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Low skeletal muscle mass is a strong predictive factor for surgical complications and a prognostic factor in oral cancer patients undergoing mandibular reconstruction with a free fibula flap

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ABSTRACT

Background: Fibula free flaps (FFF) are effective in accomplishing successful reconstruction for segmental defects of the mandible. Potential risk factors for FFF complications have been described in previous research, e.g. age, comorbidity and smoking. Low skeletal muscle mass (SMM) has shown to be an emerging predictive factor for complications and prognostic factor for survival in head and neck cancer. This study aims to identify the predictive and prognostic value of low SMM for surgical FFF related complications, postoperative complications and survival in patients who underwent mandibular reconstruction with FFF after oral cavity cancer resection.
Materials and methods: A retrospective study was performed between 2002 and 2018. Pre-treatment SMM was measured at the level of the third cervical vertebra and converted to SMM at the level of the third lumbar vertebra (L3). SMM at the level of L3 was corrected for squared height. Low SMM was defined as a lumbar skeletal muscle index (LSMI) below 43.2 cm^2/m^2.
Results: 78 patients were included, of which 48 (61.5%) had low SMM. Low SMM was associated with an increased risk of FFF related complications (HR 4.3; $p = 0.02$) and severe postoperative complications (Clavien-Dindo grade III-IV) (HR 4.0; $p = 0.02$). In addition low SMM was a prognosticator for overall survival (HR 2.4; $p = 0.02$) independent of age at time of operation, ACE-27 score and TNM stage.
Conclusion: Low SMM is a strong predictive factor for FFF reconstruction complications and other postoperative complications in patients undergoing FFF reconstruction of the mandible. Low SMM is also prognostic for decreased overall survival.

Introduction

Fibula free flaps (FFF) have become one of the main preferred choices for reconstruction of major segmental defects of the mandible, e.g. after resection of benign or malignant tumors, osteomyelitis or osteoradionecrosis.

The FFF, due to increasing refinement of surgical techniques, has a high success rate and relatively low risk of complications [1,2]. However, flap complications and loss do occur and can have severe consequences. Various risk factors for flap complications and flap loss have been identified in the literature. These include, patient characteristics and prior medical history, such as age, smoking, history of irradiation, and history of surgery in the area of the anastomosis [3–6]. Another set of risk factors are related to intra-operative and postoperative variables such as, microsurgical technique, ischemia time, intraoperative hypotension, operative time, choice of recipient vessels and anticoagulant administration [7–9].

In the last years loss of skeletal muscle mass (SMM), also known as sarcopenia, has been identified as an increasingly important independent risk factor of both survival and surgical outcomes in cancer patients [10–13]. Sarcopenia has been defined by consensus statements as a syndrome of progressive and generalized loss of skeletal muscle

Abbreviations: FFF, free fibula flap; SMM, Skeletal muscle mass; HNC, Head and neck cancer; OPSCC, Oropharyngeal squamous cell carcinoma; C3, Third cervical vertebra; L3, Third lumbar vertebra; CSMA, Cross-sectional muscle area; HU, Hounsfield Unit; Lumbar SMI, Lumbar skeletal muscle index; OS, Overall survival; DFS, Disease free survival; RCT, Randomized controlled trial

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mass and function [14,15].

In cancer patients, sarcopenia has been associated with a higher incidence of postoperative complications, chemotherapy related toxicity, longer hospital stays and lower disease-free and overall survival [12–18]. The relationship between increased postoperative complications and its negative influence on survival has been demonstrated in various surgical fields such as hepato-biliary, colon and lung surgery [12,16,19–21]. In oncologic head and neck surgery, the predictive value of low SMM for surgical complications and survival has not yet been established as thoroughly.

SMM is rarely assessed as a routine preoperative clinical measure. SMM is usually assessed on computer tomography (CT) scan of the abdomen at the level of the third lumbar vertebra (L3). However abdominal CT scanning is not routinely included in preoperative management protocols in patients with head and neck cancer (HNC) and is often only available in a subset patient group with advanced disease and increased risk for distant metastasis. Instead, SMM assessment at the level of the third cervical vertebra (C3) has been proven as a viable alternative [22].

In this study SMM is measured using CT or MRI at the level of C3. The association of low SMM with surgical complications of FFF and other postoperative complications in patients undergoing FFF reconstruction of the mandible after composite resection for malignant oral cavity tumors is investigated. Additionally its impact on overall survival in these patients is studied.

