





Article

Untailored vs. Gender- and Body-Mass-Index-Tailored Skeletal Muscle Mass Index (SMI) to Assess Sarcopenia in Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

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Simple Summary: In this study, we investigated the optimal SMI cutoff to discriminate overall survival (OS) in a cohort of consecutive advanced HNSCC patients. Untailored, BMI-tailored and gender-tailored cutoffs were analyzed, and gender-tailored SMI categorization had the highest prognostic value, which was retained in a multivariate analysis including several HNSCC-specific prognostic factors.

Abstract: (1) Background: Sarcopenia lasting >1 year might be considered a chronic condition in many HNSCC patients. CT-scan-derived Skeletal Muscle Mass Index (SMI) is an established surrogate of sarcopenia; yet, the cut-off reported in the literature (literature-based, lb-SMI < 43.2) is mainly based on the risk of chemoradiotherapy-induced toxicity, and the optimal value to discriminate OS is under-investigated. (2) Methods: The effect on OS of the lb-SMI cutoff was compared with an untailored OS-oriented SMI cutoff obtained in a cohort of consecutive advanced HNSCC patients treated with primary chemoradiotherapy, bio-chemotherapy or chemo-immunotherapy (cohort-specific, cs-SMI cutoff). Gender- and BMI-tailored (gt-SMI and bt-SMI) cut-offs were also evaluated. Cutoff values were identified by using the maximally selected rank statistics for OS. (3) Results: In 115 HNSCC patients, the cs-SMI cutoff was 31.50, which was lower compared to the lb-SMI reported cut-off. The optimal cut-off separately determined in females, males, overweight and non-overweight patients were 46.02, 34.37, 27.32 and 34.73, respectively. gt-SMI categorization had the highest effect on survival ($p < 0.0001$); its prognostic value was independent of the treatment setting or the primary location and was retained in a multivariate cox-regression analysis for OS including other HNSCC-specific prognostic factors ($p = 0.0004$). (4) Conclusions: A tailored SMI assessment would improve clinical management of sarcopenia in chemoradiotherapy-, bio-chemotherapy- or chemo-immunotherapy-treated HNSCC patients. Gender-based SMI could be used for prognostication in HNSCC patients.

Keywords: head and neck cancer; sarcopenia; skeletal muscle mass index

1. Introduction

Nearly 900,000 new diagnoses of and 500,000 deaths from head and neck squamous cell carcinoma (HNSCC) were recorded in 2020 worldwide, accounting for 9% of all cancer diagnoses and 5% of all cancer deaths [1]. More than 60% of HNSCC are locoregionally advanced or with distant metastases at diagnosis (stage III and IV, respectively) [2]. Moreover, in 15 to 40% of patients, disease recurrence occurs after definitive local treatment [2].

The current standard of care for locally advanced nonsurgical HNSCC patients is radiotherapy plus concomitant cisplatin, while in the case of recurrent disease not amenable to re-irradiation or in case of metastases, first-line systemic therapy with either chemotherapy plus anti-EGFR or anti-Programmed death protein 1 (PD-1) with or without concomitant chemotherapy is administered [3].

HNSCC patients are frequently frail and sarcopenic and require multidisciplinary care that should take into consideration multiple management aspects, such as pain, swallowing and speech dysfunction, nutritional support and psychological distress [3].

Sarcopenia is a syndrome characterized by loss of muscle mass and function that can be physiological and secondary to aging or associated with various chronic diseases such as cancer [4]. It is strongly related to impaired quality of life and depression symptoms [5]. Sarcopenia, found in approximately 20–30% of cancer patients at diagnosis, can emerge as a chronic illness [6,7], i.e., lasting >1 year (<https://www.cdc.gov/chronicdisease/about/index.htm>, accessed on 15 July 2023), and can be associated with worse surgical outcome and survival, as well as higher treatment-related toxicity [8]. More recently, its prognostic role has been confirmed also in patients treated with immune check-point inhibitors across multiple tumor types [9–11]. Computed tomography (CT)-derived skeletal muscle mass index (SMI) was proposed to quantify the total amount of skeletal muscle mass and assess sarcopenia [12]. Information for SMI can be obtained from a single lumbar or cervical CT-slice and this guarantees accessibility and good quality data for possibly all HNSCC patients [13,14]. Wong et al., in a recent meta-analysis including nine retrospective and one prospective studies [15], confirmed that radiologically defined sarcopenia is a negative predictor of OS in HNSCC, independently of the selected CT-slice. Although easily available, specific threshold values of SMI for HNSCC patients are under-investigated [15,16] and the comparability between the analysis at the cervical and lumbar level has been questioned [15,17].

