58%)		26	(9, 44)				
Not documented	33	7 (21%)		23 (70%)		10 (77%)		19 (58%)		40	(14, 46)				
Skeletal muscle status															
No sarcopenia	132	7 (5.3%)	0.3	124 (94%)	0.2	63 (73%)	0.7	35 (27%)	<0.001	10	(3, 26)	0.2			
Sarcopenia	145	13 (9.0%)		129 (89%)		68 (77%)		73 (50%)		14	(4, 34)				
No myosteatosis	49	0 (0%)	0.065	48 (98%)	0.12	19 (61%)	0.078	19 (39%)	>0.9	3	(3, 20)	0.047			
Myosteatosis	228	20 (8.8%)		205 (90%)		112 (78%)		89 (39%)		14	(4, 33)				
Skeletal muscle status—combination of features															
No features	31	0 (0%)	0.14	31 (100%)	0.2	11 (55%)	0.2	10 (32%)	<0.001	3	(2, 11)	0.2			
Sarcopenia only	18	0 (0%)		17 (94%)		8 (73%)		9 (50%)		5	(3, 32)				
Myosteatosis only	101	7 (6.9%)		93 (92%)		52 (79%)		25 (25%)		10	(5, 30)				
Sarcopenia + Myosteatosis	127	13 (10%)		112 (88%)		60 (78%)		64 (50%)		14	(4, 33)				

PG-SGA, Patient-Generated Subjective Global Assessment.

^an = 174 patients had systemic therapy.

^bStatistics presented: n (%); median (IQR).

^cStatistical tests performed: χ^2 test of independence.

^dKruskal–Wallis test.

evidence through exploration of individually or concurrently occurring body composition features in conjunction with nutritional status. Low skeletal muscle mass is a phenotypic GLIM criteria for malnutrition diagnosis, which may also arise due to involuntary weight loss or low BMI.⁸ Our study highlights the importance of understanding the complexities of human body composition and the potential impact of concurrent malnutrition on outcomes for high risk patients.

Nutritional status was independently associated with reduced OS for patients with moderate (HR 2.57; 95% CI 1.45–4.55, $P = 0.001$) and severe (HR 3.19; 95% CI 1.44–7.07, $P = 0.004$) malnutrition. Malnutrition was significantly associated with other poor outcomes including treatment discontinuation and not completing RT as planned. Malnourished patients were also more likely to require unplanned hospital admission and nutritional status significantly influenced LOS. The median (Q1, Q3) LOS for moderately malnourished [12 (5, 37)] and severely malnourished [26 (9, 44)] patients vs. those who were well-nourished [7 (3, 20)] days, $P < 0.001$. Malnutrition is a well-documented high cost diagnosis, both to patients and the healthcare system. We have previously published findings regarding economic implications of unplanned hospital admissions in patients with HNC²³ and specifically those with CT-defined sarcopenia¹⁸ with mean (SD) unplanned admission costs reported from an organizational perspective in Australian Dollars (\$AUD) of \$AUD15 846 (\$AUD17 707) for patients without sarcopenia vs. \$AUD47 945 (\$AUD82 688) for those with sarcopenia. The importance of establishing processes to facilitate early identification, intervention, and monitoring to ameliorate the detrimental sequelae of both malnutrition and skeletal muscle depletion as a contributing criterion holds potential to optimize both clinical and economic outcomes and has recently been articulated in the Clinical Oncology Society of Australia Position Statement on Cancer-Related Malnutrition and Sarcopenia.³¹

Although the association between sarcopenia and OS was not significant on adjusted analysis (HR 1.09; 95% CI 0.70–1.71), $P = 0.700$), our recent meta-analysis of pooled results from seven studies (1059 patients) showed pre-treatment L3 CT-defined sarcopenia was independently associated with reduced OS (HR 2.07; 95% CI 1.47–2.92, $P < 0.0001$, $I^2 = 49\%$).¹¹ This difference may be attributable, in part, to variation in results at the individual study level, which is improved on meta-analysis. Further, to our knowledge, other studies have not reported nutritional status using a validated nutrition assessment tool such as the PG-SGA nor subsequently controlled for this in their findings. The association between myosteatosis and OS on adjusted analysis (HR 1.28; 95% CI 0.57–2.84), $P = 0.500$) differs from our previous study ($n = 79$) (HR 8.86; 95% CI 1.12–69.88, $P = 0.038$)¹⁸ which is likely attributable to the smaller cohort in the earlier study. Myosteatosis is a demonstrated poor prognostic factor in other tumour

groups^{32,33}; however, there remains a paucity of studies in patients with HNC.

