



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com



Original Research

Prognostic value of body composition on recurrence and survival of advanced-stage head and neck cancer



Ah Ra Jung^a, Jong-Lyel Roh^{a,*}, Jae Seung Kim^b, Sung-Bae Kim^c,
Seung-Ho Choi^a, Soon Yuhl Nam^a, Sang Yoon Kim^a

^a Departments of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

^b Departments of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

^c Departments of Internal Medicine (Oncology), Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Received 16 November 2018; received in revised form 5 May 2019; accepted 11 May 2019

Available online 10 June 2019

KEYWORDS

Head and neck
squamous cell
carcinoma;
Body composition;
Skeletal muscle index;
Sarcopenia;
Prognosis

Abstract *Background:* Head and neck squamous cell carcinoma (HNSCC) is commonly associated with a high risk of malnutrition and sarcopenia, related to adverse clinical outcomes. This study evaluated the prognostic values of body composition on recurrence and survival in patients with advanced-stage HNSCC.

Methods: This study prospectively enrolled 258 consecutive patients with definitive treatments for advanced-stage HNSCC. For the determination of sarcopenia, the cross-sectional area of the skeletal muscles (SMs) was measured at the level of the third lumbar vertebra on the computed tomography images of whole-body ¹⁸F-fluorodeoxyglucose positron-emission tomography/computed tomography before and after treatments. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify the prognostic factors of disease-free survival (DFS) and overall survival (OS).

Results: Pretreatment and post-treatment diminished SM masses (sarcopenia) were found in 17 (6.6%) and 32 (12.4%) of 258 included patients, respectively. All values of body composition, SM index, visceral fat area, lean body mass, fat mass and body mass index significantly decreased after treatment (all $P < 0.05$). Multivariable analyses showed that age, Charlson comorbidity index, pretreatment and post-treatment sarcopenia, pretreatment hypoalbuminaemia, p16 status and tumour site remained the independent variables predictive of DFS and

* Corresponding author: Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea. Fax: +82 2 489 2773.

E-mail address: rohjl@amc.seoul.kr (J.-L. Roh).

OS outcomes (all $P < 0.05$). Patients with sarcopenia before or after treatment had about threefold increased risk of overall recurrence or death.

Conclusion: Diminished SM mass may predict recurrence and survival after definitive treatments in patients with advanced-stage HNSCC.

© 2019 Elsevier Ltd. All rights reserved.

1. Introduction

Depletion of skeletal muscle (SM) is associated with an adverse impact on the prognosis of patients with cancer [1]. Sarcopenia, characterised by depletion of skeletal muscle mass (SMM), strength and function, has been linked to decreased disease-free survival (DFS) and overall survival (OS) in patients with a variety of cancer types [2,3]. Moreover, increased chemotherapy toxicity and a shorter time to tumour progression were observed in cancer patients with sarcopenia [4,5].

Malnutrition and significant weight loss caused by poor oral intake is common in patients with head and neck squamous cell carcinoma (HNSCC). Malnutrition may cause the depletion of SM, defined as sarcopenia that is prevalent in up to 50% of cancer patients across the spectrum of disease at presentation [6,7]. Nutritional status and sarcopenia might impact the clinical courses and outcomes of multimodal therapy including surgery, radiotherapy and chemotherapy in HNSCC [8,9]. More studies are needed to evaluate the therapeutic outcomes or prognostic values related to body composition and sarcopenia in patients with HNSCC.

The prognostic values of sarcopenia in patients with advanced HNSCC have been rarely evaluated. Computed tomography (CT) is an accurate method for determining body composition and SMM [10,11]. Sarcopenia can be defined from the measurement of SMM using a CT cross-sectional image analysis at the third lumbar vertebra (L3) level, defined as a standard bony landmark [12]. Body composition parameters, such as total body fat-free mass and sarcopenic obesity, have clinical implications for functional status, therapy toxicity and survival in patients with cancer [4,5,10]. SMM measurement at L3 may require abdominal CT scanning that is available as whole-body ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron-emission tomography (PET)/CT for staging and post-treatment surveillance [13]. Therefore, it could be hypothesised that sarcopenia determined by L3 SMM might predict tumour recurrence and patient survival after definitive treatments for HNSCC. This study evaluated the prognostic values of sarcopenia associated with recurrence and survival after definitive treatments in these patients.

2. Materials and methods

2.1. Patients and study design

We prospectively enrolled patients older than 18 years who were initially diagnosed with primary HNSCC at our tertiary referral hospital between September 2010 and August 2015. A total of 677 patients with HNSCC arising in the oral cavity, oropharynx, larynx or hypopharynx were initially enrolled. Patients with early-stage (I-II) HNSCC ($n = 275$), previous history of cancer treatment ($n = 17$), palliative treatment ($n = 18$), incomplete initial radiotherapy or chemoradiotherapy ($n = 18$), no initiation for any treatment modality ($n = 22$) or the absence of follow-up CB data or lost to follow-up ($n = 17$) were excluded. A total of 310 patients with definitive treatments for clinically advanced (III-IV) stage HNSCC were included in the final analyses. The patients underwent examination of circulating laboratory biomarkers (complete blood count [CBC], electrolyte battery, chemical battery and C-reactive protein [CRP]) at the time of initial diagnosis and regularly after treatments. Patients were staged according to the tumour-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC 7th ed., 2010) [18]. This study was reviewed by our institutional review board, and written informed consent was obtained from each patient.