Prado et al. highlighted the importance of body mass index (BMI) and gender in the assessment of sarcopenia [17,18] and recommended that sex-specific cut-offs of SMI should be considered [17]. Importantly, gender differences in relation to sarcopenia have been reported with a higher prevalence of sarcopenic obesity found in men (defined as contemporary presence of overweight and depleted muscle mass) [19].

In the literature, SMI threshold values have been widely applied regardless of cancer type, treatment setting and patient characteristics, without appreciating potential differences in SMI cut-offs, particularly between overweight and non-overweight as well as male vs. female patients with HNSCC.

The aim of the present study was to define the optimal survival-related SMI cut-off in advanced (locoregionally and metastatic) HNSCC patients treated with primary chemoradiotherapy, bio-chemotherapy or chemoimmunotherapy and to evaluate different threshold values based on BMI and gender subgroups.

2. Materials and Methods

Patients with histologically confirmed advanced HNSCC and not candidates for surgery were treated between December 2014 and October 2022 at the ‘Tor Vergata’ University Hospital of Rome with definitive cisplatin-based chemoradiotherapy for locally advanced disease, and standard first-line bio-chemotherapy or immuno-chemotherapy for recurrent/metastatic disease was retrospectively reviewed.

Routine demographic and clinical characteristics were collected at baseline: age at diagnosis, gender, alcohol consumption, height (m), weight (kg), BMI (weight to square of height, kg/m²), primary tumor site, stage, Charlson Comorbidity Score (CCS) [20],

smoking habit, Human Papilloma Virus (HPV) status, Karnofsky Performance Status (KPS) and modified Glasgow Prognostic Score (mGPS) (a score that ranges from 0 to 2 based on the presence/absence of the following adverse factors: albuminemia < 35 g/L and C-reactive protein > 10 mg/L) [21]. Patients were classified as overweight (BMI > 25) or non-overweight (BMI < 25), according to World Health Organization (WHO) classification [22].

In order to allow SMI measurement, only patients with a pretreatment computed tomography (CT) scan with contrast reconstructed with a 1 mm slice thickness were included in the analysis. SMI was obtained according to standard procedure as follows: using C3 sagittal slice as the landmark and setting Hounsfield units (HU) within -29 HU to $+150$, corresponding to skeletal muscle density, right and left sternocleidomastoid and paravertebral muscle areas were manually selected and measured by two distinct operators (M.R. and S.G.) with discrepancies resolved by a third operator (R.A.). In Figure 1 a showing the representative SMI calculation, the sum of the selected areas corresponded to the total cross-sectional area (CSA, cm^2) of the skeletal muscle at C3, according to the method previously published by Swartz et al. [23]. In case of unilateral tumor infiltration of the muscles or surgical removal, the target area was calculated by doubling the area of the contralateral muscles [23]. CSA at L3 was finally derived by CSA at C3 using the equation described by Swartz et al. [23]. The final skeletal muscle index (SMI, cm^2/m^2) resulted from the CSA at L3 divided by the square of the height (m^2).

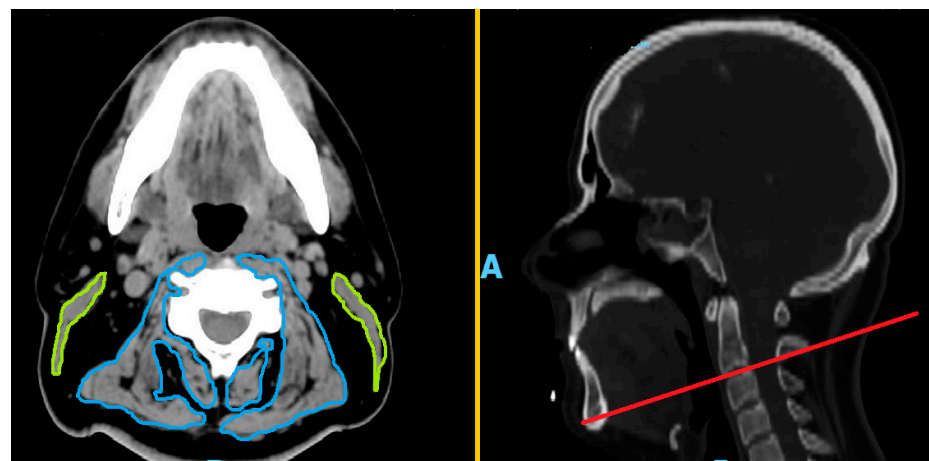


Figure 1. Representative model of C3 CT-scan slice measurement of paravertebral and sternocleidomastoid muscles.

