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Original Article

Impact of sarcopenia on survival and late toxicity in head and neck cancer patients treated with radiotherapy

Maria I. van Rijn-Dekker [a], Lisa van den Bosch [a], Johanna G.M. van den Hoek [a], Hendrik P. Bijl [a], Evert S.M. van Aken [a], Anouk van der Hoorn [b], Sjoukje F. Oosting [c], Gyorgy B. Halmos [d], Max J.H. Witjes [e], Hans P. van der Laan [a], Johannes A. Langendijk [a], Roel J.H.M. Steenbakkers [a,*]

[a] Department of Radiation Oncology; [b] Department of Radiology; [c] Department of Medical Oncology; [d] Department of Otorhinolaryngology/Head and Neck Surgery; and [e] Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, The Netherlands

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ABSTRACT

Background and purpose: Sarcopenia is emerging as an adverse prognostic factor for survival and complication risk in cancer patients. This study aims to determine the impact of sarcopenia on survival and late toxicity in a large cohort of head and neck squamous cell carcinoma (HNSCC) patients treated with definitive (chemo)radiotherapy ((C)RT).

Materials and methods: HNSCC patients treated with definitive (C)RT from January 2007 to June 2016 were included. Sarcopenia was assessed from radiation planning computed tomography (CT) scans using skeletal muscles at level C3. The impact of sarcopenia on overall survival (OS) and disease-free survival (DFS) was evaluated using the Kaplan–Meier method. Multivariable association models were developed to assess the impact of sarcopenia on late toxicity.

Results: The study population was composed of 750 HNSCC patients. Cut-off values for sarcopenia were set at SMI < 42.4 cm^2/m^2 (men) and <30.6 cm^2/m^2 (women) corresponding lowest gender specific quartile. Sarcopenic patients had significantly poorer survival rates, especially those with lower performance status and locally advanced disease. In oropharyngeal cancer patients, survival was more determined by p16 status than by sarcopenia. In multivariable analysis, sarcopenia was associated with worse OS (HR 0.72, p = 0.012) and DFS (HR 0.67, p = 0.001). In multivariable association models, sarcopenia was associated with physician-rated xerostomia six months after treatment (OR 1.65, p = 0.027) and physician-rated dysphagia six and twelve months after treatment (OR 2.02, p = 0.012 and 2.51, p = 0.003, respectively).

Conclusion: Sarcopenia in HNSCC patients receiving definitive (C)RT is an independent prognostic factor for worse survival outcomes and is associated with physician-rated toxicity.

Prognosis for head and neck cancer (HNC) patients is determined by patient- and disease-related factors, such as age, weight loss, performance status, comorbidities, prior malignancies, clinical stage, and human papilloma virus (HPV) status [1–4]. Sarcopenia is emerging as an independent adverse prognostic factor in all oncological patients [5,6], as well as in HNC patients [7–16].

Sarcopenia is defined as severe loss of muscle mass and muscle function [17]. It is associated with adverse outcomes in oncological patients, including poorer survival, more postoperative infections, increased length of hospital stay, and more chemotherapy-induced dose limiting toxicity [5,6]. Poor alimentation, an important risk factor for developing sarcopenia, is very common in patients with HNC. Approximately 35% to 60% of HNC patients present with malnutrition and over 10% weight loss [18]. In addition, HNC patients experience weight loss, gastrointestinal distress, anorexia, fatigue, and sarcopenia before, during, and after their oncological treatment [19]. Radiotherapy (RT) plays a pivotal role in most HNC patients and is associated with many toxicities, like xerostomia, dysphagia, oral mucositis, and sticky saliva, resulting in further deterioration of nutritional status [19–22]. Combining RT with systemic treatment modalities such as chemotherapy further enhances these toxicities [23].

Recent studies, consisting of 85–246 HNC patients, confirmed that sarcopenia is associated with poor overall survival (OS), disease-free survival (DFS), chemotherapy toxicity, radiation treatment breaks and post-operative wound complications after total

* Corresponding author at: Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, PO Box 30001, 9700RB Groningen, The Netherlands.
E-mail address: r.steenbakkers@umcg.nl (R.J.H.M. Steenbakkers).

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laryngectomy [7–16]. No association between radiation-induced toxicity and sarcopenia has been found yet [9].

Therefore, the purpose of this study was to investigate the association between sarcopenia and OS and DFS in a large cohort of HNC patients treated with definitive RT and to investigate the relationship between sarcopenia and late radiation-induced toxicity.

Materials and methods

Patient demographics and treatment

This single centre study used prospectively collected data which was retrospectively analysed. A total of 750 consecutive head and neck squamous cell carcinoma (HNSCC) patients were included, treated between January 2007 and June 2016 at the University Medical Center Groningen (UMCG). Patients were treated with definitive RT, either combined or not, with systemic treatment (cisplatin, carboplatin/5FU or cetuximab).