Material and methods

Ethical approval

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 17–365/C). All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients and study design

A retrospective study was performed of all consecutive patients who had undergone reconstruction of segmental mandibular defects with free fibula flaps between 2002 and 2018 at the Department of Oral and Maxillofacial Surgery and the Department of Head and Neck Surgical Oncology, of the University Medical Center, Utrecht, the Netherlands. A previously published article by our group has studied early and late surgical complications in a part of these patients [8]. Patients were included if they had recent (less than 1 month before surgery) imaging (CT or MRI scans) of the head and neck. Clinical and demographic data were collected from the medical records. Data collected included age at reconstruction, sex, smoking history, diagnosis, localization of defect, comorbidity as expressed by the Adult Comorbidity Evaluation-27 (ACE-27) score, history of radiation therapy, flap ischemia time, occurrence of complications and survival data.

All surgical procedures were performed by head and neck surgeons who are experienced in microvascular surgery. Details of surgical procedures are described in a previously published article by the same group of surgeons [8]. All patients were discussed in a tumor board meeting and underwent pre-operative angiography and Doppler examination of the lower leg to assure adequate blood supply to the foot and skin paddle.

FFF complications were defined as all complications concerning the flap, such as partial skin paddle necrosis, dehiscence, venous congestion or vascular thrombosis and failure.

All non-flap related postoperative complications were scored according to the Clavien-Dindo classification of surgical complications [23]. Complications with a Clavien-Dindo grade III-IV were graded as severe complications.

Survival data was retrieved from patients' medical record. Patients were regularly seen in the first 5 years of follow-up after reconstruction. We defined overall survival (OS) as the time between the date of diagnosis and date of death or last follow-up, whichever occurred first. We defined disease-free survival (DFS) as the time between the date of diagnosis and date of recurrence or last follow-up, whichever occurred first.

Body composition measurement

SMM was measured as muscle cross-sectional area (CSA) on pretreatment CT or MRI imaging of the head and neck area at the level of the third cervical vertebrae (C3). The axial slide of the imaging, which showed both transverse processes and the entire vertebral arc, was selected for segmentation of muscle tissue. For CT imaging, muscle area was defined as the pixel area between the radiodensity range of −29 and +150 Hounsfield Units (HU), which is specific for muscle tissue. For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. The CSA was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoideus muscles. Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (Tomovision, Canada) by a single researcher (EA) who was blinded for patient outcomes. An example of segmentation at the level of C3 is shown in Fig. 1.

CSA at the level of C3 was converted to CSA at the level of L3 using a previously published formula (1) [22]. The lumbar skeletal muscle

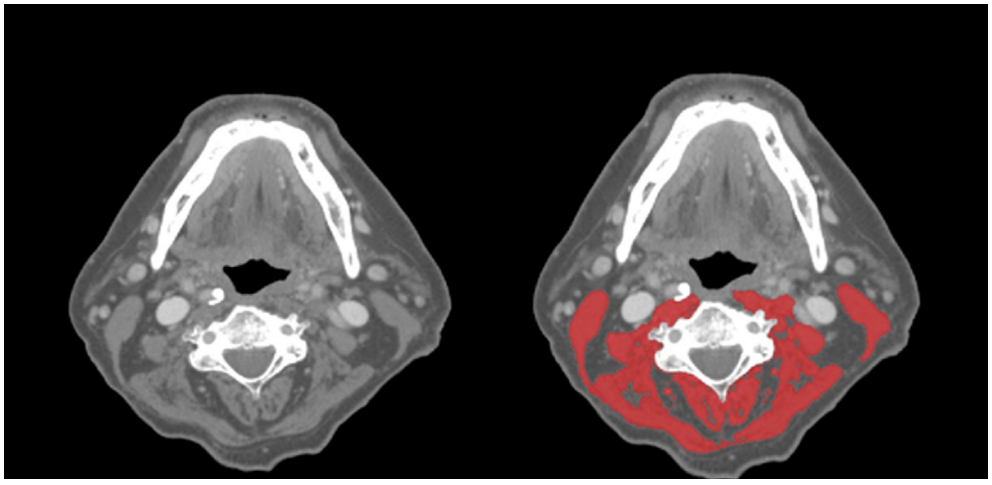


Fig. 1. Segmentation of skeletal muscle tissue at the level of the third cervical vertebra (C3). This figure displays two identical axial CT-slides at the level of C3; in the left axial slide muscle tissue is unsegmented. The right CT slide shows both sternocleidomastoideus and paravertebral muscles segmented in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

