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Original Article

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ABSTRACT

Background and purpose: Sarcopenia is related to late radiation-induced toxicities and worse survival in head and neck cancer (HNC) patients. This study tested the hypothesis that sarcopenia improves the performance of current normal tissue complication probability (NTCP) models of radiation-induced acute toxicity in HNC patients.

Material/methods: This was a retrospective analysis in a prospective cohort of HNC patients treated from January 2007 to December 2018 with (chemo)radiotherapy. Planning CT scans were used for evaluating skeletal muscle mass. Characteristics of sarcopenic and non-sarcopenic patients were compared. The impact of sarcopenia was analysed by adding sarcopenia to the linear predictors of current NTCP models predicting physician- and patient-rated acute toxicities.

Results: The cut-off values of sarcopenia in the study population (n = 977) were established at skeletal muscle index < 42.0 cm2/m2 (men) and < 31.2 cm2/m2 (women), corresponding to the lowest sex-specific quartile. Compared to non-sarcopenic patients, sarcopenic patients were more frequently smokers (61% vs. 48%, $p < 0.001$), had more often advanced stage of disease (stage III-IV, $p = 0.004$), higher age (67 vs. 63 years, $p < 0.001$) and experienced more pretreatment complaints, such as dysphagia (grade ≥ 2, $p < 0.001$). Sarcopenia remained statistically significant, next to the linear predictor, only for physician-rated grade ≥ 3 dysphagia (week 3–6 during RT, $p < 0.01$). However, sarcopenia did not improve the performance of these NTCP models ($p > 0.99$).

Conclusion: Sarcopenia in HNC patients was an independent prognostic factor for radiation-induced physician-rated acute grade ≥ 3 dysphagia, which might be explained by its impact on swallowing muscles. However, addition of sarcopenia did not improve the NTCP model performance.

Sarcopenia is defined as generalised and progressive loss of skeletal muscle mass (SMM) and muscle function [1]. Low skeletal muscle mass is a field of growing research interest due to its high prevalence in head and neck cancer (HNC) patients [2,3]. Sarcopenia can negatively influence the health status of HNC patients by impairing their daily functioning [4]. In addition, sarcopenia is associated with worse overall survival, disease-free survival and radiation-induced late toxicities such as physician-rated xerostomia and dysphagia in HNC patients treated with radiotherapy (RT) [5–7].

HNC patients have a high-risk of malnutrition due to impairment in swallowing and the passage of food due to tumour and treatment-related toxicity [8]. In general, about 70% of HNC patients are identified as either moderately or severely malnourished before treatment initiation [9]. Malnutrition has proved to be a strong predictor of sarcopenia since it is correlated with an approximately fourfold higher risk of developing sarcopenia [10]. Therefore, sarcopenia is frequently observed in these patients [7,11].

Patients with HNC treated with RT experience several different acute and late toxicities: e.g. dysphagia, xerostomia, sticky saliva, oral mucositis, mucosal infections, sensory disruptions, dermatitis, loss of taste, fatigue, aspiration, weight loss and pain. All these

Abbreviations: NTCP, Normal Tissue Complication Probability.

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toxicities have a large impact on patients' quality of life [12–17]. Therefore, HNC patients often have to deal with the dual burden of sarcopenia and treatment-induced toxicities [17–19].

However, the published evidence about the impact of sarcopenia on radiation-induced acute toxicities in HNC patients is still limited. To our knowledge, only Thureau et. al have investigated the association between sarcopenia and acute toxicity [20]. This study did not find an association between sarcopenia and radiation-induced acute toxicity [20]. However, their study only investigated two acute toxicities, i.e. oral mucositis and dysphagia.

Although new normal tissue complication probability (NTCP) models of various acute and late toxicities in HNC patients have recently been published [21], the impact of sarcopenia was not evaluated during the development of these NTCP models.

Therefore, the objective of this study was to test the hypothesis that sarcopenia improves the performance of the current NTCP models used for prediction of multiple radiation-induced acute toxicities in HNC patients treated with definitive (chemo)RT.

