Sarcopenia is associated with higher toxicity and poor prognosis of nasopharyngeal carcinoma

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Abstract

Background: Given the growing evidence that sarcopenia is associated with toxicity and survival in various cancers, we investigated its significance in patients with nasopharyngeal carcinoma (NPC) receiving concurrent chemoradiotherapy (CCRT).

Methods: In this retrospective analysis, we studied 862 NPC patients who had received CCRT between 2010 and 2014. Sarcopenia was determined using routine pre-radiotherapy computed tomography (CT) simulation scans at the third cervical vertebral level. Receiver-operating characteristic curve analyses were used to determine the optimal cutoff values. Propensity score matching (PSM) was applied to develop comparable cohorts of patients with or without sarcopenia.

Results: A total of 862 patients were included as the primary cohort, and 308 patients were matched and regarded as the matched cohort. In the primary cohort, the 5-year overall survival (OS), locoregional recurrence-free survival, and distant metastasis-free survival (DMFS) rates for the sarcopenia group *versus* non-sarcopenia group were 78.2% *versus* 93.6% ($p < 0.001$), 89.4% *versus* 87.9% ($p = 0.918$), and 82.5% *versus* 89.0% ($p = 0.007$), respectively. Univariate and multivariate survival analyses revealed that sarcopenia was an independent predictor of OS ($p < 0.001$ and $p < 0.001$) and DMFS ($p = 0.009$, $p = 0.034$). Patients with sarcopenia experienced significantly higher rates of treatment-related toxicities compared with patients without sarcopenia ($p = 0.032$). In addition, patients with sarcopenia also experienced significantly worse treatment response than those without sarcopenia ($p = 0.004$). Similar results were found in a PSM cohort.

Conclusion: The current findings support that sarcopenia is a promising indicator for predicting clinical outcomes in NPC patients receiving CCRT. A simple and rapid analysis on CT simulation images can provide information about the therapeutic toxicity and survival prognosis, consequently guiding personalized multi-modality interventions during CCRT.

Keywords: concurrent chemoradiotherapy, nasopharyngeal carcinoma, sarcopenia, survival, toxicity, treatment response

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Introduction

Nasopharyngeal carcinoma (NPC) is a common malignancy in south China that is greatly heterogeneous in its racial and geographic distributions and histopathology.[1–3] More than 70% of patients with NPC are locoregionally advanced cases at primary diagnosis.[4] Concurrent chemoradiotherapy is now recognized as the mainstay treatment for locoregionally advanced NPC.[5,6] Although adding concurrent chemotherapy to radiotherapy achieved a great survival benefit in locoregionally advanced patients, it also increases treatment-related toxicities.[7] Unfortunately, these toxicities might result in dose contraction, interruption, and termination of treatment, compromising the efficacy of CCRT. Extra toxicity can also lead to a

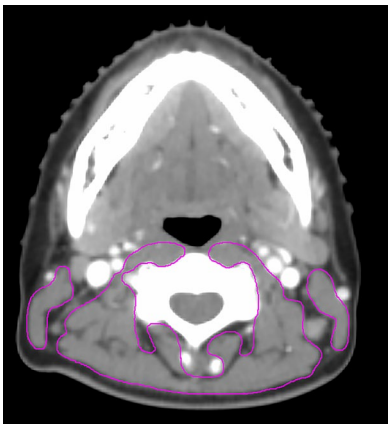

Figure 1. Slice of computed tomography (CT) simulation images of skeletal muscle at the level of the third cervical vertebra (C3).
We measured the cross-sectional area of the sternocleidomastoid and paravertebral muscles on an axial slice at the level of C3 vertebrae; the CT Hounsfield unit thresholds were −29 to +150 for skeletal muscle.

poor quality of life.[8] Therefore, identifying the patient or tumor characteristics associated with toxicity and survival can potentially help personalize treatment regimens and improve the quality of care in patients with NPC.

Depletion of skeletal muscle mass, termed sarcopenia, is common in head and neck cancer (HNC), and is related to increased treatment-related toxicity and decreased survival in HNC patients who receive comprehensive treatment of surgery/chemotherapy and/or radiotherapy.[9–13] The skeletal muscle mass can be conveniently determined by evaluating the skeletal muscle index (SMI) using computed tomography (CT) simulation scans, which are essential for the pre-treatment evaluation of radiotherapy. Sarcopenia has been shown to be a compelling prognostic factor, and it can potentially improve the survival outcomes in HNC.[14,15] Several studies have also demonstrated the relationship between sarcopenia and treatment response and toxicity in HNC.[14,16,17] Sarcopenia may also be associated with treatment response and toxicity of concurrent chemoradiotherapy (CCRT); however, its impact on patients with NPC receiving CCRT remains unclear. Thus far, only one study has investigated sarcopenia in NPC and reported that severe skeletal muscle loss might decrease the overall survival (OS); however, the sample size of that study was very small.[13]

Definitive studies on the effect of sarcopenia in NPC are scarce, as previous studies have focused primarily on the population of HNC patients, with only some cases of NPC. Here, we hypothesized that sarcopenia has a significant effect on toxicity and survival in NPC patients receiving CCRT.