index (LSMI) was calculated by correcting SMM at the level of L3 for squared height as shown in formula (2). Low SMM was defined as a LSMI below 43.2 cm^2/m^2, this cutoff value was determined in a separate cohort of head and neck cancer patients [18]

$$CSA\ at\ L3\ (cm^2) = 27.304 + 1.363 * CSA\ at\ C3\ (cm^2) - 0.671 * Age\ (years) + 0.640 * Weight\ (kg) + 26.442 * Sex\ (Sex = 1\ for\ female\ and\ 2\ for\ male) \quad (1)$$

$$Lumbar\ SMI\ (cm^2/m^2) = CSA\ at\ L3/length\ (m^2) \quad (2)$$

Statistical analysis

Data analyses was performed using IBM SPSS statistics 25. Descriptive statistics for continuous variables with a normal distribution were presented as mean with standard deviation (SD). Variables with a skewed distribution were presented as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Survival was visualized using Kaplan Meier survival curves and number at risk tables. Cox proportional hazard regression model was used for univariate and multivariate analysis of survival and surgical complications. Covariates used in the multivariate analysis were selected based on clinical significance or selected based on statistical significance ($p < 0.05$) in univariate cox regression analysis. Statistical significance was evaluated at the 0.05 level using two-sided tests.

Results

Patient characteristics

Descriptive data are presented in Table 1. In total, 78 patients were included. Of these patients, 75 (96.1%) patients had squamous cell carcinoma, 2 (2.6%) patients had sarcoma and 1 (1.3%) patient had adenoid cystic carcinoma. Low SMM was identified in 48 (61.5%) patients. Patients with low SMM were more likely to be female and to have a normal BMI.

Post-operative complications

All postoperative complication are described in Table 2. Flap complications occurred in 18 (23.1%) patients, of which 13 (72.2%) occurred in patients with low SMM.

Four of these patients finally necessitated flap revision due to vascular congestion or thrombosis and in 1 patient the flap was not salvageable and was lost.

In multivariate Cox regression analysis, low SMM was a significant predictive factor for FFF complications (HR 4.3; 95% CI 1.30–14.24; $p = 0.02$) independent of age at time of operation, ACE-27 score, ischemic time and smoking.

In total, 61 (78.2%) patients had non-flap related postoperative complications, of which 25 (32.1%) were classified as severe (Clavien-Dindo III-IV), 19 of these patients (67%) had low SMM.

Low SMM was also a significant predictive factor for postoperative complications Clavien-Dindo grade III-IV (HR 4.03; 95% CI 1.28–12.74 $p = 0.02$), again independent of age at time of operation, ACE-27 score, ischemic time and smoking.

Survival analysis

The median follow up time was 36 months (IQR 13–62 months). At the time of concluding this study, 38 (48.7%) patients of the cohort had died of any cause and 40 (51.3%) were alive.

As seen in Fig. 2, patients with low SMM showed a significant lower median OS (26 months; IQR 10–62) compared to patients without low SMM (48 months; IQR 20–79) (Log rank $\chi2 = 4.76$; $p = 0.03$). Patients with low SMM had a significantly decreased 5-year and 10-year OS rate compared to patients without low SMM (41% and 9% versus 71% and 54%, respectively; $p = 0.03$). No significant differences were seen in median DFS between patients with low SMM (22 months; IQR 6–61) and patients without low SMM (48 months; IQR 20–79) (Log rank $\chi2 = 2.54$; $p = 0.11$) (Fig. 3).

Table 3 shows the results of the univariate and multivariate Cox regression analysis for OS and DFS. In univariate Cox regression analysis, low SMM and mild-moderate ACE-27 score were significant prognosticators for OS. In multivariable Cox regression analyses

Table 1
General characteristics of patients with and without low SMM.

