The predictive and prognostic value of sarcopenia in patients undergoing (chemo)radiotherapy for laryngopharyngeal carcinoma: a retrospective cohort study

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Abstract

Introduction: Sarcopenia, characterized by skeletal muscle loss, is prevalent among cancer patients and increasingly recognized as an adverse prognostic factor influencing treatment outcomes and toxicity. The aim of this retrospective cohort study was to investigate the association between sarcopenia, overall survival, disease-free survival, and radiation-induced toxicity in primary laryngeal and hypopharyngeal cancer patients undergoing radiotherapy or chemoradiotherapy.

Methods: Eighty patients were included in this study. Data was collected from electronical patient databases. Skeletal muscle mass was assessed using cross-sectional area measurements from CT scans at the level of the third cervical vertebrae, with sarcopenia defined as lumbar skeletal muscle index (SMI) < 43.2 cm^2/m^2.

Results: The survival analysis did not show any significant association between sarcopenia and either overall survival or disease-free survival. Additionally, no statistically significant difference in radiation-induced toxicities was observed between the two groups.

Conclusion: This cohort study found no independent association between sarcopenia and survival outcomes or treatment-related toxicity.

Introduction

Laryngeal and hypopharyngeal cancers are prevalent malignancies in the head and neck region, accounting for 275,448 of new cases worldwide annually, which corresponds to 2.79% of all cancer cases[1]. Radiotherapy (RT) plays a pivotal role in the treatment of most laryngopharyngeal carcinoma patients. It is an effective modality for achieving locoregional control of solid tumors, optimizing outcomes in terms of laryngeal function, disease-free survival (DFS) and overall survival (OS)[2,3,4]. However, RT can cause adverse effects, including acute toxicity such as mucositis, dermatitis, and xerostomia, as well as late toxicity such as dysphagia and osteoradionecrosis[5]. These adverse effects can worsen the already impaired nutritional status of these patients. Combining RT with chemotherapy can further exacerbate these adverse effects[6].
Recent studies in oncology have demonstrated that sarcopenia is an independent adverse prognostic factor that can affect treatment-related toxicity, clinical response, and prognosis[7,8,9]. Sarcopenia is defined as the generalized and progressive loss of skeletal muscle mass (SMM), reduction in muscle strength and resultant functional impairment[10]. Sarcopenia is a prevalent condition among cancer patients. This increased prevalence is attributed to nutritional issues that affect patients before, during and after oncological treatment[11,2]. One of the preferred methods of evaluating sarcopenia in cancer patients is to measure the area or index of seven muscles passing through the L3 vertebra level[12,13]. However, CT imaging of the L3 is not routinely performed in laryngeal carcinoma patients. Swartz et al. found a strong correlation between the L3 cross-sectional skeletal muscle index (L3-CSMI) and the C3 cross-sectional skeletal muscle index (C3-CSMI). It was found that sarcopenia can be assessed without the need for additional imaging using this method[14].
To our knowledge, only E. Karavolia et al. and M. van Rijn-Dekker et al have investigated the association between sarcopenia and radiation-induced toxicity in head and neck cancer patients [15,16]. Their studies found that sarcopenia was an independent prognostic factor for radiation-induced outcomes such as xerostomia and dysphagia, as well as DFS and OS. However, the study included a range of head and neck cancer subtypes, without taking into account the distinct anatomical and functional characteristics of the laryngopharynx, which introduced heterogeneity into the study cohort. Furthermore, the trials were conducted separately for acute and late toxicity in different study cohorts. Therefore, the aim of this study was to investigate the association between sarcopenia, OS and DFS for primary laryngopharyngeal cancer patients undergoing RT. Additionally, the relationship between sarcopenia and both acute (mucositis, dermatitis and xerostomia) and late (dysphagia and osteoradionecrosis) radiation-induced toxicity was examined.

1. Material and Methods

Study population

This single-centre study used retrospectively collected data from 80 patients with laryngeal and hypo-pharyngeal cancer who underwent primary RT or chemoradiotherapy (CRT) at the University Medical Center Utrecht (UMCU) between 2018 and 2020. The patients received RT at a dose of 70Gy on the primary tumor, with a fractionation of 1.7-2.4 Gy/fr. Patients who received CRT were given additional cisplatin (100mg/m2) or carboplatin (400mg/m2) for a total of three doses.
The inclusion criteria for this study were a confirmed primary tumor with a pathological diagnosis of squamous cell carcinoma, the absence of distant metastatic disease, treatment with curative intent, A CT or MRI scan at least one month prior to treatment and the availability of radiation-induced toxicity data.