Patients and methods

Patients

We retrospectively enrolled 862 NPC patients who underwent CCRT from January 2010 to December 2014 at Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China. Histopathological and clinical data were obtained for all the patients. The inclusion criteria were as follows: (a) histological and radiographic findings confirmed the presence of non-metastatic NPC; (b) the patients underwent an Epstein–Barr virus (EBV) DNA test prior to treatment; (c) the patients underwent radical intensity-modulated radiotherapy (IMRT) plus weekly or triweekly platin-based concurrent chemotherapy. Plasma EBV DNA levels (copies/mL) were measured using real-time quantitative polymerase chain reaction assay, and its cutoff value was classified as previously described.[18] This study was approved by the Research Ethics Committee of SYSUCC with the number of GZR2017-224, and all the patients signed written informed consent forms for treatment and agree to cooperate with follow-up visits.

Data collection and definitions

The presence of sarcopenia was evaluated using SMI, which was defined as the skeletal muscle area (cm^2)/square of height (m^2).[19] The skeletal muscle area at the third cervical (C3) level was measured according to a validated method using CT simulation images of radiotherapy (RT) with Monaco TPS software version 5.1 (Elekta CMS, Maryland Heights, Missouri, USA). Muscle contours of the sternocleidomastoid and paravertebral muscles (Figure 1) were hand-drawn by a senior radiotherapy oncologist (LG).[14] Primary laboratory data were collected within a week of diagnosis, and clinicopathological data were retrieved from patients' medical records. Body mass index (BMI) was calculated as weight (kg)/square of the height in meters (m^2), and patients were classified as obese (BMI >24) and non-obese (BMI $\leqslant 24$) as defined by the Chinese criteria.[20]

CCRT protocol and treatment-related toxicities

The CCRT protocol comprised a triweekly (80–100 mg/m^2) or weekly (30–35 mg/m^2) administration of cisplatin concurrently with IMRT, in accordance with the guidelines of our institute.[21] The prescribed radiation dose of the gross tumor volume of the nasopharynx (GTVnx) was 68–74 Gy; the gross tumor volume of the lymph nodes (GTVnd) was 66–70 Gy; high-risk clinical target volume was 60–66 Gy and low-risk clinical target volume was 50–56 Gy. All the patients were treated once daily for weekdays only with a total of 30–33 fractions. Treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0.

Treatment response and follow-up

At the first visit three months after CCRT, nasopharyngoscopic examination and magnetic resonance imaging were conducted to evaluate the treatment response according to RECIST 1.1 criteria.[22] The patients were followed up using outpatient examination or telephonic interview. The OS, locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were defined as the time from the date of diagnosis to the date of death, to the first locoregional recurrence, and to the first distant metastasis), respectively, or to the last follow-up date.

Statistical analysis

Statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism version 6.0 software (GraphPad, La Jolla, California, USA). Receiver-operating characteristic (ROC) curve analyses were used to determine the optimal cutoff points for the SMI. Propensity score matching of 1:1 scheme with a caliper width of 0.2 was applied to develop comparable cohorts of patients with or without sarcopenia. Covariates for matching included age, gender, histological type, T stage, N stage, clinical stage, EBV DNA level, and BMI. Clinical characteristics and toxicities between the two groups were analyzed using Pearson's χ^2 test or Fisher's exact test. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model and multivariate model for variables with p values <0.20 in the univariate analysis. Two-tailed p values <0.05 were considered statistically significant.

Results

Patient characteristics

Table 1 presents the patient characteristics of 862 patients enrolled in this retrospective study. The median age at diagnosis was 45 years (range, 18–84 years). The median BMI was 23.3 kg/m^2 (range, 15.6–33.9 kg/m^2); the median SMI was 24.43 cm^2/m^2 (range, 10.96–57.48 cm^2/m^2). All 862 patients completed the treatment and thus there is no difference in chemoradiotherapy compliance between two groups. ROC curves were conducted for the SMI using survival status as an endpoint (Figure 2), and the area under the ROC curve of sarcopenia was 0.631 (95% confidence interval: 0.55–0.72; $p = 0.001$). The patients were divided into two groups (sarcopenia and non-sarcopenia) based on the SMI cutoff value of 18.82 cm^2/m^2. The characteristics of the two groups were similar, except for the gender ($p < 0.001$), clinical stage ($p = 0.011$), and BMI ($p < 0.001$). Therefore, we established a new cohort using propensity score matching (PSM) to avoid potentially confounding the findings. After PSM, 308 patients were identified, and the clinical characteristics among the two groups were well balanced (all $p > 0.05$; Table 1).