Inclusion criteria were as follows: confirmed primary tumour with pathological diagnosis of squamous cell carcinoma, no metastatic disease, treatment with curative intent, OS and DFS data available, and participation in the prospective data registry program for HNC patients, as described in previous studies [24,25]. In summary, this program includes a prospective evaluation of toxicity and quality of life prior to, weekly during, and at regular intervals after definitive or postoperative RT or chemoradiotherapy (CRT) (at 6 weeks, every 6 months up to 24 months, and every 12 months up to 60 months).

Details about the RT regimens used are described in detail in previous studies [26,27]. In summary, RT consisted of three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) using a simultaneous integrated boost (SIB) technique to a total prescribed dose of 70 Gy with fractions of 2 Gy in 6–7 weeks (6 or 5 fractions per week). Most patients received bilateral neck radiation with a prophylactic dose of 54.25 Gy. Patients with locally advanced disease below 70 years of age who were deemed fit enough received concurrent chemotherapy, or cetuximab if chemotherapy was contraindicated. Chemotherapy consisted of carboplatin 300–350 mg/m^2 on day 1, 22 and 43 followed by continuous infusion of 5-fluorouracil at a dose of 600 mg/m^2/day for 96 h. Cetuximab was started one week before radiotherapy at a loading dose of 400 mg/m^2, followed by weekly infusions of 250 mg/m^2 during radiotherapy.

Clinical parameters

All clinical parameters, including age, gender, height, weight, World Health Organization Performance Status (WHO PS), smoking history, alcohol history, p16 status, tumour location and treatment modality were derived from the prospective data registration. Mean dose of the primary tumour, positive lymph nodes and organs at risk (OARs) was derived from the RT planning system. Tumour (T) and lymph node (N) stage were defined according to the 7th edition of the American joint Committee on Cancer Staging Manual [28].

CT image analysis

Sarcopenia can be assessed on CT scans. Measurement of a single abdominal image can provide estimates of total body skeletal muscle mass and adipose tissue distribution [29]. In oncological patients, sarcopenia is determined based on single-slide CT measurement of the cross-sectional muscle area (CSA) at the level of the third lumbar vertebra (L3) [30]. Swartz et al. [31] found a strong correlation between skeletal muscle mass at level L3 and skeletal muscle mass at the level of the third cervical vertebra (C3).

For all patients, sarcopenia was assessed on the pre-treatment CT scan (Somatom Sensation Open, Siemens, Forchheim, Germany; voxel size 1.0 × 1.0 × 2.0 mm; scan voltage: 120 kV; convolution kernel: B30) with contrast enhancement acquired for RT treatment planning, according to the method previously published by Swartz et al. [31]. This method was validated by Ufuk et al. [32].

The single axial CT-slide at level of C3 first showing the entire vertebral arc when scrolling from caudal to cranial direction was selected. To avoid over- or underestimation of skeletal muscle area, the Hounsfield unit (HU) settings ranged from −29 to +150 HU [31,33]. Outer contours of both sternocleidomastoid and paravertebral muscles were delineated manually (Fig. 1) using the delineation software Mirada DBx 1.2.0. All CT-scans were delineated by a single researcher (MvR) and supervised by an experienced head and neck radiation oncologist (RS).

The cross sectional muscle area (CSA) at the level of C3 is the total volume of the delineated areas divided by the thickness of the CT-slide. The CSA (cm^2) of the skeletal muscle at C3 was used to estimate the CSA at L3 using the validated algorithm described by Swartz et al. (Eq. (1)) and was furthermore adjusted for patients height (m^2) resulting in skeletal muscle index (SMI, cm^2/m^2) (Eq. (2)) [31,32].

$$\begin{aligned} CSA\ at\ L3(cm^2) = {} & 27.304 + 1.363 * CSA\ at\ C3\ (cm^2) - 0.671 \\ & * age\ (years) + 0.640 * weight(kg) \\ & + 26.442 \\ & * sex(sex = 1\ for\ female, 2\ for\ male) \end{aligned} \quad (1)$$