SMI-based patient categorization in sarcopenic vs. non-sarcopenic (i.e., SMI low vs. high) was performed according to four different methods and the prognostic value of these categorization methods was assessed and compared, with the primary outcome measure being overall survival (OS). OS was defined as the time from the start of the main treatment (chemoradiotherapy or first-line chemotherapy) to the day of death due to any cause or last follow-up visit.

First, sarcopenia was defined a priori as an SMI of less than 43.2, based on the report by Wendrich et al. [16] that was focused on the prediction of chemotherapy dose-limiting toxicity in HNSCC (literature-based SMI, lb-SMI cutoff).

The second method was based on the identification of a prognostic ‘cohort-specific’ SMI (cs-SMI) cutoff. Taking SMI as a continuous variable, maximally selected rank statistics for overall survival (OS) [24] were applied to find the most significant cut-off associated with survival in our specific population.

Patients were then stratified by BMI (<25 vs. >25 Kg/m^2) and gender (females vs. males), and for each subgroup, a specific SMI cut-off was obtained by using the maximally selected rank statistics for OS. The third and fourth methods were therefore the definition of sarcopenia according to a BMI-tailored (bt) and a gender-tailored (gt) cutoff (i.e., two

distinct SMI cutoffs based on BMI, one for overweight and one for non-overweight patients; and two distinct cutoffs based on gender, one for males and one for females).

OS Kaplan–Meier curves were generated for patient subgroups of sarcopenia based on the four above-described categorization methods: lb-SMI, cs-SMI, gt-SMI and bt-SMI low vs. high.

Chi-square and *p* values were obtained from log-rank test in the survival analysis and the most significant categorization method of SMI was selected to be assessed in a multivariate Cox-regression model for OS with known prognostic factors that included smoking habit, HPV status, ECOG PS and mGPS [21]. Calculations were carried out for 95% confidence intervals (CIs) for the estimated hazard ratios (HRs).

Differences in prevalence of sarcopenia between patient subgroups were assessed using classic chi-square test for categorical variables.

All analyses were performed using the R software v.4.0.3 and MedCalc software version 20.006. All tests were considered statistically significant for two-tail *p* values < 0.05.

3. Results

One-hundred-fifteen patients (median age 65 years, range 35 to 86 years, 24 females, 91 males) were included in the present analysis. Fifty-three patients (46%) had oropharyngeal cancer. And 72 (63%) patients received platinum-based RT while 43 (37%) received a Cisplatin-5FU-based first-line treatment with anti-EGFR or anti-PD-1 agent (36 and 7, respectively). Table 1 depicts the main patients' characteristics. The OS endpoint was reached in 43 patients, and the median follow-up of surviving patients was 29.1 months (0.5 to 182 months). The median OS (mOS) of the entire cohort was 82.83 months (95% CI 35.75 to 106.58).

The median SMI in the cohort was 36.15 cm²/m², ranging from 18.99 cm²/m² to 53.99 cm²/m².

Taking into consideration the lb-SMI cutoff (43.2 cm²/m²) [16], 87 out of 115 patients (75.7%) were considered sarcopenic. Sarcopenic lb-SMI was associated with impaired survival (24-month OS rate 64% vs. 88% for lb-SMI low vs. high, respectively; hazard ratio (HR) 1.96; 95% confidence interval (CI) 1.03 to 3.74; *p* 0.04) (Figure 2A).

According to the maximally selected rank statistics for OS, the SMI cut-off in our cohort (cs-SMI cutoff) was 31.50 cm²/m². A total of 22 out of 115 (19%) patients were sarcopenic according to the cs-SMI. The 24-month OS rate for cs-SMI low versus high was 53% vs. 74%, respectively (HR 6.61, 95%CI 2.65 to 16.50, *p* 0.0001) (Figure 2B).

The bt-SMI and gt-SMI cut-offs were obtained using a stratified maximally selected rank statistics and were 34.73 cm²/m² for non-overweight (BMI < 25) patients, 27.32 cm²/m² for overweight (BMI > 25) patients, 34.37 cm²/m² for men and 46.02 cm²/m² for women. Patients with SMI below the reference cut-off value according to the relevant category were classified as having sarcopenia.

According to bt-SMI and gt-SMI, 26 (23%) and 55 (48%) patients were found to be sarcopenic, respectively.

Of note, sarcopenia was more prevalent in females (20 out of 24 (83%)) than in males (35 out of 91 (39%)) according to the gt-SMI (chi-square *p*-value, 0.0001).

Sarcopenia according to gt-SMI was demonstrated to have a remarkably powerful prognostic effect (24-month OS rate 55% vs. 85% for gt-SMI low vs. high, respectively; HR 3.96 (95% CI 2.12 to 7.38) *p* < 0.0001 (Figure 2D)). Bt-SMI had a prognostic impact similar to that of cs-SMI (Figure 2C).