Sarcopenia and prognosis of NPC

The median follow-up duration was 50.0 (range, 3.0–91.5) months. In the primary cohort, the 5-year OS of the whole population was 90.5%, while that in the sarcopenia group was significantly shorter (78.2%) than that in the non-sarcopenia group [93.6%; $p < 0.001$; Figure 3(A)]. The 5-year LRFS rate of the total cohort was 88.2%, and this parameter was comparable between the sarcopenia and non-sarcopenia groups [89.4% and 87.9%, respectively; $p = 0.918$; Figure 3(C)]. The 5-year DMFS rate of the total cohort was 87.7%, and this parameter was significantly shorter in the sarcopenia group (82.5%) than in the non-sarcopenia group [89.0%; $p = 0.007$; Figure 3(E)]. Then, we recalculated the effects of sarcopenia in the PSM cohort, which revealed similar differences in the prognosis of the OS ($p < 0.001$) [Figure 3(B)], LRFS [$p = 0.562$; Figure 3(D)], and DMFS [$p = 0.011$; Figure 3(F)].

Univariate Cox regression analysis in the primary cohort revealed that the T stage, N stage, EBV DNA titer, and sarcopenia were significantly associated with OS; and the N stage, EBV DNA,

Table 1. Clinicopathologic characteristics before and after matching.

Characteristic	Primary cohort			PSM cohort		
	Sarcopenia	Non-sarcopenia	*p* value	Sarcopenia	Non-sarcopenia	*p* value
Total	170	692		154	154	
Age, years	45.84 ± 10.78	45.70 ± 10.23	0.879[a]	45.55 ± 10.90	45.05 ± 10.86	0.683[a]
>45	89 (52.4%)	335 (48.4%)		79 (51.3%)	70 (45.5%)	
⩽45	81 (47.6%)	357 (51.6%)		75 (48.7%)	84 (54.5%)	
Gender			<0.001[b]			0.645[b]
Male	64 (37.6%)	576 (83.2%)		64 (41.6%)	69 (44.8%)	
Female	106 (62.4%)	116 (16.8%)		90 (58.4%)	85 (55.2%)	
Histological type			1.000[b]			0.615[b]
Non-keratinizing undifferentiated carcinoma	167 (98.2%)	682 (98.6%)		151 (98.1%)	153 (99.4%)	
Keratinizing or differentiated carcinoma	3 (1.8%)	10 (1.4%)		3 (1.9%)	1 (0.6%)	
T stage[c]			0.314[b]			0.947[b]
1	9 (5.3%)	33 (4.8%)		9 (5.8%)	9 (5.8%)	
2	33 (19.4%)	133 (19.2%)		28 (18.2%)	32 (20.8%)	
3	95 (55.9%)	429 (62.0%)		90 (58.4%)	88 (57.1%)	
4	33 (19.4%)	97 (14.0%)		27 (17.5%)	25 (16.2%)	
N stage[c]			0.168[b]			0.969[b]
0	13 (7.6%)	68 (9.8%)		12 (7.8%)	11 (7.1%)	
1	93 (54.7%)	373 (53.9%)		88 (57.1%)	91 (59.1%)	
2	50 (29.4%)	221 (31.9%)		45 (29.2%)	42 (27.3%)	
3	14 (8.2%)	30 (4.3%)		9 (5.8%)	10 (6.5%)	
Clinical stage[c]			0.011[b]			0.730[b]
Ⅱ	21 (12.4%)	100 (14.5%)		21 (13.6%)	26 (16.9%)	
Ⅲ	102 (60.0%)	471 (68.1%)		97 (63.0%)	93 (60.4%)	
Ⅳ	47 (27.6%)	121 (17.5%)		36 (23.4%)	35 (22.7%)	
EBV-DNA, copies/mL			0.895[b]			0.903[b]
>4000	54 (31.8%)	226 (32.7%)		50 (32.5%)	48 (31.2%)	
⩽4000	116 (68.2%)	466 (67.3%)		104 (67.5%)	106 (68.8%)	
BMI, kg/m^2	21.90 ± 2.92	23.48 ± 2.93	<0.001[a]	22.11 ± 2.84	22.43 ± 2.85	0.312[a]
>24	46 (27.1%)	299 (43.2%)		44 (28.6%)	44 (28.6%)	
⩽24	124 (72.9%)	393 (56.8%)		110 (71.4%)	110 (71.4%)	

[a]Student's *t* test.
[b]Pearson's χ^2 test.
[c]According to the seventh edition of the UICC/AJCC staging system.
BMI, body mass index; EBV-DNA, Epstein–Barr virus deoxyribonucleic acid.

