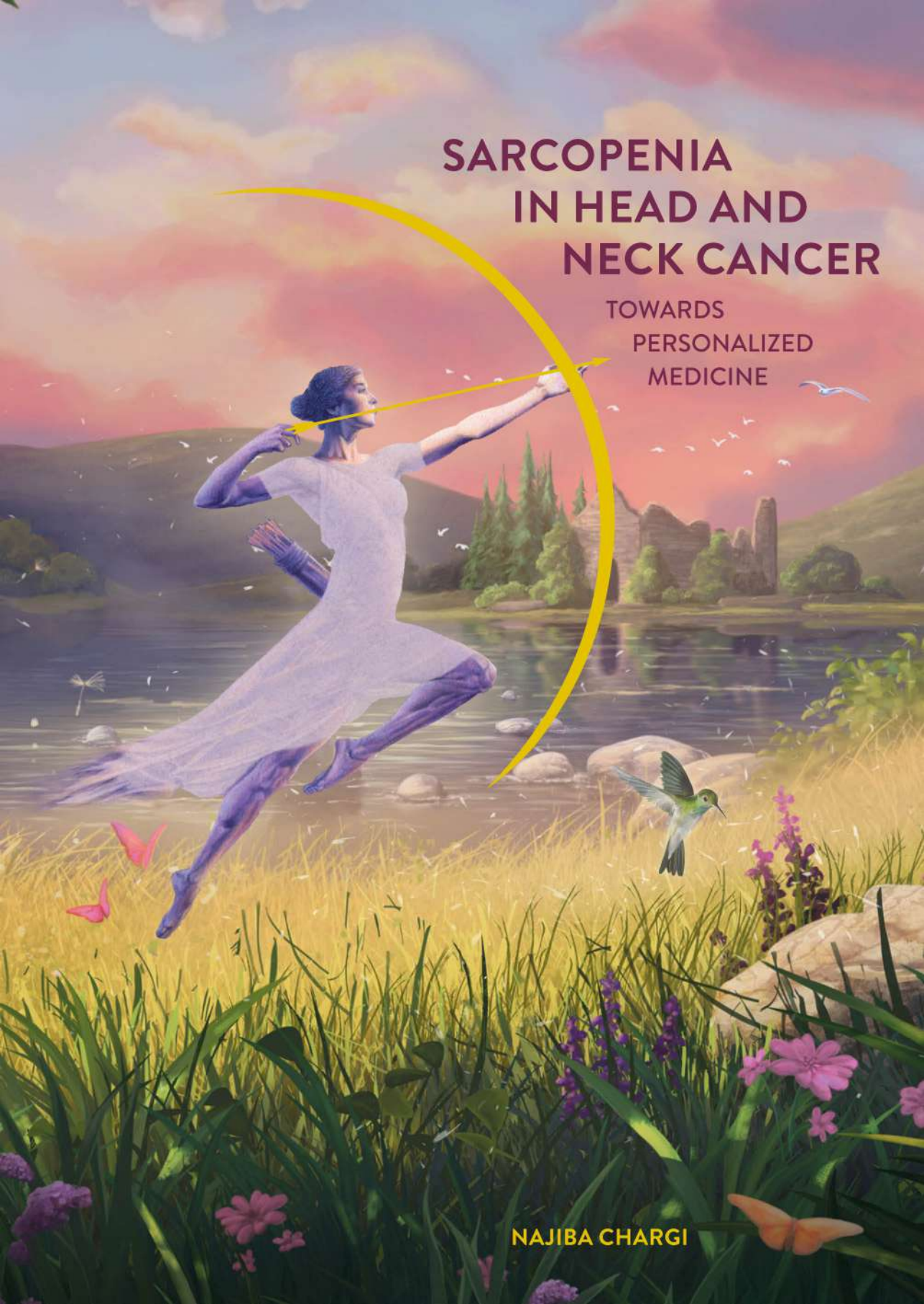
SARCOPENIA
IN HEAD AND
NECK CANCER
TOWARDS
PERSONALIZED
MEDICINE
NAJIBA CHARGI

Najiba Chargi

Sarcopenia in head and neck cancer

Towards personalized medicine

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Sarcopenia in head and neck cancer:
Towards personalized medicine

Sarcopenie en hoofd-hals kanker:
Op weg naar diagnostiek op maat
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

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Dank aan mijn ouders
voor de kansen die jullie mij geboden hebben
die jullie zelf nooit hebben gehad.

CHAPTER 1

General introduction

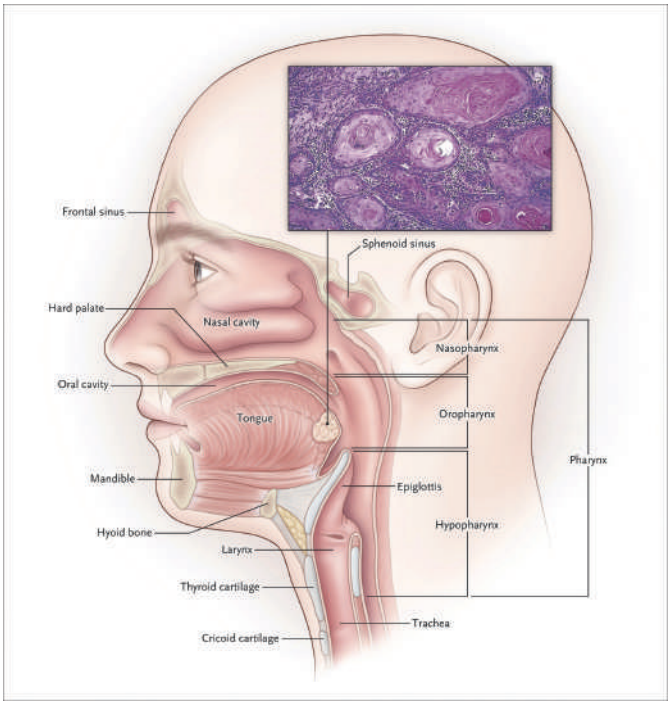
OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

The inside of the human mouth, throat and airway ducts is composed of epithelial cells who form a protective network of cells. The outer lining of these cells are squamous cells. Epithelial cells are continually replaced. A mutation during replication of squamous cells leads to mutated cells who divide uncontrollably and invade surrounding tissues. This marks the start of head and neck squamous cell carcinomas (HNSCC). The vast majority of head and neck cancers are HNSCC. Despite the fact that HNSCC arise from one cell type in the head and neck region, HNSCC are remarkably heterogeneous. This heterogeneity is in part caused by the different etiologies, complexity of the anatomical sites in which it develops and the large molecular heterogeneity.[1]

Head and neck cancer is the ninth most common cancer type worldwide with an estimated 835.000 new cases and 428.000 deaths in 2018.[2] In the Netherlands, approximately 3000 patients are newly diagnosed with head and neck cancer and approximately 900 patients die annually due to head and neck cancer.[3] Men are more frequently diagnosed with head and neck cancer. The incidence of head and neck cancer increases with age. Head and neck cancer is frequently located in the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx (figure 1). Less frequent locations are the paranasal sinuses and salivary glands.

Figure 1. Major anatomical sites of squamous cell carcinoma of the head and neck. The inset shows the typical histological features of squamous cell carcinoma of the head and neck.[4]



Heavy use of tobacco causes most head and neck cancers, and heavy use of alcohol synergistically increases the risk caused by tobacco use. The incidence of head and neck cancers caused by these risk factors is globally slowly declining, in part because of decreased use of tobacco.[5] The second most common cause of head and neck cancer is infection with the sexually transmitted human papillomavirus (HPV); commonly high-risk HPV type 16.[6] Over the past decade, there is increasing incidence of HPV-related head and neck cancers.[7] HPV leads to expression of E6 and E7 oncoproteins that inactivate the tumor-suppressor proteins p53 and the retinoblastoma protein (pRb), respectively, which leads to the malignant behavior of HPV-related tumors.[8] HPV-related head and neck cancers are typically located in the oropharynx. Patients with HPV-related head and neck cancers have unique risk factor profiles, better prognosis and have different epidemiology.[9] HPV-related head and neck cancers are more frequently seen in white men under age of 50 who usually do not smoke or use alcohol.[10]

HNSCC is staged according to the 8th edition of the American Joint Committee on Cancer (AJCC).[11] Staging is based on the size or extent of the primary tumor, involvement of lymph nodes and distant metastases, which are the T, N and M stage respectively. Combinations of these T, N and M stages are grouped in four disease stages. The TNM stage is a strong prognostic factor for disease outcome; patients with higher stages of disease are more likely to experience poorer survival outcomes. Generally, early stage head and neck cancer (stage I and II) includes smaller tumors without lymph node involvement and advanced stage head and neck cancers (stage III and IV) are characterized by more extensive local tumors with frequently invasion of surrounding structures, tumor involved lymph nodes and/or distant metastatic spread.[11]

CURATIVE TREATMENT OPTIONS FOR PATIENTS WITH HEAD AND NECK CANCER

Early-stage head and neck cancer (stage I and II) can generally be treated with primary surgery or radiotherapy. For oral cavity cancer, surgical resection of the primary tumor with elective neck dissection or sentinel node biopsy is preferred. This is followed by adjuvant radiotherapy or chemoradiotherapy depending on the presence of adverse histopathological features. At other sites, surgery is usually only performed for small and endoscopic accessible early-stage head and neck cancer. The 5-years overall survival for early-stage head and neck cancer ranges from 60 to 98% and varies between tumor sites. More than 60% percent of the patients present at diagnosis with locally advanced stage head and neck cancer (stage III and IV).[4] Treating locally advanced stage HNSCC requires evaluation by a multi-specialty team and multimodal treatment since the choice of treatment is dependent on the stage of the disease, anatomical site, surgical accessibility and preference of the patient (i.e., preserving function at the expense of survival). Multimodal treatment compromises (1) primary surgery with or without postoperative radiotherapy or chemoradiotherapy or (2) primary concomitant chemoradiotherapy or radiotherapy in combination with cetuximab (bioradiotherapy), with salvage surgery in reserve for residual or recurrent disease. In patients with locally advanced oral cavity cancer and hypopharyngeal or laryngeal cancer with cartilage invasion, extralaryngeal extension or an afunctional larynx, primary surgery is the treatment of choice. Salvage surgery can also be

considered for persistent or recurrent disease at the primary tumor site or the regional lymph nodes after definitive chemoradiotherapy. The MACH-NC meta-analysis showed that cisplatin-based chemoradiotherapy is a curative treatment option when surgical resection is less feasible or would result in poor long-term functional outcomes.[12] An absolute survival benefit of 4.5% at 5 years has been found when chemotherapy was added to locoregional treatment (radiotherapy).The most effective treatment modality was concomitant chemoradiotherapy with a hazard ratio of death of 0.81 (95% CI 0.78-0.86) and an absolute survival benefit of 6.5% at 5 years.[12] Chemoradiotherapy in the primary setting can be given for locally advanced HNSCC patients for two reasons (1) organ and function preservation or (2) unresectable disease. The Radiation Therapy Oncology Group (RTOG) found that chemoradiotherapy given in a concomitant setting was most effective for organ preservation in laryngeal cancer and locoregional control. In head and neck cancer, platinum-based drugs are the most effective and most studied chemotherapy drugs used to treat head and neck cancer. The RTOG schedule is the most commonly used schedule in head and neck cancer, consisting of cisplatin 100mg/m^2 on days 1, 22 and 43 combined with conventional radiotherapy (70 Gy in 35 fractions in 7 weeks).[13] In the adjuvant setting, after surgery, the addition of cisplatin to radiotherapy is more effective than radiotherapy alone in HNSCC patients with high-risk pathological features i.e. irradical resection (positive surgical margins) or extracapsular extension of lymph node metastasis.[14,15]

Concurrent chemoradiotherapy is associated with various in-field and systemic acute and chronic toxicities. Common side effects encountered in patients treated with cisplatin-based chemoradiotherapy are ototoxicity, nephrotoxicity and bone marrow depression, these side effects can be dose-limiting which causes patients not to complete all prescribed cisplatin cycles. Therefore, its use is predominantly for non-elderly patients who have a good performance status without major comorbidities. In patients who are not cisplatin-fit, e.g., patients with hearing problems or decreased renal function, other systemic therapeutics are carboplatin and cetuximab. Carboplatin is sometimes used when head and neck cancer patients have co-existent renal impairment, but treatment with carboplatin is less effective than high-dose cisplatin for curative therapy.[16] The combination of the epidermal growth factor receptor (EGFR) antibody cetuximab and radiotherapy, also called bioradiotherapy, improves locoregional control, progression-free survival and overall survival compared to radiotherapy alone.[17] Common side effects of bioradiotherapy include acneiform rash and infusion reactions. Recent trials have shown that locoregional control and overall survival rates are in favor for cisplatin-based chemoradiotherapy compared to cetuximab-based bioradiotherapy in patients with (mainly HPV-positive) locally advanced HNSCC.[18–20]

PROGNOSIS OF PATIENTS DIAGNOSED WITH HEAD AND NECK CANCER

Prognosis of patients with head and neck cancer varies depending on epidemiological factors (e.g. HPV-status), anatomical location and stage.[4] Recent advances such as the introduction of immunecheckpoint inhibitors for treatment of recurrent or metastatic head and neck cancer have led to increased benefit for some patients.[21] Other treatment advances such as

improvements in surgical techniques and advances in radiotherapy have also contributed to preservation of function and reduced morbidity and mortality. Despite intensive treatment, the prognosis of head and neck cancer patients is generally poor. The 5-year overall survival of patients with HNSCC is largely dependent on disease stage. Locally advanced diseases have a poor prognosis with a 5-year overall survival less than 50%.[22] As mentioned earlier, HPV-related head and neck cancers have a distinct behavior and an overall better prognosis. The 3-year survival of HPV-positive tumor patients is better than HPV-negative patients, 82% versus 57%, respectively ($p< 0.001$).[8] Due to increased prevalence of HPV-related tumors and increased treatment advances, the number of survivors of HNSCC rises. Patients with HPV-related cancers can be divided in three risk groups based on smoking habits and the T or N stage with different 3-year overall survival rates: 94% for the low risk, 67% for the intermediate risk and 42% for the high risk group.[8] In 2017, the AJCC and the Union for International Cancer Control (UICC) introduced a separate staging system for patients with HPV-positive oropharyngeal carcinoma in recognition of the improved prognosis.[11,23]

PREDICTORS AND PROGNOSTICATORS IN HEAD AND NECK CANCER

As mentioned earlier, TNM stage and HPV-status are major prognosticators for survival in patients with head and neck cancer. It is also known that incompletely resected or inoperable tumor carry a worse prognosis. For surgically treated patients, involvement of the resection margin (R1) at the primary site or extracapsular spread at different levels of lymph nodes are independent prognostic factors for overall survival in HNSCC.[11] However, for HPV-related oropharyngeal carcinoma, extracapsular spread and advanced nodal stage are not predictive for local recurrence, whereas patients with positive tumor margins, 5 or more neck node metastases and a T stage of 3 or 4 are identified as a high-risk population.[24] It has also been shown that the type of surgery used to treat HNSCC may also be an important prognostic factor in HNSCC outcomes.[25] Nevertheless, stage-dependent differences in outcomes have been consistently over the past two decades, despite the development of risk-adapted curative treatment strategies.[26] Novel strategies are thus needed to change the focus from uniform treatment for all patients with the same TNM stage, clinical and histological features to a personalized treatment guided by biomarkers that identify individual differences between patients.