Materials and methods

Patient demographics and treatment

Prospectively collected variables were retrospectively analysed in this cohort study performed in the University Medical Centre Groningen (UMCG), the Netherlands. Between January 2007 and December 2018, a total of 977 HNC patients who received definitive RT with or without systemic treatment were included. Eligibility criteria included a pathologically confirmed primary tumour of the head and neck area. Definitive radiotherapy, with or without systemic treatment, with curative intent and patient's participation in the prospective data registry program were additional inclusion criteria. Exclusion criteria were primary surgical treatment, distant metastases, re-irradiation in the head and neck area and prior malignancies in the last five years, except basal cell carcinoma or in situ carcinoma of the cervix. Lastly, since skeletal muscle mass index (SMI) used to define sarcopenia was calculated based on height, unknown height was also a reason for exclusion.

Patients received treatment with different RT techniques, i.e. three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, volumetric arc therapy or intensity-modulated proton therapy, all including a simultaneous integrated boost technique. The total prescribed dose was up to 70 Gy (fractions of 2 Gy) with or without neck irradiation to a prophylactic dose of 54.25 Gy (fractions of 1.55 Gy) in six to seven weeks (6 or 5 fractions per week). Patients below 70 years of age with locally advanced disease, who were considered fit enough, received concurrent chemotherapy or cetuximab if chemotherapy was contraindicated. Patients < 70 years who could not receive chemotherapy or cetxumiab were treated with accelerated radiotherapy (6 fractions per week). Up to 2018, chemotherapy included carboplatin 300–350 mg/m^2 on days 1, 22 and 43 followed by continuous infusion of 5-fluorouracil at dose of 600 mg/m^2/day for 96 hours. Since 2018, chemotherapy treatment has included administration of cisplatin 40 mg/m^2 weekly. Treatment with cetuximab includes a loading dose of 400 mg/m^2 one week before RT and weekly infusions of 250 mg/m^2 during radiotherapy.

Clinical parameters

Clinical data derived from medical charts included sex, age, weight, height, World Health Organisation performance status (WHO PS), alcohol and smoking history, primary tumour location and treatment modality. Dosimetric parameters of organs at risk (OARs), all delineated according to current guidelines [22], were captured from the RT planning system. In addition, tumour and lymph node stage were defined in accordance with the 7th edition of the American Joint Committee on Cancer Staging Manual (AJCC) [23].

CT image analysis

Planning CT scans, including the third cervical vertebra (C3) instead of the third lumbar vertebra (L3), were used for measuring and computing SMM at L3 as previously described by Wendrich et al. [6]. Swartz et al. found a strong correlation between SMM at level L3 and SMM at C3 [24]. Selection of the suitable axial CT slide and delineation of the outer contours of the paravertebral and sternocleidomastoid muscles were carried out using RayStation 9A Clinical software or Mirada DB Research software in the same manner as the one used by van Rijn-Dekker et al [5]. Lastly, the cross-sectional skeletal muscle area (CSA) at level of L3 was normalised for stature resulting in the lumbar SMI which is an indication of total SMM (equation 1) [25]. Sarcopenia cut-off values were defined based on the lowest sex-specific quartile.

$$\text{Lumbar SMI } (cm^2/m^2) = \text{CSA at L3 } (cm^2)/\text{height}^2\ (m^2) \quad (1)$$

Outcome measures

The outcome measures of the current study were radiation-induced acute toxicities, including dysphagia, xerostomia, sticky saliva, aspiration, oral mucositis, fatigue and weight loss. All endpoints were measured weekly during treatment, from week 3 to 7 during RT. Fatigue was the only exception to this procedure, since it was only measured 12 weeks after start of RT in our prospective data registration programme (SFP, ClinicalTrials.gov NCT02435576). In addition, if the analysis showed that sarcopenia was an independent prognostic factor for an acute toxicity, further analyses regarding this toxicity after treatment (i.e. 6 to 24 months after RT) were performed. Endpoints were similarly dichotomised and defined as described by Van den Bosch et al. [21]. To summarise, patient-rated moderate-to-severe xerostomia and sticky saliva were defined according to question 41 and 42 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Head and Neck (QLQ-H&N35) (resp. "Did you have a dry mouth?" and "Did you have sticky saliva?") [26]. Questions 10, 12 and 18 of the EORTC Quality of Life Questionnaire Cancer (QLQ-C30) (resp. "Did you have the need to rest?", "Did you feel weak?", "Did you feel tired?") were used to define moderate-to-severe fatigue [21,26]. Physician-rated toxicities were assessed weekly by the treating physician using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) [27], except for oral mucositis which was graded according to RTOG guidelines [28]. These endpoints were defined as follows: grade $\geq$ 2 and grade $\geq$ 3 dysphagia, grade $\geq$ 2 xerostomia, grade $\geq$ 2 sticky saliva, grade $\geq$ 2 aspiration, grade $\geq$ 2 and grade $\geq$ 3 oral mucositis and grade $\geq$ 2 weight loss.