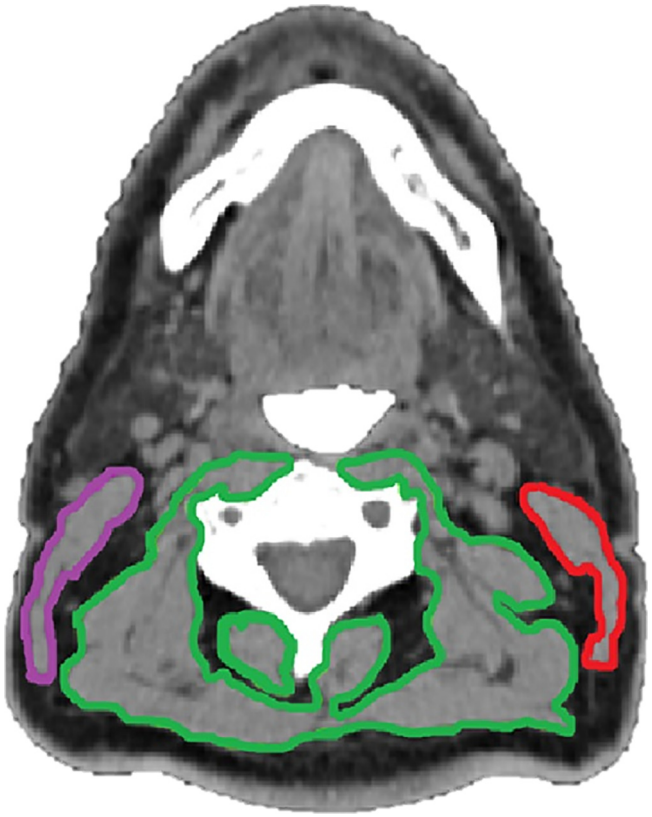

Fig. 1. A transversal CT-slice at the level of C3. Purple: right sternocleidomastoid muscle; green: paravertebral muscle; red: left sternocleidomastoid muscle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$$Lumbar\ SMI\left(\frac{cm^2}{m^2}\right) = \frac{CSA\ at\ L3\ (cm^2)}{height^2\ (m^2)} \quad (2)$$

Cut-off values for sarcopenia were set at SMI according lowest gender specific quartile.

Outcome measures

Outcome measures included OS, DFS and late radiation-induced toxicity. The time-to-event was defined from the first day of RT to the date of death or the date of disease recurrence. Patients alive or without any event were censored at the date of last follow up. For late radiation-induced toxicity endpoints were patient-rated and physician-rated xerostomia and physician-rated dysphagia, six and twelve months after treatment. Patient-rated xerostomia was defined as moderate-to-severe patient-rated xerostomia using the European Organisation for Research and Treatment of Cancer EORTC QLQ-H&N35 questionnaires [34]. Physician-rated xerostomia and dysphagia were both defined as grade 2 $\geq$ toxicity using the Common Terminology Criteria for Adverse Events (CTCAE, v4.03) [35].

Data analysis

Descriptive statistics were calculated, the continuous variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR) and discrete variables were presented as frequency counts and percentages. The *T*-test and Chi-square test were used to calculate differences between groups.

Kaplan–Meier estimates of survival proportions over time were calculated for patients with or without sarcopenia using log-rank tests or Wilcoxon tests in case of crossing survival curves. Stratified survival analysis was performed by WHO PS, i.e. WHO PS 0 versus WHO PS 1–3, by stage of disease, i.e. stage I–II versus stage III–IV and by p16 status in patients with oropharynx tumours, i.e. p16-negative vs. p16-positive. The risk factors for time to death and disease progression or recurrence were analysed using Cox proportional hazards models. Univariable models were fit to determine the hazard associated with sarcopenia, age, gender, WHO PS, smoking history, alcohol history, p16 status, tumour stage, tumour location, treatment modality, and RT technique. Covariates for the multivariable Cox proportional hazards regression models were selected using stepwise-forward selection with the condition *p*-value = 0.157.

Association models, using multivariable logistic regression, were developed to analyse the association of sarcopenia with the toxicity endpoints [36]. Association models are used to estimate the relationship between an outcome variable and a determinant while correcting for confounding. Potential confounders, i.e. age, gender, body mass index (BMI), WHO PS, smoking history, tumour stage, tumour location, treatment modality, RT technique, and mean dose on OARs, were evaluated with Pearson's Chi-Squared test or Spearman's Rank Correlation coefficient. Variables with $p < 0.10$ were selected and added to the analysis as potential confounders. Confounders resulting in more than 10% change of the regression coefficient were considered relevant confounders for the effect of sarcopenia on the endpoints.

Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 23. Data from all included patients were used and missing values were not imputed in analysis.

Results

The median follow up for the entire cohort was 24 months (IQR 12–56) and 315 deaths (42.0%) were observed. SMI was calculated in 744 patients, since information on patient height was missing in six patients. Mean SMI of the total population was 43.4 (SD 7.8) cm^2/m^2, significantly higher in men than in women (resp. 46.3 and 34.9 cm^2/m^2, $p < 0.001$). Sarcopenia cut-off values corresponding with the lowest gender specific quartile were set at SMI < 42.4 cm^2/m^2 in men and <30.6 cm^2/m^2 in women.

Patients with sarcopenia were more likely to be older (66 vs. 62 years, $p < 0.001$), or to have a worse WHO PS, i.e. WHO PS 1–3 (50.3% vs. 29.7%, $p < 0.001$). They were less likely to have a tumour located in the larynx (30.7% vs. 49.2%, $p < 0.001$), to have stage I or II disease (23.8% vs. 33.3%, $p < 0.001$), or to have

Table 1a
Baseline characteristics of the patients.