AN EMERGING PREDICTIVE AND PROGNOSTIC BIOMARKER IN THE FIELD OF CANCER: SARCOPENIA

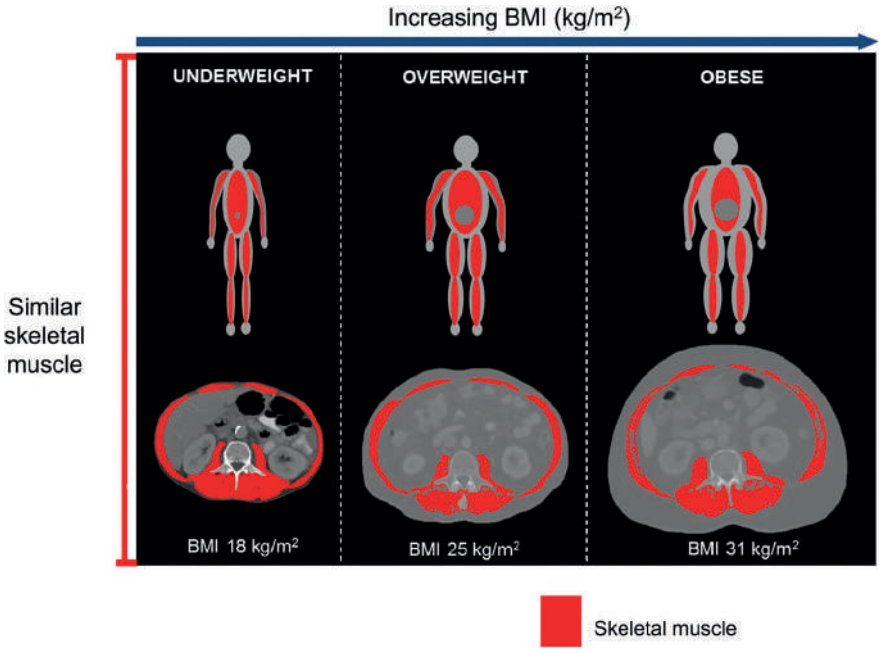
Over the last decade, research on body composition has gained increased attention in oncological and surgical literature. Body composition consists of fat mass and fat-free mass also called lean body mass. The skeletal muscle mass is the largest contributor to the lean body mass.[27] Low skeletal muscle mass is also referred to as sarcopenia. Sarcopenia lends its name from the Greek words ''sarx'' meaning flesh and ''penia'' meaning lack of. Sarcopenia can be primary due to ageing 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 skeletal muscle mass and a decrease in muscle function.[28] Muscle function is not routinely measured; therefore, the terms sarcopenia and low skeletal muscle mass are often

used interchangeably in literature. It is estimated that the prevalence of primary sarcopenia in the general population is 5-13% for people aged 60-70 years, and up to 50% for those aged 80 years or above.[29] Secondary sarcopenia is due to chronic systemic inflammation, malnutrition and immobilization.[28] It is suggested that for cancer patients, a chronic systemic inflammatory state caused by the tumor microenvironment leads to the presence of secondary sarcopenia.[28] Low skeletal muscle mass is associated with adverse outcomes in oncological patients and in particular when a state of both low skeletal muscle mass and a disproportional surplus of fat mass is present (sarcopenic obesity).[30–34] Head and neck cancer patients are at risk for low skeletal muscle mass (secondary sarcopenia) due to tumor site which leads to dysphagia and difficulty of swallowing, leading to malnutrition and a catabolic state. At diagnosis, up to 50% of patients with HNSCC present with signs of malnutrition.[35]

SKELETAL MUSCLE MASS INVESTIGATION

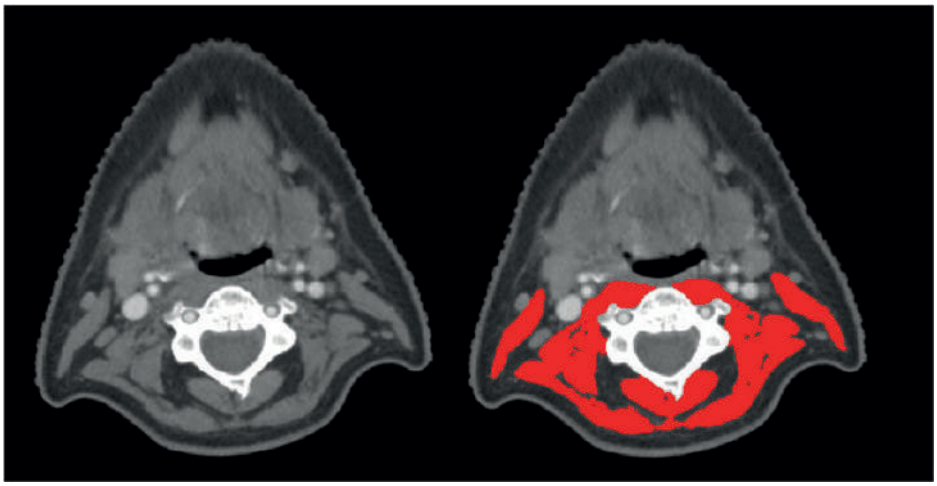
There are several methods to measure body composition and skeletal muscle mass. These methods include 'dual-energy X-ray'-absorptiometry (DEXA) scan, bioelectrical impedance analysis (BIA) and modern imaging techniques including Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).[36,37] BIA is based on the difference in electrical conductance of the different body compartments; muscle mass has a high water content and therefore low electrical resistance, whereas fat mass has a lower water content and higher resistance. Both DEXA and BIA are generally low cost and easy to use. These diagnostic tools are however confounded by alterations in hydration, edema and food intake. Therefore, its use in assessing body composition of patients with cancer is not favored. Both CT and MRI allow for the detailed assessment of all body compartments including skeletal muscle mass. In 2004, Shen et al. showed a high correlation between the cross-sectional skeletal muscle area on a single MRI slice at the level of the third lumbar vertebra (L3) and whole body total skeletal muscle volume as measured on whole body MRI.[38] In contrast to skeletal muscle mass measurement on MRI, in which skeletal muscle mass measurement is fully manually performed, measurement on CT imaging can be performed using semi-automatic software programs and with predefined Hounsfield unit range that are muscle specific. In most studies, a Hounsfield unit range between -29 and +150 is accepted as being skeletal muscle mass.[39] For abdominal imaging, the area of the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques and rectus abdominis muscles on level L3 are segmented on a single axial-slice (figure 2).

Figure 2. Skeletal muscle mass segmentation (red) at the level of L3 for three different patients with different body mass index (BMI) but same skeletal muscle mass.[27]



Abdominal CT is routinely performed during diagnostic work-up and follow-up of many cancer patients, and thus imaging is routinely available for analysis without any extra burden for the patient or healthcare-related costs. In 2008, Prado et al. showed that there is a linear relationship between a person's height and the skeletal muscle area at the level of L3.[40] Therefore the skeletal muscle area at the level of L3 is adjusted for squared height, to calculate the skeletal muscle index (SMI; cm^2/m^2), as a estimation of a person's total skeletal muscle mass in proportion to stature.[40] Prado et al were the first to investigate the relationship between low skeletal muscle mass (low skeletal muscle mass index) and adverse outcomes in patients with cancer.[40,41] Since 2008, various studies have shown that low skeletal muscle mass is associated with increased rates of postoperative complications, chemotherapy-related toxicity, prolonged hospital stay, increased healthcare related costs, and decreased overall and disease-specific survival rates in patients with colon cancer, breast cancer, lung cancer, bladder cancer, pancreatic cancer and hematological malignancies, amongst others.[42–50] Abdominal CT imaging is not routinely performed in head and neck cancer patients and is often only available in patients with locally advanced disease. In 2016, Swartz et al. published a novel assessment method for skeletal muscle mass using a single CT slice at the level of the third cervical vertebra (C3), which is featured on regular head and neck CT imaging.[51] Figure 3 shows an example of skeletal muscle mass segmentation on the level of C3 in which both sternocleidomastoid muscles and the paravertebral muscles are segmented.

Figure 3. Skeletal muscle mass segmentation at the level of C3 in which the sternocleidomastoid and paravertebral muscle are segmented in red.



A good correlation between skeletal muscle mass area at the level of C3 and L3 was found (r = 0.785). A multivariate formula to estimate the skeletal muscle mass area at the level of L3 from the skeletal muscle mass area at the level of C3 was formulated; the correlation between the estimated skeletal muscle mass area at the level of L3 and the actual skeletal muscle mass area at the level of L3 was excellent (r = 0.891). This allows for skeletal muscle mass measurements on routinely performed head and neck CT imaging for head and neck cancer diagnosis and treatment evaluation. Due to heterogeneity in patients with head and neck cancer, research is necessary to understand what, and if any, relationship exists between skeletal muscle mass and treatment outcomes. This knowledge may aid in individualizing curative goals which aims at structural and functional preservation, amelioration of treatment outcomes and the maintenance of quality of life.

AIM AND OUTLINE OF THIS THESIS

The introduction describes the poor prognosis of patients with HNSCC and in particular of patients with locally advanced HNSCC. Besides the poor prognosis, treatment of HNSCCC is also associated with a high frequency of severe toxicities. Over the past decade, research on body composition cancer is rapidly increasing. The main of the research described in this thesis is to evaluate diagnostic measurements of skeletal muscle mass, to evaluate the predictive and prognostic value of low skeletal muscle mass in patients with HNSCC who are surgically treated and who are treated with systemic therapy (chemoradiotherapy and bioradiotherapy).

Part I of this thesis presents the diagnostic research on skeletal muscle mass measurements. Before investigating the predictive and prognostic value of skeletal muscle mass the measurement method has to be validated and its robustness tested.

Therefore, in **Chapter 2** we correlate skeletal muscle mass measurement on head and neck computed tomography imaging at the level of the third cervical vertebra and on abdominal imaging at the level of the third lumbar vertebra in a large cohort of patients. Because sometime only MRI of the head and neck is available and CT not, we correlate in **Chapter 3** measurement of skeletal muscle mass at the level of the third cervical vertebrae using computed tomography imaging and magnetic resonance imaging. In an attempt to find an alternative skeletal mass measurement on head and neck CT, we investigate the association of muscle segmentation of the musculus masseter and muscle segmentation at the level of the third cervical and lumbar vertebra in **Chapter 4**. Because gender specific cut-off values for defining low skeletal muscle mass on head and neck are missing, we developed new cut-off values for low skeletal muscle mass obtained by image-analysis in patients with head and neck cancer in **Chapter 5**.

Part II of this thesis presents the predictive and prognostic impact of skeletal muscle mass in surgically treated head and neck cancer patients. The predictive and prognostic value of skeletal muscle mass may differ for specific head and neck cancer patient groups. Thereore, groups of head and neck cancer patient undergoing surgical procedures with high and low risk of complications are investigated. **In Chapter 6** we investigated the predictive and prognostic impact of low skeletal muscle mass on postoperative morbidity and survival in oral cavity cancer patients undergoing surgical resection and mandibular microvascular reconstruction with a free fibula flap. Besides skeletal muscle mass, systemic inflammation may also influence treatment outcomes of head and neck cancer patients undergoing microvascular free flap reconstruction. Therefore, in **Chapter 7** we investigated the predictive and prognostic impact of low skeletal muscle mass and elevated systemic inflammation on postoperative morbidity and survival in head and neck cancer patients undergoing microvascular free flap reconstruction using a variety of free flaps. The predictive impact of skeletal muscle mass on perioperative complications is further investigated in patients with oral squamous cell carcinoma and presented in **Chapter 8**. Besides skeletal muscle mass, arterial calcification is also assessed on routine diagnostic CT imaging and could be used as an additional image-based biomarker.

Therefore, in **Chapter 9** we investigated the predictive impact of low skeletal muscle mass and arterial calcification on the occurrence of pharyngocutaneous fistula in patients with laryngeal cancer undergoing total larynx extirpation.

Part III of this thesis presents the predictive and prognostic impact of skeletal muscle mass in head and neck cancer patients treated with systemic therapy. Because the effect of skeletal muscle mass on (dose limiting) toxicity and survival may be different for different anti-cancer drugs, we investigate, besides cisplatin, also other anti-cancer drugs. The impact of low skeletal muscle mass may also differ for specific subgroups with favourable treatment outcome; therefore, we investigate its predictive and prognostic impact in patients with oropharyngeal cancer. Moreover, we also investigate the association of skeletal muscle mass and functional outcome after non-surgical treatment of head and neck cancer. **In Chapter 10**, we investigated the predictive impact of low skeletal muscle mass on cisplatin dose-limiting toxicity in patients with locally advanced head and neck cancer who were treated with chemoradiotherapy. **Chapter 11** presents the same study as described in Chapter 10 in another hospital to validate the predictive impact of low skeletal muscle mass on cisplatin dose-limiting toxicity and to investigate the prognostic impact for survival in patients with head and neck cancer treated with chemoradiotherapy. Sometimes head and neck cancer patients are not fit enough to receive cisplatin-based chemoradiotherapy and these patients are offered cetuximab-based bioradiotherapy. Therefore, in **Chapter 12** we present the predictive and prognostic impact of low skeletal muscle mass on cetuximab dose-limiting toxicity and survival in patients with head and neck cancer treated with bioradiotherapy. Besides the impact of skeletal muscle mass on cisplatin toxicity and cetuximab toxicity in patients with head and neck cancer, we investigated the impact on other anti-cancer drug toxicity in a variety types of cancers by a systematic review and meta-analysis presented in **Chapter 13.** To further investigate the hypothesis of the relationship between cisplatin pharmacokinetics and skeletal muscle mass in locally advanced head and neck cancer patients treated with chemoradiotherapy, we performed a prospective observational study, presented in **Chapter 14.** Because cislaptin itself is also thought to influence skeletal muscle mass changes, we investigated in **Chapter 15** the patterns, predictors and prognostic impact of skeletal muscle mass loss after cisplatin-based chemoradiotherapy in patients with head and neck cancer. For the subgroup of oropharyngeal cancer patients, in **Chapter 16** we investigated the prognostic impact of low skeletal muscle mass for decreased survival in patients with oropharyngeal squamous cell carcinoma. In **Chapter 17** we present a prospective observational study describing the impact of low skeletal muscle mass on functional outcomes after radiation-based treatment in patients with locally advanced oropharyngeal carcinoma.

Approximately a quarter of HNSCC patients is older than 70 years at diagnosis. This percentage is expected to increase in the upcoming decades. Therefore, in **Part IV** of this thesis we present the predictive and prognostic impact of skeletal muscle mass in elderly head and neck cancer patients. Because both low skelatal muscle mass and frailty are prognostic and predictive factors and are both common in the elderly, we investigate their association and

their predictive and prognostic impact in elderly head and neck cancer patients. **Chapter 18** presents the prognostic impact of low skeletal muscle mass and low muscle function on overall survival in elderly patients with head and neck cancer. **Chapter 19** presents the predictive impact of sarcopenia measured with skeletal muscle mass and muscle strength on frailty in elderly patients with head and neck cancer. **Chapter 20** presents the association of sarcopenia measured with skeletal muscle mass and muscle function and frailty in elderly patients with head and neck cancer. In **Chapter 21** a summary and general discussion is presented with future perspectives and in **Chapter 22** a Dutch summary is presented.

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PART I

Image-based analysis
of skeletal muscle mass

CHAPTER 2

Validation of skeletal muscle mass assessment at the level of the third cervical vertebra in patients with head and neck cancer

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Submitted ■

ABSTRACT

Background

Low skeletal muscle mass (SMM) is associated with adverse outcomes. SMM is often assessed at the third lumbar vertebra (L3) on abdominal imaging. Abdominal imaging is not routinely performed in patients with head and neck cancer (HNC). We aim to validate SMM measurement at the level of the third cervical vertebra (C3) on head and neck imaging.