Data analysis

Descriptive statistics for continuous variables were presented as median (interquartile range, IQR) or as mean (standard deviation, ± SD), depending on their distribution. Categorical variables were illustrated as frequencies (n) and percentages (%). All reported p-values were two-sided and were statistically significant for $\alpha \leq 0.05$. Missing data were imputed, resulting in ten imputation sets [29]. Analysis of these endpoints were carried out in all imputation sets and results were pooled based on the Rubin's Rule [30].

The association between sarcopenic status and clinical parameters and several toxicity outcomes was assessed by pooled Welch

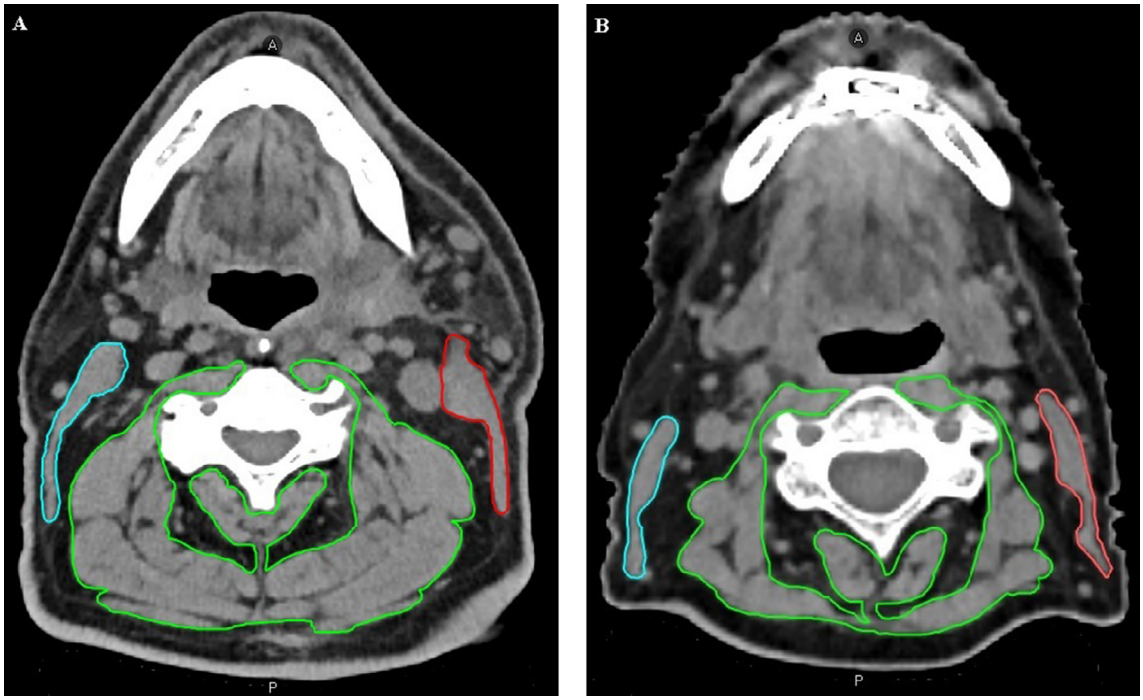

Fig. 1. Comparison axial CT slide non-sarcopenic and sarcopenic patient. (A) Non-sarcopenic patient with SMI 65,17 cm/m^2 and (B) sarcopenic patient with SMI 25.5 cm/m^2. *Legend:* green = paravertebral muscles; blue = right sternocleidomastoid muscle; red = left sternocleidomastoid muscle. *Abbreviations:* CT = computed tomography; SMI = skeletal muscle index.

t-tests and pooled Chi-square tests, respectively for continuous and categorical variables. The following clinical parameters were compared: sex, age, weight, BMI, SMI, WHO PS, alcohol and smoking history, RT technique, treatment modality, tumour and nodal stage, primary tumour stage according to AJCC 7th edition [23] and pretreatment toxicities.

The first step to determine the impact of sarcopenia on the different radiation-induced toxicities was an univariate logistic regression analysis. Secondly, it was explored whether sarcopenia would improve the recently published NTCP models [21]. The linear predictor for each endpoint from 3 to 7 weeks during treatment was calculated based on these NTCP models [21]. Subsequently, the addition of sarcopenia to the linear predictor was analysed with multivariable logistic regression analysis using a forward selection method based on the Bayesian information criterion [29]. If sarcopenia remained significant next to the linear predictor, the likelihood-ratio test was performed to test whether the NTCP model including sarcopenia performed significantly better than the original NTCP model.