We prospectively enrolled patients older than 18 years who were treated for treatment-naïve HNSCC at our tertiary referral hospital between September 2010 and December 2015. The primary end-point was the impact of PET/CT imaging and circulating biomarkers on recurrence and survival after definitive treatment for HNSCC. The patients were requested to undergo whole-body ^{18}F -FDG PET/CT prior to and around 3–6 months after definitive treatment. The imaging and biomarkers were performed for initial staging and post-treatment surveillance. The research ethics board of our institution reviewed and approved the study proposal, and all patients gave written informed consent. A total of 672 patients with HNSCC arising in the oral cavity, oropharynx, larynx or hypopharynx were initially enrolled. Patients with early I or II stage ($n = 275$), palliative treatment or no treatment initiation ($n = 40$), incomplete initial radiotherapy or chemoradiotherapy

($n = 18$), previous cancer treatment ($n = 17$) or lost to follow-up ($n = 17$) were excluded. Forty-seven patients were also excluded due to unavailable post-treatment images assessing SM area at the L3 level. A total of 258 patients with definitive treatment for stage III or IV HNSCC were included. Tumours were clinically staged using the TNM system proposed by the American Joint Committee on Cancer (7th edition).

2.2. CT assessment of body composition

The SMM was manually delineated along the SM outlines at the level of L3 from the CT images of pre-treatment and post-treatment whole-body ^{18}F -FDG PET/CT. The images were analysed to determine cross-sectional area (CSA, cm^2) and total fat area (cm^2) including visceral plus subcutaneous fat regions using the CT Hounsfield unit thresholds of -29 to $+150$ for SM and -50 to -150 for adipose tissue [14–16]. The CSA of the delineated area was automatically retrieved as the sum of delineated pixels. The criteria for determining sarcopenia were derived from the CSA sum (lean tissue area) of all SMs at the L3 level [14,15]. Skeletal muscle index (SMI) was derived as the ratio of lean tissue area (cm^2) to the square of height (m^2). Sarcopenia was defined as SMI less than $52.4 \text{ cm}^2/\text{m}^2$ for men and less than $38.5 \text{ cm}^2/\text{m}^2$ for women [4,14,17]. Visceral obesity was defined as a visceral fat area less than 163.8 cm^2 for men and 80.1 cm^2 for women [15]. Lean body mass (LBM) was defined using the formula: $\text{LBM (kg)} = 0.30 \times [\text{lean tissue area (cm}^2\text{)}] + 6.06$ [14]. Fat mass (FM) was defined using the formula: $\text{FM (kg)} = 0.042 \times [\text{total fat area (cm}^2\text{)}] + 11.2$ [4].

2.3. Variables

Patient demographic data were included as variables: patient age (>65 years), sex, history of smoking (>20 pack-years) and alcohol consumption (≥ 1 drink/day), body mass index (BMI, $<18.5 \text{ kg}/\text{m}^2$), Charlson comorbidity index (≥ 2), Karnofsky performance status (≤ 80) and second cancer [18,19]. Clinical tumour, node and metastatic stage were also included [20]. Body composition parameters from the measurement of CT images were included: SMI, visceral obesity, LBM, and FM. CBC and chemistry parameters were measured without any evidence of infection in study patients before treatment and around 2–4 months after treatment. The reference limits of baseline biomarkers were defined from previous reports and our institutional normal ranges as leucocytosis (white blood cell count $>10,000/\mu\text{L}$) [21,22], anaemia (haemoglobin $<11 \text{ g}/\text{dL}$ in both genders) [23], hypoalbuminaemia ($<3.5 \text{ g}/\text{dL}$) [24], hypoproteinaemia ($<6.0 \text{ g}/\text{dL}$) [24], neutrophilia ($>7500/\mu\text{L}$) [21], lymphocytopenia ($<1000/\mu\text{L}$) [25] and neutrophil-lymphocyte ratio (>2.5) [26]. Patients who underwent primary surgery with/without postoperative

radiotherapy or chemoradiotherapy were allocated to the surgery group, whereas those who received definitive radiotherapy or chemoradiotherapy were allocated to the non-surgery group. Variables were selected based on recursive partitioning analysis with influences on survival in HNSCC [27].