Clinical parameters

All clinical parameters: age, sex, weight, height, smoking history, heavy alcohol consumption[17], treatment modality, tumor site, pathological stage (AJCC)[18], radiation/chemoradiation schedule, DFS, OS, and radiation-induced toxicity data were obtained from electronic patient records.

Imaging protocol

All patients underwent contrast-enhanced CT scanning prior to radiation treatment on a Philips Brilliance iCT scanner (Philips Healthcare, Best, The Netherlands) using a standardized protocol for head and neck cancer patients. The imaging was performed in treatment position in a radiotherapy immobilization mask. Scanning parameters included slice thickness 1 mm with a 2 mm interslice gap[19].

CT image analysis

The cross-sectional area (CSA) of the muscle was measured by CT scans of the head and neck at the C3 level[14]. In summary, the slide that displays both transverse processes and the entire vertebral arc at the level of the third cervical vertebrae (C3) when scrolling from caudal to cranial direction was chosen for segmenting skeletal muscle tissue[20]. For CT imaging, skeletal muscle area was defined as the pixel area within a radiodensity between -29 and +150 Hounsfield units (HU), which is specific for skeletal muscle tissue [21]. The skeletal muscle tissue segmentation was manually performed by a single independent researcher (B.E.G.D.) using the commercially available software package SliceOmatic (Tomovision, Magog, Quebec, Canada). The 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 of the third lumbar vertebrae (L3) using the validated algorithm developed by Swartz et al. using the following formula:

$$CSA\ at\ L3\ (cm^2) = 27.304 + 1.363 * CSA\ at\ C3\ (cm^2) - 0.671 * Age\ (years) + 0.640 * weight\ (kg) + 26.442 * sex\ (sex = 1\ for\ female, 2\ for\ male)$$

The skeletal muscle area at L3 was then normalized for height to calculate the lumbar skeletal muscle index (SMI).

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

Low SMM or radiological sarcopenia, was defined as a lumbar SMI lower than 43.2 cm^2/m^2. This definition is based on a separate cohort of patients with head and neck cancer[22].

Outcome measures

This study analyzes the impact of radiation therapy on overall survival (OS), disease-free survival (DFS), and radiation-induced toxicity. The time to event was measured from the first day of therapy until the date of death or recurrent disease. Patients who remained alive or had no events were censored at the date of the last follow-up. Acute radiation-induced toxicity was assessed based on physician-rated mucositis, xerostomia and dermatitis while late radiation-induced toxicity was evaluated based on physician-rated dysphagia and osteoradionecrosis. The study assessed radiation-induced toxicity using the Common Terminology Criteria for Adverse Events (CTCAE, v5.0) for both acute and late effects [23].

Statistical analysis

R 4.3.2 software (The R Foundation for Statistical Computing, Vienna, Austria; 'gtsummary and 'survival' package) was used for all statistical analyses. Descriptive statistics were calculated using Pearson's Chi-squared test, Fisher's exact test and Wilcoxon rank sum test to compare group demographics and toxicity. The study identified univariate and multivariate confounding characteristics for both OS and DFS using the Cox proportional hazards model. To assess survival differences between sarcopenic

and non-sarcopenic groups, the Kaplan-Meier test was used. Results were considered statistically significant at a P-value of less than 0.05.

2. Results

Patient characteristics

Of the cohort, 49 patients were identified as radiologically sarcopenic, while 31 were not. The mean follow-up time for the entire cohort was 41 months (SD = 18.18). Patients with sarcopenia (N=49) were more likely to be female ($p < 0.001$), have a lower BMI ($p < 0.001$), and a lower SMI ($p < 0.001$). Other characteristics were evenly distributed between the two groups (Table 1).