Variables	All patients N = 78	Low SMM N = 48	Without low SMM N = 30	*p-value*
Sex (n, %)				
Female	24 (30.8)	24 (50.0)	–	**0.0001****
Male	54 (69.2)	24 (50.0)	30 (1 0 0)	
Age (years) (M, SD)	62.4 (10.2)	63.3 (10.9)	60.9 (8.8)	0.31
BMI (kg/m^2) (n, %)				**0.004****
< 18.5	20 (25.6)	8 (17.6)	12 (40.0)	
18.5–24.9	27 (34.6)	27 (56.3)	–	
25–29.9	26 (33.3)	12 (25.0)	14 (64.7)	
≥30	5 (6.4)	1 (2.1)	4 (13.3)	
Smoker (n, %)				0.82
No	32 (41.0)	19 (39.6)	13 (43.3)	
Yes	46 (59.0)	29 (60.4)	17 (56.7)	
ACE-27 score (n, %)				0.86
Non	28 (35.9)	18 (37.5)	10 (33.3)	
Mild	19 (24.4)	12 (25.0)	7 (23.3)	
Moderate	27 (34.6)	15 (31.3)	12 (40.0)	
Severe	4 (5.1)	3 (6.3)	1 (3.3)	
Diagnosis				0.29
Squamous cell carcinoma	75 (96.1)	46 (95.8)	29 (96.7)	
Osteosarcoma	2 (2.6)	2 (4.2)	–	
Adenoid cystic carcinoma	1 (1.3)	–	1 (3.3)	
Tumor stage (n, %)				
T1	1 (1.3)	1 (2.1)	–	0.46
T2	4 (5.1)	2 (4.2)	2 (6.7)	
T3	4 (5.1)	1 (2.1)	3 (10.0)	
T4a	67 (85.9)	42 (87.5)	25 (83.3)	
T4b	2 (2.6)	2 (4.2)	–	
Nodal stage (n, %)				0.35
N0	37 (47.4)	21 (43.8)	16 (53.3)	
N1	15 (19.2)	12 (25.0)	3 (10.0)	
N2a	–	–	–	
N2b	19 (24.4)	10 (20.8)	9 (30.0)	
N2c	7 (9.0)	5 (10.4)	2 (6.7)	
N3	–	–	–	
TNM stage (n, %)				0.10
I	1 (1.3)	1 (2.1)	–	
II	3 (3.8)	2 (4.2)	1 (3.3)	
III	3 (3.8)	–	3 (10)	
IV	71 (91.0)	45 (93.8)	26 (86.7)	
Localization defect (n, %)				0.08
Lateral mandible	30 (38.5)	12 (25.0)	18 (60.0)	
Lateral mandible with hemi-symphysis	13 (16.7)	8 (16.7)	5 (16.8)	
Lateral mandible with total symphysis	15 (19.2)	12 (25.0)	3 (10)	
Bilateral mandible with total symphysis	17 (21.8)	13 (27.1)	4 (13.3)	
Flap ischemic time (M, SD)	2.5 (0.6)	2.45 (0.7)	2.6 (0.6)	0.26

** Correlation is significant at the 0.01 level (2-tailed).

Table 2
All postoperative complications.

Postoperative complications	All patiënts N = 78 N (%)	Low SMM N = 48 N (%)	Without SMM N = 30 N (%)
CD 0	17 (21.8)	9 (18.8)	8 (26.7)
CD I-II	36 (46.2)	20 (41.7)	16 (53.3)
CD III-IV	25 (32.1)	19 (39.6)	6 (20.0)
FFF related complications			
Congestion	5	5 (38.5)	0 (0.0)
Partial skin paddle necrosis	6	3 (23.1)	3 (60.0)
Flap dehiscence	4	2 (15.4)	2 (40.0)
Thrombosis	2	2 (15.4)	0 (0.0)
Failure	1	1 (7.7)	0 (0.0)

corrected for age at time of operation, ACE-27 score and TNM stage, low SMM remained a significant negative prognostic factor for OS (HR 2.4; 95% CI 1.1–5.1; p = 0.02).

Discussion

Low skeletal muscularity has been associated with increased mortality of all cause in the elderly [24–26]. The prognostic significance of sarcopenia on survival and treatment complications is of increasing interest in cancer patients. Sarcopenia has been studied broadly in patients with colorectal, esophageal and lung cancers. In these groups of cancer patients, it is associated with increased surgical morbidity and mortality [12,27,28].