All analyses were performed in RStudio Version 1.1.463.

Results

The study population consisted of 977 HNC patients treated with definitive (chemo)radiotherapy. Mean SMI of the total population was 42.9 ± 7.9 cm^2/m^2. SMI was significantly higher in men (46.2 cm^2/m^2) than in women (35.5 cm^2/m^2) ($p < 0.001$). Sarcopenia cut-off values were set at SMI < 42.0 cm^2/m^2 (men) and SMI < 31.2 cm^2/m^2 (women), according to the lowest sex-specific quartile. To illustrate the difference between non-sarcopenic patients and sarcopenic patients, the delineated cross-sectional muscle area at C3 of two patients are shown in Fig. 1.

All clinical and dosimetric parameters were complete. Due to loss to follow up, tumour recurrence or death, and non-compliance, not all toxicity measurements were complete (Table Supplementary Materials S1). Characteristics of non-sarcopenic and sarcopenic patients are shown in Table 1. Sarcopenic patients were generally older (mean age of 67 vs. 63 years, $p < 0.001$), active smokers (61% vs. 48%, $p < 0.001$), in worse performance status, i.e., WHO PS ≥ 1 (52% vs. 29%, $p < 0.001$) and had more advanced stages of disease, i.e., stage III-IV (77% vs. 67%, $p = 0.004$). In addition, sarcopenic patients were more likely to have physician-rated grade ≥ 2 and grade ≥ 3 dysphagia (32% vs. 20%, $p < 0.001$ and 12% vs. 6%, $p = 0.003$, respectively), patient-rated moderate-to-severe xerostomia (17% vs. 11%, $p = 0.01$) and more weight loss (4.2 vs. 2.4 kilogram, $p < 0.001$) before the onset of treatment.

Univariable logistic regression analysis showed that sarcopenia was significantly associated with the following radiation-induced toxicities: physician-rated grade ≥ 2 and ≥ 3 dysphagia week 3 to 7, patient-rated moderate-to-severe sticky saliva week 3, physician-rated grade ≥ 2 sticky saliva week 6, physician-rated grade ≥ 2 mucositis week 4 to 7, and physician-rated grade ≥ 3 mucositis week 7 (Table S2). The addition of sarcopenia to the current NTCP models for radiation-induced acute toxicity, remained only significant next to the linear predictor, for physician-rated grade ≥ 3 dysphagia from 3 to 6 weeks during RT (Table 2, Table S3-8). However, these models including sarcopenia did not perform significantly better than the original NTCP models for acute grade ≥ 3 dysphagia (likelihood-ratio test $p = 1.0$ and $p = 0.99$, respectively for week 3 to 5 and week 6).

Considering the results with regard to the physician-rated acute dysphagia, these analyses were repeated for physician-rated late dysphagia. Univariate analysis showed that sarcopenia was significantly associated with physician-rated grade ≥ 2 and ≥ 3 dysphagia from 6 to 24 months after treatment (Table S9). In addition, multivariable analysis showed that the addition of sarcopenia to the current NTCP models for late dysphagia was significant for both grade ≥ 2 and grade ≥ 3 physician-rated dysphagia from 6 to 24 months after treatment (Table 3). Nonetheless, these NTCP models with sarcopenia, had no significantly better performance than the NTCP models without sarcopenia (likelihood-ratio test $p = 1.0$ for all endpoints).

Table 1
Baseline characteristics of the head and neck cancer patients.