Table 1: Baseline characteristics

Characteristic	Overall, N = 80[1]	No Sarcopenia, N = 31[1]	Sarcopenia, N = 49[1]	p-value[2]
Gender				**<0.001**
Female	22/80 (28%)	1/31 (3.2%)	21/49 (43%)	
Male	55/80 (73%)	30/31 (97%)	28/49 (57%)	
Age	69.88 (10.43)	68.65 (9.07)	70.65 (11.22)	0.4
BMI	25.36 (5.32)	28.46 (6.05)	23.40 (3.69)	**<0.001**
Heavy alcohol use[a]	46/77 (60%)	17/30 (57%)	29/47 (62%)	0.7
Smoking history	72/79 (91%)	27/31 (87%)	45/48 (94%)	0.4
Follow-up time[b]	41.13 (18.18)	42.06 (17.08)	40.53 (18.99)	>0.9
Tumor				0.6
Hypopharynx	21/80 (26%)	7/31 (23%)	14/49 (29%)	
Larynx	59/80 (74%)	24/31 (77%)	35/49 (71%)	
AJCC stage[c]				0.3
1	8/80 (10%)	3/31 (9.7%)	5/49 (10%)	
2	22/80 (28%)	8/31 (26%)	14/49 (29%)	
3	26/80 (33%)	13/31 (42%)	13/49 (27%)	
4A	18/80 (23%)	7/31 (23%)	11/49 (22%)	
4B	6/80 (7.5%)	0/31 (0%)	6/49 (12%)	
Treatment modality				0.7
Chemoradiotherapy	9/80 (11%)	4/31 (13%)	5/49 (10%)	
Radiotherapy	71/80 (89%)	27/31 (87%)	44/49 (90%)	
KPS[d]				0.2
50	1/61 (1.6%)	1/22 (4.5%)	0/39 (0%)	
70	6/61 (9.8%)	3/22 (14%)	3/39 (7.7%)	
80	28/61 (46%)	7/22 (32%)	21/39 (54%)	
90	7/61 (11%)	4/22 (18%)	3/39 (7.7%)	
100	19/61 (31%)	7/22 (32%)	12/39 (31%)	
WHO score[e]				0.5
0	19/61 (19%)	7/22 (32%)	12/39 (31%)	
1	35/61 (73%)	11/22 (50%)	24/39 (62%)	
2	6/61 (7.7%)	3/22 (14%)	3/39 (7.7%)	
3	1/61 (1.6%)	1/22 (4.5%)	0/39 (0%)	
SMI[f]	41.18 (7.36)	48.45 (4.10)	36.58 (5.07)	**<0.001**

[1] n/N (%); Mean (SD)
[2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test
[a] According to National Institute on Alcohol Abuse and Alcoholism (NIAAA)
[b] Follow-up time in months
[c] Stage according to American Joint Committee on Cancer
[d] Karnofsky Performance Scale
[e] World Health Organisation Performance score
[f] Skeletal Muscle Index

Survival analysis

Following adjustments for confounding variables, including age, BMI, tumor site, treatment and SMI. The analysis revealed a significant independent association between tumor site and OS (p = 0.020). This association remained significant after controlling for other contributing factors (p = 0.015). No other characteristics showed a significant association with either OS or DFS (Table 2).