Characteristic	No sarcopenia (*n* = 555) (%)	Sarcopenia (*n* = 189) (%)	*P* value
Gender			0.697[b]
Male	412 (74.2)	143 (75.7)	
Female	143 (25.8)	46 (24.3)	
Age at diagnosis (median ± SD) (years)	62 ± 10	66 ± 10	<0.001[c]
WHO PS			<0.001[b]
0	390 (70.3)	94 (49.7)	
1–3	165 (29.7)	95 (50.3)	
SMI at diagnosis (median ± SD) (cm^2/m^2)	45.7 ± 7.2	36.7 ± 5.3	<0.001[c]
Smoking history			0.002[b]
Never	53 (9.5)	13 (6.9)	
Yes, current smoker	256 (46.1)	118 (62.4)	
Yes, in the past	244 (44.0)	58 (30.7)	
Missing	2 (0.4)	0 (0.0)	
Alcohol history			0.022[b]
Never	117 (21.1)	24 (12.7)	
Yes, current drinker	381 (68.8)	135 (71.4)	
Yes, in the past	53 (9.6)	29 (15.3)	
Missing	3 (0.5)	1 (0.5)	
Tumour site			<0.001[b]
Hypopharynx	38 (6.8)	33 (17.5)	
Larynx	273 (49.2)	58 (30.7)	
Oral cavity	27 (4.9)	16 (8.5)	
Oropharynx	189 (34.1)	80 (42.3)	
Nasopharynx	28 (5.0)	2 (1.1)	
P16 status (oropharynx tumours)			0.001[b]
Positive	83 (43.9)	16 (20.0)	
Negative	91 (48.1)	57 (71.3)	
Missing	15 (8.0)	7 (8.7)	
T stage[a]			<0.001[b]
Tis	3 (0.5)	1 (0.5)	
T1	105 (18.9)	17 (9.0)	
T2	180 (32.4)	54 (28.6)	
T3	142 (25.6)	39 (20.6)	
T4	125 (22.5)	78 (41.3)	
N stage[a]			0.002[b]
N0	267 (48.1)	62 (32.8)	
N1	48 (8.6)	16 (8.5)	
N2	223 (40.2)	106 (56.1)	
N3	17 (3.1)	5 (2.6)	
Clinical stage[a]			<0.001[b]
Stage I	71 (12.8)	13 (6.9)	
Stage II	114 (20.5)	32 (16.9)	
Stage III	110 (19.8)	22 (11.6)	
Stage IV	260 (46.8)	122 (64.6)	
Treatment modality			0.072[b]
RT only	338 (60.1)	101 (53.4)	
RT with systemic treatment	217 (39.1)	88 (46.6)	
RT technique			0.534[b]
Conventional	65 (11.7)	19 (10.1)	
IMRT	490 (88.3)	170 (89.9)	

Abbreviations: SMI = skeletal muscle index; WHO PS = World Health Organization performance score; T = tumour, N = lymph node; RT = radiotherapy; IMRT = intensity modulated radiotherapy.

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

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

[c] *P* value was calculated using the independent samples *t*-test.

p16-positive oropharyngeal cancer (20.0% vs. 43.9%, p = 0.001) (Table 1a).

Three-year OS and DFS in sarcopenic patients were 56% and 48% versus 75% and 69% in non-sarcopenic patients, respectively (both p < 0.001). The effect of sarcopenia was most pronounced in the first two years after treatment (Fig. 2).

In patients with WHO PS 0, or early stage disease, (stage I–II), sarcopenia was not significantly associated with OS (p = 0.154 and p = 0.532 resp.), whereas in patients with worse performance (WHO PS 1–3), or locally advanced disease (stage III-IV), sarcopenic patients had a significantly worse OS Estimated three-year OS in sarcopenic patients with worse performance and sarcopenic patients with locally advanced disease were 37% and 48% (p < 0.001) versus 59% and 70% (p < 0.001) in non-sarcopenic patients, respectively. No significant association between sarcopenia and OS was found in patients with an oropharynx tumour after stratification by p16 status, i.e. p16-negative (p = 0.561 and p = 0.118, resp. log-rank test and Wilcoxon test) versus p16-positive (p = 0.150) (Fig. 3). Results regarding DFS were similar.

Sarcopenia was a independent predictor for worse OS and DFS. After adjustment for confounders including age, WHO PS, smoking history, p16 status, primary tumour site, tumour stage, and treatment modality, multivariable Cox proportional hazards models showed that for patients without sarcopenia the HR for OS was 0.72 (95% CI 0.56–0.93, p = 0.012) and 0.67 (95% CI 0.53–0.86, p = 0.001) for DFS (Table 2).

