Sarcopenia and its impact in head and neck cancer treatment

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Purpose of review
The aim of this review is to discuss recent studies on the assessment of sarcopenia and its predictive and prognostic value in head and neck cancer (HNC) patients.

Recent findings
There is increasing evidence that low skeletal muscle mass (SMM), often named sarcopenia, can easily be assessed on cross-sectional imaging of the head and neck and is associated with chemotherapy (dose limiting) and radiotherapy toxicity and survival.

Summary
SMM measurement at the level of the third cervical vertebra (C3) on routine computed tomography and magnetic resonance imaging is easy and robust to perform. Several studies have shown a significantly higher incidence of cisplatin dose limiting toxicity in HNC patients with a low SMM. In HNC patients pretreatment low SMM is associated with acute and late toxicity and adverse events of radiotherapy, complications of major head and neck surgery and decreased disease-specific and overall survival. This information can be used for individualized treatment planning in HNC patients with low SMM.

Keywords
head and neck cancer, sarcopenia, skeletal muscle mass, survival, toxicity

INTRODUCTION

Over the last decade, research on body composition has gained attention in oncological and surgical research. Body composition consists of fat mass and fat-free mass also called lean body mass. The skeletal muscle mass (SMM) is the largest contributor to the lean body mass. Low SMM is also often referred to as sarcopenia. Sarcopenia lends its name from the Greek words 'sarx' meaning flesh and 'penia' meaning lack of [1]. Sarcopenia can be primary due to aging and secondary due to an underlying disease. The proposed definition of sarcopenia of the European Working Group on Sarcopenia in Older People (EWGSOP) requires a decrease in SMM and a decrease in muscle function, e.g. hand grip strength or gait speed [2,3]. Also the Sarcopenia Definition and Outcomes Consortium (SDOC), supports the use of both SMM and measures of muscle function for defining sarcopenia [4]. Muscle function is not frequently measured, whereas SMM can often be retrospectively determined. Therefore, the terms sarcopenia and low SMM are often used interchangeably in the literature. Sarcopenia can occur across all body mass index (BMI) categories. In the elderly, sarcopenia is a risk factor for various adverse outcomes including physical disability, decreased quality of life, and ultimately early death. Independent of age, sarcopenia can exist secondary to chronic systemic inflammation, malnutrition, and immobilization. In cancer patients, a risk factor for secondary sarcopenia inherently present is the malignant tumor and its microenvironment, which may trigger a chronic systemic inflammatory process in the body as a reaction to the tumor [2]. Head and neck cancer (HNC) patients are at risk for secondary sarcopenia due to the tumor site which may lead to dysphagia and difficulty of swallowing, leading to malnutrition and a catabolic state [5]. SMM does not simply reflect physical condition, but acts also as an endocrine organ that secretes several specific cytokines, also called myokines.

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KEY POINTS

- Skeletal muscle mass can be assessed on routinely performed CT or MRI of the head and neck by an easy and robust method.
- Low skeletal muscle mass is associated with cisplatin (dose limiting) toxicity.
- Patients with low skeletal muscle mass experience more acute and late toxicity of radiotherapy.
- Skeletal muscle mass measurement can identify frail patients.
- Low skeletal muscle mass is associated with decreased disease free and overall survival in head and neck cancer patients.

In recent years, body composition research in cancer patients has accelerated due to the use of routinely performed, diagnostic computed tomography (CT) or magnetic resonance imaging (MRI) for quantification of the different body compartments. Evidence is mounting that an abnormal body composition, in specific a low SMM, is an adverse predictive and prognostic factor in HNC patients [6].

SKELETAL MUSCLE MASS MEASUREMENT METHODS

There are several methods to measure body composition and SMM. These methods include 'dual-energy X-ray'-absorptiometry scan, bioelectrical impedance analysis and imaging techniques including CT and MRI [7,8].