Material and methods

Patients with pre-treatment whole-body computed tomography (CT) between 2010 and 2018 were included. Skeletal muscle mass area (SMA) was manually delineated at the level of C3 and L3. Correlation coefficients and intraclass correlation coefficients (ICCs) were calculated. Cohen's kappa was used to assess the reliability of identifying a patient with low SMM.

Results

Two hundred patients were included. Correlation between SMA at the level of C3 and L3 was good ($r = 0.75$, $p<0.01$). When using a multivariate formula to estimate SMA at L3, including gender, age, and weight, correlation improved ($r = 0.82$, $p<0.01$). The agreement between estimated and actual SMA at L3 was good (ICC 0.78, $p<0.01$). There was moderate agreement in the identification of patients with low SMM based on the estimated lumbar skeletal muscle mass index (LSMI) and actual LSMI (Cohen's κ: 0.57, 95%CI 0.45-0.69).

Conclusions

SMA at C3 correlates well with SMA at L3. There is moderate agreement in the identification of patients with low SMM based on the estimated LSMI (based on measurement at C3) and actual LSMI.

INTRODUCTION

Over the last decade, research into the specific body composition of cancer patients and its relationship with clinical outcomes has tremendously increased due to the use of diagnostically performed imaging for quantification of different body compartments, including skeletal muscle mass (SMM) and adipose tissue mass.[1,2] Specifically a state of low SMM, sometimes termed sarcopenia, has gained interest as a novel risk factor for negative short- and long-term outcomes. In breast, gastro-intestinal, hepato-pancreatic-biliary and respiratory cancer, amongst others, low SMM is associated with increased incidence of postoperative complications, chemotherapy-related toxicity, prolonged hospital stay and shorter disease-free and overall survival.[3,4] SMM is most commonly assessed on a single CT slice at the level of the third lumbar vertebra (L3), which has shown to have excellent correlation with whole body skeletal muscle volumes as measured using whole body MRI.[5,6] The cross-sectional skeletal muscle area (SMA) at the level of L3 is then most commonly normalized for stature, to calculate the lumbar skeletal muscle index (lumbar SMI).[5] The lumbar SMI is used as a proxy for SMM as a whole, and several cut-offs have been published to identify patients with low SMM.[4]

In head and neck cancer (HNC), abdominal CT imaging is not commonly performed as part of the routine diagnostic work-up. Therefore, abdominal CT imaging to quantify SMM is not routinely applicable in HNC patients. To overcome this, a measurement method for SMM at the level of the third cervical vertebra (C3), which is featured on standard CT imaging of the head and neck area, was published by Swartz et al.[7] A multivariate formula to calculate SMA at the level of L3 from SMA at the level of C3 was also published, to allow for comparison to other oncological research.[7] Wendrich et al. published a cut-off value for low SMM in HNC patients based on this method.[8] The measurement method for SMM at the level of C3 was used in several studies in HNC patients. The incidence of low SMM was high in several studies; typically 50% of patients and sometimes up to 77% of patients had low SMM prior to start of treatment.[8–11] In HNC patients, low SMM was associated with negative short- and long-term outcome such as chemotherapy dose-limiting toxicity, postoperative complications and decreased survival.[8,9,12,13] Only one previous study by Ufuk et al. has investigated the correlation between SMA measurement at the level of C3 and L3. They showed that SMA at the level of C3 was best associated with SMA at the level of L3, and that the correlation between SMA at the level of C3 and SMA at the level of L3 was excellent.[14] Ufuk et al. segmented the sternocleidomastoid(SCM) and paravertebral muscles (PVM) separately, Swartz et al. recommends using the SMA at C3 of both the SCM and PVM. Ufuk et al. also used cut-off values for low SMM based on the study of Prado et al. which did not include HNC patients and did not validate the formula proposed by Swartz et al.

Our current study aimed to reevaluate the association between SMA at the level of C3 and the level of L3 in a larger cohort of treatment naïve HNC patients. It also aimed to investigate the accuracy of identifying patients with low SMM using a previously published cut-off value.

PATIENTS AND METHODS

ETHICAL CONSIDERATIONS

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 16/595 C). All data was retrieved retrospectively and processed in an anonymized fashion.

STUDY POPULATION

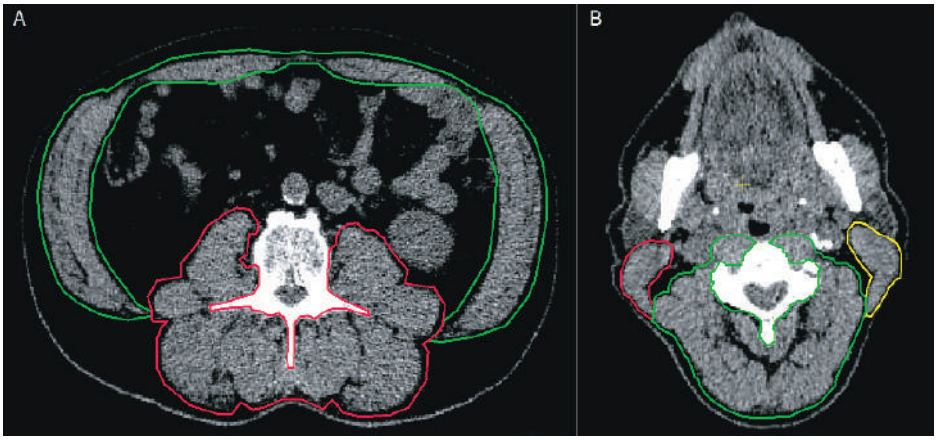
Patients who were diagnosed at the University Medical Center Utrecht, The Netherlands between 2010 and 2018 with a primary head and neck squamous cell carcinoma were evaluated for this study. Since the effect of previous treatments of the neck on SMA measurement at the level of C3 is not known, patients previously treated with surgery or radiotherapy of the neck were excluded.

Patients were included if a pre-treatment whole body FDG-PET/CT scan in radiation mould (as part of radiotherapy treatment planning) was available. Other relevant parameters, including length and weight at the time of imaging, sex, age, tumor localization and clinical TNM stage (7^{th} and 8^{th} edition) were retrospectively retrieved. In total, 200 patients were selected.

ASSESSMENT OF CROSS-SECTIONAL SKELETAL MUSCLE AREA

Pre-treatment FDG-PET/CT-imaging was performed in all patients according to a standardized protocol. Muscle tissue was identified using Hounsfield Unit (HU) range settings from -29 to +150 HU, which is specific for muscle tissue. Muscle tissue was delineated at the level of the third lumbar vertebra (L3) and the third cervical vertebra (C3). The SMA was defined as the pixel area within the delineated area with a radiodensity between -29 and +150 HU.[15,16] Delineation of muscle tissue was manually performed using the Volumetool v.1.6.5 Research Software Package, designed in our center as an image evaluation, registration and delineation system for radiotherapy planning.[17] For delineation of muscle tissue at the level of L3, the first slide when scrolling from caudal to cranial direction to show the entire vertebral arc and both transverse processes was selected. The contours of the abdominal wall and paraspinal muscles were manually traced. SMA at the level of L3 was calculated by adding up the abdominal wall and paraspinal muscle area. For delineation of muscle tissue at the level of C3, the first slide when scrolling from caudal to cranial direction to show both transverse processes and the entire vertebral arc was selected. The contours of the paravertebral muscles and both sternocleidomastoid muscles were manually traced. The SMA at the level of C3 was calculated as the sum of the paravertebral muscle and both sternocleidomastoid muscles. If evident lymph node metastasis hindered accurate delineation of one sternocleidomastoid muscle, the SMA of the contralateral sternocleidomastoid muscle was used as an estimation of the SMA of the affected sternocleidomastoid muscle.[7] After delineation, SMA was automatically retrieved from Volumetool. First, all head and neck CT scans (C3) were delineated, and afterwards all abdominal scans (L3). Figure 1 shows muscle tissue delineation at the level of C3 and L3.

Figure 1. Delineation of skeletal muscle tissue on transversal CT imaging at the level of L3 (A) and at the level of C3 (B). A Hounsfield Unit window of -29 to +150 was used to accentuate skeletal muscle tissue.



CROSS-SECTIONAL SKELETAL MUSCLE AREA AT THE LEVEL OF L3

As well as the actually measured SMA at the level of L3, the SMA at the level of L3 was also estimated from the SMA at the level of C3 using the prediction formula as described by Swartz et al, see formula 1.[7]

Formula 1:

*SMA at L3 (cm^2) = 27.304 + 1.363 * CSA at C3 (cm^2) – 0.671*Age (years) + 0.640 * Weight (kg) + 26.442*Gender (Gender=1 for female and 2 for male)*

The lumbar SMI was then calculated using the formula published by Prado et al, see Formula 2.[5]

Formula 2:

*LSMI (cm^2/m^2) = SMA at L3/(height*height)*

Low SMM was defined as a LSMI ≤43.2cm^2/m^2, as previously published by Wendrich et al.[8]

STATISTICAL ANALYSIS

All statistical analyses were performed using the IBM SPSS Statistics version 25.0 software package (Chicago, Illinois, USA). There were no missing data. A test for normality (Shapiro-Wilk test) was performed to assess whether continuous variables were normally distributed. For table 1 continuous data are represented as mean ± standard deviation (SD) if normally distributed, and median ± range if skewed. Categorical data are represented as a number and percentage of total. The student's *t*-test, one-way ANOVA, Mann-Whitney U test were used where appropriate. Depending on normality of variables, Pearson or Spearman Rank correlation coefficients were calculated to assess correlation between SMA at the level of C3, at the level of L3 and predicted SMA at the level of L3. To assess the agreement between measurements, we calculated intraclass correlation coefficients (ICCs) using a two-way mixed single

measures model with absolute agreement. The ICCs were rated as poor (0.00 – 0.49), fair to good (0.50 – 0.74), good (0.75-0.90) and excellent (>0.90).[18] For agreement in classification of patients with low SMM, Cohen's κ was used. The agreement was rated as no agreement (<0), slight (0.01-0.20), fair (0.21 - 0.40), moderate (0.41 - 0.60), substantial (0.61 - 0.80) and almost perfect (0.81 - 1.00).[19] A two-tailed test of significance ($p = 0.05$) was used.

RESULTS

PATIENT CHARACTERISTICS

For this study, 200 patients were included for analyses. Baseline patient characteristics are shown in Table 1. Patients were predominantly male and often presented with advanced disease (T3-4; N+). Weight and body mass index (BMI) at diagnosis were normally distributed. On average, patients had a normal BMI.

Table 1. Patient characteristics

Characteristic	n (% or SD), total n = 200
Gender	
Male	147 (73.5)
Female	53 (26.5)
Age at diagnosis (years)	
Mean (SD)	63.5 (8.3)
Range	44.9–85.6
Weight at diagnosis (kg)	
Mean (SD)	74.1 (16.4)
Range	40.0–122.0
Body mass index (weight/height²)	
Mean (SD)	24.2 (4.6)
Range	14.0–40.0
Localization	
Oral cavity	12 (6.0)
Nasopharynx	5 (2.5)
Oropharynx	83 (41.5)
Hypopharynx	57 (28.5)
Larynx	40 (20.0)
Unknown primary	3 (1.5)
T-status	
T1-2	92 (46.0)
T3-4	108 (54.0)
N-status	
N0	73 (36.5)
N1-2a	61 (30.5)
N2b-3b	66 (33.0)
M-status	
M0	183 (91.5)
M+	10 (5.0)
Mx	7 (3.5)

IMAGE ANALYSIS

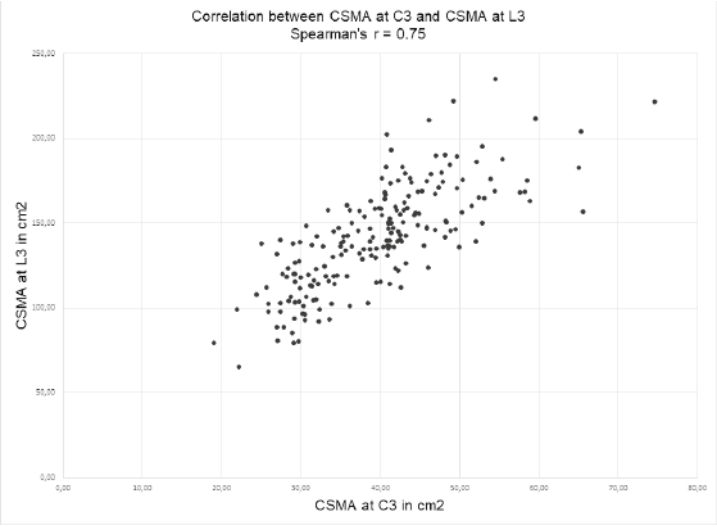
Delineation of muscle tissue at the level of C3 was successful in all patients. Six patients (8.6%) had evident growth of a lymph node metastasis into the SCM muscles. In these 6 patients, the SMA of the affected SCM muscle was substituted by the SMA of the unaffected, contralateral SCM muscle.

CORRELATION BETWEEN SMA AT C3 AND L3

SMA at the level of C3 was not normally distributed (Shapiro-Wilk test <0.05). Spearman rank correlation analysis showed a good correlation between SMA at C3 and SMA at L3 (Spearman's $r_s = 0.75$; $p < 0.01$). Figure 2 shows the direct correlation between SMA measurements at the level of C3 and L3.

Correlation between SMA at C3 and SMA at L3 was higher than the correlation between cross-sectional area of the paravertebral muscles only at C3 and SMA at L3 (Spearman's $r_s = 0.75$ versus $r_s = 0.70$).

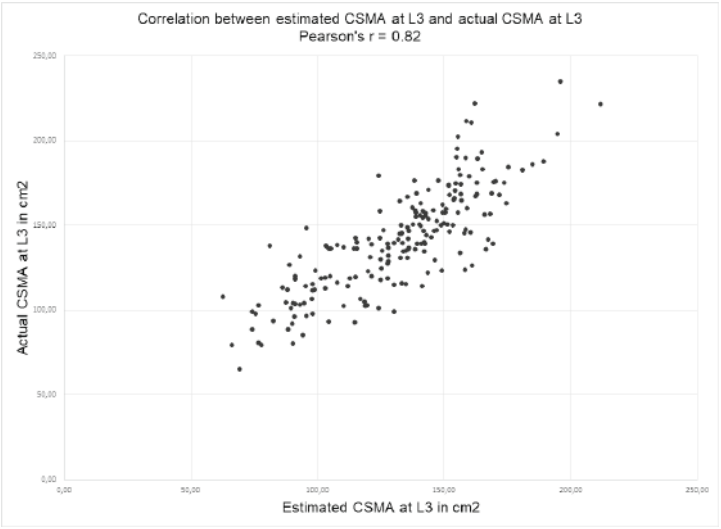
Figure 2. Correlation between cross-sectional SMA (CSMA) at the level of C3 and (actual) cross-sectional SMA (CSMA) at the level of L3



SMA at L3 was estimated from SMA at C3 using the multivariate formula as described earlier (Formula 1). Actual SMA at L3 and estimated SMA at L3 were normally distributed (Shapiro-Wilk test: $p > 0.05$). Figure 3 shows the correlation between the estimated SMA at L3 and the actual SMA at L3. Pearson correlation analysis showed a high correlation between the estimated SMA at L3 and the actual SMA at L3 ($r = 0.82$; $p < 0.01$). The mean difference between the estimated SMA at L3 and the actual SMA at L3 was calculated (mean -3.1 cm^2, SD 5.9 cm^2), meaning that the estimated SMA at L3 was slightly lower than the actual SMA at L3. In 13 of 200 patients (7%) the estimated and actual SMA at L3 differed more than 1.96 standard deviation from the

average, suggesting a reasonably good agreement. The ICC between estimated SMA at L3 and actual SMA at L3 was good: 0.78 (95% CI: 0.61 – 0.86, p < 0.01).