2.4. Statistical analysis

Categorical data were expressed as number and percentage, and continuous data were expressed as median and interquartile range (IQR). Primary end-points of interest were DFS and OS. DFS was defined as the time from the start of treatment to the first event of recurrence at any site or last visit. OS was defined as the time from the start of treatment to the day of death due to any cause or last visit. Univariate Cox proportional hazard regression analyses were used to identify associations between variables and DFS or OS. Variables significant in the univariate analyses with P values of <0.05 were included in the multivariate analyses. Multivariate analyses were performed using a stepwise variable selection procedure based on Akaike information criterion (AIC) methods [28]. Variables with the lowest AIC values were used in the final multivariate model. A stratified Cox regression model was used to address the violation of the proportional hazards assumption. The multivariate Cox regression model was also stratified for variables with non-proportional hazards, and variables with multicollinearity were separately fit [29]. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. The Kaplan–Meier and log-rank tests were used to determine survival and statistical significance, respectively. The pretreatment and post-treatment values were compared using the paired t -test with Bonferroni correction. P -values less than 0.05 were considered statistically significant, and all statistical tests were two tailed. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

The 258 patients comprised 223 (86.4%) males and 35 (13.6%) females, with a median age of 64 years (IQR 56–73). Patient characteristics are presented in Table 1. Karnofsky performance status ≤ 80 and Charlson comorbidity index ≥ 2 were found in 111 (43.0%) and 29 (11.3%) patients, respectively. The median BMI, pre-treatment SMI and post-treatment SMI were 23.0 (20.8–25.3), 62.3 (57.1–67.1) and 58.5 (53.8–63.2), respectively. The most common tumour site was the oropharynx ($n = 94$, 36.4%), followed by the oral cavity ($n = 56$, 21.7%), the larynx ($n = 54$, 20.9%) and the hypopharynx ($n = 54$, 20.9%). P16 positivity was found

Table 1
Patient characteristics (N = 258).

Variables	N	%
Gender, male	223	86.4
Age (years), median (IQR)	64 (56–73)	
Smoking, >20 pack-years	93	36.0
Alcohol consumption, ≥1 drink/day	110	42.6
KPS, 100/90/≤80	102/45/111	39.5/17.4/43.0
CCI, 0/1/≥2	176/53/29	68.2/20.5/11.3
Second cancer	73	28.3
BMI (kg/m ²), median (IQR)	23.0 (20.8–25.3)	
SMI, median (IQR)	62.3 (57.1–67.1)	
Tumour site		
Oropharynx	94	36.4
Oral cavity	56	21.7
Larynx	54	20.9
Hypopharynx	54	20.9
p16, positive	72	27.9
T classification, T1/T2/T3/T4	35/79/63/81	13.6/20.6/24.4/31.4
N classification, N0/N1/N2/N3	50/42/16/2/4	19.4/16.3/62.8/1.6
Overall TNM stage, III/IV	69/189	26.7/73.3
Primary treatment		
Surgery alone	61	23.6
Surgery + RT/CRT	70/32	21.1/12.4
RT alone/CRT	2/93	0.8/36.0
Follow-up information		
Periods (months), median (IQR)	53.6 (26.3–70.5)	
Recurrence, overall/local/regional/distant ^a	83/36/27/35	32.2/14.0/10.5/13.6
Last status, NED/DOD/DOC/AD	158/56/29/16	61.2/21.7/11.2/6.2

AD, alive with disease; BMI, body mass index (kg/m²); C3, the third cervical vertebra; CCI, Charlson comorbidity index; CRT, chemoradiotherapy; DOC, died of other causes; DOD, died of disease; IQR, interquartile range; KPS, Karnofsky performance status; L3, the third lumbar vertebra; NED, no evidence of disease; SMI, skeletal muscle index (cm²/m²); RT, radiotherapy; TNM, tumour-node-metastasis staging proposed by the AJCC (7th edition).

^a There was overlapping of recurrent sites in some patients.

in 72 patients (27.9%). Advanced T classification was found in 144 patients (55.8%), nodal positivity in 208 patients (20.6%) and overall IV stage in 189 patients (73.3%). The patients underwent primary surgery alone or surgery plus radiotherapy/chemoradiotherapy in 163 patients (63.2%) and definitive radiotherapy alone or chemoradiotherapy in 95 patients (36.8%). The median follow-up period was 53.6 (26.3–70.5) months. At last follow-up, 158 patients (61.2%) were alive without disease, 56 (21.7%) died of disease, 29 (11.2%) died of other causes and 16 (6.2%) were alive with disease. During follow-up, any site recurrence was found in 83 patients (32.2%): 36 (14.0) at the primary site, 27 (10.5%) at the regional site and 35 (13.6%) at distant sites with overlapping of recurrent sites in some patients. Five-year DFS and OS rates were 66.8% (63.7–69.9%) and 66.2% (63.1–69.3%), respectively.

3.2. Changes in body composition and circulating biomarkers before and after treatment

All values of body composition, BMI, SMI, visceral fat area, LBM and FM, significantly decreased after treatment (all $P < 0.001$) (Table 2). Regarding circulating biomarkers, the levels of haemoglobin, total protein, albumin and white blood cells significantly decreased,

while the levels of lymphocyte count, neutrophil-to-lymphocyte ratio and CRP significantly increased (all $P > 0.05$). Pretreatment sarcopenia and visceral obesity were found in 17 (6.6%) and 13 (5.0%) patients, respectively. Post-treatment sarcopenia and visceral obesity were found in 32 (12.4%) and 4 (1.6%) patients, respectively. Anaemia, hypoalbuminaemia and leucocytosis were found in 22 (8.5%), 25 (9.7%) and 18 (7.0%) patients, respectively, before treatment, and 61 (23.6%), 87 (33.7%) and 24 (9.3%), respectively, after treatment.