Cross-sectional muscle area (CSMA) measurement on CT at the level of the third lumbar vertebra (L3) is highly associated with whole body total skeletal muscle volume and became the most often used measurement method for SMM [9]. To correct for person's height CSMA is adjusted for squared height to calculate the skeletal muscle index (SMI; cm^2/m^2) [10]. Because abdominal CT imaging is not routinely performed in HNC patients and is often only available in patients with locally advanced disease, Swartz *et al.* developed a novel method for SMM assessment using a single CT slice at the level of the third cervical vertebra (C3), which is featured on regular head and neck CT imaging. See for examples of segmentation of SMM tissue at level C3 (paravertebral and sternocleidomastoid muscles) Fig. 1. A good correlation between CSMA at the level of C3 and L3 was found ($r = 0.785$). A multivariate formula to estimate the CSMA at the level of L3 from the CSMA at the level of C3 including gender, age, and weight resulted in a very high correlation ($r = 0.891$) between the estimated CSMA at the level of L3 and the actual CSMA at the level of L3 [11]. This method was recently validated [12▪] and had a very good intraobserver and interobserver agreement [13,14]. A strong correlation of predicted and measured L3 CSMA was also found using slightly different prediction formulas [15,16]. Although recently this strong correlation was questioned for patients with low SMI [17], a study with 200 Dutch HNC patients showed for patients with low and normal SMI a similar high correlation between estimated and measured SMI at L3 [18]. For CSMA measurements at the level of C3 on CT and MRI a high correlation (intraclass correlation

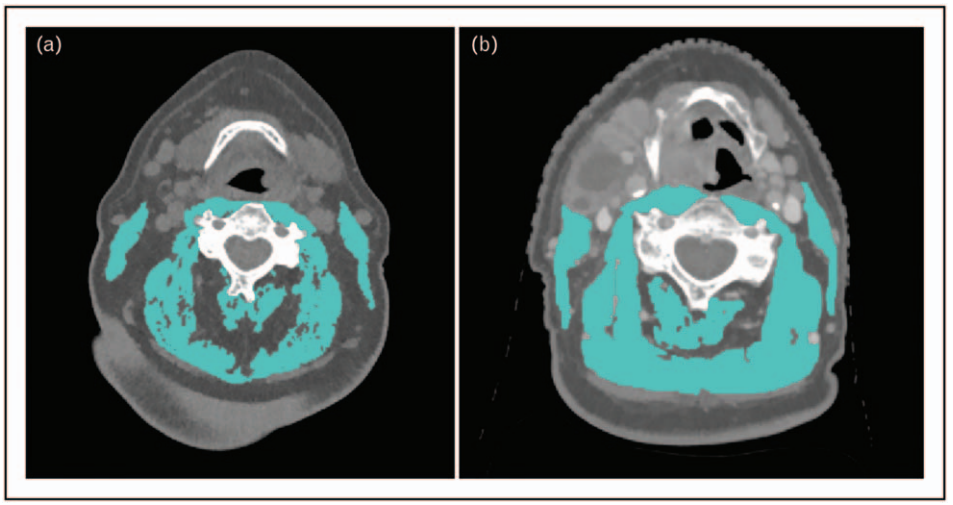

FIGURE 1. Examples of segmentation of skeletal muscle mass tissue (paravertebral and sternocleidomastoid muscles) at level C3: (a) low and (b) normal skeletal muscle mass.

coefficient (ICC) = 0.97) was found [19] and recently confirmed ($r = 0.958–0.998$) [18]. Also for CSMA measurement on MRI, an excellent intra-observer agreement was found (ICC 0.961–0.998) [20]. Several cut-off values for low SMI exist, most of which have not been formulated in HNC patients [10,21–25]. Future research is needed to identify an optimal cut-off value for low SMI in HNC patients that is most prognostic and predictive of clinically relevant adverse outcomes. Nevertheless, the above findings allow for easy and robust SMM measurements at level C3 on routinely performed CT or MRI for HNC diagnosis and treatment evaluation.