Twenty-four-month OS rate, univariate HR with 95% CI and *p* values, and chi-square statistics for the four SMI categorization methods are summarized in Table 2.

Table 1. Baseline patients' characteristics.

| Variable * | Locally Advanced Disease | Metastatic Disease |
|--|--------------------------|---------------------|
| | No. of patients [%] | No. of patients [%] |
| Gender | | |
| male | 59 [81.94] | 32 [74.41] |
| females | 13 [18.06] | 11 [25.59] |
| Median age (range) in years | 66 (40–86) | 64 (35–83) |
| Body Mass Index | | |
| <25 Kg/m ² | 43 [59.72] | 24 [55.81] |
| ≥25 Kg/m ² | 29 [40.28] | 19 [44.19] |
| Tumor stage | | |
| III | 72 [100] | - |
| IV | - | 43 [100] |
| Tumor site | | |
| Oropharyngeal HPV-positive | 18 [25.00] | 9 [20.93] |
| Oropharyngeal HPV-negative | 16 [22.22] | 10 [23.25] |
| Non-oropharyngeal | 38 [52.78] | 24 [55.82] |
| Smoking habits | | |
| former/current | 63 [87.50] | 33 [76.75] |
| never | 9 [12.50] | 10 [23.25] |
| Alcohol consumption | | |
| yes | 53 [73.61] | 14 [32.56] |
| no | 19 [26.39] | 29 [67.44] |
| Charlson Comorbidity Score | | |
| <9 | 57 [79.17] | 30 [69.77] |
| ≥9 | 15 [20.83] | 13 [30.23] |
| Treatment | | 36 [83.75] |
| Cisplatin-5FU-Cetuximab first-line | - | 7 [16.28] |
| Cisplatin-5FU-Pembrolizumab first-line | - | - |
| Cisplatin-based CRT | 72 [100] | |
| mGPS | | |
| 0 | 19 [26.39] | 12 [27.91] |
| 1–2 | 53 [73.61] | 31 [72.09] |
| KPS | | |
| 100–90 | 53 [73.61] | 26 [60.46] |
| ≤80 | 19 [26.39] | 17 [39.54] |

5FU: 5-Fluorouracil; CDDP: cisplatin; CRT: chemoradiotherapy; HPV: Human Papilloma Virus; KPS: Karnofsky Performance Status; mGPS: modified Glasgow Prognostic Score, which is based on the number of the following adverse factors that are present: C-reactive protein > 10 mg/L, albumin < 3.5 g/dL. * values refer to n. of patients [percentage], unless otherwise specified (e.g., median age).

The prognostic value of the gt-SMI was confirmed both in patients with locally advanced disease treated with definitive chemoradiotherapy [HR 4.18, 95%CI 1.36 to 12.85, p 0.01] (Figure 3A) and in metastatic patients treated with CDDP-5FU-based first-line treatment [HR 2.63, 95%CI 1.26 to 5.49, p 0.01] (Figure 3B) and in both oropharyngeal and non-oropharyngeal cancer patients (HR 5.56 (95%CI 2.07 to 14.96), p 0.0007; and HR 3.04 (95%CI 1.36 to 6.81), p 0.007, respectively) (Figures 3C and 3D, respectively).

To investigate whether gt-SMI remained an independent prognostic factor for OS when other HNSCC-specific prognostic factors (KPS, smoking habit, mGPS, HPV status and treatment setting) were considered, we fitted a multivariate Cox regression model (Table 3). When all the variables were entered into the model, gt-SMI sarcopenia was demonstrated to be an independent prognostic factor together with HPV positivity and treatment setting (HR for gt-SMI low vs. high 3.62 (95%CI 1.78 to 7.37), p 0.0004 (Table 3)).