3.3. Variables for survival

Univariable analyses showed that age (>65 years), Karnofsky performance scale (≤80), Charlson comorbidity index (≥2), second cancer, tumour site, tumour differentiation, p16 positivity and T classification were significantly associated with DFS and OS outcomes (all $P < 0.05$) (Table 3). Regarding body composition, BMI (<18.5 kg/m²) and sarcopenia were significantly associated with DFS and OS outcomes (all $P < 0.05$). However, visceral obesity was not a predictive factor for survival. Among circulating biomarkers, the pretreatment levels of haemoglobin, albumin, white blood cells, absolute neutrophil count, neutrophil-to-lymphocyte ratio and CRP were significantly associated with DFS

Table 2
Changes in body composition and circulating biomarkers before and after treatment.

Variables	Before treatment (N = 258)	After treatment (N = 258)	P ^a
Body mass index	23.2 (3.6)	22.2 (3.6)	<0.001
Skeletal muscle index (cm ² /m ²)	61.7 (8.4)	57.9 (4.7)	<0.001
Visceral fat area (cm ²)	50.1 (41.0)	42.2 (33.9)	<0.001
Lean body mass (kg)	56.9 (8.5)	53.7 (7.6)	<0.001
Fat mass (kg)	17.9 (3.4)	17.1 (3.1)	<0.001
Haemoglobin, g/dL	13.7 (1.8)	12.3 (2.2)	<0.001
Total protein, g/dL	6.9 (0.5)	6.7 (0.7)	0.009
Albumin, g/dL	4.0 (0.4)	3.6 (0.6)	<0.001
WBC, × 10 ⁶ /L	6642 (2259)	6068 (3354)	0.027
CNC, × 10 ⁶ /L	4008 (1982)	4188 (3069)	0.088
CLC, × 10 ⁶ /L	1942 (712)	1274 (1407)	0.023
NLR	2.59 (3.18)	4.61 (5.52)	<0.001
CRP, mg/L	1.7 (2.6)	3.2 (2.5)	0.001

The values indicate the mean (standard deviation).

CLC, circulating lymphocyte count; CNC, circulating neutrophil count; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PV, pre-vertebral; SCM, sternocleidomastoid; WBC, white blood cell.

^a Compared between the values before and after treatment using paired *t*-test with Bonferroni correction. *P* < 0.05.

Table 3
Univariable analyses of body composition and circulating biomarkers in association with disease-free and overall survival.

Variables	Disease-free survival		Overall survival	
	HR (95% CI)	P ^a	HR (95% CI) ^a	P ^a
Before treatment				
BMI, <18.5 kg/m ²	2.67 (1.47–4.85)	0.001	1.54 (0.77–3.08)	0.223
Sarcopenia	2.34 (1.17–4.69)	0.016	3.24 (1.79–5.87)	<0.001
Visceral obesity	0.57 (0.18–1.81)	0.339	0.35 (0.09–1.43)	0.143
Haemoglobin, <11 g/dL	2.13 (1.13–4.03)	0.020	2.58 (1.43–4.58)	0.001
Total protein, <6.0 g/dL	2.65 (1.07–6.56)	0.035	1.28 (0.41–4.06)	0.673
Albumin, <3.5 g/dL	3.87 (2.23–6.71)	<0.001	3.48 (2.03–5.94)	<0.001
WBC, >10 × 10 ⁹ /L	3.23 (1.66–6.27)	0.001	3.21 (1.70–6.05)	<0.001
CNC, >7.5 × 10 ⁹ /L	3.66 (1.83–7.34)	<0.001	3.24 (1.62–6.48)	0.001
CLC, <1.0 × 10 ⁹ /L	1.12 (0.49–2.56)	0.794	1.11 (0.49–2.55)	0.800
NLR, >2.5	1.65 (1.07–2.57)	0.025	1.67 (1.08–2.58)	0.021
CRP, >2 mg/L	3.41 (1.54–7.56)	0.003	2.40 (1.06–5.45)	0.036
After treatment				
BMI, <18.5 kg/m ²	2.79 (1.70–4.57)	<0.001	1.95 (1.16–3.30)	0.012
Sarcopenia	2.42 (1.42–4.13)	0.001	3.15 (1.94–5.13)	<0.001
Visceral obesity	0.59 (0.08–4.27)	0.605	0.48 (0.08–4.54)	0.386
Haemoglobin, <11 g/dL	1.03 (0.61–1.73)	0.922	1.45 (0.91–2.31)	0.119
Total protein, <6.0 g/dL	1.02 (0.54–1.93)	0.943	1.22 (0.67–2.19)	0.519
Albumin, <3.5 g/dL	1.63 (1.05–2.52)	0.030	1.94 (1.26–2.97)	0.002
WBC, >10 × 10 ⁹ /L	2.40 (1.30–4.44)	0.005	2.50 (1.38–4.53)	0.002
CNC, >7.5 × 10 ⁹ /L	1.43 (0.74–2.77)	0.290	1.91 (1.05–3.45)	0.033
CLC, <1.0 × 10 ⁹ /L	1.26 (0.81–1.95)	0.301	1.15 (0.75–1.76)	0.511
NLR, >2.5	1.34 (0.84–2.14)	0.213	1.48 (0.93–2.35)	0.103
CRP, >2 mg/L	1.47 (0.93–2.33)	0.100	1.65 (1.04–2.61)	0.034