Sarcopenic patients were more likely to experience moderate-to-severe patient-rated xerostomia (15.9% vs. 8.1%, p < 0.001) and grade 2 $\geq$ physician-rated dysphagia (33.9% vs. 20.0%, p = 0.001) at baseline (Table 1b). The percentages of sarcopenic and non-sarcopenic patients with radiation-induced toxicities six and twelve months after treatment, are shown in Fig. 4. Patients with sarcopenia seemed to have grade 2 $\geq$ physician-rated xerostomia and grade 2 $\geq$ physician-rated dysphagia more often, both six and twelve months after treatment. In multivariable analysis, after correction for confounders, such as toxicity at baseline, i.e. the pre-existing experienced toxicity at start of treatment, and mean dose at OARs, a significant association was found between sarcopenia and physician-rated xerostomia six months after treatment (OR 1.65 (95% CI 1.06–2.57), p = 0.027) and physician-rated dysphagia both six and twelve months after treatment (OR 2.02 (95% CI 1.17–3.51), p = 0.012 and OR 2.51 (95% CI 1.36–4.65), p = 0.003, resp.) (Supplements, Tables 1–3). However, for patient-rated xerostomia no significant association was found with sarcopenia.

Discussion

This large cohort study of 750 HNSCC patients confirmed that sarcopenia is an independent adverse prognostic factor for OS and DFS, especially in patients with worse performance, (WHO PS 1–3), or locally advanced disease, (stage III–IV). In addition, this study shows that sarcopenia is associated with radiation-induced physician-rated xerostomia at six months and dysphagia six and twelve months after treatment.

Our study confirmed that sarcopenia in HNC patients treated with definitive (C)RT is strongly associated with worse OS and DFS (7,9,10,13,14). Additionally, we were the first to investigate the impact of sarcopenia on survival outcomes when stratified for WHO PS or disease stage and found that sarcopenia is strongly associated with worse outcomes in patients with worse performance. This finding is supported by a recent study from Zwart et al. in which sarcopenia was associated with frailty in HNC patients with locally advanced disease [37]. A hypothesis is that skeletal muscle depletion is a marker of more advanced disease. However, no studies confirmed this, partly because most studies only included patients with locally advanced disease.

Our study showed that sarcopenia was not a significant factor with regard to OS in HNSCC patients with oropharyngeal carcinoma when stratified for p16 status. This finding is in contrast to a smaller study consisting of 113 patients with advanced oropharyngeal cancer, which showed that sarcopenia was a prognostic factor affecting OS independent of HPV status [10]. However, after

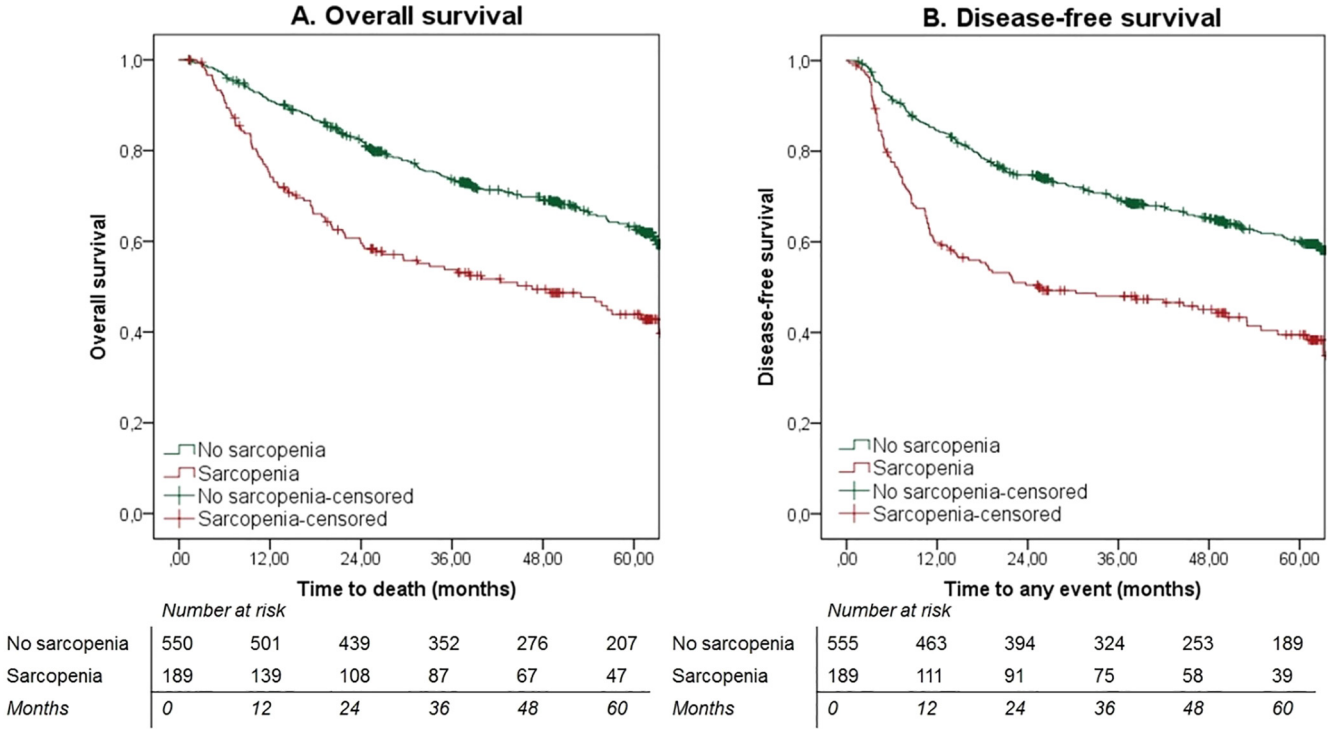

Fig. 2. Kaplan-Meier curves of overall survival, p < 0.001 (A) and disease-free survival, p < 0.001 (B).