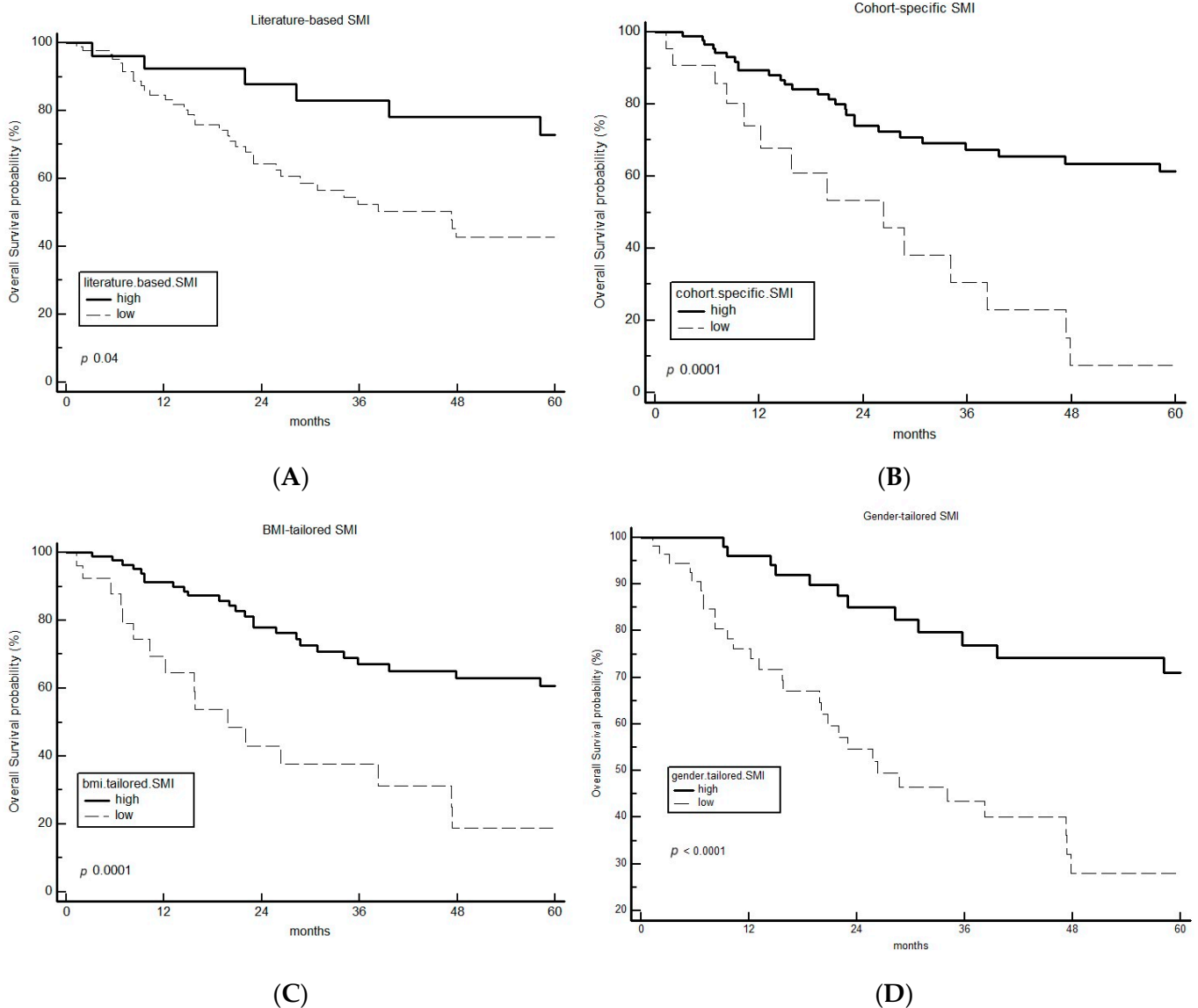


Figure 2. Kaplan–Meier curve of OS for the entire population selected for sarcopenia by using literature [14] (A), cohort-specific (obtained through maximally selected rank statistic) (B) and BMI- (C) and gender- (D) tailored SMI cut-offs. BMI: body mass index; OS: overall survival; SMI: sarcopenic mass index.

Table 2. Univariate Cox-regression analysis for overall survival, chi-square and *p*-values from Log Rank test for comparison between survival curves obtained by using literature, cohort-specific, and BMI- and gender-tailored SMI cut-offs in HNSCC patients.

| SMI | <i>p</i> Value | 24-Month-OS (%) | Univariate HR (95%CI) |
|-----------------------------------|----------------|-----------------|-----------------------|
| Literature-based-SMI low vs. high | 0.04 | 64 vs. 88 | 1.96 (1.03 to 3.74) |
| Cohort-specific-SMI low vs. high | 0.0001 | 53 vs. 74 | 6.61 (2.65 to 16.50) |
| BMI-tailored SMI low vs. high | 0.0001 | 43 vs. 78 | 5.52 (2.40 to 12.73) |
| Gender-tailored SMI low vs. high | <0.0001 | 55 vs. 85 | 3.96 (2.12 to 7.38) |

BMI: body mass index; HNSCC: head and neck squamous cell carcinoma; SMI: sarcopenic mass index.