	No sarcopenia	Sarcopenia	*P* value
	(*n* = 733)	(*n* = 244)	
Patient characteristics			
Sex (*n* (%))			1.0[b]
Male	506 (69)	168 (69)	
Female	227 (31)	76 (31)	
Age at diagnosis (years) (mean ± SD)	63 ± 10	67 ± 10	<0.001*[c]
WHO PS (*n* (%))			<0.001*[b]
0	518 (71)	117 (48)	
1–4	215 (29)	128 (52)	
Weight (in kg) (mean ± SD)	83 ± 16	66 ± 12	<0.001*[c]
BMI (in kg/m^2) (mean ± SD)	27 ± 4.5	21 ± 2.9	<0.001*[c]
SMI at diagnosis (in cm^2/m^2) (mean ± SD)	45 ± 7.1	36 ± 5.3	<0.001*[c]
Smoking history (*n* (%))			<0.001*[b]
No, not smoking at this moment	379 (52)	94 (39)	
Yes, current smoker	354 (48)	150 (61)	
Alcohol history (*n* (%))			<0.50[b]
No, not drinking at the moment	231 (32)	83 (34)	
Yes, current drinker	502 (68)	161 (66)	
Tumour characteristics			
Tumour site (*n* (%))			<0.001*[b]
Larynx	363 (50)	73 (30)	
Other locations	370 (50)	171 (70)	
Tumour stage[a] (*n* (%))			0.002*[b]
Tis-T2	369 (50)	94 (39)	
T3-T4	364 (50)	150 (61)	
Nodal stage[a] (*n* (%))			<0.001*[b]
N0	364 (50)	84 (34)	
N1-N3	369 (50)	160 (66)	
Clinical stage[a] (*n* (%))			0.004*[b]
Stage I-II	242 (33)	56 (23)	
Stage III-IV	491 (67)	188 (77)	
Treatment characteristics			
Treatment modality (*n* (%))			0.04*[b]
RT alone	461 (63)	135 (55)	
RT and systemic treatment	272 (37)	109 (45)	
RT technique (*n* (%))			<0.001*[b]
Conventional (3D CRT)	65 (9)	20 (8)	
IMRT/VMAT	654 (89)	209 (86)	
IMPT	14 (2)	15 (6)	
Toxicity prior to treatment			
Physician-rated dysphagia, grade ≥ 2 (*n* (%))			<0.001*[b]
Grade 0–1	585 (80)	165 (68)	
Grade 2–3	148 (20)	79 (32)	
Physician-rated dysphagia, grade ≥ 3 (*n* (%))			0.003*[b]
Grade 0–2	688 (94)	214 (88)	
Grade 3	45 (6)	30 (12)	
Patient-rated xerostomia (*n* (%))			0.01*[b]
None	432 (59)	126 (52)	
A little	219 (30)	76 (31)	
Moderate-severe	82 (11)	42 (17)	
Physician-rated xerostomia (*n* (%))			0.32[b]
Grade 0	616 (84)	198 (81)	
Grade 1–3	117 (16)	46 (19)	
Patient-rated sticky saliva (*n* (%))			0.07[b]
None	432 (59)	126 (51)	
Any	301 (41)	118 (49)	
Physician-rated sticky saliva (*n* (%))			0.15[b]
Grade 0	646 (88)	206 (84)	
Grade 1–3	87 (12)	38 (16)	
Physician-rated aspiration (*n* (%))			0.83[b]
Grade 0–1	698 (95)	230 (94)	
Grade 2 or higher	35 (5)	14 (6)	
Patient-rated fatigue (*n* (%))			0.06[b]
None-Mild	655 (89)	206 (84)	
Moderate-severe	78 (11)	38 (16)	
Weight loss (in kg) (mean ± SD)	2.4 ± 17	4.2 ± 8.0	0.001*[c]

Abbreviations: *n* = number; SD = standard deviation; WHO PS = world health organisation performance status; kg = kilogram; BMI = body mass index; SMI = skeletal muscle index; RT = radiotherapy; 3D CRT three-dimensional conformal radiation therapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc therapy; IMPT = intensity modulated proton therapy. * Statistically significant, $\alpha \leq 0.05$.

[a] According to the 7th edition of the AJCC/UICC staging system [23].

[b] *p* value was calculated using the pooled chi-square test.

[c] *p* value was calculated using pooled welch t-test.

Table 2
Addition of sarcopenia to NTCP models for physician-rated grade ≥ 2 and ≥ 3 dysphagia during radiotherapy.