TOXICITY OF ANTI-CANCER DRUGS

Low SMM is increasingly recognized for its value to predictive adverse events in cancer patients. In specific, the predictive value of low SMM has been demonstrated for anticancer drug toxicity in a variety of cancer types and anticancer drugs [26]. Several studies investigating the predictive value of low SMM on dose limiting toxicity (DLT) in HNC patients are performed.

Wendrich *et al.* [22] were the first to show that low SMM is a predictive factor for chemotherapy DLT in 112 patients with locally advanced HNC treated with high-dose cisplatin-based chemoradiotherapy (CRT). Chemotherapy DLT was defined as any toxicity resulting in any dose-reduction of $\geq$50% (e.g. due to neutropenia or nephrotoxicity), a postponement of treatment of $\geq$4 days (e.g. in the case of bone marrow suppression) or a definite termination of chemotherapy after the first or second cycle of therapy. Patients with low SMM (54.5%) experienced DLT more frequently than patients with normal SMM (44.3% vs. 13.7%) and received a higher dose per lean body mass. A multivariate analysis, low SMM was independently inversely associated with DLT (OR 0.93, 95% CI: 0.88–0.98). Patients experiencing DLT had a significantly lower overall survival (OS) than patients who did not (mean 36.6 vs. 54.2 months) [22]. In a more recent study of 153 consecutive HNC patients treated with primary chemoradiotherapy with high-dose cisplatin, any toxicity leading to a cumulative cisplatin dose below 200 mg/m^2 was defined as DLT. Patients with low SMM (54.9%) experienced significantly more DLT than patients with normal SMM (35.7% vs. 10.1%). Low SMM (OR 3.99, 95% CI: 1.56–10.23) was an independent predictor for DLT. Although patients with low SMM did not have a decreased OS, patients who experienced DLT did have a significantly decreased OS (HR 2.11) [27]. In 300 HNC patients treated with definitive chemoradiotherapy, patients with low SMI were more likely to experience moderate to severe toxicities and more treatment gaps [28]. In 82 nasopharyngeal cancer patients treated by concurrent platin-based chemoradiotherapy, low SMM (91%) was associated with DLT defined as the need to reduce the drug dose, to delay, or definitively to discontinue the protocol (OR 4.00, 95% CI: 1.20–13.36) [29]. Also, Shodo *et al.* reported that low SMM (OR 22.33, 95% CI 1.29–386.31) and age over 70 years (OR 26.67, 95% CI 1.56–456.62) were significant predictors of incompletion of concurrent chemoradiotherapy in 41 male HNC patients [30]. Despite slightly different definitions of low SMM and DLT, the conclusions of aforementioned studies are comparable: a significant higher incidence of cisplatin DLT in low SMM patients and a significantly lower OS in patients experiencing DLT.

In contrast with cisplatin DLT, low SMM has no predictive value for cetuximab DLT and immune-related adverse events of immune checkpoints inhibitors in HNC patients [31,32].

An explanation for the relationship between low SMM and toxicity might be that hydrophilic drugs, including cisplatin, mainly distribute into the fat-free body mass of which SMM is the largest contributor. Cisplatin is dosed based on body surface area and not body composition. It is hypothesized that an altered distribution of cisplatin, which is reflected by differences in cisplatin plasma concentrations, could explain why patients with low SMM are more prone to experience cisplatin toxicity. In a prospective study by Chargi *et al.* [33], a significant relationship between cisplatin pharmacokinetics and SMM, weight, fat-free mass, and body surface area was found in 45 HNC patients. In a simulation, patients with a low SMM (<25.8 kg) were predicted to reach higher-bound cisplatin concentrations. The higher concentration of bound cisplatin could be seen as a reflection of the smaller volume of distribution. Because of this smaller volume, less tissue is available where, the hydrophilic and highly reactive cisplatin can distribute to and bind with, without inducing toxicity [33].