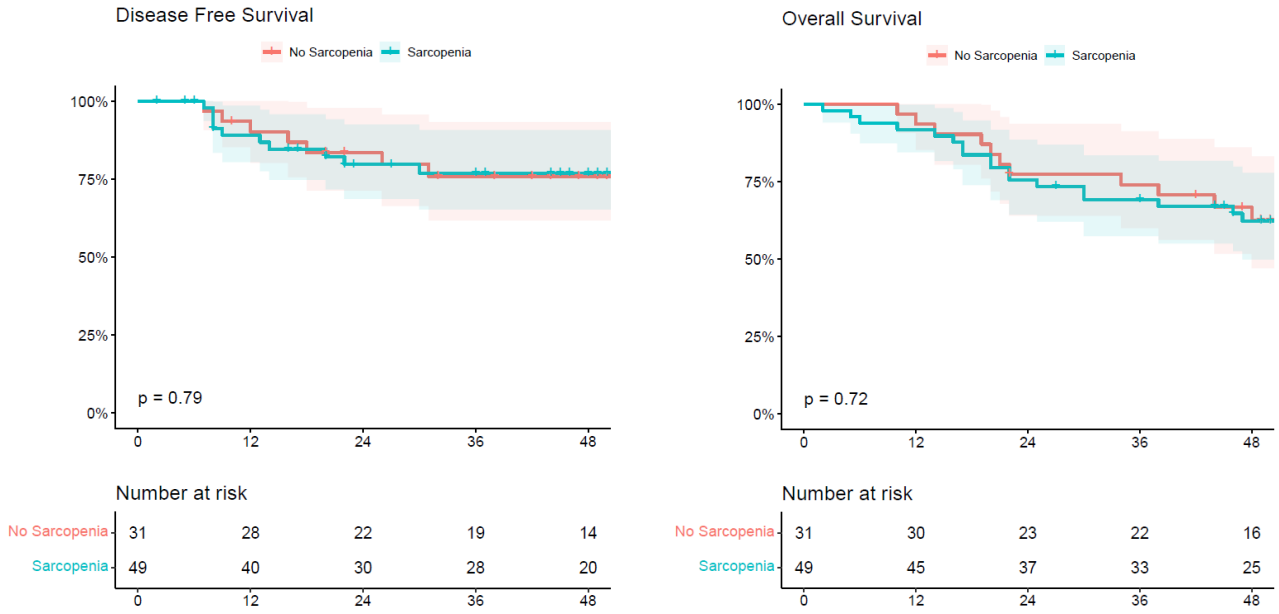
Table 2: Cox proportional hazards model

			Overall Survival		**Disease Free Survival**	
Characteristic		**Overall, N = 29[1]**	HR[2] (univariable)	HR[2] (multivariable)	HR[2] (univariable)	HR[2] (multivariable)
Age		69.9 (10.4)	1.00 (0.96-1.03, p=0.773)	0.99 (0.96-1.03, p=0.635)	0.96 (0.92-1.00, p=0.078)	0.96 (0.91-1.01, p=0.102)
BMI		25.4 (5.3)	1.01 (0.96-1.07, p=0.651)	1.04 (0.97-1.11, p=0.285)	0.96 (0.87-1.07, p=0.457)	0.97 (0.87-1.08, p=0.570)
Tumor	Hypopharynx	21/80 (26%)	-	-	-	-
	Larynx	59/80 (74%)	**0.44 (0.22-0.88, p=0.020)**	**0.41 (0.20-0.84, p=0.015)**	0.45 (0.18-1.17, p=0.104)	0.43 (0.16-1.15, p=0.092)
Treatment	CRT[a]	9/80 (11%)				
	RT[b]	71/80 (89%)	0.57 (0.22-1.47. p=0.245)	0.61 (0.23-1.65, p=0.331)	0.53 (0.15-1.83, p=0.315)	0.72 (0.20-2.56, p=0.607)
SMI	≤ 43.2	31/80 (39%)	-	-	-	-
	> 43.2	49/80 (61%)	1.14 (0.56-2.31, p=0.715)	1.45 (0.64-3.26, p=0.371)	0.88 (0.35-2.24, p=0.792)	0.84 (0.29-2.45, p=0.751)

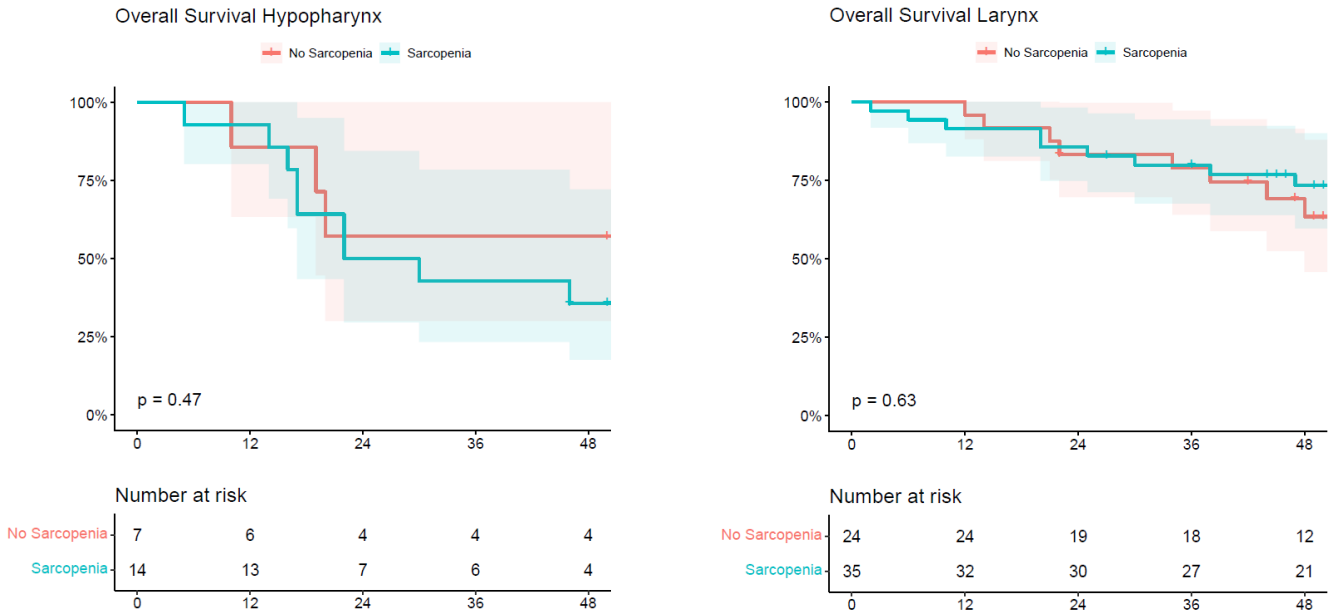
[1] n/N (%); Mean (SD)
[2] Hazard Ratio (HR)
[a] Chemoradiotherapy (CRT)
[b] Radiotherapy (RT)