Model predictors	W03		W04		W05		W06		W07	
Grade ≥ 2 (events n (%))	482 (49)		642 (66)		693 (71)		744 (75)		726 (74)	
	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P value*	coefficient (SE)	*P* value	coefficient (SE)	*P* value
Intercept	−0.020 (0.074)	0.79	−0.060 (0.090)	0.51	−0.063 (0.098)	0.52	−0.150 (0.114)	0.19	−0.255 (0.154)	0.10
Linear predictor[a]	1.027 (0.076)	<0.001*	1.015 (0.073)	<0.001*	1.003 (0.069)	<0.001*	1.030 (0.073)	<0.001*	0.951 (0.072)	<0.001*
Sarcopenia	–		–		–		–		–	
Grade ≥ 3 (events n (%))	232 (24)		358 (37)		432 (44)		497 (51)		528 (54)	
	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P* value
Intercept	−0.215 (0.120)	0.07	−0.245 (0.939)	0.009*	−0.299 (0.094)	0.002*	−0.237 (0.098)	0.02*	0.103 (0.086)	0.23
Linear predictor[b]	1.058 (0.089)	<0.001*	0.991 (0.071)	<0.001*	0.791 (0.050)	<0.001*	0.886 (0.054)	<0.001*	0.906 (0.057)	<0.001*
Sarcopenia	0.712 (0.189)	<0.001*	0.516 (0.178)	0.004*	0.529 (0.183)	0.004*	0.500 (0.191)	0.009*	-	

Abbreviations: n = number; W03 – W07 = week during radiotherapy; - = not selected during multivariable logistic regression analysis; RT = radiotherapy. * Statistically significant, $\alpha \leq 0.05$.
[a] Original model consisted of mean dose to the oral cavity and the PCM superior, and treatment modality (conventional RT vs. accelerated RT vs. chemoradiation vs. accelerated RT with cetuximab) [21].
[b] Original model consisted of mean dose to the oral cavity and the PCM superior, and treatment modality (conventional RT vs. accelerated RT vs. chemoradiation vs. accelerated RT with cetuximab) [21].

Table 3
Addition of sarcopenia to NTCP models physician-rated grade ≥ 2 and ≥ 3 dysphagia after radiotherapy.

Model predictors	M06		M12		M18		M24	
Grade ≥ 2 (events n (%))	293 (30)		235 (24)		232 (24)		264 (27)	
	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P value*	coefficient (SE)	*P value*
Intercept	−0.306 (0.108)	0.005*	−0.696 (0.176)	<0.001*	−0.550 (0.152)	<0.001*	−0.550 (0.123)	<0.001*
Linear predictor[a]	0.868 (0.084)	<0.001*	0.703 (0.081)	<0.001*	0.837 (0.103)	<0.001*	0.723 (0.068)	<0.001*
Sarcopenia	0.699 (0.220)	0.001*	0.837 (0.208)	<0.001*	0.549 (0.289)	0.06	0.660 (0.226)	0.004*
Grade ≥ 3 (events n (%))	165 (17)		129 (13)		118 (12)		167 (17)	
	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P* value	coefficient (SE)	*P* value
Intercept	−0.386 (0.171)	0.02*	−0.737 (0.357)	0.04*	−0.569 (0.343)	0.10	−0.033 (0.272)	0.90
Linear predictor[b]	0.816 (0.090)	<0.001*	0.757 (0.105)	<0.001*	0.921 (0.118)	<0.001*	0.983 (0.104)	<0.001*
Sarcopenia	0.793 (0.243)	0.001*	0.828 (0.279)	0.003*	0.653 (0.302)	0.03*	0.874 (0.234)	<0.001*

Abbreviations: n = number; W03 – W07 = week during radiotherapy; - = not selected during multivariable logistic regression analysis; PCM = pharyngeal constrictor muscle. * Statistically significant, $\alpha \leq 0.05$.
[a] Original model consisted of mean dose to the oral cavity, the PCM superior, the PCM middle and the PCM inferior, baseline toxicity (grade 0–1 vs. grade 2 vs. grade 3–4) and primary tumour location (pharynx vs. larynx) [21].
[b] Original model consisted of mean dose to the oral cavity, the PCM superior, the PCM middle and the PCM inferior, baseline toxicity (grade 0–1 vs. grade 2 vs. grade 3–4) and primary tumour location (pharynx vs. larynx) [21].

Since sarcopenia was only an independent predictor for physician-rated dysphagia, its impact was further illustrated by comparing the prevalence of physician-rated grade ≥ 2 and ≥ 3 dysphagia during and after treatment in sarcopenic and non-sarcopenic patients. Dysphagia complaints gradually increased throughout treatment for both sarcopenic and non-sarcopenic patients (Fig. 2). However, this univariate analysis showed that sarcopenic patients experience grade ≥ 2 and ≥ 3 dysphagia during and after treatment significantly more often (Fig. 2).