BMI, body mass index (kg/m²); C3, third cervical vertebra; CLC, circulating lymphocyte count; CNC, circulating neutrophil count; CRP, C-reactive protein; L3, third lumbar vertebra; NLR, neutrophil-lymphocyte ratio; SMI, skeletal muscle index; WBC, white blood cell; HR, hazard ratio; CI, confidence interval.

^a Univariate Cox proportional hazard regression models, *P* < 0.05.

and OS outcomes (all *P* < 0.05). The post-treatment albumin level was also significantly associated with DFS and OS outcomes (all *P* < 0.05). Multivariable analyses showed that age, Charlson comorbidity index, pretreatment and post-treatment sarcopenia, pretreatment hypoalbuminaemia, p16 status and tumour site remained the independent variables predictive of DFS

and OS outcomes (all *P* < 0.05) (Table 4). Patients with sarcopenia before or after treatment had about a threefold increased risk of overall recurrence or death. Five-year DFS rates of patients without and with pretreatment sarcopenia were 68.4% (65.2–71.6%) and 45.4% (33.9–57.9%), respectively (*P* = 0.013). The five-year OS rates of patients without and with pretreatment

Table 4
Multivariable analyses of variables in association with disease-free and overall survival.

Variables	Disease-free survival		Overall survival	
	HR (95% CI)	<i>P</i> ^a	HR (95% CI) ^a	<i>P</i> ^a
Age, >65 years	1.64 (1.02–2.62)	0.040	1.97 (1.21–3.21)	0.006
CCI, ≥2	2.12 (1.15–3.91)	0.016	2.63 (1.49–4.64)	0.001
Pretreatment sarcopenia	3.06 (1.25–7.54)	0.015	3.93 (2.36–6.56)	<0.001
Post-treatment sarcopenia	3.34 (1.70–6.55)	<0.001	2.92 (1.68–5.07)	<0.001
Pretreatment albumin, <3.5 g/dL	3.29 (1.81–6.00)	<0.001	2.64 (1.49–4.69)	0.001
Pretreatment WBC, >10 × 10 ⁹ /L	–	–	2.85 (1.45–5.58)	0.002
p16, negative	2.39 (1.27–9.29)	0.001	2.38 (1.28–7.94)	0.001
Tumour site				
Oropharynx	Reference		Reference	
Oral cavity	2.53 (1.32–4.86)	0.005	2.34 (1.21–4.52)	0.011
Larynx	1.74 (0.85–3.54)	0.127	1.62 (0.75–3.52)	0.219
Hypopharynx	2.78 (1.46–5.29)	0.002	2.51 (1.26–5.00)	0.009

CCI, Charlson comorbidity index; KPS, Karnofsky performance status; WBC, white blood cell; HR, hazard ratio; CI, confidence interval.

^a The multivariate models were performed using a backward stepwise selection procedure with all clinically relevant variables from the univariate analysis (*P* < 0.05) (Table 3 and Supplementary Table S1).

sarcopenia were 69.4% (66.3–72.5%) and 23.5% (13.2–33.8%), respectively (*P* < 0.001). The same findings were observed with the absence and presence of post-treatment sarcopenia. Fig. 1 represents the Kaplan–Meier estimates for absence and presence of sarcopenia in patients with advanced-stage HNSCC.

4. Discussion

The present study showed the prognostic values of sarcopenia on recurrence and survival in 258 patients with advanced HNSCC. Pretreatment and post-treatment sarcopenia were found in 6.6% and 12.4% of patients, respectively, when determined for SMM from CT images at L3. Most body composition parameters including SMI, LBM, FM and BMI significantly decreased in most patients after treatment. Pretreatment sarcopenia was the independent risk factor for DFS and OS after definitive treatment, showing about threefold increased risk of overall recurrence or death. Therefore, this study might first suggest the use of sarcopenia for risk stratification as predicting recurrence and death after definitive treatment in patients with advanced-stage HNSCC.