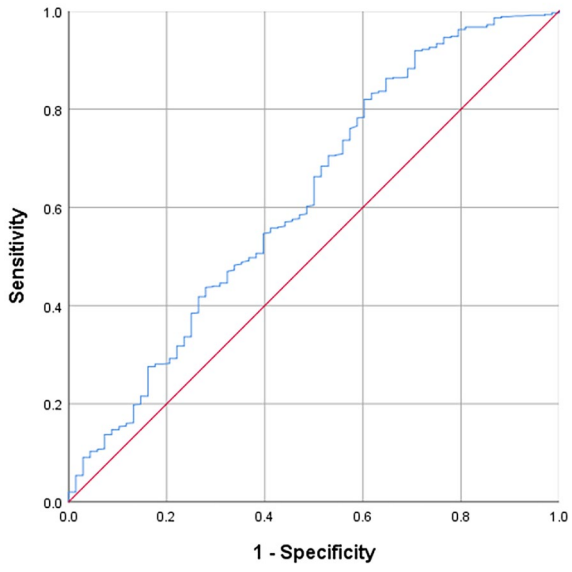

Figure 2. Predictive ability of sarcopenia by receiver-operating characteristic curve (ROC) analysis.
ROC curve analyses by overall survival status were used to determine the optimal cutoff points for the skeletal muscle index. Area under the ROC curve of sarcopenia was 0.631 (95% confidence interval: 0.55–0.72; $p = 0.001$).

and sarcopenia were significantly associated with DMFS. Multivariate survival analysis revealed that sarcopenia could independently predict OS ($p < 0.001$; Table 2) and DMFS ($p = 0.034$; Table 3). In the PSM cohort, the results of the multivariate analysis were consistent with the results of the primary cohort (Tables 2 and 3).

As shown in Table 4, the sarcopenia group had significantly higher rates of treatment-related toxicities in both the primary and PSM cohorts [Grade 0 (25.9%), Grade 1–2 (40.6%), and Grade 3–4 (33.5%) *versus* Grade 0 (36.6%), Grade 1–2 (34.5%), and Grade 3–4 (28.9%), $p = 0.032$ and Grade 0 (25.9%), Grade 1–2 (40.3%), and Grade 3–4 (33.8%) *versus* Grade 0 (39.6%), Grade 1–2 (33.8%), and Grade 3–4 (26.6%), $p = 0.038$, respectively]. The main treatment-related effects included anemia [Grade 0 (72.5%), Grade 1–2 (26.9%), and Grade 3–4 (0.6%) *versus* Grade 0 (82.8%), Grade 1–2 (17.1%), and Grade 3–4 (0.2%), $p = 0.009$ and Grade 0 (68.8%), Grade 1–2 (30.4%), and Grade 3–4 (0.7%) *versus* Grade 0 (76.2%), Grade 1–2 (23.8%), and Grade 3–4 (0.0%), $p = 0.135$, respectively], tinnitus [Grade 0 (90.6%), Grade 1–2 (9.4%), and Grade 3–4 (0.0%) *versus* Grade 0 (91.5%), Grade 1–2 (1.3%), and Grade 3–4 (0.0%), $p < 0.001$ and Grade 0 (90.3%), Grade 1–2 (9.7%), and Grade 3–4 (0.0%) *versus* Grade 0 (98.1%), Grade 1–2 (1.9%), and Grade 3–4 (0.0%), $p = 0.004$, respectively], xerostomia [Grade 0 (53.8%), Grade 1–2 (44.4%), and Grade 3–4 (1.8%) *versus* Grade 0 (55.3%), Grade 1–2 (44.6%), and Grade 3–4 (0.1%), $p = 0.020$ and Grade 0 (53.2%), Grade 1–2 (44.8%), and Grade 3–4 (1.9%) *versus* Grade 0 (59.5%), Grade 1–2 (40.5%), and Grade 3–4 (0.0%), $p = 0.166$, respectively], and mucositis [Grade 0 (44.7%), Grade 1–2 (21.8%), and Grade 3–4 (33.5%) *versus* Grade 0 (46.5%), Grade 1–2 (24.4%), and Grade 3–4 (29.0%), $p = 0.492$ and Grade 0 (43.0%), Grade 1–2 (23.8%), and Grade 3–4 (33.1%) *versus* Grade 0 (45.2%), Grade 1–2 (33.5%), and Grade 3–4 (21.3%), $p = 0.038$, respectively].

As shown in Table 4, 613 (74.4%) patients reached complete response, 180 (21.8%) patients reached partial response, 27 (3.3%) patients reached stable disease, and four (0.5%) patients reached progressive disease. Patients in the sarcopenia group experienced significantly worse treatment response than those in the non-sarcopenia group in both the primary ($p = 0.004$) and PSM ($p = 0.020$) cohorts (Table 4).