Discussion

With 977 patients, this study was the largest prospective study aiming to test the hypothesis that sarcopenia improves the performance of recently published NTCP models to predict acute toxicity in HNC patients treated with definitive (chemo)RT [21]. Sarcopenia was specifically chosen because it is the most common cause of lean body mass loss in cancer patients [31]. HNC patients receiving (chemo)RT frequently lose more than 5% of their total muscle mass in less than 6 months [31]. This study showed that sarcopenia was an independent prognostic factor for the development of physician-rated acute grade ≥ 3 dysphagia and late grade ≥ 2 and grade ≥ 3 dysphagia. However, sarcopenia did not improve the performance of these NTCP models. This is the first time that the relationship between sarcopenia and acute RT-induced side effects in HNC patients has been investigated directly.

Our study proved a significant association of sarcopenia with both grade ≥ 2 and ≥ 3 dysphagia after correcting for the necessary confounders, based on the recently published NTCP models [21]. Dysphagia complaints gradually increased throughout treatment for both sarcopenic and non-sarcopenic patients (Fig. 2). However, sarcopenic patients experienced grade ≥ 2 and ≥ 3 dysphagia during and after treatment significantly more often (Fig. 2). Karsten et al. showed that HNC patients have an increased risk of developing swallowing complaints due to the extent of tumour and treatment consequences [32]. Furthermore, loss of muscle mass and function that accompany sarcopenia leads to muscle atrophy, aggravating the patients' swallowing ability even more [32]. One of the most crucial modulators in human health is nutritional intake [10]. Poor nutritional status observed in HNC patients leads to loss of swallowing muscle mass and function, and therefore to swallowing difficulties due to non-use atrophy of these muscles [32]. Sarcopenia could be one of the main factors worsening this vicious spiral by limiting the reserves with regards to muscle mass and function even more [32]. This assertion could explain why sarcopenic HNC patients experience grade ≥ 2 and grade ≥ 3 dysphagia more frequently, at all stages of treatment. However, sarcopenia did not improve the performance of the current NTCP models to predict physician-rated dysphagia. Sarcopenia was not