The incidence of sarcopenia ranges from 11% to 74% in adult patients with solid tumours when defined with its cut point from 36.2 to 55.4 cm²/m² for men and from 29.6 to 55.4 cm²/m² for women [30]. A retrospective study reported the incidence of sarcopenia as 35.3% (67 of 190 patients with HNSCC) before definitive radiotherapy [17]. SM depletion was significantly increased up to 65.8% (125 of 170) after radiotherapy. The incidence of sarcopenia did not differ by tumour stage, radiation or chemotherapy dose, treatment modality and provision of the feeding tube. Low SMM less than 43.2 cm²/m² was found in 54.4% of 112 patients with locally advanced HNSCC when the SMM was estimated using the prediction rule of CSA

measured at the third cervical vertebral (C3) level [31]. A recent study showed that the prevalence of pre-treatment sarcopenia was 15.9% and differed between oesophageal cancer patients with (43.0%) and without (6.3%) visceral obesity [32]. Among surgical patients, the prevalence of sarcopenia was 6.9% at baseline, 21.1% after neoadjuvant therapy and 34.7% at one year [32]. The prevalence of sarcopenia increased to 25.5% among all patients and 44.0% among viscerally obese patients at the time of resection after neoadjuvant chemotherapy. Sarcopenia might be associated with lower body weight and BMI (*P* < 0.001) but can present in normal weight (25.3%) and overweight (10.8%) patients [32]. Therefore, a recent review article indicated the prognostic awareness of sarcopenic obesity in obese patients with severe muscle depletion [33]. The prevalence of sarcopenia appeared to be low compared to that previously reported [17,30–32], which might result from the different SMI cut-off points, cancer types and ethnic groups.

Most body composition parameters can decrease during or after chemotherapy, radiotherapy, surgery or combination therapy. The LBM and BMI significantly decreased during platinum-based neoadjuvant chemoradiotherapy for oesophageal cancer [32]. Post-neoadjuvant sarcopenia affected performance status and disease progression, and preoperative sarcopenia increased the comprehensive complication index and major complications including postoperative pneumonia and prolonged intubation (all *P* < 0.05) [32]. A recent study also suggested that pretreatment sarcopenia caused more frequent chemotherapy dose-limiting toxicity (CDLT) from platinum-based concurrent chemoradiotherapy when the CDLT was defined as any toxicity resulting in ≥50% reduction in chemotherapy dose from neutropenia, nephrotoxicity, bone marrow suppression or early termination after one- or two-cycle chemotherapy [31].