Figure 3. Correlation between estimated cross-sectional SMA (CSMA) at the level of L3 and actual cross-sectional SMA (CSMA) at the level of L3



AGREEMENT AND ACCURACY IN IDENTIFICATION OF PATIENTS WITH LOW SKELETAL MUSCLE MASS

Using Formula 2, the estimated LSMI and actual LSMI were calculated. The previously published cut-off value of ≤43.2cm^2/m^2 was used to determine low SMM. Using this cut-off value, 96 patients were determined to have low SMM using the estimated LSMI, and 77 patients had low SMM using the actual LSMI; see Table 2. The sensitivity of identifying patients with low SMM using the estimated LSMI and a cut-off of ≤43.2cm^2/m^2 was 84.4% and the specificity was 74.8%. The positive predictive value (PPV) of the estimated LSMI was 67.7% and the negative predictive value (NPV) was 88.5%. The false positive value, indicating the number of patients that incorrectly were identified as having low SMM, was 25.2%. Cohen's kappa for agreement between low SMM using the estimated and the actual LSMI was 0.57, indicating moderate agreement.

Table 2. Agreement between estimated and actual low SMM, defined as a LSMI ≤43.2 cm^2/m^2

		Low skeletal muscle mass: actual LSMI ≤43.2 cm^2/m^2		Sum	
		Yes	No		
Low skeletal muscle mass: estimated LSMI ≤43.2 cm^2/m^2	Yes	*65 (A)*	*31 (B)*	*96*	PPV=68%
	No	*12 (C)*	*92 (D)*	*104*	NPV=88%
sum		*77*	*123*	*200*	
		Sens 84%	Spec 75%		Acc=79%

Legend: Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, Acc: accuracy

DISCUSSION

There is a need for a robust, easy and widely available SMM quantification tool specifically for HNC patients, to allow for routine assessment of SMM without the need for additional diagnostics. Swartz et al proposed a measurement of SMA at the level of C3 as an alternative to measurement of SMA at the level of L3, using standard head and neck CT imaging. Our current study shows that measurement of SMA at the level of C3 provides a good estimation of SMA at the level of L3 (r_s = 0.75). Total SMA at the level of C3 had a higher correlation with SMA at the level of L3 than cross-sectional area of paravertebral muscles only (r_s = 0.75 versus r_s = 0.70), which is in agreement with results of a previous study, albeit slightly lower.[14] Using the same multivariate formula as described earlier, in a different set of patients, we found a very good correlation (r = 0.82) between SMA at the level of C3 and L3. The agreement in identification of patients with low SMM was moderate and the probability that a patient with low SMM according to C3 has a low SMM with the L3 method is 68%. A measurement of SMA at the level of C3 provides a good estimation of SMA at the level of L3 and subsequent analysis without the need for additional testing. Interobserver agreement was not further tested in this study; a previous study showed excellent interobserver agreement for SMA measurement at the level of C3.[20]

There was some variation in the identification of patients with low SMM based on the estimated LSMI compared to the actual LSMI. The estimated LSMI however was on average -3.9 cm^2 lower than the actual LSMI; classifying more patients as having low SMM than there actually are. Because the cut-off value for low SMM (LSMI ≤43.2 cm^2/m^2) is based on estimated LSMI by use of segmented SMA at the level of C3, other cut-off values for LSMI may apply when segmentation of SMA at the level of L3 is performed directly. This may explain the false positive rate of 25.2%. However, we acknowledge that an estimation of SMA at the level of L3 based on SMA at the level of C3 is not ideal and probably is not sufficient in the future as the most accurate estimation of a patient's total SMM. Indeed, Baracos published an article concluding that using single muscle as a sentinel muscle for whole body SMM is a flawed premise.[21] This problem probably also applies to SMA on a single CT slice as a representation of whole body skeletal muscle volume.

We do believe that at the current time, the SMA at C3 can provide a good estimation of SMM of HNC patients without the need for additional diagnostics and at minimal effort, with considerable accuracy. To facilitate implementation of SMM measurement in clinical practice, we believe the long-term focus should shift towards using artificial intelligence such as deep learning and machine learning to develop an automatic, whole muscle volume analysis based on routinely available CT imaging or MRI. Research into these methods are ongoing, and the expectation is that whole- or portion-of-body measurement of SMM will provide a much more accurate representation of a patients overall body composition and skeletal muscle status than the SMA on a single CT slide or a single muscle, with no or very little manual work involved.[22–24] Indeed, the use of the SMA at the level of L3 as an estimation of whole body skeletal muscle volume is based on studies using whole-body MRI for manual segmentation and calculation of whole-body skeletal muscle volume; in these studies, whole body MRI is referenced as the gold standard.[6,25] Manual segmentation of whole body MRI is time-consuming and therefore clinically not feasible. However, when software is available to perform automatic skeletal muscle volume analysis, a whole-body analysis approach seems preferred. In the short term, future studies may be aimed at developing gender-specific references values for SMA at the level of C3, to allow for the use of SMA at the level of C3 as a direct measure of SMM and to overcome the problem of several different cut-offs for low SMM that are currently available.[26,27]

There are limitations to our study that need to be addressed. Most patients in our study presented with advanced stage disease; in our center, the indication for FDG-PET/CT is a suspected advanced stage disease. Inherently to the use of FDG-PET/CT, patients with limited disease are underrepresented in this study. We excluded patients who had received prior treatment for HNC for this validation study, because the effect of prior local treatment (e.g., radiotherapy or surgery) on the accuracy of delineation of SMA at C3 is not known and may cloud its relationship with SMA at L3. It is well-known that patients with tobacco-related cancers of the upper aero-digestive tract have a substantial risk of developing a second primary malignancy in the same region. In another study by our group, also imaging of patients who had undergone prior treatment was also used, and found that low SMM as identified at the level of C3 was associated with adverse outcomes in patients with and without prior treatment.[9] Some patients with HNC will undergo MRI instead of CT imaging. In this study we only used CT imaging, according to the protocol described by Swartz et al.[7] Two recent studies also showed excellent correspondence between SMA on CT imaging and MRI, and concluded that CT and MRI can be used interchangeably.[28,29] The effect of different posture and different angles (e.g. in laryngeal cancer, CT scans are often angulated to better visualize the vocal cords) was not evaluated in this study, but may influence SMA.[30] Future research should clarify this, but we expect that this problem will be overcome by using whole-body or portion-of-body skeletal muscle volumes using artificial intelligence.

Our current study confirms the previously found strong correlation between SMA at the level of C3 and SMA at the level of L3. This method allows for research into the predictive and prognostic effect of low SMM in HNC patients, using routinely performed imaging of the head

and neck region without any additional costs or burden for the patient. It may also be used to identify patients with low SMM at high risk of adverse clinical outcomes, who may benefit from treatment adaptation or additional supportive treatment; acknowledging that there is some uncertainty in the identification of patients with low SMM.

CONCLUSION

A measurement of SMA at the level of C3 is a reliable method for evaluation of SMM in HNC patients and allows for investigating the predictive and prognostic value of low SMM in HNC patients using routinely performed CT imaging of the head and neck area. There is reasonable accuracy in the identification of patients with low SMM based on the estimated lumbar SMI and the actual lumbar SMI. Future research should be aimed at optimizing methods to use routinely performed imaging for body composition analysis.

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CHAPTER 3

Agreement between skeletal muscle mass measurements using computed tomography imaging and magnetic resonance imaging in head and neck cancer patients

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Research on skeletal muscle mass (SMM) has increasingly gained interest over the past several decades. Pre-treatment low SMM, often referred to as sarcopenia, has shown to be a predictive and prognostic factor in a variety type of cancers.[1–6] In head and neck cancer (HNC), sarcopenia has shown to be a predictive factor for dose-limiting toxicity[7,8] and for the development of fistulas after total laryngectomy.[9,10] Sarcopenia has also shown to have negative prognostic impact in HNC patients.[11-13]

Computed tomography (CT) has become the most used imaging modality in research on SMM because of relatively easy, fast and accurate segmentation of muscle by use of the muscle specific radiodensity range of -29 to +150 Hounsfield units (HU). Currently, the most used method is to assess SMM on abdominal CT, which uses the axial slice at the level of the third lumbar vertebra (L3) for segmentation of abdominal muscles as cross-sectional area (CSA). However, abdominal CT imaging is not routinely performed in HNC patients and is often only available in patients with advanced disease. Measurements of CSA of both sternocleidomastoid muscles and the paravertebral muscles at the level of the third cervical vertebra (C3) have shown to correlate well with CSA measurements at the level of L3.[17] In order to avoid selection bias in research on SMM in HNC, measurement at the level of C3 is the preferred method.[17]

Magnetic resonance imaging (MRI) does not allow for segmentation of muscle tissue based on a muscle specific radiodensity range, and therefore it is subject to the interpretation of the observer. However, MRI is considered one of the most accurate methods for analyzing quantitative and qualitative changes in body composition and is associated with an error in quantifying muscle that ranges between 1.1% and 4.4%.[14] CT, like MRI, is also considered as a highly precise imaging modality in investigating human body composition and has a reported precision error of about 1.4% for tissue areas.[15] Both scanning methods are able to distinguish muscle mass from fat. CT imaging can reveal fat infiltration within muscle by identifying areas in the range of −190 to −30HU.[16]

In the management of HNC, not all patients receive routinely CT scans. A large proportion of HNC patients receive MRI only. The agreement of CSA measurements of skeletal muscle mass (SMM) based on CT and MRI at the level of C3 is unknown. In order for SMM to be analyzed and routinely (without additional imaging and eventually retrospectively) used in the clinical practice of oncologic patients, it is paramount to study the concordance between SMM measurements based on CT and MRI. For this reason, we investigated the correlation in CSA measurements of SMM on CT and MRI in HNC patients.

We conducted a brief retrospective study in patients with oropharyngeal squamous cell carcinoma (OPSCC), who were diagnosed and treated at the University Medical Center Utrecht, The Netherlands, between 2010 and 2015. Patients were included if they had pretreatment head and neck CT and MRI imaging of sufficient quality performed within 1 month of each other.

Segmentation of muscle tissue on CT and MRI was manually performed using the Volumetool v.1.6.5 research software package[18] by a single researcher (N.C). The researcher was blinded to the outcome since all CSA values were retrieved at the end of the study. The axial imaging slide which showed both the transverse processes and the entire vertebral arch 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 sternocleidomastoid muscles. CSA at the level of C3 measured by CT and MRI was used for variability analysis. Data analysis was performed using IBM SPSS statistics 25. Variability between CT and MRI in CSA measurements of SMM was determined by the intraclass correlation coefficient (ICC) which is based on analysis of variance.[19] The ICC was calculated using a two-way mixed-effects model with absolute agreement. An ICC of 1 represents no variance in CSA assessment of SMM by CT and MRI. Bland and Altman method were used to calculate the mean difference and to evaluate the 95% limits of agreements between CSA measurements of SM by CT and MRI.[20]

In total, 50 OPSCC patients were included. Demographic and clinical data are presented in table 1. Low SMM was identified by MRI in 30 (60%) patients and by CT in 31 (62%) patients. The overall ICC for the CSA measurements of SMM obtained by CT and MRI was excellent (0.97; 95% CI 0.94 - 0.98, $p < 0.01$). Figure 1 shows the scatter plot of the correlation between CSA measurements by CT and MRI. As shown in this figure, there is a positive linear and a statistically significantly strong ($r^2 = 0.94$, $p<0.01$) relationship. Figure 2 shows the Bland and Altman plot with the corresponding 95% limits of agreements; the mean difference of CSA measurements between CT and MRI was less than 1 cm^2 (mean difference 0.87 cm^2; 95% CI -5.24 - 6.98).

Table 1. Demographic and clinical characteristics of included patients

Variables	N	%
Human papillomavirus status		
Positive	18	36
Negative	21	42
Unknown	11	22
Gender		
Female	14	28
Male	36	72
Age (years) (M, SD)	61.3	9.4
Body mass index (kg/m²)		
<20 kg/m²	9	18
20-24.9 kg/m²	24	48
25-29.9 kg/m²	8	16
≥30 kg/m²	9	18

Table 1. (Continued)

Variables	N	%
Weight loss 6 months prior to diagnosis		
None	32	64
<10%	9	18
≥10%	9	18
Smoking status		
Never smoked	3	6
Former	29	58
Current	18	36
Pack-years (years)		
0	3	6
1-15	9	18
16-25	5	10
26-40	12	24
≥41	11	22
Alcohol use		
No	3	6
Current	36	72
Former	11	22
Alcohol units/day (M, SD)	3.7	3.6
Adult Comorbidity Evaluation-27		
None	12	24
Mild	14	28
Moderate	17	34
Severe	7	14
Tumor localization		
Tonsil	12	24
Base of tongue	7	14
Soft palate	1	2
Oropharynx not otherwise specified	30	60
Tumor stage		
T1	8	16
T2	20	40
T3	11	22
T4a	10	20
T4b	1	2
Nodal stage		
N0	16	32
N1	11	22
N2a	2	4
N2b	7	14
N2c	12	24
N3	2	4
Tumor, Node, Metastasis (TNM) stage		
I	3	6
II	8	16
III	11	22
IV	28	56

Legend: N:number of patients, M:Mean, SD:standard deviation

Figure 1. Scatterplot of the correlation between CSA measurements on CT and MRI

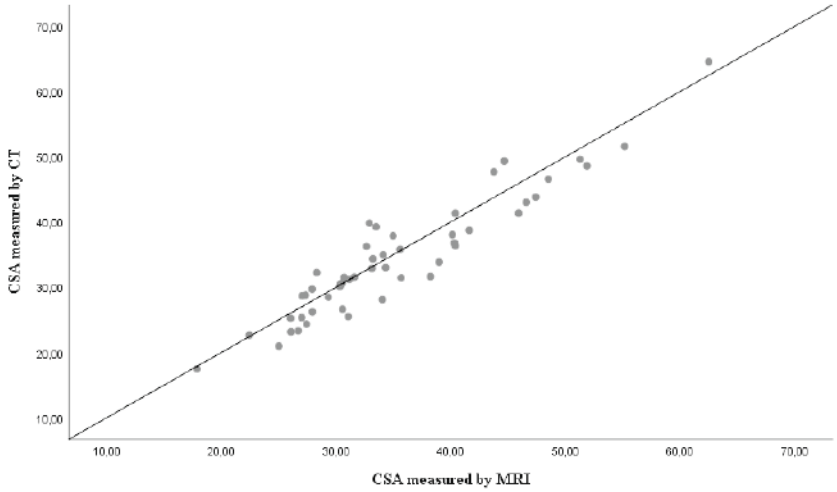
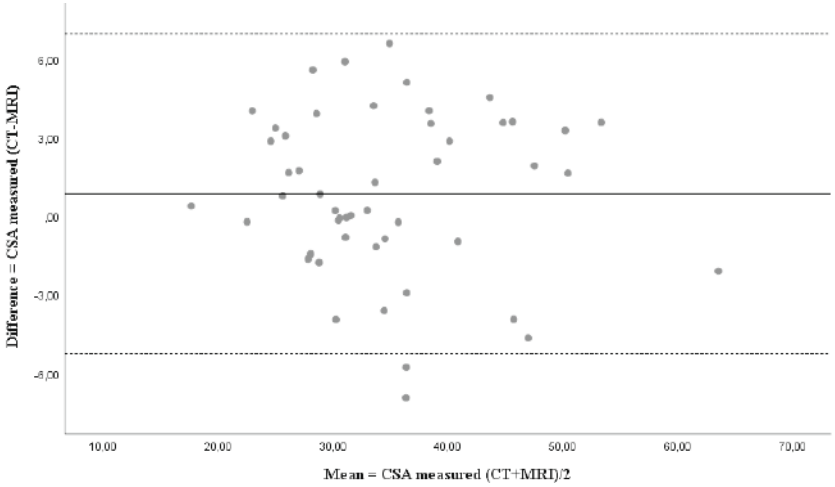


Figure 2. Bland-Altman Plot showing the mean difference (straight line) and 95% limits of agreement (dotted lines) between CSA measurement on CT and MRI



The main finding from this study is that the two different imaging modalities CT and MRI show significant correlation in quantifying SMM when measured by CSA at the level of C3. In a study on liver transplant patients a significant intraclass correlation coefficient between CT and MRI to measure CSA at L3 was found.[21] Consistent with this, measurements based on MRI and CT can also be used interchangeably for measuring CSA at the level of C3. This knowledge contributes to the growing knowledge concerning the role of SMM in head and neck oncology and could be used to conduct further research using both CT and MRI for the assessment of SMM.