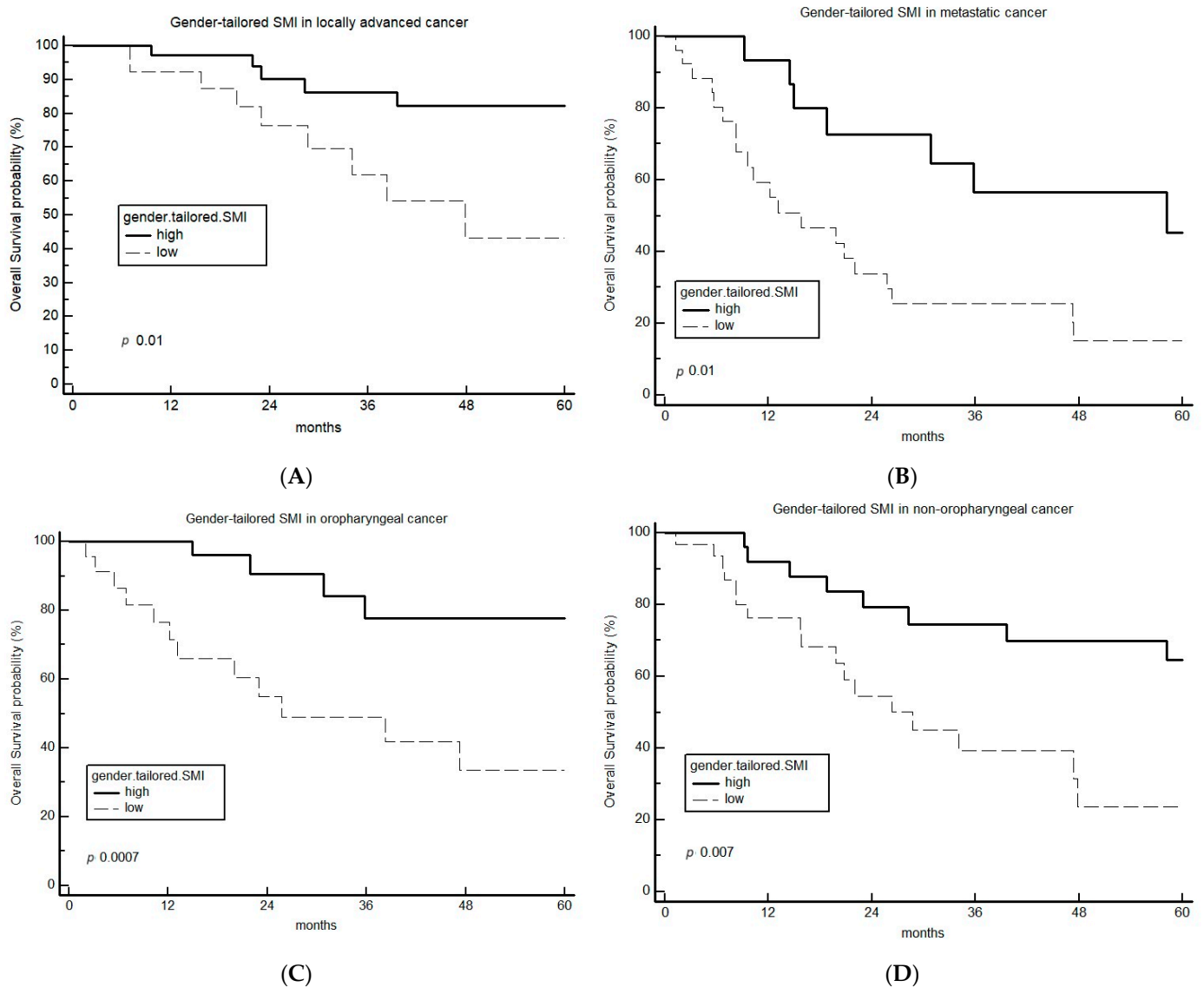


Figure 3. Kaplan–Meier curves of OS according to gender-tailored SMI sarcopenic assessment in locally advanced CRT-treated (A) and metastatic 1st-line-treated (B) patients and in oropharyngeal (C) and non-oropharyngeal (D) primary site. CRT: chemoradiotherapy; OS: overall survival; SMI: skeletal muscle index.

Table 3. Multivariate Cox-regression analysis of several sarcopenic-related prognostic factors for overall survival of HNSCC patients.

| Prognostic Factor | HR | 95% CI | p Value |
|--|------|--------------|---------|
| Gender-tailored SMI (low vs. high) | 3.62 | 1.78 to 7.37 | 0.0004 |
| HPV status (positive vs. negative) | 0.22 | 0.09 to 0.52 | 0.0006 |
| KPS (≤ 80 vs. 100–90) | 0.87 | 0.46 to 1.67 | 0.68 |
| mGPS (0 vs. 1–2) | 0.54 | 0.25 to 1.17 | 0.12 |
| smoking habit (current or former vs. never) | 1.30 | 0.59 to 2.83 | 0.51 |
| Line of treatment (CRT vs. first-line treatment) | 4.79 | 2.47 to 9.29 | <0.0001 |

BMI: body mass index; CI: confidence interval; CRT: chemoradiotherapy; HNSCC: head and neck squamous cell carcinoma; HR: Hazard ratio; KPS: Karnofsky Performance Status; mGPS: modified Glasgow Prognostic Score; SMI: Sarcopenic Mass Index.