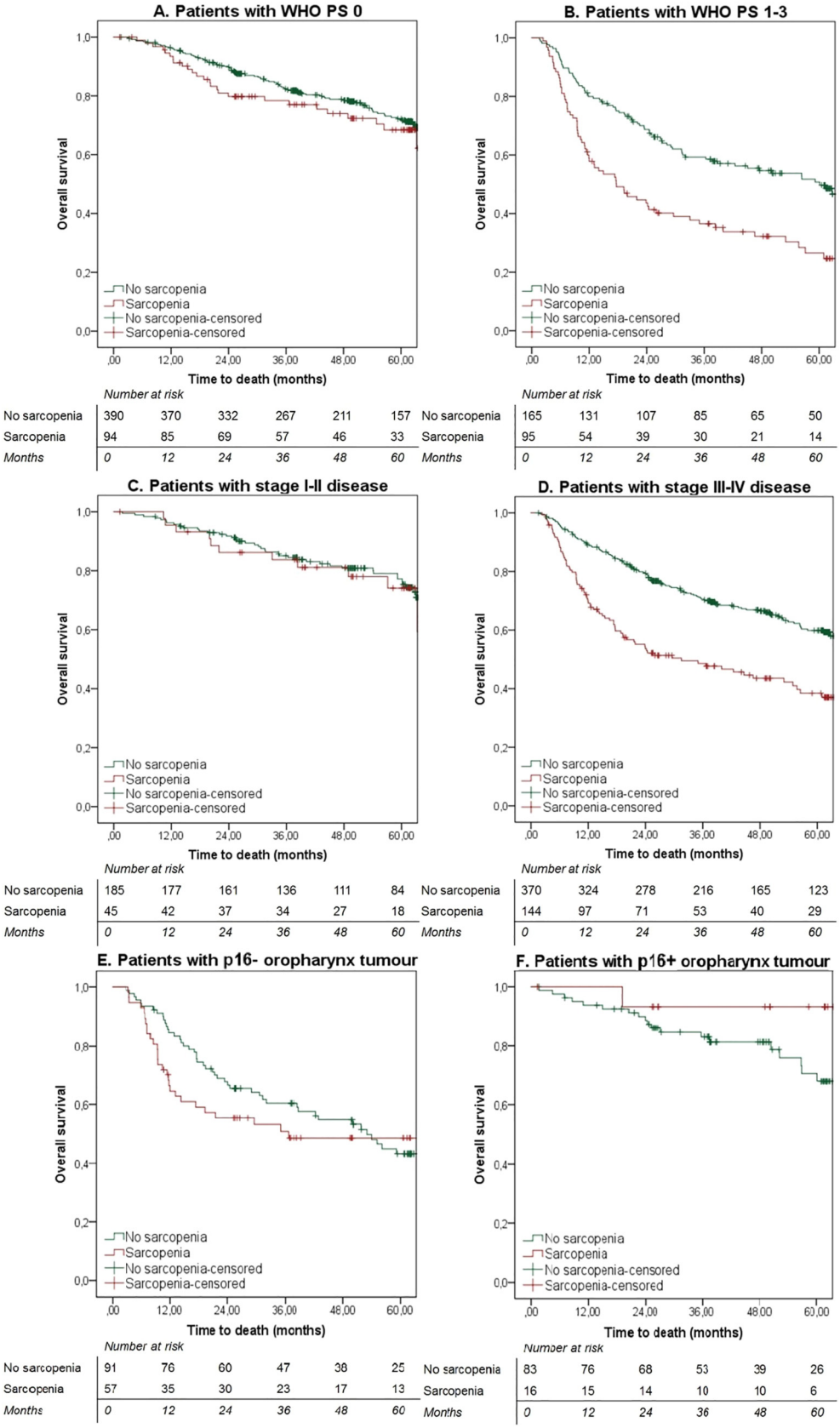

Fig. 3. Kaplan-Meier curves of overall survival stratified by WHO PS (WHO PS 0, $p = 0.154$ (A) and WHO PS 1–3, $p < 0.001$ (B)), stage of disease (stage I–II, $p = 0.532$ (C) and stage III–IV, $p < 0.001$ (D)), and p16 status in patients with an oropharynx tumour (p16 negative, $p = 0.541$ (E) and p16 positive, $p = 0.150$ (F)). *Abbreviation:* WHO PS = World Health Organization performance status.

Table 1b
Baseline toxicities of the patients.