Discussion

In recent years, many studies have investigated skeletal muscle loss (sarcopenia) in HNC. Thus far, however, only one study has explored the prognostic significance of sarcopenia in NPC, and its sample size was small.[13] To our knowledge, this is the largest study to date of patients receiving CCRT in NPC endemic areas, and our results demonstrated that sarcopenia is underrated, highly prevalent, and related to a significantly poor prognosis. We also found a correlation between sarcopenia and treatment-related toxicities, suggesting that this may be useful in identifying toxicity-related treatment delays and reductions in the chemotherapeutic dose. In addition, we found a negative correlation between sarcopenia and treatment response, which could be useful in predicting treatment efficacy. The prognostic measure of skeletal muscle mass can be easily integrated into routine clinical practice, using existing radiotherapy assessments and evaluation system software to generate highly accurate body composition measurements from clinically collected CT scans.

This is the first large-scale study to establish a cutoff for sarcopenia in a large population of NPC

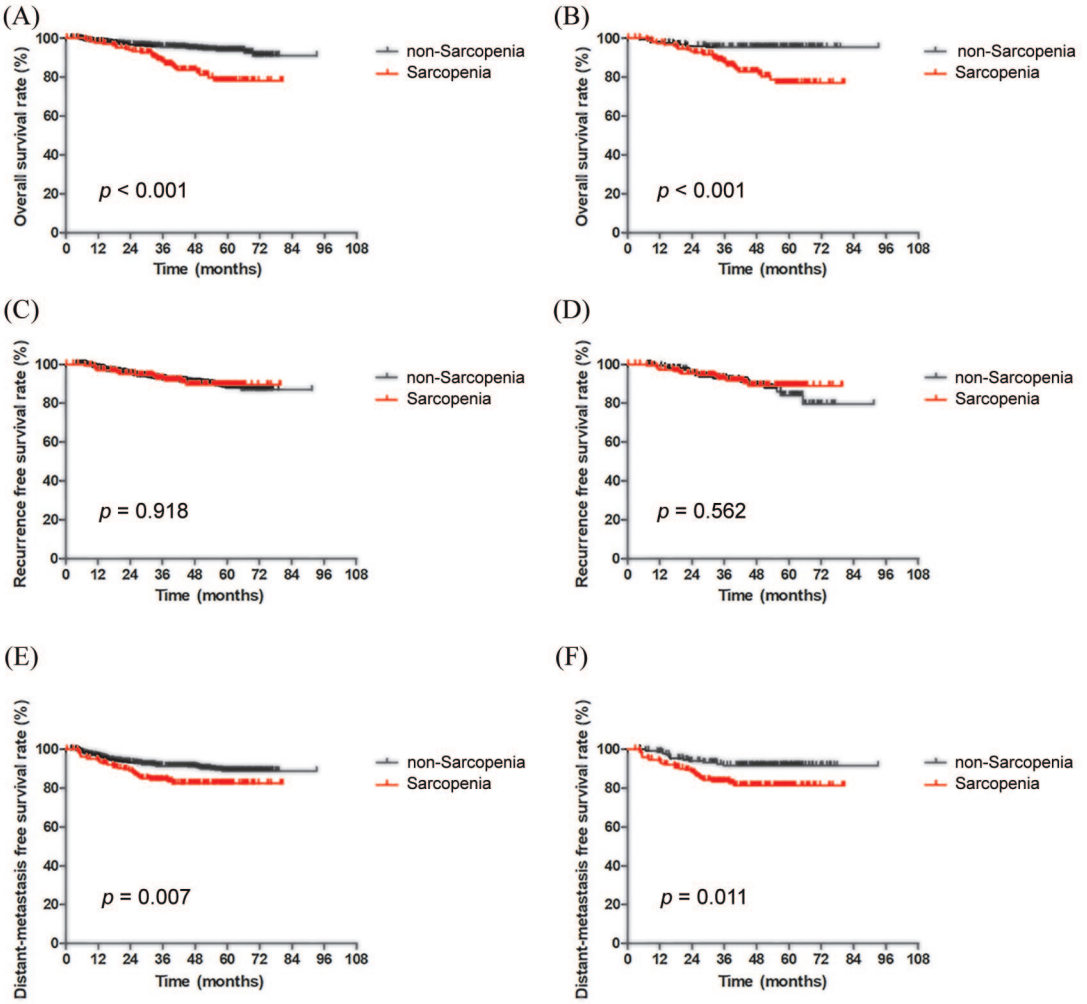

Figure 3. Kaplan–Meier survival curves for overall survival (OS), locoregional recurrence-free survival-free survival (LRFS), and distant metastasis-free survival (DMFS) in the primary cohort and the propensity score matching (PSM) cohort.