RADIOTHERAPY

In a systematic review of the literature published (11 studies) between January 2004 and June 2019, low SMM was independently associated with prolonged radiotherapy breaks and chemotherapy-related toxicities in 3,461 HNC patients who completed radiotherapy of curative intent with or without other treatment modalities. Pretreatment sarcopenia was independently associated with prolonged radiotherapy breaks and chemotherapy-related toxicities [34].

In 60 patients with oral cancer undergoing adjuvant concurrent chemoradiotherapy, low SMM

(18.3%) was an independent risk factor for severe oral mucositis (HR 18.1, 95% CI: 3.4–96.0) [35]. On the contrary, Huang *et al.* could not find an association between low SMM and severe acute radiation oral mucositis and dermatitis in 82 nasopharyngeal cancer patients treated by concurrent chemoradiotherapy [29]. Lee *et al.* found that acute grade ≥3 mucositis or grade ≥2 dysphagia was associated with more SMM loss from baseline to 3 months after treatment in 155 oral cancer patients undergoing surgery and adjuvant (chemo)radiotherapy [36]. Endo *et al.* investigated whether pretreatment SMI is a predictor for the risk of aspiration pneumonia in 159 HNC patients receiving CRT. In 159 HNC patients, low SMM was the only independent predictor of aspiration pneumonia defined as the presence of both subjective symptoms, e.g. included wet cough, purulent sputum, and fever, and objective symptoms, e.g. increased inflammatory or consolidation on chest imaging [37]. Low SMM was also found to be predictive for the length of hospital stay and unplanned admission in HNC patients treated with (chemo)radiotherapy [38].

Van Rijn-Dekker *et al.* found that low SMM was associated with physician-rated xerostomia six months after treatment (OR 1.65, 95%: CI 1.06–2.57) and physician-rated dysphagia six and twelve months after treatment (OR 2.02, 95% CI: 1.17–3.51 and OR 2.51, 95% CI: 1.36–4.65, respectively) in 750 HNC patients treated with definitive (chemo)radiotherapy [39▪]. Karsten *et al.* reported that patient-rated swallowing outcome 6 months after radiotherapy was worse in patients with pretreatment sarcopenia in 108 patients during the first year after radiation-based treatment for stage III-IV oropharyngeal carcinoma. For other functional outcome parameters as speech and trismus no association with sarcopenia was found [40].

It can be concluded that pretreatment SMM is predictive for acute and late toxicity and adverse events in HNC patients treated with radiotherapy.

SURGERY

There is compelling evidence that sarcopenia is associated with higher rates of surgical complications that delay recovery and increase mortality.

Surov and Wienke [41▪] found in a meta-analysis (search date December 2020) that low SMM was associated with the occurrence of severe postoperative complications (OR 4.79, 95% CI: 2.52–9.11) in three studies (481 patients with HNC) [42–44]. In a prospective study of 190 HNC patients aged ≥65 years who underwent primary surgery with curative intent pretreatment low SMM, found in 33.7% of patients, was significantly associated with early complications (3.2-fold increase) and readmission [45].

In a prospective cohort study of patients 251 patients undergoing major head and neck surgery the predictive and prognostic value of sarcopenia, defined as low SMI with either low muscle strength (grip strength) or low muscle performance (timed walk test), was investigated. Presarcopenia (low SMI only) was present in 34.9% and sarcopenia in 15.6% of patients. The presence and severity of sarcopenia were associated with the development of medical complications, higher grade of complications, length of hospital stay, and OS. Sarcopenia was associated with an increased risk of grade 3 or higher complications (OR 5.42; 95% CI 1.51–19.42), whereas presarcopenia was not. Sarcopenia was an independent predictor of increased length of hospital stay [46▪]. Comparable results were also found by Alwani *et al.* in 168 patients receiving free flap reconstruction after resection for HNC. Postoperatively, patients with low SMM had higher rates of pneumonia, venous thromboembolism, prolonged ventilation, delirium, fistula, wound disruption, and longer intensive care unit stays. Overall these patients had higher rates of general postoperative complications and flap-specific complications [44]. In another study low, SMM was a predictor of blood transfusion requirements in 239 HNC patients who underwent free flap reconstruction [47].