Baseline toxicity	No sarcopenia (n = 555) (%)	Sarcopenia (n = 189) (%)	P value
Patient-rated xerostomia			<0.001[a]
None – a bit	458 (82.5)	127 (67.2)	
Moderate-to-severe	45 (8.1)	30 (15.9)	
Missing	52 (9.4)	32 (16.9)	
Physician-rated xerostomia			0.437[a]
Grade 0	478 (86.1)	154 (81.5)	
Grade 1	71 (12.8)	30 (15.9)	
Grade 2	1 (0.2)	0 (0.0)	
Missing	5 (0.9)	5 (2.6)	
Physician-rated dysphagia			0.001[a]
Grade 0–1	434 (78.2)	121 (64.0)	
Grade 2	76 (13.7)	38 (20.1)	
Grade 3	22 (4.0)	17 (9.0)	
Grade 4–5	13 (2.3)	9 (4.8)	
Missing	10 (1.8)	4 (2.1)	

[a] P value was calculated using the chi-square test.

inclusion of p16 status in the multivariable Cox proportional hazards model of all our HNSCC patients sarcopenia remained an independent significant adverse prognostic factor for OS and DFS.

Apart from worse survival outcomes, we also found that sarcopenia is significantly associated with grade 2 $\geq$ physician-rated xerostomia six months after treatment, and grade 2 $\geq$ physician-rated dysphagia at both six and twelve months after treatment, after correction for baseline toxicity and other confounders. However, no significant association was found between sarcopenia and patient-rated xerostomia six and twelve months after treatment, and physician-rated xerostomia 12 months after treatment, after correction for confounders. A possible explanation for the significant association between sarcopenia and physician-rated xerostomia while association between sarcopenia and patient-rated xerostomia is lacking, might be that grade 2 $\geq$ physician-rated xerostomia is defined as a multi-item endpoint, considering dietary changes next to xerostomia. Therefore, we hypothesize that sarcopenia affects swallowing, and not salivary gland functioning.

To our knowledge, only Nishikawa et al. [9] have investigated the correlation between sarcopenia and radiation-induced toxicities in HNC patients. These investigators did not find an association between sarcopenia and acute toxicities, including dermatitis, mucositis and aspiration pneumonia, and late toxicities such as xerostomia, dysgeusia and hypothyroidism, but this study only included 39 patients which is perhaps not a large enough sample. Other studies found a significant association between skeletal muscle mass and increased acute grade $\leq$ 3 toxicities in patients with oesophageal cancer treated with CRT [38] and in patients with pancreatic cancer receiving stereotactic body RT [39]. Murimwa et al. suggest that the increased radiation-induced acute toxicities in sarcopenic patients may be due to the pro-inflammatory state of these patients [38].

This increased radiation-induced toxicity in sarcopenic patients, negatively impacts their quality of life since Langendijk et al. showed that xerostomia and dysphagia have a significant impact on quality of life [40]. Moreover, a recent literature review showed that sarcopenia itself was associated with an obvious decline in quality of life [41]. Therefore, quality of life in this patient population might be affected by both radiation-induced toxicities and sarcopenia.

Despite intensive nutritional support, nutritional status generally deteriorates during RT [19,22]. Loss of skeletal muscle mass during (C)RT cannot be prevented by tube-feeding [7,16]. In contrast, recent studies showed that intensive nutritional, physical and psychological interventions minimize weight loss, increase muscle mass and strength, improve treatment tolerance and result in less fatigue and better quality of life [42–46]. Therefore, it might be interesting to investigate whether sarcopenia is a potentially modifiable risk factor to improve patient outcome.

The current study has some limitations. First, in this retrospective cohort analysis, the patients were divided into two groups,

Table 2
Cox regression analysis of overall survival and disease-free survival.

Variable	Overall survival (n = 720) HR (95% CI)	P value	Disease-free survival (n = 720) HR (95% CI)	P value
Univariate analysis				
Gender (male vs. female)	1.05 (0.81–1.36)	0.712	1.13 (0.88–1.45)	0.342
Age	1.02 (1.01–1.03)	0.002*	1.02 (1.00–1.03	0.007*
WHO PS (0 vs. 1–3)	0.38 (0.31–0.48)	<0.001*	0.43 (0.35–0.54)	<0.001*
Sarcopenia (no vs. yes)	0.52 (0.41–0.66)	<0.001*	0.51 (0.40–0.64)	<0.001*
Smoking history (never vs. ever)	0.68 (0.42–1.08)	0.098	0.61 (0.39–0.96)	0.031*
Alcohol history (never vs. ever)	0.88 (0.66–1.19)	0.413	0.89 (0.67–1.18)	0.426
P16 status (negative vs. positive)	1.81 (1.18–2.78)	0.006*	0.51 (0.34–0.76)	0.001*
Tumour stage (I–II vs. III–IVb)	0.52 (0.39–0.67)	<0.001*	0.54 (0.42–0.69)	<0.001*
Primary tumour site (larynx vs. other)	0.50 (0.39–0.63)	<0.001*	0.53 (0.42–0.66)	<0.001*
Treatment modality (RT alone vs. RT with systemic treatment)	0.64 (0.51–0.81)	<0.001*	0.70 (0.57–0.87)	0.001*
Technique (conventional vs. IMRT)	0.68 (0.48–0.96)	0.030*	0.65 (0.46–0.91)	0.013*
Multivariable analysis				
Age	1.03 (1.01–1.04)	<0.001*	1.02 (1.01–1.03)	0.004*
WHO PS (0 vs. 1–3)	0.44 (0.35–0.56)	<0.001*	0.53 (0.42–0.67)	<0.001*
Sarcopenia (no vs. yes)	0.72 (0.56–0.93)	0.012*	0.67 (0.53–0.86)	0.001*
Smoking history (never vs. ever)			0.62 (0.38–0.99)	0.044*
P16 status (negative vs. positive)	0.51 (0.33–0.80)	0.003*	0.47 (0.31–0.71)	<0.001*
Primary tumour site (larynx vs. other)	0.58 (0.43–0.78)	<0.001*	0.53 (0.41–0.70)	<0.001*
Tumour stage (I–II vs. III–IVb)			0.69 (0.51–0.94)	0.018*
Treatment modality (RT alone vs. RT with systemic treatment)	0.65 (0.48–0.87)	0.004*		