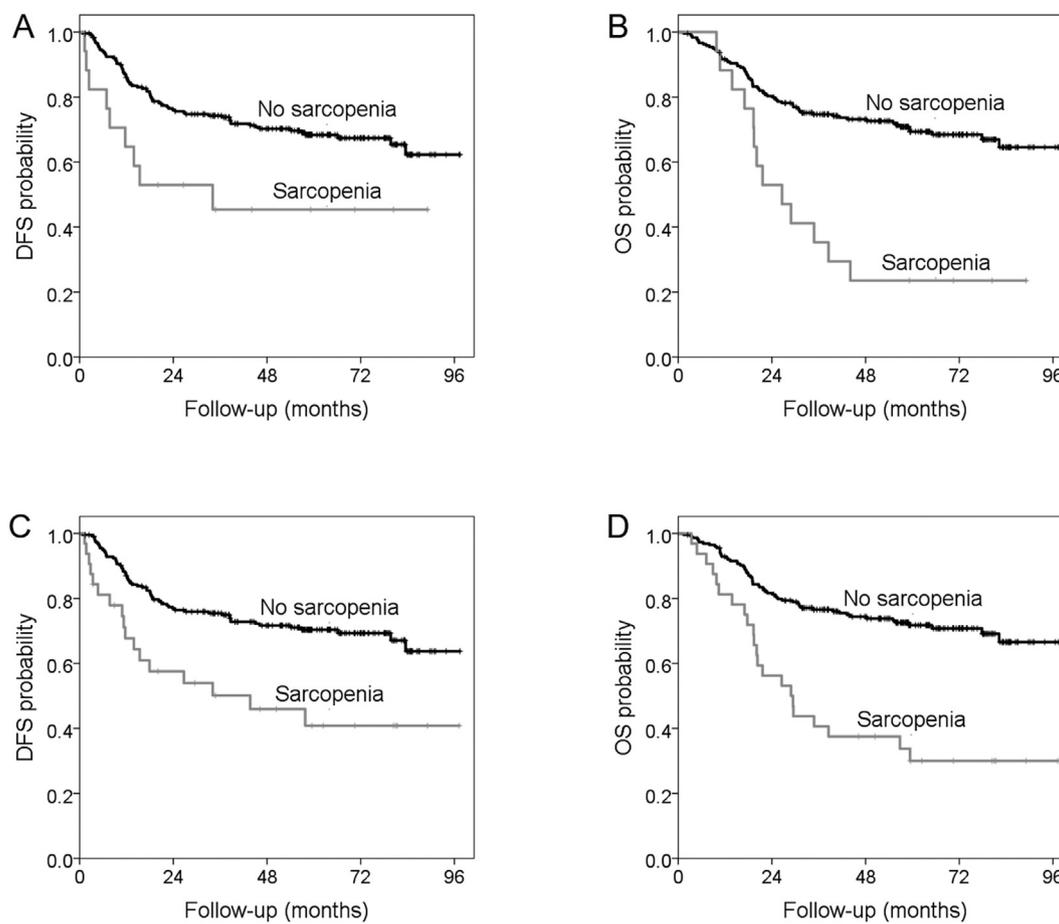


Fig. 1. Kaplan–Meier curves estimating survival according to absence and presence of sarcopenia in patients with advanced-stage HNSCC. (A–B) Disease-free survival (DFS) and overall survival (OS) according to pretreatment sarcopenia. (C–D) DFS and OS according to post-treatment sarcopenia. The log-rank test, $P < 0.05$. HNSCC, head and neck squamous cell carcinoma.

Another study involving 215 patients with HNSCC showed the significant decrease of LBM after curative radiotherapy, from mean 55.2 kg before therapy to 49.27 kg after therapy [11]. In the present study, most body composition indicators, such as LBM, VFA, FM and BMI, significantly decreased at 3–6 months after definitive treatment. Changes in body composition parameters might be accompanied by those of circulating biomarkers measured from the peripheral blood [24]. Pretreatment and post-treatment sarcopenia was not associated with low values of most circulating biomarkers, including haemoglobin, albumin, total protein and other cell counts ($P > 0.05$).

This study also showed that pretreatment and post-treatment sarcopenia and some circulating biomarkers were associated with increased disease recurrence and mortality after definitive treatment for advanced-stage HNSCC. A recent meta-analysis involving 7843 patients with solid tumours showed a strong association between sarcopenia and poorer OS as well as DFS: the pooled HR for OS, 1.44 (95% CI, 1.32–1.56, $P < 0.001$); that for DFS, 1.16 (95% CI, 1.00–1.30, $P = 0.014$) [30]. This suggests the wide use of CT scanning to detect SM

depletion in patients with cancer, predict treatment outcomes and thereby improve the outcomes of future intervention. A recent study examined the prognostic value of sarcopenia in 190 HNSCC patients with definitive radiotherapy [17]. This study showed the association between OS outcomes and sarcopenia before radiotherapy (HR = 1.92; 95% CI, 1.19–3.11; $P = 0.007$) and after radiotherapy (HR = 2.03; 95% CI, 1.02–4.24; $P = 0.04$). Post-treatment weight loss without sarcopenia did not affect survival outcomes. The present study also showed a strong association between DFS or OS outcomes and diminished SMM, particularly after definitive treatment. However, the BMI at diagnosis and after treatment was not associated with survival outcomes, different from recent observations [17], which might result from different treatment modalities and ethnic groups. Changes in body composition might occur with circulating biomarkers that indicate their prognostic role in systematic inflammatory response and nutritional status, such as leucocytosis and hypoalbuminaemia [24]. The prognostic significance of p16 and tumour site has been already well established [34]. Therefore, these risk factors will not be described further.

Our current investigation is the largest prospective study to evaluate the prognostic values of body composition and their changes measured from the CT images of ¹⁸F-FDG PET/CT scanning in patients with HNSCC undergoing definitive treatment. In terms of limitations, however, this study included different tumour sites and treatment modalities that varied from surgery, radiotherapy, chemoradiotherapy to combination therapy. However, all study patients had completed definitive treatments determined by the consensus of our multidisciplinary tumour board teams. Our results may be confirmed by further multi-institutional studies involving a large cohort of HNSCC and CT-based imaging ensuring the measurement of LBM and FM.

In conclusion, the present study suggests the prognostic values of sarcopenia at baseline and after treatment on recurrence and survival in patients with advanced-stage HNSCC. Sarcopenia is the independent risk factor for poorer DFS and OS outcomes after definitive treatments, showing about threefold increased risk of overall recurrence or death. Post-treatment depletion of SM is more associated with unfavourable survival outcomes. Therefore, our study might indicate the routine use of pretreatment and post-treatment CT image-based measurement of LBM to identify at-risk HNSCC patients associated with high recurrence and mortality.

Conflict of interest statement

None declared.

Acknowledgements

No funding was received in support of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.05.006>.