4. Discussion

Cancer cachexia, or cancer sarcopenia, is a syndrome that comprises loss of both body weight and muscle mass. In HNSCC patients, it might accompany the disease course for a long time and emerge as a true chronic illness. Moreover, it is often linked to poor prognosis and worse treatment tolerability. The prognostic role of sarcopenia in HNSCC patient candidates for local treatment has been highlighted by two recent meta-analyses demonstrating that sarcopenia represents a poor prognostic factor in patients with localized cancer treated with surgery and/or radiotherapy [25,26].

Sarcopenia assessment is important, especially when cachexia is subclinical [27], and in certain settings, it has a stronger prognostic effect than the primary tumor site and patient performance status [28]. Furthermore, it can be present independently of the basal BMI [28].

CT scan is a feasible alternative to study and measure muscle mass. Although the L3-CT scan slice is the most commonly applied diagnostics for this purpose [29], it is not always available in HNSCC patients, since most scans only report on the cervicofacial area, without considering a whole-body CT scan [30]. In our analysis, C3-slice was used to calculate SMI in accordance with previous research, reporting a strong correlation between the measurement of sarcopenia at the cervical and the lumbar level [23].

In previous works [31–35], SMI threshold values obtained from non-HNSCC patients [18] were applied in HNSCC patients. However, due to the lack of consensus on the use of cut-off values of sarcopenia and the unique characteristics of each patient group, we are in favor of using a disease-specific one.

Wendrich et al. for the first time identified an HNSCC-specific cut-off of sarcopenia by analyzing a cohort of 112 locally advanced HNSCC [16]. Specifically, they demonstrated that $SMI > 43.2 \text{ cm}^2/\text{m}^2$ could predict the dose-limiting toxicity of standard chemotherapy [16]. In our work, we focused on the potential association between sarcopenia as measured using SMI and survival outcome. We observed that $31.50 \text{ cm}^2/\text{m}^2$ was the SMI cut-off value with the greatest discrimination power in terms of OS in our cohort (cs-SMI). Based on our threshold value of sarcopenia, only about one quarter of patients who would have been defined as sarcopenic according to the ‘toxicity’ SMI cut-off by Wendrich et al. [16] were actually found sarcopenic according to the cs-SMI. The lower cutoff for survival deterioration simply indicates that the muscle mass required to be lost before having a significant impact on overall survival is higher than that posing the risk for toxicity.

Considering that skeletal muscle mass can differ in specific patient subgroups, we looked at differences in SMI cut-offs based on BMI (< vs. ≥ 25) and gender (male vs. female).

BMI is a simple tool, representative of adipose tissue, obtainable at baseline visit. Sarcopenia has been demonstrated to have a negative impact on prognosis both in severely cachectic underweight patients with a contemporary loss of fat and lean tissue [31,34,36] and in sarcopenic obese patients [18,37,38]. Lean muscle tissue can vary according to the BMI [31]. Myo-steatosis, defined as the lipid content of skeletal muscle, is increased in obesity, and this might influence the CT-scan based measurement of the lean muscle tissue [39]. Sarcopenic assessment by using SMI cut-offs adjusted for BMI could therefore partly overcome this risk. Indeed, we found that overweight patients may tolerate a higher muscle loss before survival deterioration as compared to non-overweight patients (SMI cut-off of 27.32 and 34.73, respectively), possibly because of a higher energy reserve (so-called obesity paradox) [18].

Gender might be implicated in sarcopenia assessment because of the difference in proportion of specific body components per body surface area between males and females [17]. In an era of personalized medicine, physiological differences between men and women, as well as the potential role played by sex-hormones in tumor biology, should be taken into account [40]. Importantly, a mounting body of evidence is supporting our hypothesis in terms of outcome, treatment benefit and adverse events between men and women in non-sex-related cancers [41]. Discrepancies in gene expression in skeletal muscle tissue as well as in thyroid hormone, estrogen and testosterone levels might result in a

different fiber-type composition and contractility between men and women [42]. Moreover, Park et al., by analyzing the intestinal microbiota using 16S rRNA gene sequencing in more than 1000 Korean patients, showed that sex-specific gut microbiome diversity might be associated with different skeletal mass tissue amounts [43]. Finally, recent reports conducted on community-dwelling adults have evidenced that different risk factors might lead to sarcopenia in men and women, suggesting that gender-tailored preventing activities (particularly resistance training versus nutritional support) should be designed [44]. These data suggest that gender should be considered when muscle tissue measurement is performed.