Kaplan-Meier curves for: (A) OS in the primary cohort; (B) OS in the PSM cohort; (C) LRFS in the primary cohort; (D) LRFS in the PSM cohort; (E) DMFS in the primary cohort; (F) DMFS in the PSM cohort. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test.

patients by calculating the SMI using the skeletal muscle area at the C3 vertebral level. The results of this study could be applied to other patients with newly diagnosed non-metastatic NPC. Most studies used routine clinical diagnostic CT scans to determine skeletal muscle mass at the third lumbar (L3) vertebral level.[12] Unfortunately, abdominal CT scans, including L3, are not routinely applied in NPC. Therefore, the lack of widely available diagnostic tools to determine sarcopenia in NPC may lead to the absence of adequate studies on sarcopenia in NPC. Some scholars have confirmed that the C3 level can be used to determine skeletal muscle mass in HNC in both western and eastern cohorts;[14,23,24] however, the cutoff value established at the L3 level was still chosen to diagnose sarcopenia. In this study, we used routine CT simulation scans of radiotherapy, without any additional expense or radiation exposure to the patients, to evaluate the skeletal muscle mass at the C3 level, and we established a cutoff value to define sarcopenia. In our study, the incidence of sarcopenia was 170/862 (19.72%), which is within the incidence range of 6.6–64.6% reported in other studies on HNC.[9,11,14,15,25] Assessment at the C3 level using routine CT simulation scans of radiotherapy is a reasonable and efficient method in NPC, as this method does not involve any additional expense or radiation exposure to the patients.

Table 2. Univariate and multivariate analyses of overall survival.

Characteristic	Primary cohort				PSM cohort			
	Univariate analysis		Multivariate Cox regression analysis		Univariate analysis		Multivariate Cox regression analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age, years	1.598 (0.985–2.593)	0.058	1.574 (0.966–2.566)	0.069	1.772 (0.881–3.562)	0.109	1.756 (0.866–3.564)	0.119
Gender	0.745 (0.413–1.341)	0.326			0.406 (0.199–0.825)	0.013*	0.643 (0.292–1.417)	0.273
Histological type	0.468 (0.212–1.033)	0.060	0.716 (0.327–1.566)	0.403	8.244 (0.001–8×10^4)	0.656		
T stage[a]	1.563 (1.091–2.240)	0.015*	1.595 (1.106–2.299)	0.012*	1.918 (1.147–3.207)	0.013*	1.937 (1.131–3.316)	0.016*
N stage[a]	1.780 (1.291–2.453)	<0.001*	1.710 (1.234–2.369)	0.001*	2.064 (1.338–3.183)	0.001*	2.001 (1.232–3.251)	0.005*
EBV-DNA	1.686 (1.042–2.729)	0.033*	1.351 (0.815–2.239)	0.244	2.372 (1.198–4.695)	0.013*	1.532 (0.738–3.183)	0.252
Sarcopenia	3.066 (1.884–4.990)	<0.001*	2.811 (1.718–4.599)	<0.001*	4.205 (1.823–9.698)	0.001*	4.020 (1.737–9.307)	0.001*
BMI	0.815 (0.495–1.342)	0.422			1.074 (0.511–2.257)	0.851		

*$p < 0.05$.
[a]According to the seventh edition of the UICC/AJCC staging system.
BMI, body mass index; CI, confidence interval; EBV–DNA, Epstein-Barr virus deoxyribonucleic acid; PSM, propensity score matching.

In a recent study by the US Kansas Medical Cancer, sarcopenia was reportedly related to worse OS and progression-free survival in patients with HNC receiving chemoradiotherapy,[14] and another, Korean, study reported that sarcopenia can predict survival and recurrence in HNC patients receiving definitive radiotherapy.[15] In addition, researchers have suggested that sarcopenia combined with tumor-related inflammations enhanced the prognostic significance in HNC.[11] In contrast, the only published study on sarcopenia in NPC reported that skeletal muscle loss during treatment was associated with survival, whereas the presence of sarcopenia before and after treatment was not associated with survival. This may be because the cutoff value used to define sarcopenia in the previous study was adopted from research in gastric cancer. Our study demonstrated that patients with sarcopenia had significantly worse OS and DMFS than patients without sarcopenia, which is consistent with the results of other studies on sarcopenia in HNC, indicating that skeletal muscle loss does play a role in the prognosis of NPC.

Many studies have found that patients with sarcopenia experienced higher rates of treatment-related toxicities in various cancers, including HNC.[16,26–31] A European study revealed that sarcopenia was an independent predictor for treatment-related toxicity in locally advanced cases of HNC,[16] and another study reported that sarcopenia can predict treatment-related toxicity and tolerance in HNC cases receiving chemoradiotherapy.[14] Similarly, other studies have suggested that patients with sarcopenia have a higher risk of postoperative infection and longer hospital stays.[32,33] Therefore, we concluded that sarcopenia may be a meaningful risk factor for toxicity, and our results verified that sarcopenia is closely related to higher rates of CCRT-related toxicity in NPC. This finding suggests that sarcopenia may be used as a reference for chemoradiotherapy dose selection to better balance individual pharmacokinetic differences.