Most research on CT-defined body composition in patients with HNC has to date reported findings regarding sarcopenia alone; however, our study explores whether skeletal muscle depletion features occur in isolation or concurrently appears to also influence outcomes. Patients with no features were less likely to require unplanned hospital admission (0%) than those with sarcopenia alone (50%), myosteatorsis only (25%), concurrent sarcopenia and myosteatorsis (50%), $P < 0.001$. Similarly, a clinically relevant difference in median (Q1, Q3) LOS was observed for those with sarcopenia only [5 (3, 32)], myosteatorsis only [10 (5, 30)], concurrent sarcopenia and myosteatorsis [10 (4, 33)] vs. those with no features [3 (2, 11)] days, $P = 0.2$. This harmonizes with findings of Martin *et al.*¹⁹ in patients undergoing elective surgery for colorectal cancer, which demonstrated that CT-defined multidimensional body habitus was independently associated with hospital admission and LOS. Xiao *et al.* (2020) also identified even higher risk of overall mortality where sarcopenia and myosteatorsis occurred concurrently in colon cancer surgical patients.³⁴ Human body composition is multifaceted, and therefore, reducing an individual feature to a binary proposition is an oversimplification of what are complex body habitus parameters.³⁵

In our study, validated methods in line with the GLIM criteria were used to diagnose both malnutrition and skeletal muscle depletion; however, no single method currently exists to detect both. With the epidemiological shift towards obesity in Western societies, both may well be occult diagnoses, with high risk patients going undetected or unrecognized. Early identification of high risk patients is vital to improving outcomes; however, clinical utility in a practical, real-world setting must also be given consideration. CT-defined body composition analysis requires considerable financial and resource investment in software, analyst training, time to locate scans, isolate the CT DICOM file of PET-CT scans, and undertake the necessary landmarking and analysis which in our study is estimated to be approximately 1 h per scan per patient even with auto-segmentation software functionality that still requires quality assurance checks. Whereas nutrition assessment with a validated assessment tool, the PG-SGA, as recommended in evidence-based guidelines,²² can be undertaken as part of routine clinical practice in approximately 15 min. Further, availability of scans for analysis is beholden to diagnostic and staging imaging protocols while nutritional status can be reassessed at regular intervals as part of best-practice nutrition monitoring with minimal resource utilization. In the quest to optimize patient care and outcomes, adhering to the fundamentals of nutrition care and clinical practice for assessment of nutritional status may also offer a timely and efficient mechanism for flagging and monitoring high risk patients.

Study strengths include the first to employ validated methods for evaluation of both nutritional status that align with the GLIM criteria and the gold standard of skeletal muscle evaluation at the tissue-organ level. Limitations of our study include its retrospective nature and the availability of nutritional status at baseline only. Given patients with HNC are known to often present as well-nourished at baseline but experience significant decline in nutritional status throughout the course of care, addressing this through prospective study design in a larger cohort to capture the nature of nutritional status and skeletal muscle status inter-relationships and change over time would be of value for future research. Given malnutrition and skeletal muscle depletion are related, we acknowledge that a larger sample size may provide clarity regarding the inter-relationships of these prognostic factors. Future prospective studies that explore the alignment between skeletal muscle depletion and malnutrition using validated methods are recommended. Overall, research in the field of CT-defined body composition would benefit from agreed definitions of sarcopenia and myosteatorsis and standardized reporting criteria to ultimately improve the certainty and applicability of the growing evidence base.

Conclusions

In this study, malnutrition was a more powerful prognostic indicator than CT-defined skeletal muscle depletion and was independently associated with reduced OS in patients undergoing RT or CRT of curative intent for HNC. It was also associated with poor outcomes including treatment discontinuation and RT not completed as planned. Malnutrition and also the combination of skeletal muscle status features were associated with unplanned hospital admissions and LOS. Studies of CT-defined skeletal muscle depletion should recognize the multifaceted nature of human body composition; and as such, the inclusion of validated measures of nutritional status is warranted in order to develop a typology of high risk criteria for this complex patient group. Consideration should also be given to the clinical utility of methods to assess nutritional status and skeletal muscle status in routine practice.

Funding

Chief Investigator (M.F.) was supported by a Sydney Research PhD Scholarship through the Sydney Local Health District.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

The author's contribution was as follows: Conceptualization, M.F., K.W., and J.B.; methodology, M.F., K.W., C.B., and J.B.; software, M.F.; validation, M.F. and J.B.; formal analysis, M.F. and C.B.; investigation, M.F.; resources, M.F.; data curation, M.F.; writing—original draft preparation, M.F.; writing—review and editing, M.F., K.W., C.B., and J.B.; visualization, M.F.; supervision, K.W., C.B., and J.B.; project

administration, M.F.; funding acquisition, M.F., K.W., and J.B. All authors have read and agreed to the published version of the manuscript and confirm compliance with the Ethical guidelines for authorship and publishing in this journal.³⁶

Acknowledgements

We thank Professor Michael Fulham, Ms Patricia Knebl, and staff in the Department of Molecular Imaging, Royal Prince Alfred Hospital, Sydney New South Wales, Australia. We also thank Ms Dan Luo and Ms Michelle Lai, Cancer Nursing Research Unit at the University of Sydney for research officer support.

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