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CHAPTER 4

The association of muscle segmentation of the musculus masseter and muscle segmentation at the level of the third cervical and lumbar vertebrae

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Article in press ■

ABSTRACT

Background

Patients with head and neck cancer (HNC) are at increased risk of developing low skeletal muscle mass (sarcopenia), which is associated with adverse treatment outcomes and prognosis. Sarcopenia is most commonly assessed by the skeletal muscle cross sectional area (CSA) at the third lumbar vertebra (L3) or more recently the third cervical vertebra (C3). L3 is not routinely imaged and C3 may be impacted by disease or treatment. As alternative we analyzed masseter muscle characteristics and their relationship with L3 and C3 skeletal muscle CSA and overall survival.

Methods

In this single-center retrospective study, 113 patients with HNC who underwent whole body FDG-PET/CT-scans were reviewed. Of these patients, L3 CSA, C3 CSA, masseter CSA, masseter thickness, masseter volume, masseter Hounsfield Unit values, lumbar skeletal muscle mass index (LMSI), cervical skeletal muscle mass index (CSMI) and masseter skeletal muscle mass index (MSI) were recorded and correlated with each other and with overall survival.

Results

We included 81 male and 32 female patients. The masseter muscle parameters differed significantly between sexes. The Spearman correlation coefficients between C3 CSA and Masseter volume and between L3 CSA ad Masseter volume were 0.67 and 0.54 ($p < 0.001$) respectively. In multivariate analysis, low MSI was a significant predictor for decreased overall survival (HR 3.0, $p<0.01$).

Conclusion

There is a strong association between masseter muscle volume and C3 CSA and L3 CSA. Low SMM (MSI) predicts decreased overall survival. Further research should investigate the relationship between muscle function and masseter muscle parameters and impacting factors on masseter muscle dimensions.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common type of cancer worldwide with 890.000 new cases and 450.000 deaths in 2018. It is commonly diagnosed in elderly patients in association with heavy alcohol and tobacco use.[1] Human papillomavirus (HPV) associated oropharyngeal cancer is found in younger patients and has a more favorable prognosis due to better responses to chemo- and radiotherapy and these patients have fewer comorbidities than patients with HPV-negative HNSCC. Approximately 30 to 40% of patients present with early-stage disease, which is defined as stage I or II, meaning at least 60% of patients present with advanced stage disease defined as stage III or IV. Advanced stage disease is characterized by large tumors with local invasion, regional lymph node involvement and/or distant metastases. HNSCC at this stage is associated with a high risk of locoregional recurrence and distant metastasis resulting in a poor 5-year overall survival of less than 50%. There is a need for accurate prognostic factors to tailor treatment for HNSCC patients, and sarcopenia is emerging as a novel candidate in HNSCC.[2–4]

Sarcopenia is defined as the loss of skeletal muscle mass (SMM) and muscle function[5], although measurements of only SMM are often used in literature. Sarcopenia was first thought to be a physiological state in the elderly, however scientific research has changed the perception of the condition and uncovered a myriad of causes. Sarcopenia can be the result of cancer cachexia, a disruption in energy and protein balance caused by reduced food intake and hypermetabolism. Cancer cachexia can be divided in three clinical stages: precachexia, cachexia and refractory cachexia. Progression between stages is dependent on factors such as cancer type and stage, decreased food intake and therapy resistant disease.[6,7]

Patients with HNSCC are at an increased risk for cancer related cachexia and sarcopenia. Partly this is due to dysphagia caused by tumor localization or its treatment and side effects thereof. Moreover, patients with HNSCC might present with underlying malnutrition caused by poor diet, tobacco use or alcohol abuse.[8,9]

Sarcopenia, and particularly low SMM, has been associated with adverse treatment outcome in patients with cancer. Sarcopenic cancer patients treated with surgery are at risk for complications and decreased survival.[10] In HNSCC, low SMM has been associated with and increased risk of surgical complications and cisplatin dose-limiting toxicity and with decreased survival.[11–13] Low SMM can be considered as an emerging biomarker for the clinical setting in HNSCC patients.[14]

While the gold standard for total SMM assessment is full body imaging, earlier research has shown that the muscle cross-sectional area (CSA) measured on a single abdominal cross-sectional slice at the level of the third lumbar vertebra (L3) on computed tomography (CT) imaging can provide accurate estimates of patient's total SMM.[15] Unfortunately, patients treated for head and neck cancers do not usually have imaging performed at this level. Therefore, a

method was developed to assess SMM on a single CT slide at the level of the third cervical vertebra (C3) in HNC patients.[16] In this method the CSA of both sternocleidomastoid and paravertebral muscles were measured. However, CSA assessment at this level may be impaired by extension of primary tumor and/or lymph nodes or previous treatment. Moreover, accurate assessment is time consuming.[17,18] There is a need for a reliable index muscle that is consistently present on routine imaging, is rarely impacted by disease or treatment and is quick and easy to characterize using commonly used imaging software. For this purpose, we propose the masseter muscle. The masseter muscle has been shown to be adequate in determining SMM and predicting mortality in other fields of medicine.[19–21]

The purpose of this study was firstly to investigate whether masseter muscle quantity measures such as masseter cross-sectional area (MCSA), masseter muscle volume (MV), masseter muscle maximum thickness (MT) and measurements of muscle quality defined by the Hounsfield unit (HU) and expressed as the average HU of all measured tissue (HU_{tot}) and in a region of interest (HU_{ROI}) obtained on routine CT-imaging, correlate with the CSA at C3 and L3. Secondly, we sought to investigate the predictive impact of these masseter muscle parameters and overall survival.

METHODS AND MATERIALS

ETHICAL CONSIDERATIONS

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.

PATIENT AND STUDY DESIGN

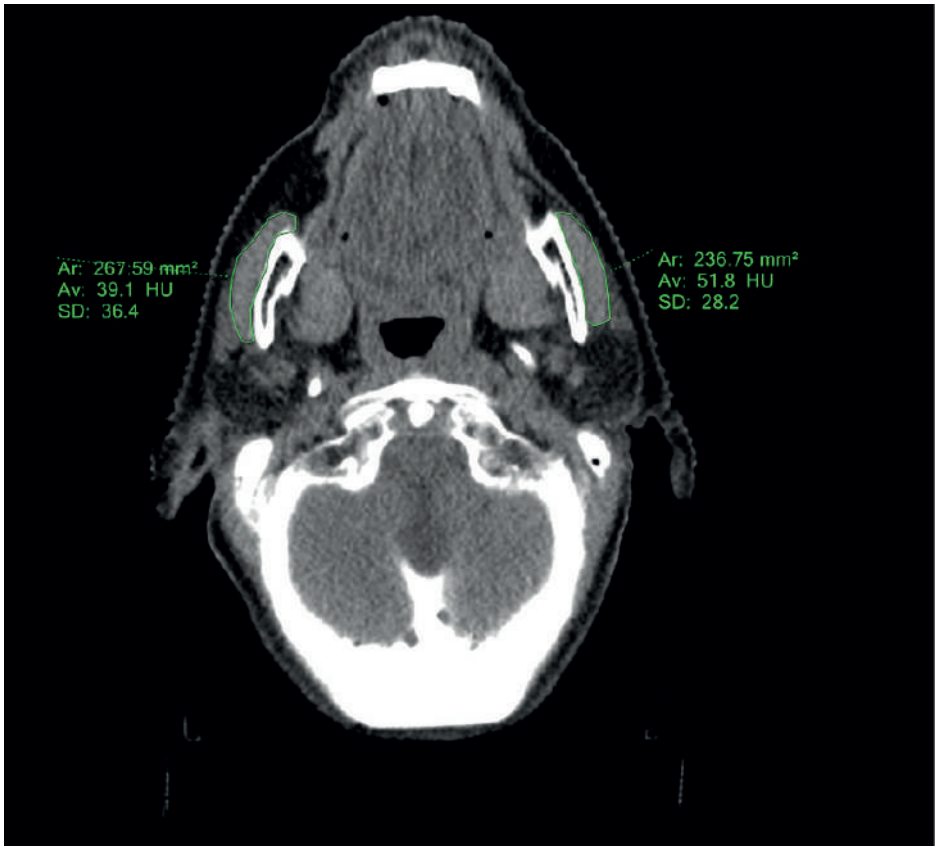
We reviewed patients with newly diagnosed, pathologically proven advanced stage HNSCC who underwent a whole body FDG-PET/CT-scan between 2010 and 2018 at the University Medical Center Utrecht (UMCU), the Netherlands. Patient scans who were incomplete, of insufficient quality or incompatible with current imaging software were excluded from further analysis. Patient factors with known or expected relation to HNC outcome measures or development of sarcopenia were collected: age at diagnosis, gender, histological diagnosis, comorbidities scored using the Charlson Comorbidity Index (CCI) and the ACE-27 score, tumor site and tumor staging according to the 7th edition of the UICC TNM classification system, human papillomavirus (HPV) status for oropharyngeal carcinomas, weight loss 6 months prior to diagnosis and treatment regimens.

RADIOLOGICAL ASSESSMENT

Segmentation of muscle tissue at the level of C3 and L3 was manually performed using the commercially available software package SliceO-matic (Tomovision, Canada). For analysis

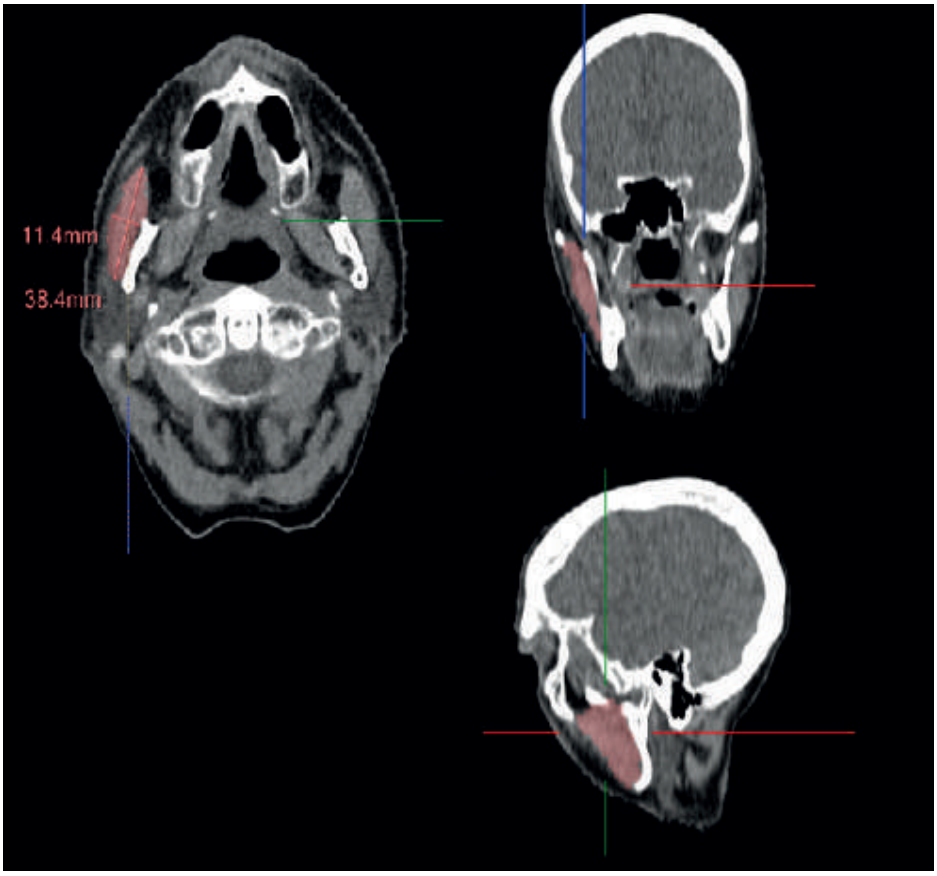
of the CSA at the level of C3, a standard method for slide selection was used, where the first slide to show the entire vertebral arc and the transverse and spinous process when scrolling in a cephalad to caudad direction was selected. Skeletal muscle tissue was identified using HU range settings from -29 to 150 HU and the outer contours of the sternocleidomastoid and paravertebral muscles were traced manually. The CSA at the level of C3 was determined as the sum of delineated areas of the paravertebral muscles and both sternocleidomastoid muscles within a HU range of -29 to 150HU in cm^2. For analysis of the CSA at level L3 the muscle groups analyzed were the psoas, paravertebral and the anterior abdominal wall. For assessment of the masseter muscle, Intellispace (version 14, Phillips, Netherlands) was chosen for its ability to measure the volume of a selected structure (e.g., the masseter muscle) using the Tumor-Tracking feature which allows for rapid tissue volume assessment. Masseter CSA was measured at the level of the dens of the second cervical vertebra (Figure 1).

Figure 1. Assessment of the masseter cross sectional area at the level of the 2nd cervical vertebrae.



Coronal tilt alignment was made according to a tangent running through the dens and hard palate. Masseter CSA was measured by outlining the outer surfaces of masseter after which IntelliSpace automatically calculated the surface area (mm2), a method independent of the HU value of the defined area. Masseter volume (MV) (cm3) and the total Hounsfield Unit value (HUtot) were automatically calculated after segmenting the entire muscle (Figure 2).

Figure 2. Assessment of the Masseter volume.



Maximum thickness of the masseter was determined using the measuring-tool included in Intellispace (mm). HUROI was determined in a 1-centimeter diameter circle on the same level as Masseter CSA.

Since the state of a patient's teeth may impact masseter function and size each patient was examined for the presence of dental elements.[22] Dental status was scored as follows: (0) no missing dentition, (1) one or more missing teeth, (2) total absence of dentition. Presence of scattering cause by (dental) implants was scored as follows: (0) no scattering present, (1) slight scattering present, (2) significant scattering present. Measurements were performed bilaterally for each patient and an average was calculated and used for further analysis.

Earlier research has shown that there is excellent agreement between image scoring software programs used for measuring CSA.[23] Therefore, we found it acceptable to use the two programs independently and compare the data.

BODY COMPOSITION MEASUREMENTS

Weight and height were recorded during patient's first consultation at our out-patient clinic and used to calculate Body Mass Index (BMI) and Body Surface Area (BSA) using the Mosteller formula.[24] Lumbar skeletal muscle index (LSMI), cervical skeletal muscle index (CSMI) and masseter skeletal muscle mass index (MSMI) were calculated by dividing the corresponding patient's CSA values by patient's squared height. There is, to our knowledge, no scientific consensus on a cut-off value for MSMI. We therefore designated patients present in the lowest quartile of MSMI for their specific gender as "low MSMI".