Table 3. Univariate and multivariate analyses of distant metastasis-free survival.

Characteristic	Primary cohort				PSM cohort			
	Univariate analysis		Multivariate Cox regression analysis		Univariate analysis		Multivariate Cox regression analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age, years	1.001 (0.666–1.503)	0.998			0.929 (0.451–1.914)	0.843		
Gender	0.793 (0.483–1.300)	0.358			0.588 (0.311–1.112)	0.102	0.687 (0.356–1.328)	0.265
Histological type	0.560 (0.255–1.233)	0.150	0.627 (0.291–1.351)	0.233	6.745 (0.006–7×10^3)	0.595		
T stage[a]	1.190 (0.887–1.597)	0.247			1.362 (0.853–2.173)	0.196	1.480 (0.926–2.366)	0.101
N stage[a]	1.850 (1.406–2.433)	<0.001*	1.632 (1.237–2.152)	0.001*	1.957 (1.285–2.982)	0.002*	1.919 (1.229–2.996)	0.004*
EBV-DNA	2.398 (1.597–3.603)	<0.001*	2.110 (1.390–3.202)	<0.001*	1.598 (0.834–3.063)	0.158	1.158 (0.589–2.277)	0.671
Sarcopenia	1.825 (1.165–2.857)	0.009*	1.639 (1.038–2.588)	0.034*	2.365 (1.193–4.690)	0.014*	2.285 (1.147–4.556)	0.019*
BMI	0.668 (0.431–1.036)	0.072	0.710 (0.455–1.107)	0.130	0.880 (0.403–1.920)	0.748		

*$p < 0.05$.
[a]According to the seventh edition of the UICC/AJCC staging system.
BMI, body mass index; CI, confidence interval; EBV-DNA, Epstein–Barr virus deoxyribonucleic acid; PSM, propensity score matching.

In this study, it was found that patients with sarcopenia exhibited significantly worse treatment responses, which is consistent with the reports of previous studies in which sarcopenia was found to be associated with a decreased response to chemotherapy. One possible explanation for such findings is that sarcopenia can reflect an individual's nutritional and immune status, and therapeutic effect is closely related to the host's nutritional and immune status. In addition, in our previous study on NPC, we found that chemotherapy response was closely related to the survival prognosis.[34] Therefore, we hypothesized that patients with sarcopenia may experience more severe treatment-related toxicities (resulting in treatment delays, chemotherapy dose reduction, and treatment termination) and worse therapeutic response, leading to a poorer prognosis than in patients without sarcopenia.

There are some limitations in our study. First, our conclusions are drawn from a single-center retrospective study and may therefore be biased. Second, our study targeted non-metastatic NPC receiving CCRT; thus, the conclusions are based on this particular characteristic of the patients. Third, many studies determine cutoff values by gender. In this study, there are only 222 (25%) female patients. Considering the small number of female patients, bias may be caused if we still followed different cutoff values by gender. Therefore, we used a uniform cut-off value after consulting the statistical expert. Thus, more studies are required to verify the cutoff value established in this study.

Conclusion

In summary, we found that sarcopenia (as assessed by CT simulation scans of radiotherapy) was associated with therapeutic toxicity, therapeutic response, and survival prognosis in patients with non-metastatic NPC receiving CCRT. These findings suggest that a simple and rapid

Table 4. Treatment-related toxicities and treatment response before and after matching.