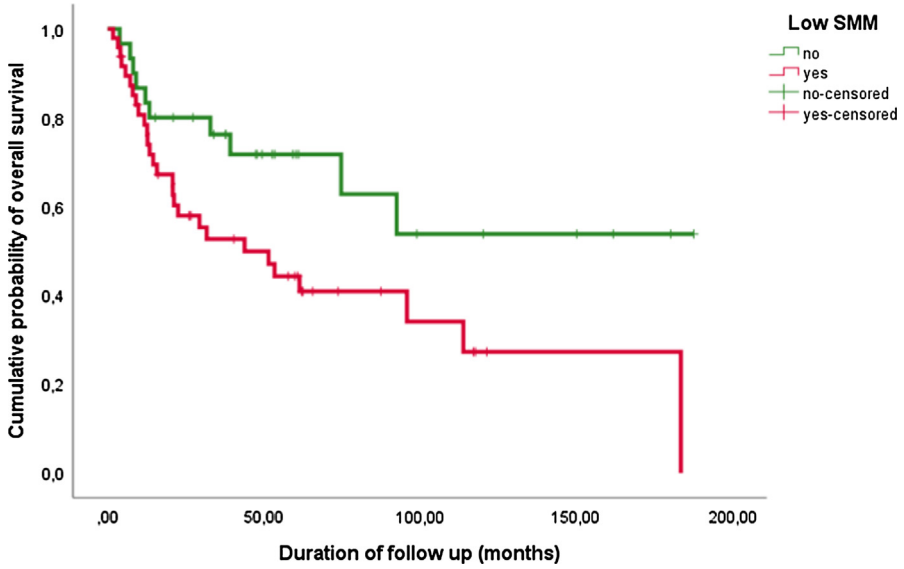
To the best of our knowledge this is the first study to study the influence of SMM on microvascular free flap reconstruction outcomes in patients undergoing surgery for oral cavity cancer.

In this study low SMM was a powerful independent and negative predictive factor for the occurrence of flap failure and complications after mandibular reconstruction in HNC patients.

Patients with skeletal muscle depletion were significantly more likely to develop early or late flap related complications such as flap dehiscence, skin island necrosis, thrombosis and failure. Low SMM was also seen as a risk factor for patients in this study cohort to develop severe (non-flap related) postoperative complications, which were graded by the Clavien-Dindo Classification.

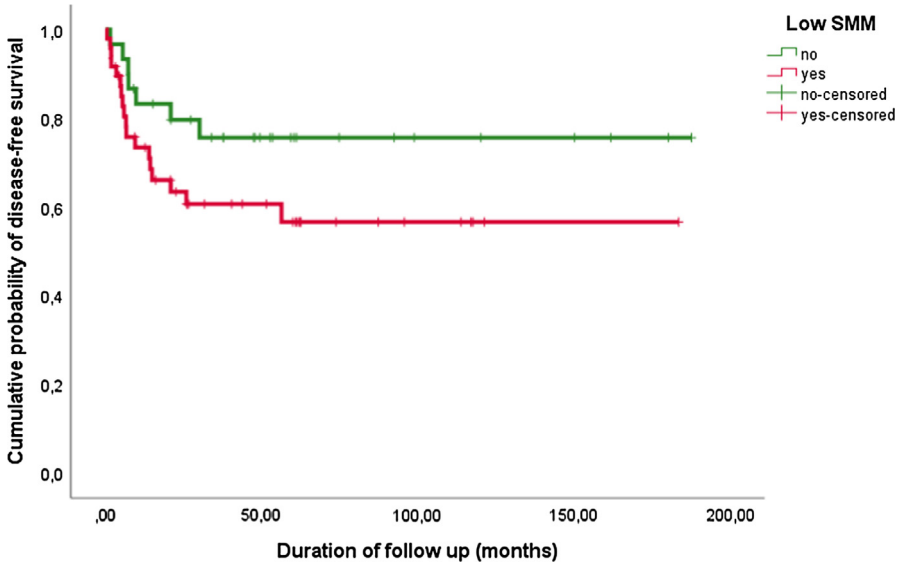
In line with this study are recent studies that have investigated the effects of low SMM in HNC patients undergoing total laryngectomy [29,30]. These studies reported prolonged hospital stay, wound related complications, pharyngo-cutaneous fistula and diminished overall survival. Low skeletal muscularity was also found to be an independent prognostic factor influencing OS, independent of HPV status, in patients with advanced oropharyngeal cancer [31,32]. In patients undergoing primary chemoradiotherapy with advanced stage head and neck squamous cell carcinoma it is associated with increased chemotherapy dose-limiting toxicity (CLDT) and decreased OS [18].