In some institutes, HNC patients undergoing free flap reconstruction are discharged to post-acute care facilities, including skilled nursing facilities, inpatient rehabilitation facilities, and long-term care hospitals, for extended support and recuperation beyond the immediate postoperative setting. In a cohort of 206 HNC patients, SMM was found to be independently associated with discharge to these facilities, with such as discharge. The authors concluded that SMI should be considered in preoperative planning of these patients [48].

It can be concluded that low SMM and sarcopenia predict complications in major head and neck surgery. Identification of high-risk patients allows for alternative surgical treatment planning, e.g. less extensive surgery, less complex reconstructions and use of pectoralis major myofascial flap for reinforcement of mucosal closure, and perioperative management and counseling.

FRAILTY

SMM assessment can also be used to identify frail patients. Frailty is associated with adverse outcomes and is diagnosed by a time-consuming comprehensive geriatric assessment (CGA). Frailty screening questionnaires are used to select patients for CGA.

Zwart *et al.* were the first to demonstrate that low SMM is independently associated with frailty based on the frailty screening G8 questionnaire in 112 HNC patients [14]. Meerkerk *et al.* confirmed this finding in 150 HNC patients (≥60 years old) and found a significant though weak correlation between G8 frailty score and SMM, but not when combined with handgrip strength [49]. In a sequel study in 73 elderly (≥70 years) HNC patients low SMM was the only significant predictor for frailty diagnosed by CGA independent of comorbidity and muscle strength [50]. From these studies it can be concluded that low SMM predicts frailty and may be a promising time-efficient and routinely available tool for clinical practice to select the (un)suitable patients for therapy.

SURVIVAL

Several studies report on the decreased survival of HNC patients with low SMM. Most of these studies were discussed in recent systematic reviews. Surov and Wienke investigated in a meta-analysis (search date December 2020) the association between sarcopenia and disease-free survival (DFS) in five studies with 1284 patients who underwent different curative treatment strategies and found that sarcopenia predicted DFS in HNC patients (HR 2.00, 95% CI: 1.63–2.45) [41▪]. In another systematic review (search date February 7, 2021) and meta-analysis of 7 studies, low SMM was associated with DFS in patients treated with surgery (2.59, 95% CI: 1.56–4.31) and in patients treated with radiotherapy for HNC (1.56, 95% CI: 1.24–1.97). Comparable associations for disease-specific survival (DSS) were found in 5 studies for patients treated by surgery (HR 2.96, 95% CI: 0.73–11.95) and radiotherapy (HR 2.67, 95% CI: 1.51–4.73) [51]. These results were confirmed in more recent studies [28,52,53].

Wong *et al.* performed a systematic review (search date July 12, 2019) and meta-analysis of 10 studies with 2,181 HNC patients and found a worse OS for HNC patients with low SMM (HR = 1.98; 95% CI: 1.64–2.39) [54]. Hua *et al.* systematically reviewed data (search date August 30, 2019) from 11 studies involving 2,483 HNC patients and found similar results. There was no difference between groups where L3 SMI was calculated from the C3 SMI and primary L3 SMI. There was also no difference between the Asia and non-Asia studies [55]. Findlay *et al.* analyzed data from seven studies (published between January 2004 and May 2020) consisting of 1,059 HNC patients treated with radiotherapy with or without another treatment modality with curative intent and found that pretreatment low SMI was associated with reduced OS (HR 2.07; 95% CI, 1.47–2.92) with similar findings for posttreatment low SMI (HR 2.93; 95% CI, 2.00–4.29) [56]. In a meta-analysis (search date December 2020) of 18 studies with 6388 HNC patients sarcopenia was associated with lower OS after different curative treatment strategies (HR 1.96, 95% CI: 1.71–2.24). Associations of sarcopenia and OS for HNC patients treated with primary surgery with or without adjuvant (chemo)radiotherapy (five studies with 933 patients) and HNC patients treated with primary radiotherapy and/or chemotherapy (six studies with 2878 patients) were comparable: HR 2.21, 95% CI 1.72–2.84 and HR 1.95, 95% CI: 1.61–2.36, respectively [41▪]. However, more recently Takenaka *et al.* reported their systematic review (search date February 7, 2021) and meta-analysis of 18 studies with 3,233 HNC patients treated with surgery or radiotherapy and found that the OS was significantly higher for the surgery group (HR 2.50, 95% CI 1.95–3.21) than for the radiotherapy group (HR 1.63, 95% CI 1.40–1.90). A subgroup analysis demonstrated a similar prognostic capability between L3 and C3 level-based measurements of SMM [51]. These findings were confirmed in more recent studies [52,53,57]. SMM was also an imaging biomarker for decreased survival in subgroups of patients with oral cancer [58,59] and oropharyngeal squamous cell carcinoma [60], and in elderly HNC patients (when combined with muscle function) [61].