OVERALL SURVIVAL

The status of the patient (alive/deceased) was acquired from the UMCU electronic patient data system on date of last follow-up. Overall survival (OS) was defined as the time between the date of histologic diagnosis and death, or date of last follow-up. UMCU patient system is linked to the provincial government register and is updated continuously for patients living in the Utrecht province. Patients were considered alive if no date of death was available on date of last follow-up or if there was no physician note reporting on their death. Cause of date was determined by physician's notes.

STATISTICAL ANALYSIS

SPSS 26 for Windows (IBM, Armonk, NY, U.S.A.) was used for analysis. Descriptive statistics were calculated with the continuous variables presented as mean (standard deviation) or median (interquartile range). Discrete variables were displayed as counts (percentages). Normality was investigated by using the Kolmogorov-Smirnov test. Characteristics and muscle measurements were analyzed using independent-samples t-test for normally distributed variables, independent-samples test for skewed variables and Fisher's exact test or Pearson's chi-squared test for categorical variables. Spearman correlation coefficients were calculated to establish the relationship between L3 measurements, C3 measurements and masseter measurements. A correlation coefficient of (-)0.8 to (-)1 was interpreted as a very strong correlation, (-)0.6 – 0.8 as strong, (-)0.4 to (-)0.6 as moderate, and (-)0.2 to (-)0.4 as a low correlation.[25] Radiological measurements and patient characteristics were analyzed using Cox regression proportional hazards first as univariate analysis. Variables with a p-value lower than 0.05 and dental status were included for multivariate analysis. The backward step-method was chosen for multivariate analysis. The influence of MSMI and low lumbar SMI using the cut-off established by Wendrich et al.[11] on overall survival was evaluated using Kaplan-Meier curves and associated Log-Rank tests.

RESULTS

SEARCH AND INCLUSION

In total 139 patients who had undergone a CT-scan were screened for study viability. Of these patients 15.2% (n=21) had (partially) missing imaging and were subsequently excluded. Furthermore, in 3.6% (n=5) of included patients the available imaging was of insufficient quality for analysis either due to low resolution or poor image quality. In total, 113 whole body FDG-PET/CT-scans were included for further image analysis.

PATIENT CHARACTERISTICS

In total 113 patients were included, with a median age of 61.9 (IQR 56.0 – 68.40) years. Of the included patients, 81 (71.3%) were male. A minority of patients had no history of alcohol consumption (n=32, 28.3%) or smoking (n=6, 14.2%). Forty-six patients (40.7%) were categorized as having normal weight based on body mass index score (BMI). Most patients presented with a primary tumor (n= 99, 87.6%), commonly localized in the oropharynx (n= 73, 64.6%) of which 16 (14.2%) were HPV-positive. Most patients presented with a clinical TNM stage IV tumor (n= 71, 62.8%) and patients were most commonly treated with a combination of radiotherapy and systemic therapy (n= 53, 46.9%, Table 1). Twenty-nine patients were designated as "Low MSMI" and eighty-four as "Normal MSMI". There was a statistically significant difference between these groups for L3 SMI, C3 CSA and BMI (p = 0.001, 0.007 and, 0.003, respectively).

Table 1. Baseline characteristics of included patients and differences between normal and low masseter muscle index

Characteristics	All patients (n = 113) N (%) or Mean (±SD)	Normal MSMI (n = 84) N (%) or Mean (±SD)	Low MSMI (n = 29) N (%) or Mean (±SD)	p-value
Median age (years) (IQR)	61.7 (56.0 – 68.4)	63.0 (55.9 – 69.2)	61.4 (56.6 – 64.6)	0.3
Male	81 (71.7)	61 (72.6)	20 (69.0)	0.8
Deceased	43 (53.1)	41 (48.2)	19 (67.9)	0.08
Alcohol intake				0.5
Never	32 (28.3)	23 (27.4)	9 (31.0)	
Light (≤1 units/day)	26 (23.0)	17 (20.2)	9 (31.0)	
Moderate (>1-<4 units/day)	32 (28.3)	26 (31.0)	6 (20.7)	
Heavy (>4 units/day)	23 (20.4)	18 (21.4)	5 (17.2)	
Smoking status				
Never	16 (14.2)	15 (17.9)	1 (3.4)	
Current	57 (50.4)	36 (42.9)	21 (72.4)	

Table 1. (Continued)

Characteristics	All patients (n = 113) N (%) or Mean (±SD)	Normal MSMI (n = 84) N (%) or Mean (±SD)	Low MSMI (n = 29) N (%) or Mean (±SD)	p-value
Former	30 (35.4)	33 (39.3)	7 (24.1)	
Adult Comorbidity Evaluation-27				1.0
None	18 (15.9)	13 (15.5)	5 (17.2)	
Mild	38 (33.6)	29 (34.5)	9 (31.0)	
Moderate	34 (30.1)	25 (29.8)	9 (31.0)	
Severe	23 (20.4)	17 (20.2)	6 (20.7)	
Charlson Comorbidity Index				0.4
No risk (0)	2 (1.8)	2 (2.4)	0 (0.0)	
Low risk (1-2)	43 (38.1)	30 (35.7)	13 (44.8)	
Moderate risk (3-4)	41 (36.3)	29 (34.5)	12 (41.4)	
High risk (5)	27 (23.9)	23 (27.4)	4 (13.8)	
Body Mass Index (BMI) (kg/m^2)				**0.003**
<20 (underweight)	23 (20.4)	11 (13.1)	12 (41.4)	
20-24.9 (normal weight)	46 (40.7)	34 (40.5)	12 (41.4)	
25-29.9 (overweight)	34 (30.1)	29 (34.5)	5 (17.2)	
≥30 (obese)	10 (8.8)	10 (11.9)	0 (0.0)	
BSA	3.62 (±0.92)	3.71 (±0.93)	3.33 (±0.85)	0.05
C3 CSA	37.97 (±8.53)	39.19 (±8.23)	34.25 (±8.44)	**0.007**
L3 SMI	45.43 (±8.08)	46.83 (±7.66)	41.18 (±7.95)	**0.001**
Tumor type				0.5
Primary	99 (87.6)	72 (85.7)	27 (93.1)	
Recurrent	9 (8.0)	8 (9.5)	1 (3.4)	
Second primary	5 (4.4)	4 (4.8)	1 (3.4)	
Localization				0.9
Oral cavity	8 (7.1)	5 (6.0)	3 (10.3)	
Oropharynx	73 (64.6)	55 (65.5)	18 (62.1)	
Nasofarynx	3 (2.7)	2 (2.4)	1 (3.4)	
Hypopharynx	18 (15.9)	2 (2.4)	5 (17.2)	
Larynx	8 (7.1)	7 (8.3)	1 (3.4)	
Lymph node	3 (2.7)	2 (2.4)	1 (3.4)	
Human Papillomavirus Status				0.1
Negative	70 (61.9)	51 (60.7)	19 (65.5)	
Positive	16 (14.2)	15 (17.9)	1 (3.4)	
Not recorded	27 (23.9)	18 (21.4)	9 (31.0)	

Table 1. (Continued)

Characteristics	All patients (n = 113) N (%) or Mean (±SD)	Normal MSMI (n = 84) N (%) or Mean (±SD)	Low MSMI (n = 29) N (%) or Mean (±SD)	p-value
T-staging				0.2
T0	1 (0.9)	1 (1.2)	0 (0.0)	
T1	21 (18.6)	17 (20.2)	4 (13.8)	
T2	37 (32.7)	29 (34.5)	8 (27.6)	
T3	24 (21.2)	16 (19.0)	8 (27.6)	
T4a,b	29 (25.7)	20 (23.8)	9 (31.0)	
Tx	1 (0.9)	1 (1.2)	0 (0.0)	
N-staging				0.6
N0	44 (38.9)	33 (39.3)	11 (37.9)	
N1	18 (15.9)	13 (15.5)	5 (17.2)	
N2a,b,c	50 (50.3)	37 (44.0)	13 (44.9)	
N3	1 (0.9)	1 (1.2)	0 (0.0)	
M-staging				
M0	104 (92.0)	78 (92.9)	26 (89.7)	0.4
M1	2 (1.8)	2 (2.4)	0 (0.0)	
Mx	7 (6.2)	4 (4.8)	3 (10.3)	
Tumor, Node, Metastasis (TNM) stage				0.9
Stage I	4 (3.5)	3 (3.6)	1 (3.4)	
Stage II	18 (15.9)	14 (16.7)	4 (13.8)	
Stage III	20 (17.7)	16 (19.0)	4 (13.8)	
Stage IV	71 (62.8)	51 (60.7)	20 (69.0)	
Treatment modality				0.4
Surgery with or without (chemo)radiotherapy	34 (30.1)	28 (33.3)	6 (20.7)	
Radiotherapy	26 (23.0)	18 (21.4)	8 (27.6)	
Radiotherapy with concurrent cisplatin, carboplatin or cetuximab	53 (46.9)	38 (45.2)	15 (51.7)	

Comparison of patient characteristics based on MSMI classification. Statistically significant differences are shown in bold.

BODY COMPOSITION MEASUREMENT

Table 2 shows a significant difference based on gender for BMI (p=0.02), BSA, L3 CSA, C3 CSA, MCSA, MV, MT, L3 SMI and MSMI (all p<0.001). There was no significant difference based on gender for HU_{tot} and HU_{ROI} (Table 2).

Table 2. Body composition measurements

Characteristic	Total (n=113)	Male (n=81)	Female (n=32)	p
BMI at diagnosis Median (IQR) [Range]	24.2 (20.8–26.6) [14.9-40.0]	24.6 (21.8– 26.8) [14.9–38.4]	21.8(18.7 – 25.9) [15.8- 40.1]	**0.02**
BSA at diagnosis Mean (SD) [Range]	3.6 (0.9) [1.7–6.5]	3.9(0.9) [1.7–6.5]	3.0 (0.8) [2.0– 5.8]	**<0.001**
Muscle CSA L3 (cm^2) Mean (SD) [Range]	139.6 (30.4) [65.3–235.0]	148.9 (28.5) [85.4–235]	116.2 (21.0) [65.3–158.5]	**<0.001**
Muscle CSA C3 (cm^2) Mean (SD) [Range]	38.0 (8.5) [19.0– 58.8]	40.8 (7.7) [25.9–58.8]	30.8 (5.9) [19.0–44.7]	**<0.001**
Muscle CSA masseter (mm^2) Mean (SD) [Range]	395.3 (84.3) [234.1–624.4]	415.7 (85.5) [243.0–624.4]	343.8 (54.7) [234.1–509.1]	**<0.001**
Masseter volume (cm^3) Mean (SD) [Range]	18.2 (5.5) [8.3– 36.1]	19.4 (5.3) [8.4–36.1]	15.2 (4.9) [9.0–30.2]	**<0.001**
Masseter maximum thickness (mm) Median (IQR) [Range]	12.8 (10.8 – 15.0) [8.5–21.1]	13.9 (11.1-15.4) [8.5–21.1]	11.4 (10.3 – 12.8) [8.9–18.0]	**0.001**
HU_{tot} Median (IQR) [Range]	110.2 (95.0 – 128.4) [59.5-474.0]	111.8 (95.7– 129.3) [61.7–192.3]	104.9 (89.6–127.0) [59.5–474.0]	**0.3**
HU_{ROI} (HU) Median (IQR) [Range]	56.2 (48.2– 65.6) [22.0-310.6]	56.9 (49.4 – 65.5) [28.8–310.6]	52.3 (46.6– 60.9) [22.0–83.2]	**0.07**
L3 SMI (cm^2/m^2) Mean (SD) [Range]	45.4 (8.1) [39.8-50.8]	47.2 (7.9) [27.4–65.1]	41.0 (6.9) [23.7–52.8]	**<0.001**
MSMI (mm^2/m^2) Mean (SD) [Range]	129.0 (24.1) [75.4-189.3]	132.1 (26.0) [75.4–189.3]	121.2 (16.3) [80.1– 148.1]	**<0.001**

Comparison of body composition measurements between sexes. Statistically significant differences are shown in bold.

Table 3. Masseter muscle parameters left-right deviation.

Measurement	Total
MCSA Median (IQR) [Range] (mm^2)	33.8 (16.7 – 61.1) [0.0 - 184.6]
MV Median (IQR) [Range] (cm^3)	1.0 (0.5 - 2.3) [0.02 - 5.4]
MT Median (IQR) [Range] (mm)	1.0 (0.5 – 1.9) 1.0 [0.0 - 8.0]
HU_{tot} Median (IQR) [Range]	4.7 (1.5 - 9.0) [0.0 - 374.0]
HU_{ROI} Median (IQR) [Range]	9.7 (4.3 – 18.5) [0.1 - 548.9]

Illustration of the deviation between the left and right-sides masseter parameters in individual patients. All variables are shown as median values with interquartile range (IQR) and range. MCSA = Masster cross sectional area, MV = Masseter volume, MT = Masseter maximum thickness, HUtot (tot in lowerscript) = The total HU-value of the measured tissue, HUroi (roi in lowerscript) = The HU value of a 1cm diameter circle in the measured tissue.

Generally, there was some amount of left-right difference present. The deviations are shown as median (percentage of average masseter characteristic). The median left-right difference for MCSA, MV, MT, HU_{tot} and HU_{ROI} were 33.78 mm^2 (8.55%), 0.99 cm^3 (5.45%), 1.0 mm (7.67%), 4.70 HU (4.09%) and 9.70 HU (16.62%) respectively (Table 3). There was a significant difference in left-right deviation of median MV and HU_{tot} for different scattering scores ($p < 0.001$; Table 4). MV and HU_{tot} had a significant negative relationship with dental score ($p = 0.017$ and 0.010, respectively; Table 5).

CORRELATION BETWEEN MASSETER PARAMETERS AND MUSCLE MASS MEASURED AT C3 AND L3

All masseter and muscle mass parameters had a highly significant correlation with each other ($p = 0.002$ to $p < 0.001$). The strongest correlation was between L3 CSA - C3 CSA ($r = 0.715$), followed by C3 CSA – MV ($r = 0.671$) and L3 CSA – MV ($r = 0.573$). MT was moderately correlated to C3 CSA ($r = 0.527$) and L3 CSA ($r = 0.439$), and low to LSMI ($r = 0.342$). MCSA had low to moderate correlation with L3 CSA and C3 CSA ($r = 0.469$, 0.573). MSMI had a low correlation with LSMI, L3 CSA and C3 CSA ($r = 0.291$, $r = 0.193$, $r = 0.349$, respectively; Table 6)).

Table 4. Effect of scattering on masseter left-right deviation.