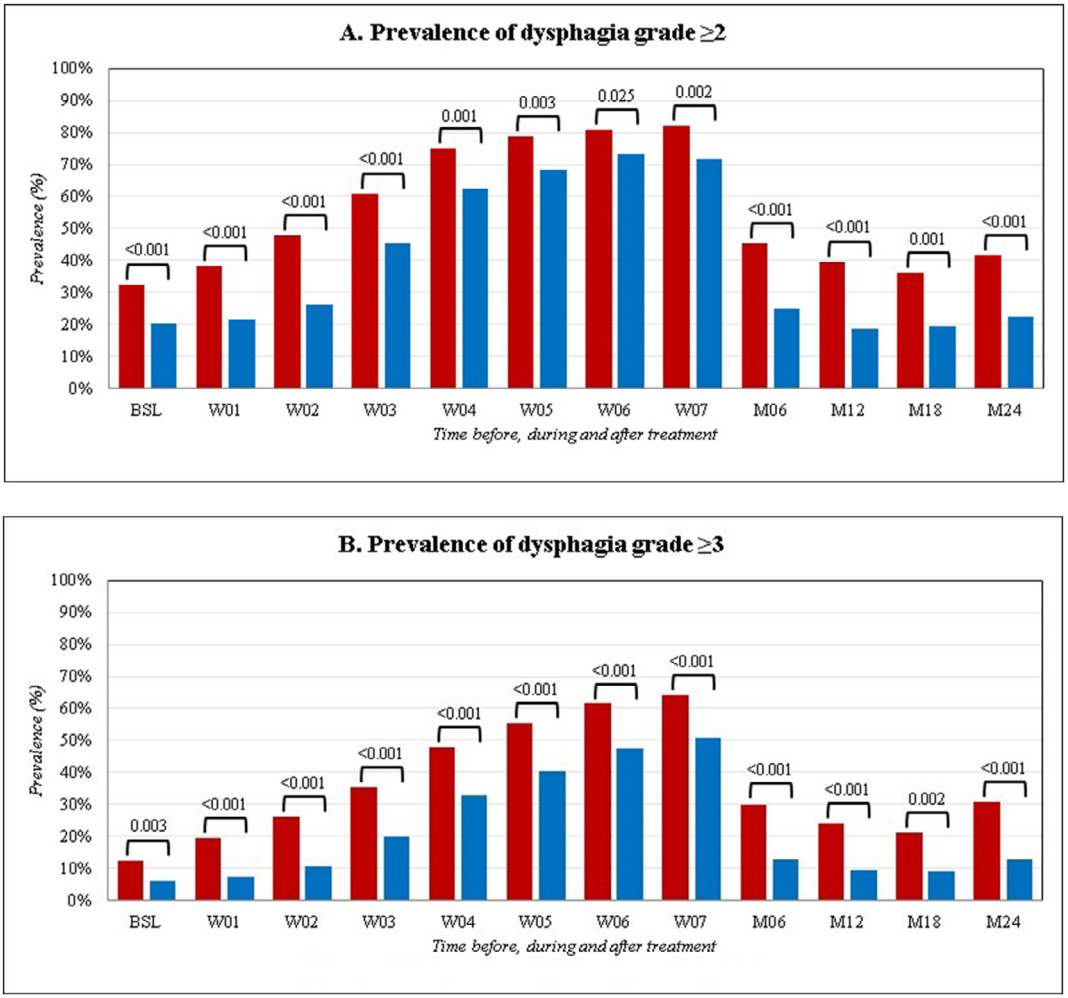

Fig. 2. Prevalence of dysphagia in sarcopenic and non-sarcopenic HNC patients. (A) Physician-rated grade ≥ 2 dysphagia and (B) physician-rated grade ≥ 3 dysphagia. *Legend:* red = Sarcopenic HNC patients; blue = non-sarcopenic HNC patients. *Abbreviations:* HNC = head and neck cancer; BSL = baseline (prior to treatment); W01 - W07 = weeks during radiotherapy; M06 - M24 = months after radiotherapy. *P* values were calculated using pooled Chi-square tests.

an independent prognostic predictor for the other acute toxicities investigated by our study in HNC patients treated with definitive RT.

After comparing the characteristics of sarcopenic and non-sarcopenic patients, it was found that sarcopenic patients were more likely to deal with greater weight loss at baseline. Our study was in accordance with Chargi et al. who proved that low food intake, increased inflammation and catabolic pathways associated with malignancy and old age can lead to weight loss [4]. Furthermore, sarcopenic HNC patients were more likely to have a worse performance and more advanced stage of disease. Additionally, it was shown that sarcopenic HNC patients were more likely to be current smokers. An explanation for this could be that components of the cigarette smoke such as reactive oxygen and nitrogen species enter the bloodstream, reach the skeletal muscles and accelerate muscle wasting, as suggested by Steffl et al. [33]. Moreover, differentiation was observed regarding the type of RT treatment technique the two patient groups received. The patient selection for proton therapy in the Netherlands is partly based on dysphagia complaints before treatment. This might be one of the reasons why sarcopenic patients receive proton therapy more often. However, conclusions cannot be drawn due to the small number of patients receiving proton therapy.

This study had some limitations. Firstly, since no validated sex-specific cut-off values for sarcopenia in HNC patients could be found in literature [4,6,34,35], the cut-off values in the current study were arbitrary chosen according to the lowest sex-specific quartile, based on the strategy used in the article of van Rijn-Dekker et al. [5]. As soon as new non-arbitrary, sex-specific cut-off values are established, this research could be repeated, and the results could be compared. Secondly, this study's design was defined after the data collection and therefore it was a retrospective study. However, its data was prospectively collected according to the department's standardised follow up protocol (SFP, ClinicalTrials.gov NCT02435576). Lastly, the focus of this study was on the effect of sarcopenia on the performance of recently published NTCP models to predict acute toxicity. However, the study of Wang et al showed that the total psoas area, lean psoas area, and psoas density decreased significantly from pretreatment to 3 months after treatment [36]. It would be of great research interest to assess in a follow-up study how worsening sarcopenia after therapy, compared with baseline, affects subacute and late NTCPs which could be calculated based on posttreatment followed up CT scans.

In conclusion, sarcopenia did not improve the performance of the current NTCP models to predict acute toxicity in HNC patients treated with definitive RT. However, this study illustrated that sarcopenia in HNC patients treated with RT was an independent prognostic factor for the development of physician-rated acute grade ≥ 3 dysphagia and late grade ≥ 2 and grade ≥ 3 dysphagia,

which might be explained by its impact on the swallowing muscles. In addition, sarcopenia based on SMI according to the lowest sex-specific quartile had no significant impact on the other examined toxicities. Nevertheless, this study did shed light on the importance of detecting sarcopenia in HNC patients and on knowing its impact on the toxicities during RT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.03.009.

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