References

- [1] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis report of the European Working Group on Sarcopenia in older people. *A. J. Cruz-Gentoft et al Age Ageing* 2010;39:412–23.
- [2] Levolger S, Van Vledder MG, Muslem R, Koek M, Niessen WJ, de Man RA, et al. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *J Surg Oncol* 2015;112:208–13.
- [3] Psutka SP, Carrasco A, Schmit GD, Moynagh MR, Boorjian SA, Frank I, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* 2014;120:2910–8.
- [4] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenia in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;9:629–35.
- [5] Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 2009;15:2920–6.
- [6] Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck: J. Sci. Spec. Head and Neck* 2005;27:659–68.
- [7] Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;31:1539–47.
- [8] Peters L, Ang K, Thames H. Accelerated fractionation in the radiation treatment of head and neck cancer—a critical comparison of different strategies. *Acta Oncol* 1988;27:185–94.
- [9] Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;324:1685–90.
- [10] Prado CM. Body composition in chemotherapy: the promising role of CT scans. *Curr Opin Clin Nutr Metab Care* 2013;16:525–33.
- [11] Chamchod S, Fuller CD, Mohamed AS, Grossberg A, Messer JA, Heukelom J, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: a challenge of height-weight formulae using computed tomography measurement. *Oral Oncol* 2016;61:62–9.
- [12] Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004;97:2333–8.
- [13] Chong A, Ha JM, Han YH, Kong E, Choi Y, Hong KH, et al. Preoperative lymph node staging by FDG PET/CT with contrast enhancement for thyroid cancer: a multicenter study and comparison with neck CT. *Clin Exp Otorhinolaryngol* 2017;10:121–8.
- [14] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metabol* 2008;33:997–1006.
- [15] Doyle SL, Bennett AM, Donohoe CL, Mongan AM, Howard JM, Lithander FE, et al. Establishing computed tomography-defined visceral fat area thresholds for use in obesity-related cancer research. *Nutr Res* 2013;33:171–9.
- [16] Lee Y, Park M. Relationships among factors relevant to abdominal fat and age-related hearing loss. *Clin Exp Otorhinolaryngol* 2017;10:309–14.
- [17] Grossberg AJ, Chamchod S, Fuller CD, Mohamed AS, Heukelom J, Eichelberger H, et al. Association of body composition with survival and locoregional control of radiotherapy-treated head and neck squamous cell carcinoma. *JAMA Oncol* 2016;2:782–9.
- [18] Ahn SH, Hong HJ, Kwon SY, Kwon KH, Roh JL, Ryu J, et al. Guidelines for the surgical management of laryngeal cancer: Korean society of thyroid-head and neck surgery. *Clin Exp Otorhinolaryngol* 2017;10:1–43.
- [19] Kim BH, Park SJ, Jeong WJ, Ahn SH. Comparison of treatment outcomes for T3 glottic squamous cell carcinoma: a meta-analysis. *Clin Exp Otorhinolaryngol* 2018;11:1–8.
- [20] Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. The American Joint Committee for Cancer (AJCC) cancer staging manual. 7th ed. ed. New York, NY: Springer-Verlag; 2010. p. p54–96.

- [21] Schernberg A, Escande A, Rivin Del Campo E, Ducreux M, Nguyen F, Goere D, et al. Leukocytosis and neutrophilia predicts outcome in anal cancer. *Radiother Oncol* 2017;122:137–45.
- [22] Mabuchi S, Matsumoto Y, Kawano M, Minami K, Seo Y, Sasano T, et al. Uterine cervical cancer displaying tumor-related leukocytosis: a distinct clinical entity with radioresistant feature. *J Natl Cancer Inst* 2014;106.
- [23] Holgersson G, Sandelin M, Hoyer E, Bergstrom S, Henriksson R, Ekman S, et al. Swedish lung cancer radiation study group: the prognostic value of anaemia, thrombocytosis and leukocytosis at time of diagnosis in patients with non-small cell lung cancer. *Med Oncol* 2012;29:3176–82.
- [24] Park MJ, Roh JL, Kim SB, Choi SH, Nam SY, Kim SY. Prognostic value of circulating biomarker score in advanced-stage head and neck squamous cell carcinoma. *Eur J Cancer* 2018;92:69–76.
- [25] Schernberg A, Moureau-Zabotto L, Rivin Del Campo E, Escande A, Ducreux M, Nguyen F, et al. Leukocytosis and neutrophilia predict outcome in locally advanced esophageal cancer treated with definitive chemoradiation. *Oncotarget* 2017;8:11579–88.
- [26] Cho Y, Kim KH, Yoon HI, Kim GE, Kim YB. Tumor-related leukocytosis is associated with poor radiation response and clinical outcome in uterine cervical cancer patients. *Ann Oncol* 2016;27:2067–74.
- [27] Cooper JS, Farnan NC, Asbell SO, Rotman M, Marcial V, Fu KK, et al. Recursive partitioning analysis of 2105 patients treated in Radiation Therapy Oncology Group studies of head and neck cancer. *Cancer* 1996;77:1905–11.
- [28] Yamashita T, Yamashita K, Kamimura R. A stepwise AIC method for variable selection in linear regression. *Commun Stat Theor Methods* 2007;36:2395–403.
- [29] Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in regression analyses conducted in epidemiologic studies. *Epidemiology* 2016;6.
- [30] Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. *Eur J Cancer* 2016;57:58–67.
- [31] Wendrich AW, Swartz JE, Bril SI, Wegner I, de Graeff A, Smid EJ, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncol* 2017;71:26–33.
- [32] Elliott JA, Doyle SL, Murphy CF, King S, Guinan EM, Beddy P, et al. Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. *Ann Surg* 2017;266:822–30.
- [33] Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. *Ann Oncol* 2018;29:iii1–9.
- [34] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35.