Also changes between SMI values before and 3 and 9 months after radiotherapy were independently associated with significantly worse OS [36]. The combination with parameters of systemic inflammation in blood, e.g. platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, serum C-reactive protein and albumin levels, improved the prognostic value of sarcopenia [59,62].

From these meta-analyses and recent studies it can be concluded that low SMM is associated with reduced survival in HNC patients for different areas (e.g., Asia and non-Asia), sites (e.g., oral cavity, oropharynx), treatment modalities (surgery, radiotherapy and chemoradiotherapy), measurement methods (calculated (from C3) or measured L3 SMI) and time point (pre and posttreatment). Sarcopenia assessment can be used for improved treatment decision-making.

Potential explanations for the prognostic impact of sarcopenia are that it reflects general physical status, it is associated with postoperative complications through which adjuvant therapy is hindered or delayed, it is associated with more complications during radiotherapy which may lead to treatment cessation, it is associated with chemotherapy DLT trough which planned therapy is not completed, it is associated with more late toxicity,

e.g. dysphagia, which affects survival, and it changes the characteristics of circulating myokines, which are cytokines secreted by muscle cell. Altogether, sarcopenia reflects the status of the patient and the tumor, and increases the risk of adverse events, all of which can lead to a poorer prognosis.

PERSPECTIVES

Not only SMI, but also other body (composition) features, e.g. myosteatosis (intramuscular adipose tissue) and BMI (sarcopenic obesity), alone, combined or in combination with nutrition status have a predictive and prognostic value in HNC patients undergoing (chemo)radiotherapy and should be considered in future sarcopenia research [34,38,63].

Body composition analysis via CT or MRI imaging taken as routine care holds the potential to become a viable adjunct to care of patients with HNC through guiding management and clinical decision making. Consensus regarding sarcopenia assessment and definitions is warranted in order to substantiate these findings and support the implementation of body composition assessment as a clinically meaningful prognostic tool into practice. Studies are warranted to identify effective preoperative exercise and nutrition programs to improve low SMM and subsequently treatment outcomes and survival [64,65].

CONCLUSION

SMM can be assessed by an easy and robust method on routinely performed CT or MRI of the head and neck. However, research is needed to identify the optimal cut-off values for low SMI that are most prognostic and predictive of clinically relevant adverse outcomes in HNC patients. HNC patients with low SMM experience more acute and late toxicity of cisplatin and radiotherapy leading to significantly more frequent DLT and radiotherapy breaks. Alternative cisplatin dosing and other anticancer drugs need to be investigated in patients with low SMM. Low SMM can predict complications in major head and neck surgery. Alternative surgical treatment planning in patients with low SMM at high risk for complications should be investigated. HNC patients with low SMM have decreased disease free and OS. In HNC patients, low SMM predicts frailty and may be a promising time-efficient and routinely available tool for counseling and individualized treatment planning in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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