Kaplan-Meier curves were plotted to compare the DFS and OS of sarcopenic and non-sarcopenic patients. The first two plots do not distinguish between tumor sites. The x-axis represents the time interval in months, while the vertical stripes in the graph represent censored patients. The coloured boundaries in the graph indicate confidence intervals. Below the curve, a table of patients at risk is shown, which includes patients for whom the event did not occur at that time.
Both sarcopenic and non-sarcopenic patients had a 4-year DFS rate of 75% and a 4-year OS rate of 67.5%. The study found no statistically significant difference in OS or DFS rates between sarcopenic and non-sarcopenic patients, as demonstrated in Figures 1 and 2.

Furthermore, a stratified plot was generated to illustrate the correlation between OS and tumor site (Figures 3 and 4). The 4-year OS rate for hypopharyngeal cancer was 37.5% in sarcopenic patients and 60% in non-sarcopenic patients. However, there was no statistically significant difference between the two groups (p = 0.47). For laryngeal cancer, the 4-year OS rate was 80% in sarcopenic patients and 67.5% in non-sarcopenic patients. Again, there was no statistically significant difference between the two groups (p = 0.63).



Figures 1 & 2: Kaplan-Meier curves for disease-free survival and overall survival in all patients



Figures 3 & 4: Kaplan-Meier curves for overall survival in patients with laryngeal and hypopharyngeal cancer

Toxicity

Out of 80 patients, 59 had mucositis, 63 had dermatitis, 41 had xerostomia, and 55 had dysphagia. Radionecrosis was found in 7 out of 80 patients. The percentage of grades 0 and 3-4 toxicities was the same for both the sarcopenic and non-sarcopenic groups. However, the sarcopenic group exhibited a higher number of toxicities for grade 1-2 dermatitis, xerostomia, and dysphagia. Nevertheless, no statistically significant difference was observed (Table 3).

Table 3: Therapy-induced toxicity

Characteristic	**Overall, N = 80[1]**	**No Sarcopenia, N = 31[1]**	**Sarcopenia, N = 49[1]**	**p-value[2]**
Mucositis[a]				>0.9
Grade 0	21/80 (26%)	8/31 (26%)	13/49 (29%)	
Grade 1-2	45/80 (56%)	17/31 (55%)	28/49 (41%)	
Grade 3-4	14/80 (18%)	6/31 (19%)	8/49 (29%)	
Dermatitis[a]				0.2
Grade 0	17/80 (21%)	9/31 (29%	8/49 (24%)	
Grade 1-2	60/80 (75%)	20/31 (65%)	40/49 (76%)	
Grade 3-4	3/80 (3.8%)	2/31 (6.5%)	1/49 (0%)	
Xerostomia[a]				0.11
Grade 0	39/80 (49%)	19/31 (61%)	20/49 (35%)	
Grade 1-2	41/80 (51%)	12/31 (39%)	29/49 (65%)	
Grade 3-4	0/80 (0%)	0/31 (0%)	0/49 (0%)	
Dysphagia[a]				0.2
Grade 0	25/80 (31%)	13/31 (42%)	12/49 (24%)	
Grade 1-2	43/80 (54%)	15/31 (48%	28/49 (65%)	
Grade 3-4	12/80 (15%)	3/31 (9.7%)	9/49 (12%)	
Radionecrosis[a]				0.8
Grade 0	73/80 (91%)	29/31 (94%)	44/49 (88%)	
Grade 1-2	5/80 (6.3%)	1/31 (3.2%)	4/49 (5.9%)	

Grade 3-4	2/80 (2.5%)	1/31 (3.2%)	1/49 (5.9%)