The exact underlying mechanism of how preoperative sarcopenia attributes to increased microsurgical flap complications and other adverse surgical outcomes is still subject to further investigation. Low skeletal muscularity is a multifactorial syndrome which is induced by heterogeneous conditions which can be cancer-specific and non-cancer-specific. Cancers constitute a micro environment of inflammation induced by the presence of inflammatory cells, chemokines and cytokines, a phenomenon known as cancer-related inflammation [33]. Feliciano et al. have studied in a large cohort of colorectal cancer patient the association between sarcopenia and systemic inflammation measured by the neutrophil-to-lymphocyte (NLR) ratio [34]. They have found that an increased NLR ratio is associated with sarcopenia and hypothesized that this is an intertwined mechanism in which inflammation underlies muscle wasting and is in itself reinforced by it. These inflammatory mediators promote a catabolic mechanism in which there is a rise in protein breakdown coupled with decreased synthesis. This can lead to increased muscle wasting due to myocyte apoptosis and decreased regeneration [35,36]. Low SMM may therefore also impair wound healing and increase wound related complications



	T=0	T=12	T=24	T=36	T=48	T=60	T=72	T=84	T=96	T=108	T=120
Low SMM	48	35	25	20	18	14	8	7	5	5	2
Without low SMM	30	26	22	19	14	10	8	7	6	5	5

Fig. 2. Kaplan Meier curves shows a significant decreased overall survival for patients with low SMM compared to patients without low SMM (Log rank test $\chi 2 = 4.8$, p = 0.03).



	T=0	T=12	T=24	T=36	T=48	T=60	T=72	T=84	T=96	T=108	T=120
Low SMM	48	31	23	18	16	13	8	7	5	5	2
Without low SMM	30	24	21	18	14	10	8	7	6	5	5

Fig. 3. Kaplan Meier curves show no significant decreased disease specific for patients with low SMM compared to patients without low SMM (Log rank test $\chi 2 = 2.5$, $p = 0.11$).

[29].

Success of microvascular free flaps strongly depend on an environment of low thrombogenicity, favorable endothelialization at the anastomotic sites and a wound microenvironment where essential healing processes such as fibroblast collagen synthesis and the production of reactive oxygen species can be unhindered [37,38]. An increased inflammatory microenvironment impedes these processes and may consequently be deleterious to the outcomes of microsurgical flaps.

In this study, sarcopenia had a significant prognostic impact on OS but not on disease free survival. A recent study by Tamaki et al. and a study by Grossberg et al. showed also sarcopenia's negative impact on OS [31,39]. DFS was not found to be affected by sarcopenia. However, both studies found an increase in disease recurrence in sarcopenic patients. This may be attributed to a relatively new insight that skeletal muscle mass may be considered to be an endocrine organ. Different research groups have displayed that skeletal muscle cells secrete cytokines, known as myokines [40,41]. These myokines have been shown induce apoptosis in the cells of some tumors [41,42]. A myokine of specific interest has been interleukin-6. Pedersen et al. demonstrated its antitumorigenic effects in mouse models through increased mobilization of natural killer cells in tumor surveillance [42].

Preventing head and neck cancer-related sarcopenia is challenging, due to high risk of malnutrition in this patient population secondary to odynophagia, dysphagia, aspiration and prior radiotherapy exposure. Yet, it is of interest to study if interventions aimed at preservation of muscle mass such as multimodal preoperative rehabilitation programs that include physical therapy and nutritional intervention before surgery are effective in improving SMM and outcomes. For instance, exercise and nutrition intervention during and after radiotherapy in HNC patients is shown to be feasible and is effective in diminishing muscle

Table 3
Univariate and multivariate Cox regression analysis: overall survival and disease free survival.