Characteristic	Primary cohort			PSM cohort		
	Sarcopenia	Non-sarcopenia	*p* value	Sarcopenia	Non-sarcopenia	*p* value
Treatment-related toxicities			0.032[a]			0.038[a]
Grade 0	44 (25.9%)	253 (36.6%)		40 (25.9%)	61 (39.6%)	
Grade 1–2	69 (40.6%)	239 (34.5%)		62 (40.3%)	52 (33.8%)	
Grade 3–4	57 (33.5%)	200 (28.9%)		52 (33.8%)	41 (26.6%)	
Leucopenia			0.092[a]			0.191[a]
Grade 0	84 (49.4%)	379 (54.8%)		79 (51.3%)	78 (50.6%)	
Grade 1–2	68 (40.0%)	270 (39.1%)		59 (38.3%)	68 (44.2%)	
Grade 3–4	18 (10.6%)	42 (6.1%)		16 (10.4%)	8 (5.2%)	
Anemia			0.009[a]			0.135[b]
Grade 0	116 (72.5%)	547 (82.8%)		95 (68.8%)	112 (76.2%)	
Grade 1–2	43 (26.9%)	113 (17.1%)		42 (30.4%)	35 (23.8%)	
Grade 3–4	1 (0.6%)	1 (0.2%)		1 (0.7%)	0 (0.0%)	
Thrombocytopenia			0.214[b]			0.206[b]
Grade 0	142 (87.1%)	604 (90.1%)		128 (85.9%)	137 (91.3%)	
Grade 1–2	19 (11.7%)	62 (9.3%)		19 (12.8%)	11 (7.3%)	
Grade 3–4	2 (1.2%)	4 (0.6%)		2 (1.3%)	2 (1.3%)	
Liver dysfunction			0.007[a]			0.184[b]
Grade 0	65 (77.4%)	242 (71.6%)		54 (74.0%)	57 (81.4%)	
Grade 1–2	17 (20.2%)	96 (28.4%)		17 (23.3%)	13 (18.6%)	
Grade 3–4	2 (2.4%)	0 (0.0%)		2 (2.7%)	0 (0.0%)	
Renal dysfunction			0.348[a]			0.934[a]
Grade 0	76 (90.5%)	293 (86.7%)		66 (90.4%)	6390.0 (%)	
Grade 1–2	8 (9.5%)	45 (13.3%)		7 (9.6%)	7 (10.0%)	
Grade 3–4	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Vomiting			0.761[a]			0.833[a]
Grade 0	100 (58.8%)	423 (61.1%)		90 (58.4%)	88 (57.1%)	
Grade 1–2	58 (34.1%)	216 (31.2%)		52 (33.8%)	51 (33.1%)	
Grade 3–4	12 (7.1%)	53 (7.7%)		12 (7.8%)	15 (9.7%)	
Mucositis			0.492[a]			0.038[a]
Grade 0	76 (44.7%)	322 (46.5%)		65 (43.0%)	70 (45.2%)	

(Continued)

Table 4. (Continued)

Characteristic	Primary cohort			PSM cohort		
	Sarcopenia	Non-sarcopenia	*p* value	Sarcopenia	Non-sarcopenia	*p* value
Grade 1–2	37 (21.8%)	169 (24.4%)		36 (23.8%)	52 (33.5%)	
Grade 3–4	57 (33.5%)	201 (29.0%)		50 (33.1%)	33 (21.3%)	
Radiodermatitis			0.503[a]			0.017[b]
Grade 0	80 (47.1%)	328 (47.4%)		68 (44.2%)	87 (56.5%)	
Grade 1–2	84 (49.4%)	350 (50.6%)		80 (51.9%)	65 (42.2%)	
Grade 3–4	6 (3.5%)	14 (2.0%)		6 (3.9%)	2 (1.3%)	
Tinnitus			<0.001[a]			0.004[a]
Grade 0	154 (90.6%)	633 (91.5%)		139 (90.3%)	151 (98.1%)	
Grade 1–2	16 (9.4%)	9 (1.3%)		15 (9.7%)	3 (1.9%)	
Grade 3–4	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Xerostomia			0.020[a]			0.166[b]
Grade 0	91 (53.8%)	382 (55.3%)		82 (53.2%)	91 (59.5%)	
Grade 1–2	75 (44.4%)	308 (44.6%)		69 (44.8%)	62 (40.5%)	
Grade 3–4	3 (1.8%)	1 (0.1%)		3 (1.9%)	0 (0.0%)	
Treatment response			0.004[a]			0.020[b]
CR	115 (71.4%)	498 (75.1%)		103 (71.0%)	120 (80.5%)	
PR	33 (20.5%)	147 (22.2%)		30 (20.7%)	24 (16.1%)	
SD	10 (6.2%)	17 (2.6%)		9 (6.2%)	5 (3.4%)	
PD	3 (1.9%)	1 (0.2%)		3 (2.1%)	0 (0.0%)	

[a]Pearson's χ^2 test.
[b]Fisher's exact test.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

analysis of CT simulation images can provide information about the therapeutic toxicity and survival prognosis in NPC, thus guiding personalized multi-modality interventions during CCRT.

Author contributions

Conceptualization, Xin Hua; Data curation, Xin Hua and Jun-Fang Liao; Formal analysis, Xin Hua; Funding acquisition, Ling Guo and Huan-Xin Lin; Investigation, Jun-Fang Liao, Xin Huang, Han-Ying Huang, Wen Wen and Zhi-Qing Long; Methodology, Xin Hua and Jun-Fang Liao; Project administration, Zhong-Yu Yuan and Huan-Xin Lin; Software, Xin Hua, Xin Huang and Wen Wen; Supervision, Ling Guo, Zhong-Yu Yuan and Huan-Xin Lin; Validation, Jun-Fang Liao, Han-Ying Huang and Wen Wen; Visualization, Xin Huang; Writing – original draft, Xin Hua; Writing – review & editing, all authors. All authors have read and approved the paper.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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