[1] n/N (%)
[2] Pearson's Chi-squared test; Fisher's exact test
[a] Physician graded, adhering to CTCAE version 5

3. Discussion

The aim of this study was to investigate the association between sarcopenia, OS, DFS, and radiation-induced toxicity in primary laryngeal and hypopharyngeal cancer patients undergoing RT or CRT. The research findings revealed important insights into the relationship between sarcopenia and treatment outcomes in this specific patient population. Contrary to previous studies in broader head and neck cancer cohorts, this study found no statistically significant association between sarcopenia and OS, DFS, or radiation-induced toxicity in laryngeal and hypopharyngeal cancer patients undergoing RT or CRT. Despite expectations based on existing literature, the presence of sarcopenia did not independently predict survival outcomes or increase the risk of treatment-related toxicity in this cohort[15,16,24].

This study contributes to the current literature on the influence of sarcopenia on cancer treatment outcomes, particularly in relation to laryngeal and hypopharyngeal cancer. As mentioned in the introduction, previous studies have demonstrated the predictive value of sarcopenia in radiation-induced outcomes and survival for patients with head and neck cancer[15,16].
Their inclusion of diverse cancer subtypes may have introduced variability within study cohorts. Furthermore, examining acute and late toxicity separately in different cohorts may have introduced complexities in data interpretation, potentially affecting the robustness and applicability of their findings.

Our study focused specifically on patients with primary laryngeal and hypopharyngeal cancer, resulting in a more homogeneous cohort. This allowed for a targeted analysis of treatment outcomes relevant to this distinct anatomical site[25,26]. Additionally, our study addressed a methodological limitation present in previous research by comprehensively evaluating both acute and late toxicity in a single cohort of patients undergoing radiotherapy or chemoradiotherapy for laryngeal and hypopharyngeal cancer.

This study unexpectedly showed no association between sarcopenia and treatment outcomes, despite previous evidence suggesting a significant impact of sarcopenia on radiation-induced toxicity and survival in head and neck cancer patients.
It is important to consider several limitations inherent in this study. The nature of retrospective data collection introduces inherent biases and limitations, including selection bias and incomplete data capture. Furthermore, the small sample size of 80 patients may limit the generalizability of the findings and reduce the statistical power to detect significant associations. Moreover, utilizing CT imaging at the C3 level for sarcopenia evaluation may not fully capture the range of muscle mass variation and could introduce measurement variability[14]. Additionally, the subjective nature of toxicity assessment using CTCAE, V5.0 may lead to inter-rater variability and bias in toxicity scoring[23]. Furthermore, it is important to consider that differences in treatment methods, such as varying radiation therapy schedules and types of chemotherapy, may impact treatment response and toxicity profiles. This could potentially obscure the effects of sarcopenia on outcomes. Finaly, it is good to realize that we only investigated radiological sarcopenia and not the combination with muscle function, which used in the preferred definition of sarcopenia according to the European Working Group on Sarcopenia (EWGSOP)[27]. It is important to note that muscle function is critical in diagnosing and predicting sarcopenia. Excluding muscle function assessment may overestimate sarcopenia prevalence in our cohort, as functional impairment may exclude individuals who meet sarcopenia criteria based on muscle mass alone[28].

Despite the limitations of this study, there are several avenues for future research that merit exploration. Larger, multicenter studies with more extensive patient cohorts are needed to validate the findings of this study and provide more robust evidence on the relationship between sarcopenia and treatment outcomes in patients with laryngeal cancer. Prospective studies with standardized methods for sarcopenia assessment (with muscle function) and toxicity evaluation are necessary to overcome the limitations associated with retrospective data analysis and subjective toxicity scoring. Additionally, investigations into the underlying mechanisms linking sarcopenia to treatment response and toxicity may provide insights into potential therapeutic targets to mitigate treatment-related morbidity and improve outcomes in patients with laryngeal cancer[29,30].

4. Conclusion

In conclusion, this study contributes to our understanding of the role of sarcopenia in treatment outcomes and toxicity in primary laryngeal and hypopharyngeal cancer patients undergoing RT or CRT. Although sarcopenia was not found to be independently associated with survival outcomes or treatment-related toxicity in this cohort, the findings highlight the need for further research to clarify the complex interplay between sarcopenia, treatment response, and toxicity in laryngeal and hypopharyngeal cancer. To improve outcomes for these patients, larger (prospective) studies should be conducted to address the limitations of this study and build upon its findings. This may ultimately inform personalized treatment strategies.

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