Abbreviations: HR = hazard ratio; CI = confidence interval; WHO PS = World Health Organization performance status; RT = radiotherapy, IMRT = intensity modulated radiotherapy.
*Wald test statistically significant.

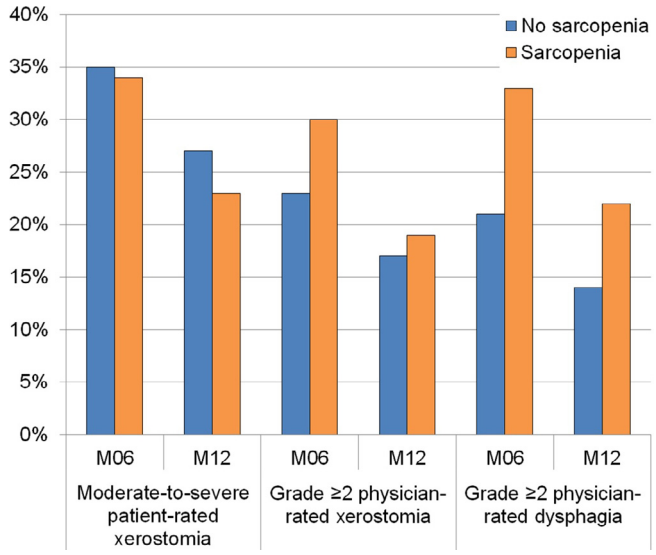

Fig. 4. Percentage of patients without and with sarcopenia with late radiation-induced toxicity. *Abbreviations:* M06 = six months after treatment; M12 = twelve months after treatment.

based on sarcopenia, defined as SMI according the lowest gender specific quartile. Therefore, the two study arms are not statistically balanced. Instead, this study shows that sarcopenic patients had other baseline characteristics than non-sarcopenic patients. Second, CSA at L3 is estimated based on the CSA at C3, resulting in some uncertainty, although two other recent studies showed the L3-method used for delineation provides reproducible measurements and is robust [47,48]. Jung et al. developed another prediction model for estimating the CSA at L3 with the same variables as Swartz et al. [31], but other coefficients [49]. Moreover, they showed high predictability of skeletal muscle mass at C3 alone for estimating OS after curative treatment for advanced stage HNC [49], which might make the conversion to CSA at L3 unnecessary. However, this method has not yet been externally validated. Third, no consensus regarding cut-off values for sarcopenia has been reached in the literature, which makes it more difficult to compare results. Our study, like some others, used a gender specific threshold corresponding to the lowest 25th percentile [50,51]. We considered using existing cut-off values of a comparable patient cohort [8,52]. Wendrich et al. developed one optimal cut-off value for low skeletal muscle mass as a predictor for chemotherapy dose limiting toxicity, which was set at $\leq$43.2 cm/m^2 for both men and women [8]. The female patients in the current cohort had significantly lower SMI-values than males. Therefore, we decided to use a gender specific cut-off value. If cut-off values of Prado et al. [52] would have been used in the current study population, the majority (i.e. 82%) of our patients would have been classified as sarcopenic. In addition, the cut-off values of Prado et al. [52] were based on an obese population (mean BMI 34.3 kg/m^2), whereas the mean BMI in our population was 25.6 kg/m^2.

In conclusion, sarcopenia is a common and relevant problem in HNC patients and is associated with poor OS and DFS, especially in patients with worse performance and locally advanced disease. In contrast, sarcopenia is not a significant factor with regard to survival outcomes in oropharyngeal cancer patients. In addition, sarcopenia might be associated with radiation induced toxicities. Given that the SMI can be easily assessed on CT scans, clinical introduction is easy and adds important and clinically relevant information to assess patient outcome.

Conflict of interest

The authors state that the research presented in this manuscript is free of conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.03.014.

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