OVERALL SURVIVAL							DISEASE FREE SURVIVAL					
Variables	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95%CI	p-value	HR	95% CI	p-value
Low SMM	2.2	1.1–4.5	**0.03***	2.4	1.1–5.1	**0.02***	2.0	0.8–4.8	0.12	**1.9**	**0.8–4.6**	**0.18**
Age (years)	1.0	1.0–1.1	0.41	1.0	1.0–1.0	0.90	1.0	1.0–1.0	0.73	1.0	1.0–1.0	0.98
ACE-27												
Non	Ref			Ref			Ref			Ref		
Mild	3.3	1.3–8.4	**0.01***	3.3	1.2–9.2	**0.02***	1.5	0.5–4.2	0.48	1.3	0.4–4.1	0.69
Moderate	2.4	1.0–5.5	**0.04***	2.5	1.2–6.1	0.05	1.5	0.6–3.7	0.43	1.4	0.5–3.8	0.47
Severe	1.9	0.4–9.1	0.41	1.6	0.3–7.4	0.58	1.0	0.1–7.8	0.98	0.8	0.1–6.8	0.88
TNM stage												
I	Ref			Ref			Ref			Ref		
II	0.2	0.0–3.5	0.29	0.5	0.0–8.7	0.61	0.4	0.0–6.7	0.54	0.60	0.0–11.8	0.73
III	1.0	0.0–∞	0.98	–	–	–	–	–	–	–	–	
IV	0.4	0.1–3.3	0.44	1.0	0.1–8.0	1.00	0.4	0.1–2.9	0.35	0.50	0.1–4.4	0.54

loss [43]. A randomized controlled trial (RCT) in patients with lung cancer undergoing 1-week intensive rehabilitation, which consisted of exercise endurance and resistance training prior to lung cancer lobectomy, showed a significant decrease in hospital stay after surgery, and less severe pulmonary postoperative complications. Though information on pre-treatment SMM was not provided [44].

Because of increasing surgical experience and technological advancement, the success rate of microvascular free tissue transfer is reported to be above 95% [9]. Still, flap failures have dreaded consequences for both functional and cosmetic outcomes and can have a devastating psychological impact on patients.

The selection of an optimal flap for the reconstruction of a mandibular defect depends on site-specific factors such as the length and location of the segmental defect, extent of the external cutaneous defect and volume of the residual tongue among others [45]. Also, patient specific factors play a role in the decision-making process of optimal flap choice. Determining sarcopenia could provide valuable information to aid surgical decision analysis and whether or not to opt for a direct microvascular reconstruction.

Exact definitions and cutoff values for sarcopenia differ between studies and a uniformed definition has not been stated for patient groups and ethnicities. The cutoff value to define low SMM in our study, is based on the SSM cutoff value developed in a separate cohort of patients with HNC in The Netherlands [18]. To our knowledge, no sex-specific cut-off values to define low SMM have been established in head and neck cancer patients.

In spite of the different cutoff values used throughout the literature for sarcopenia, low muscularity seems to be strongly linked with poorer surgical outcomes and decreased survival in cancer patients.

In this study, SMI at the level of C3 was measured, since imaging at this anatomical site is almost always readily available as part of a head and neck cancer workup. We included both CT scans and MRI scans of the head and neck area to evaluate SMM, since some patients did not have CT scans as part of their workup. Most published articles on SMM in patients with cancer is performed using CT imaging. However, the CT measurement method for SMM was formulated on MRI-based research [13,46]. Since both methods are accurate for evaluating SMM, there should be no difference between CT imaging and MRI for assessing SMM.

The retrospective design and the relatively limited number of cases, 78 patients in 16 years, are limitations of this study. The present study, however is the only report that has sought to examine the impact of skeletal muscle mass on fibula free flap reconstruction, but it remains a single-center analysis. Therefore, other independent confirmatory studies would be required before extending these findings into surgical treatment planning. One other essential limitation is that cancer-related skeletal muscle depletion is a continuous process, this study only assessed SMM preoperatively, there at a single point in time. Changes in SMM can occur over time and its relationship with cancer survival is of considerable interest and should be the subject of future research.

In conclusion, low SMM at initial diagnosis had a negative effect on fibula flap related complications, other postoperative complications and OS in patients undergoing resection for locally advanced oral cavity cancers. Future prospective studies should be performed to find an effective prehabilitation strategy to improve skeletal muscle status and to establish if SSM might be part of a selection plan for surgical reconstruction of large oromandibular defects.

Informed consent

All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A formal informed consent procedure was waived due to the retrospective nature of this study. The design of this study was approved by the Medical Ethical Research Committee of our center (approval ID 17–365). All data were handled according to general data protection regulation (GDPR).

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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