Measurement	Scatter score 0 (n=38)	Scatter score *1* (n=44)	Scatter score *2* (n=31)	p-value
MCSA Median (IQR) (mm^2) [Range]	35.15 (17.78 – 61.12) [0.78 – 117.42]	36.90 (17.93 – 64.65) [0.00 – 158.55]	29.62 (14.57 – 52.52) [3.82 – 184.62]	0.83
MV Median (IQR) (cm^3) [Range]	1.22 (0.67 – 2.40) [0.02 – 5.31]	0.62 (0.27 – 1.51) [0.02 – 5.41]	1.48 (0.82 – 2.32) [0.05 - 4.25]	**<0.001**
MT Median (IQR) (mm) [Range]	0.85 (0.5 – 1.88) [0.00 – 8.00]	1.15 (0.5 – 1.78) [0.00 – 6.10]	1.00 (0.4 – 1.9) [0.00 – 3.20]	0.25
HU_{tot} Median (IQR) [Range]	2.65 (1.08 – 4.33) [0.00 – 25.50]	5.30 (2.48 – 8.73) [0.30 – 374.00]	8.40 (4.2 – 17.0) [0.50 – 26.60]	**<0.001**
HU_{ROI} Median (IQR) [Range]	9.50 (4.68 – 18.23) [0.10 – 38.98)	7.60 (4.25 – 16.83) [1.00 – 58.60]	12.90 (4.2 – 19.7) [0.20 – 548]	0.53

Effect of scattering on deviations in masseter assessment. Scatter score is defined as follows: 0 = no scattering present, 1 = slight scattering present, 2 = significant scattering present. Statistically significant differences are shown in bold

Table 5. Effect of dental status on masseter measurements

Measurement	Dental score *0 (n=77)*	Dental score *1 (n=16)*	Dental score *2 (n=20)*	p-value
MCSA Mean (SD) (mm^2)	403.71 (88.68)	380.04 (71.90)	375.30 (73.73)	0.34
MV Mean (SD) (cm^3)	19.17 (5.90)	16.68 (4.90)	15.57 (2.84)	**0.02**
MT Median (IQR) (mm)	12.75 (10.98 – 15.45)	13.05 (10.45 – 15.13)	12.10 (10.41 – 13.78)	0.94
HU_{tot} (IQR)	115.60 (98.15 – 133.15)	108.55 (96.3 – 116.35)	95.85 (83.78 – 112.08)	**0.01**
HU_{ROI} Median (IQR)	56.85 (48.85 – 65.83)	56.05 (47.73 – 61.34)	53.03 (47.33 – 60.58)	0.35

Effect of dental status on masseter parameters. Dental score is defined as follows: Dental status was scored as follows: 0 = no missing dentition, 1 = one or more missing teeth, 2 = total absence of dentition.

Table 6. Spearman correlation coefficients of the different skeletal mass measurements

Relation	Correlation coefficient	p-value
LSMI - MSMI	0.291	**0.002**
LSMI – MCSA	0.335	**<0.001**
LSMI – MV	0.418	**<0.001**
LSMI - MT	0.342	**<0.001**
L3 CSA - MSMI	0.193	**<0.001**
L3 CSA - MCSA	0.469	**<0.001**
L3 CSA - MV	0.542	**<0.001**
L3 CSA - MT	0.439	**<0.001**
C3 CSA - MSMI	0.349	**<0.001**
C3 CSA – MCSA	0.573	**<0.001**
C3 CSA – MV	0.671	**<0.001**
C3 CSA - MT	0.527	**<0.001**
L3 CSA – C3 CSA	0.715	**<0.001**

Correlation between different masseter parameters, lumbar skeletal muscle index, cross-sectional area at level L3 and cross-sectional area at level C3 are shown.

UNIVARIATE AND MULTIVARIATE COX REGRESSION ANALYSIS

All clinically relevant characteristics or characteristics relevant to masseter muscle parameters were tested using Cox univariate regression analysis. In univariate analysis, MCSA, MSMI, L3 CSA, C3 CSA, BSA, CCI were all significantly associated with overall survival (Table 7). For variables that were strongly correlated or dependent on each other (e.g., MSMI, low MSMI and MCSA) the variable with the lowest p-value was included in the multivariate analysis. As to not exceed the >10 events per variable rule BSA was excluded from multivariate analysis based on expert opinion. This left Low MSMI-classification, C3 CSA, L3 CSA and CCI as included variables. Low MSMI and CCI score remained as the only independent predictors of overall survival (HR 3.032, p=0.002 and HR 1.338, p<0.001, respectively; Table 8).

Table 7. Univariable Cox regression analysis

Risk factor	HR	95% CI	p-value
MCSA	1.0	0.99 - 1.0	0**.02**
MV	0.95	0.91 – 1.0	0.06
MT	0.5	0.86 – 1.0	0.27
HU_{tot}	1.0	0.99 – 1.0	0.23
Masseter ROI	1.0	0.98 – 1.1	0.55
Low MSMI	2.2	1.2 – 4.3	**0.02**
CSMI	0.92	0.80 – 1.1	0.28
LSMI	0.97	0.93 – 1.0	0.13

Table 7. (Continued)

Risk factor	HR	95% CI	p-value
L3 CSA	0.99	0.98 – 1.0	**0.03**
C3 CSA	0.95	0.91 – 1.0	**0.04**
Body mass index (kg/m²)			
<20 (underweight)	*Ref.*		
20-24.9 (normal weight)	1.61	0.84 – 3.10	0.29
25-29.9 (overweight)	0.52	0.26 – 1.03	0.06
≥30 (obese)	1.40	0.61 – 3.22	0.43
Body mass index	0.95	0.90 – 1.01	0.13
Body surface area	0.71	0.52 – 0.96	**0.02**
Charlson comorbidity index	1.28	1.15 – 1.44	**<0.001**
Teeth (categorized)			
No teeth missing	*ref*		
One or more dental elements missing	1.07	0.52 – 2.22	0.85
Complete lack of denture	0.12	0.64 – 2.41	0.52
Smoking status (never vs. ever)	1.41	0.61 – 3.29	0.42
Alcohol status (never vs. ever)	1.01	0.50 – 2.06	0.97
Localization (oropharynx vs. other)	0.70	0.41 – 1.18	0.18
Stage (I-II vs. III-IV)	1.17	0.62 – 2.21	0.62
T-stage (T1-T2 vs. T3-T4)	1.08	0.65 – 1.80	0.76
Treatment (CRT vs. other)	0.63	0.35 – 1.15	0.13
Surgery (yes vs. no)	1.21	0.70 – 2.10	0.44

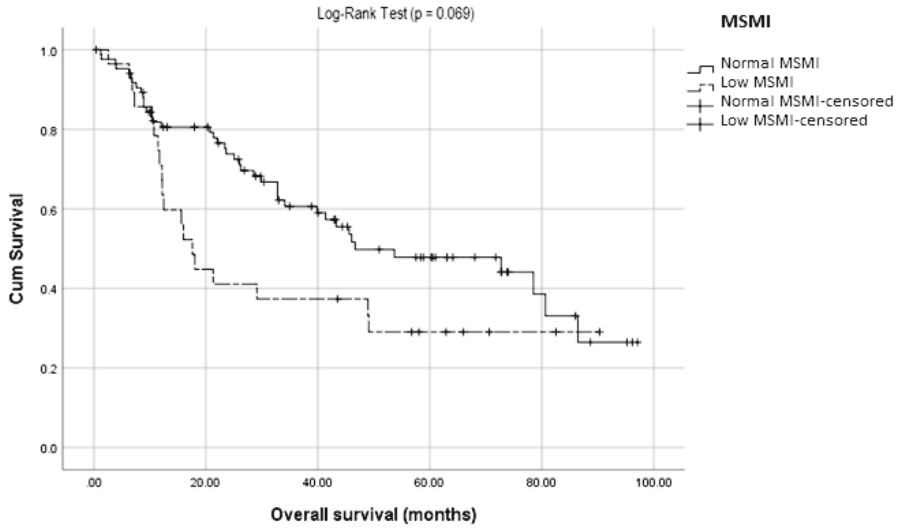
Table 8. Multivariable Cox regression analysis

Risk factor	HR	95% CI	p-value
Charlson comorbidity index	1.34	1.16 – 1.53	**<0.001**
Low MSMI	3.03	1.52 – 6.03	**0.002**
L3 CSA	1.00	0.98 – 1.02	0.99
C3 CSA	1.00	0.95 – 1.06	0.93

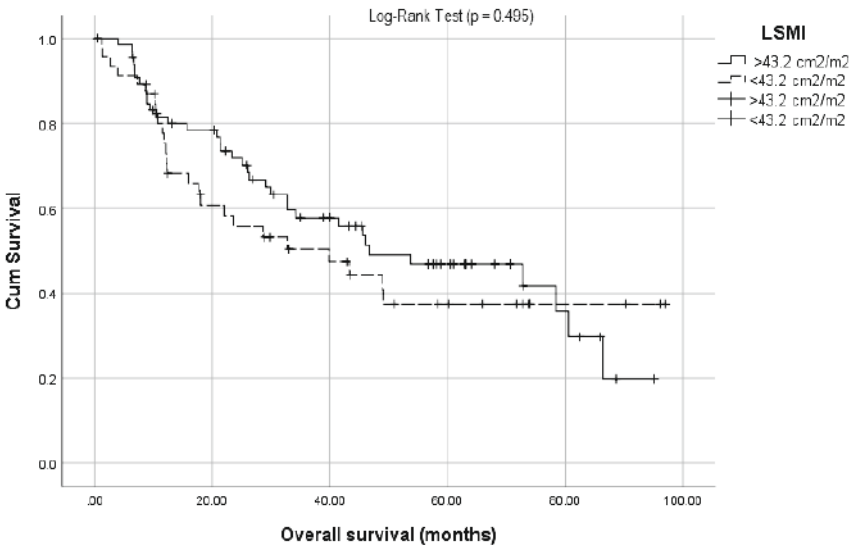
OVERALL SURVIVAL

Mean overall survival for patients with low MSMI was 16.81 months (IQR 10.92 – 54.86) compared to 32.82 months (IQR 12.21 – 59.55) for patients with normal MSI (log rank p = 0.07; Figure 3). There was no significant difference in overall survival between patients with low and normal LSMI using the previously established cut-off value of LSMI ≤43.2 cm^2/m^2 (Figure 4).[11]

■ **Figure 3.** Kaplan Meier survival curve for patients with normal and low MSMI.



■ **Figure 4.** Kaplan Meier survival curve for patients with normal and low LSMI



DISCUSSION

Patients with head and neck cancers are at an increased risk of sarcopenia compared to patients with other types of cancer. [8,9,26] Previous reports have established that measuring muscle mass at the level of L3 on CT-scans is a reliable method for assessing total body skeletal muscle mass. Unfortunately, scans at this lumbar level are rarely available in patients with HNSCC. Previously published findings by Swartz et al. show that the CSA of skeletal muscles at level of C3 strongly correlates with the CSA of skeletal muscles at the level of L3, indicating that this is a viable alternative method. However, determining the CSA at C3 is time consuming and can be impacted by either treatment (e.g., neck dissection) or disease (e.g., invading lymph node in the SCM). We therefore investigated to what degree masseter muscle parameters are associated with levels L3 and C3, and their relationship on overall survival. We found moderate to strong associations for most masseter parameters with muscle mass on level L3 and C3, with MV being the strongest followed by masseter CSA. Low MSMI was shown to be an independent prognostic for decreased overall survival in multivariate analysis.

We found that the scatter-score had a significant impact on MV and masseter HU measurements. It stands to reason that scattering results in unreliable masseter HU-measurements, as scattering generally causes a larger spread of pixel values shown on imaging. The method we used to determine MV used the Tumor Tracking feature included in IntelliSpace which utilizes the pixel values recorded and inputs them into an algorithm to determine whether certain areas are related to each other. It follows that a larger spread in pixel-values decreases the reliability of the algorithm. Manual adjustment of the measured area was often required to fully include all masseter muscle tissue, although this too becomes unreliable when significant scattering is present. However, we found no significant relationship between scatter-score and MT, HU_{ROI} and MCSA (and subsequently MSI) leaving these as viable options when significant scattering is present. Our included patient group had 8 (7.1%) patients with tumors in the oral cavity. Based on expert opinion none of those significantly impacted the masseter muscle. If present, one solution could be that in the rare cases where the muscle is unilaterally significantly affected, a contralateral masseter measurement is counted twice.

Our findings are consistent with other studies which determine that masseter CSA predicts mortality in patients suffering from blunt trauma, traumatic brain injury or undergoing carotid endarterectomy. [19–21] However, differences between our study and earlier scientific reports should be noted. Oksala et al, Wallace et al and Hu et al. all used the masseter CSA measured at 2cm below the arcus zygomaticus. In our study, we chose the first slice showing the dens of the C2 vertebra as our landmark as this was easily identifiable when scrolling in cephalad-to-caudad fashion.

Secondly, whereas Wallace et al. and Hu et al. did not correct for head tilt, Oksala et al. adjusted their CT-scans for both sagittal and coronal head tilt. Based on expert opinion we chose to

only adjust for coronal head tilt. Using our center's patient positioning protocol, we expected very little to no sagittal tilt in our imaging.

We corrected the observed MCSA by dividing by squared body height to determine a masseter muscle mass index (MSMI). The masseter muscle characteristics are dependent on various factors such as dental status and craniofacial structure.[22,27] MCSA was adjusted by body height, as it has been established that muscle mass corrected by body height is an accurate adjustment method for other CSA measurements.[28] Although we found a significant difference in skeletal muscle mass and body composition indicators for groups based on MSMI, we only found a near significant difference in overall survival between patients classified as normal or low MSMI (p=0.069). Conversely, in multivariate analysis low MSI classification significantly predicted all-cause mortality.

Another limitation of our retrospective design is that patient frailty and sarcopenia as defined by the European Working Group on Sarcopenia in Older People (EWGSOP) could not be assessed. Sarcopenia is diagnosed by evaluating muscle mass and muscle function.[6] Further prospective studies are needed that correlate masseter findings with muscle strength (e.g., by grip strength) and physical performance (e.g., by the Short Physical Performance Battery and the Timed Up and Go-test).

Finally, whole-body PET-CT-scans are only performed in patients with advanced disease (stage III and IV). We expected that this would not cause any significant bias in our study as Swartz et al. found no significant difference in C3 or L3 CSA between patients with traumatic injury and head and neck cancer allowing for extrapolation to both healthy patients and patients with malignant disease.

CONCLUSION

We conclude that several masseter muscle parameters, namely MV, masseter CSA and MT, are significantly correlated (varying from moderate to strong) with cross-sectional muscle area at cervical and lumbar level. Additionally, MSMI, defined as masseter CSA divided by squared patient's height in meters, proved to be a significant prognostic factor for decreased overall survival (HR 3.03). In patients without cross-sectional imaging at the level L3 or C3 or with impaired C3 measurements, masseter muscle parameters could serve as an alternative for assessment of skeletal muscle mass. We recommend further studies to determine factors influencing masseter parameters as to formulate an improved method to correct for individual patient factors, e.g., dental status, previous dental disease, previous cancer treatment and facial morphologic features. Subsequently, this research should correlate masseter parameters with muscle strength and physical performance.

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CHAPTER 5

Cut-off values for low skeletal muscle mass at the level of C3 in patients with head and neck cancer

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Submitted ■

ABSTRACT

Background

Low skeletal muscle mass is associated with adverse outcomes. For patients with head and neck cancer, skeletal muscle mass is often assessed at the third cervical vertebra (C3) on head and neck imaging. Various cut-off values for low skeletal muscle mass are proposed in literature. We aim to provide cut-off values for low skeletal muscle mass in head and neck cancer patients.

Material and methods

In total, 1415 patients with pre-treatment head and neck imaging between 2008 and 2018 were included. Skeletal muscle area was manually delineated at the level of C3 and corrected for patients squared height to obtain the cervical skeletal muscle mass index (CSMI). Gender and body-mass specific cut-off values for low skeletal muscle mass were calculated based on mean CSMI – 2 standard deviations (SD) as suggested by the European Working Group on Sarcopenia in Older People (EWGSOP).

Results

Of the 1415 included patients, the majority was male (69.8%) and had a body mass index (BMI) below 25 kg/m^2 (59.2%). A primary tumor localization in the oropharynx (35.3%) and a tumor, node, metastasis (TNM) stage IV tumor (60.5%) were most frequently observed. CSMI was significantly correlated with gender (r^2=0.4, p<0.01) and BMI (r^2=0.4, p<0.01). For male patients with a BMI <25 kg/m^2, a CSMI ≤6.8 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤8.5cm^2/m^2 was defined for low SMM. For female patients with a BMI <25 kg/m^2, a CSMI ≤5.3 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤6.4 cm^2/m^2 was defined for low SMM.

Conclusions

This study is the first to provide standardized cut-off values for low SMM at the level of C3 in patients with HNC. This information may aid in the uniformity of low SMM definition in research.