Only few studies have previously taken into account gender to define sarcopenia in HNSCC patients [45–49]. However, all of them focused on treatment toxicity and did not evaluate survival endpoints. Moreover, threshold values were identified using quintiles and not cut-off optimization methods [45–47]. We focused on identifying specific cutoffs for patients with HNSCC undergoing definitive chemo-radiotherapy or first-line bio-chemotherapy by using distinct thresholds for males and females, since these HNSCC populations might have different risk factors and cancer biology.

Also, Ye et al. [50] recently developed an image-based deep learning platform for SMI calculation to evaluate associations with survival and treatment toxicity outcomes and used separate thresholds for males and females. However, they used literature-based cutoffs [19] established on a mixed population of 250 patients with different types of cancer (mostly colon, rectum and other gastrointestinal or respiratory tract sites.). We consider this a clear limitation given the heterogeneity between different cancer types. The novelty of our study relies on the improved prognostication obtained by tuning the SMI cutoff based on gender and a specific cancer setting.

The high prognostic effect of gt-SMI found in our study (p value < 0.0001) provides support for the interaction between body composition, sex and lean tissue. Interestingly, the prevalence of sarcopenia assessed by gt-SMI cut-off is consistent with that reported by Surov et al. in a recent meta-analysis including 7704 HNSCC patients [7]. We found a superior SMI threshold to define survival-associated sarcopenia in women. No clear explanation could be identified for this finding. A higher sensitivity to muscle mass reduction impacting on survival can be hypothesized in women, but further investigation in this respect is highly warranted.

The prognostic role of sarcopenia defined by gt-SMI was observed regardless of the treatment setting and the primary tumor site (Figure 3). Moreover, gt-SMI retained its independent effect on survival when included in a multivariable model with other well-known HNSCC-specific prognostic factors, including inflammatory biomarkers such as mGPS. Further analyses are needed to confirm that sarcopenia has a prognostic role independently of systemic inflammation, although the strong link between these two conditions has been repeatedly reported in cancer and other chronic diseases [21].

Early identification of sarcopenia and the application of effective rehabilitation programs would be of great value for HNSCC patients. Previous works have shown that physical exercise focused on resistance activity to increase strength and muscle mass, and nutritional interventions such as the increase in protein intake up to 2 g a day and the supplementation of essential amino acids and β -hydroxy β -methylbutyric acid are able to improve the sarcopenic status [4,48,49].

Chemotherapy-dose-limiting toxicities reported in sarcopenic patients [16] also deserve special attention with a need to quickly recognize this status to eventually tailor drug dosing [51]. For example, cisplatin, a key chemotherapeutic drug used in HNSCC, is partly absorbed in the muscle tissue where it is metabolized with mild toxic effects [52]. Charki et al., by analyzing cisplatin pharmacokinetics in 45 HNSCC patients, confirmed that patients with lower muscle mass were more prone to cisplatin-related toxicity because of the higher drug concentration in non-muscle tissues, where it exerted toxic effects [53].

The retrospective nature of our work is a major limitation, but the results should generate a hypothesis in prospectively evaluating our findings in a more defined patient population. Moreover, we included a mixed population of locally advanced and metastatic

HNSCC patients and a distinct analysis with adequate sample size of these two subgroups of patients would be highly desirable. A further drawback is that the cross-sectional area (CSA) to measure SMI was manually derived by reviewing available CT scans. An automated measurement of CSA would be preferable to minimize operator-dependent errors in the analytic procedure. Finally, external validation of the identified SMI cut-offs in larger cohorts is highly recommended.

Sarcopenia has been demonstrated to be strongly related to the immune system [48,54]. Several studies have confirmed a negative prognostic role of sarcopenia in cancer patients treated with immune-checkpoint inhibitors, probably due to increased release of proinflammatory cytokines dysregulating T-cell activity [55]. Further studies are needed to evaluate if sarcopenia could directly affect PD-L1 expression in HNSCC patients, considering the potential therapeutic implications.

5. Conclusions

Our study confirmed the negative correlation between sarcopenia, derived from CT-scans of the head and neck region, and survival in an HNSCC patient cohort, treated with standard chemotherapy +/- RT. Gender should be taken into account in the assessment of sarcopenia, to allow adequate preventive programs as well as to evaluate personalized treatment plans.

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