INTRODUCTION

Research on body composition in cancer patients, and in particular on skeletal muscle mass (SMM), has increasingly gained interest over the past several decades. Low SMM is often referred to as sarcopenia, although a more comprehensive definition of sarcopenia is the combination of low SMM and low muscle function.[1] Due to the unavailability of routinely performed muscle function tests, most research in oncological patients focusses on radiologically assessed SMM, measured on routinely performed computed tomography (CT) or magnetic resonance imaging (MRI). Radiologically assessed low SMM at diagnosis has shown to predict adverse outcomes in a variety of cancer types and treatments.[2–6]

For HNC, low SMM has shown to be a significant predictive factor for cisplatin dose-limiting toxicity[7], the occurrence of a fistula after total laryngectomy[8] and flap-related complications in microvascular free flap head and neck reconstructive surgery.[9] It has also been shown that low SMM is prognostic for decreased survival in patients with HNC.[10–14]

Several diagnostic imaging modalities can be used to quantify SMM such as magnetic resonance imaging (MRI), computed tomography (CT), bioimpedance analysis (BIA) and dual energy X-ray absorptiometry (DEXA). BIA and DEXA are confounded by alterations in hydration, edema and food intake. Therefore, its use in assessing body composition of patients with cancer is not favored. First research on body composition was performed by measurement of skeletal muscle area (SMA) on a single axial-slice at the level of the third lumbar vertebra (L3).[15,16] The skeletal muscle area (SMA) at the level of L3 is then normalized for height to calculate the lumbar skeletal muscle index (lumbar SMI), which is used as a proxy of whole body skeletal muscle mass.[16] Abdominal CT imaging is not routinely performed in patients with HNC and is often only available in patients with advanced disease and those at risk for distant metastasis.

Measurements of SMM at the level of the third cervical vertebra (C3) have shown to correlate well with SMM measurements at the level of L3.[17] Therefore, in order to avoid selection bias (i.e. only patients with abdominal CT included) in research on SMM in HNC, measurement of SMA at the level of C3 is the preferred method. Measurement of SMA at the level of C3 consists of segmentation of both sternocleidomastoid muscles and the paravertebral muscles. If preferred, the SMA at the level of C3 can be converted to SMA at the level of L3 by using a previously published and validated prediction formula.[17]

Accurate diagnosis of low SMM in clinical practice is impeded by heterogeneous cut-off values used to diagnose patients with low SMM. In oncological literature different cut-off values for low SMM are used. The most used cutoff values in the field of research on body composition are the ones defined by Prado et al. and Martin et al.[15,18] Prado et al. used optimum stratification analyses between muscle mass and mortality in a population of 250 obese (body mass index (BMI) ≥ 30 kg/m^2) patients with respiratory or gastro-intestinal malignancies and found cut-off values for low muscle mass to be 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women as the

best predictor for mortality. Martin et al. also utilized optimum stratification analysis for low SMM as a predictor of mortality in a population of 1.473 patients with lung or gastrointestinal malignancies and incorporated both gender-specific and BMI-specific cutoffs: 41.0 cm^2/m^2 for women and 43.0 cm^2/m^2 for men with a BMI <25 kg/m^2 and 53.0 cm^2/m^2 for men with a BMI > 25 kg/m^2. These cut-off values are based on SMA at the level of L3 and are not applicable for patients with HNC in whom SMM segmentation at the level of C3 is performed.

The European Working Group of Sarcopenia in Older People (EWGSOP) recommends that low SMM should be defined as SMM less than 2 standard deviations (SD) below the mean SMM of typical healthy adults.[1] It is unknown whether this recommendation also implies to patients with cancer, but reference values may provide a better direct comparison in between patients. Recently a study in a Dutch cohort of healthy persons revealed gender- and BMI-specific reference values for SMM at the level of L3[19], which may be used to uniformly identify patients with a significantly lower SMM than a reference patient of the same gender and BMI.

The aim of this study is to provide gender- and BMI-specific cut-off values for low SMM as measured at the level of C3 in a large cohort of patients diagnosed with HNC. This information will contribute to the knowledge about the distribution of low SMM in HNC patients and will provide more uniformity in the definition of low SMM in HNC research.

METHODS

ETHICAL CONSIDERATIONS

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 16/595 C and 17-365/C). All data was retrieved retrospectively and used in an anonymized fashion.

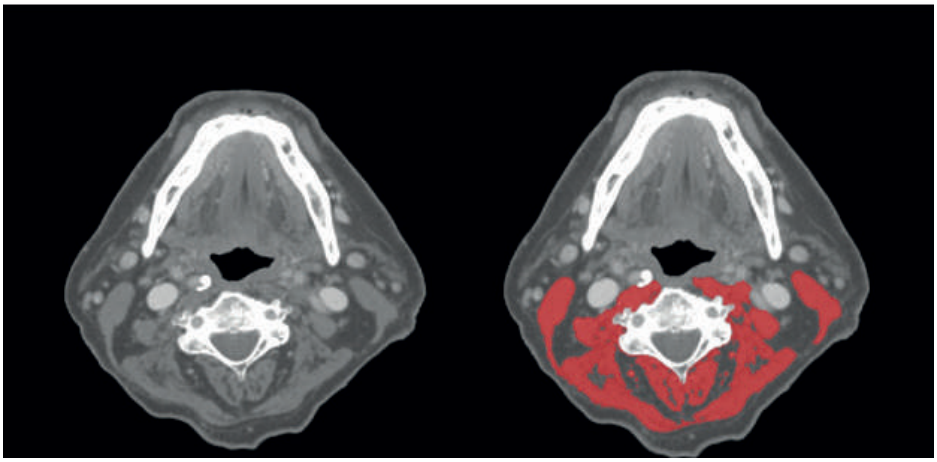
STUDY POPULATION

Patient data collected in several earlier retrospective studies of our group that evaluated skeletal muscle mass in head and neck cancer patients were combined in a new database. Patients were diagnosed and treated with a curative intent at the University Medical Center Utrecht, The Netherlands between 2008 and 2018 with a primary head and neck cancer and include cohorts of patients planned for microvascular free-flap mandibular reconstruction[9], patients undergoing chemoradiotherapy[7] or bioradiotherapy[20], elderly patients with HNC[10] and patients with oropharyngeal cancer[11]. Relevant parameters, including length and weight at the time of imaging, sex, age, tumor localization and clinical TNM stage (7^{th} and 8^{th} edition) were retrospectively retrieved. After completion of the new database, the database was checked for duplicates and all duplicate patients were removed.

ASSESSMENT OF CROSS-SECTIONAL MUSCLE AREA AT THE LEVEL OF C3

Muscle tissue was identified using Hounsfield Unit (HU) range settings from -29 to +150 HU, which is specific for muscle tissue. Muscle tissue was delineated at the level of the third cervical vertebra (C3). The SMA was defined as the pixel area within the delineated area with a radiodensity between -29 and +150 HU.[21] Delineation of muscle tissue was manually performed using the Slice-O-matic software v 5.0. Muscle tissue delineation at the level of C3 was performed by selecting the first slide showing both transverse processes and the entire vertebral arc when scrolling from caudal to cranial direction. The contours of the paravertebral muscles and both sternocleidomastoid muscles were manually traced. The SMA at the level of C3 was calculated as the sum of the paravertebral muscle and both sternocleidomastoid muscles. If evident lymph node metastasis hindered accurate delineation of one sternocleidomastoid muscle, the SMA of the contralateral sternocleidomastoid muscle was used as an estimation of the SMA of the affected sternocleidomastoid muscle. After delineation, SMA was automatically retrieved from Slice-O-matic. For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. The overall intraclass correlation coefficient (ICC) for the muscle SMA obtained by CT and MRI has shown to be excellent (ICC 0.9, $p<0.01$)[22], and can therefore be used interchangeably for measuring CSA at the level of C3. The cervical SMI (CSMI) was calculated by dividing the SMA at the level of C3 by the squared height of the patient. Figure 1 shows muscle tissue delineation at the level of C3.

Figure 1. 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 sternocleidomastoid and paravertebral muscles segmented in red.



STATISTICAL ANALYSIS

A test for normality (Kolmogorov-Smirnov) was performed to assess whether continuous variables were normally distributed. Continuous data are represented as mean ± standard deviation (SD) if normally distributed, and median ± range if skewed. Categorical data are represented as a number and percentage of total. The student's *t*-test, one-way ANOVA, Mann-Whitney

U test were used where appropriate. Percentiles were used to describe the distribution of SMA and CSMI. Chi-square test was used to investigate the association between gender and various clinical and demographic variables. Spearman correlation was used for correlation analysis of SMI and patients' characteristics such as BMI, age and gender. All statistical analyses were performed using the IBM SPSS Statistics version 25.0 software package (Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

PATIENTS' CHARACTERISTICS

In total, the skeletal muscle mass data of 1763 study subjects were entered in this study database. After deduplication, 1415 unique patients were included for analysis in this study. Roughly two-third of patients was male, and one-third was female. Continuous variables were not normally distributed (Kolmogorov-Smirnov $p < 0.05$). The median age of the included patients was 63.7 years at diagnosis, ranging between 19.6 and 97.6 years. The median BMI was 24.0 (range 13.3 - 48.2; only a minority of patients were underweight at diagnosis with a BMI ≤18.5: n=129, 9.1%. This study included tumors of all tumor head and neck sites and all tumor stages. The most common diagnosis was oropharyngeal carcinoma (n=500, 35.3%), and most patients were diagnosed with a stage IV tumor (n=800, 59.4%). Significant differences between male and female patients were seen in age, height and TNM-stage; female patients were older, shorter of height and were less frequently diagnosed with a TNM-stage IV tumor compared to male patients, all p<0.01. Full patient and disease characteristics are shown in table 1.

Table 1. Patient's characteristics of the total study population (n=1415)

	All subjects (n = 1415)	**Men (n = 988)**	**Women (n = 427)**	**P-value**
Age (years)	63.6 [57.0 - 69.8]	63.2 [56.6 - 69.6]	64.9 [58.0 - 70.0]	**<0.01**
Height (cm)	174 [168 - 180]	177 [172 - 182]	167 [162 - 172]	**<0.01**
Weight (kg)	73.9 [62.2 - 84.0]	77.2 [66.0 - 87.0]	66.5 [55.6 - 75.1]	**<0.01**
Body mass index (BMI)	24.0 [21.2 - 27.2]	24.5 [21.6 - 27.2]	23.9 [20.3 - 27.0]	**<0.01**
BMI categorical				**<0.01**
Below 25	838 (59.2)	567 (57.4)	271 (63.5)	
25 or above	577 (40.8)	421 (42.6)	156 (36.5)	

Table 1. (Continued)

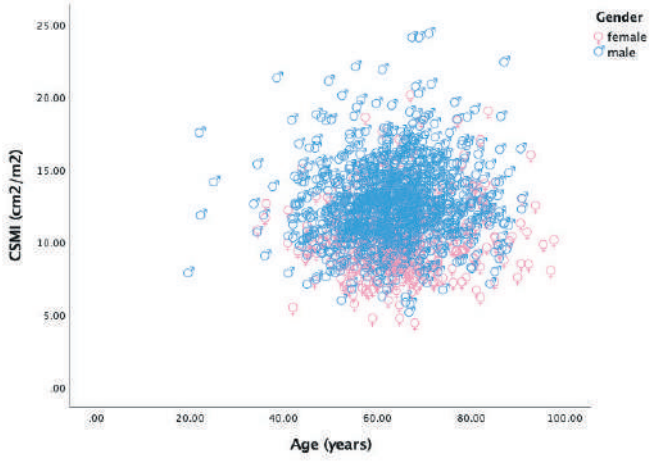
	All subjects (n = 1415)	Men (n = 988)	Women (n = 427)	P-value
Localization of tumor				
Oropharynx	500 (35.3)	334 (33.8)	166 (38.9)	**<0.01**
Hypopharynx	207 (14.6)	174 (17.6)	33 (7.7)	
Larynx	267 (18.9)	209 (21.2)	58 (13.6)	
Oral cavity	319 (22.5)	188 (19.0)	131 (30.7)	
Nasopharynx	51 (3.6)	37 (3.7)	14 (3.3)	
Paranasal sinus	21 (1.5)	13 (1.3)	8 (1.9)	
Salivary gland	20 (1.4)	10 (1.0)	10 (2.3)	
Unknown primary	18 (1.3)	14 (1.4)	4 (0.9)	
Skin (lip, ear, face)	12 (0.8)	9 (0.9)	3 (0.7)	
AJCC stage				
I	103 (7.3)	57 (5.8)	46 (10.8)	**<0.01**
II	165 (11.7)	118 (11.9)	47 (11.0)	
III	280 (19.8)	178 (18.0)	102 (23.9)	
IV	856 (60.5)	628 (63.6)	228 (53.4)	
x	11 (0.8)	7 (0.7)	4 (0.9)	

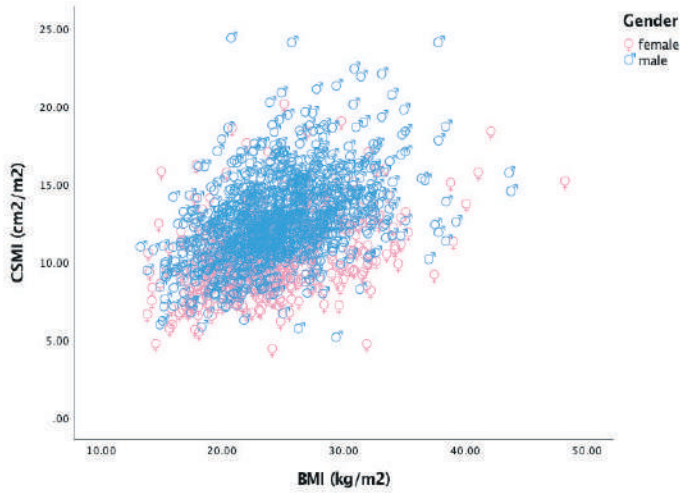
Legend: AJCC stage: American Joint Committee on Cancer staging system for describing the extent of disease progression. P-value of <0.05 was considered statistically significant.

CORRELATION ANALYSIS

The SMA at the level of C3 and CSMI were not normally distributed (Kolmogorov-Smirnov $p<0.05$). SMM (CSMI) had a significantly low correlation with age at diagnosis (Spearman $r^2=0.1$, $p<0.05$) and a significantly moderate correlation with BMI (Spearman $r^2=0.4$, $p<0.01$) and gender (Spearman $r^2=0.4$, $p<0.01$). Figure 2 shows the scatter plots of the association between CSMI and age and CSMI and BMI in females and males.

Figure 2. Scatterplots of the association between CSMI and age and CSMI and BMI.





Legend: BMI: body mass index, CSMI: cervical skeletal muscle mass index

DISTRIBUTION OF SMM

The median SMA at the level of C3 was 39.0 cm^2 for men (IQR 28.4-49.6 cm^2) and 27.8 cm^2 for women (19.2-36.2 cm^2). The median CSMI was 12.3 cm^2/m^2 for men (IQR 8.9-15.7 cm^2/m^2) and 10.0 cm/m^2 for women (IQR 6.9-13.1 cm^2/m^2). The distribution of SMA at the level of C3 and from the 5th percentile up to the 95th percentile is shown in Table 2.

Table 2. Distribution of SMM from the 5th until the 95th percentile

	SMA at the level of C3 (cm^2)		CSMI (cm^2/m^2)	
	Male N = 988	**Female N = 427**	**Male N = 988**	**Female N = 427**
Total mean (SD)	39.4 (8.3)	28.6 (6.8)	12.6 (2.7)	10.3 (2.4)
P5	26.9	19.1	8.4	7.0
P10	29.4	20.9	9.4	7.5
P25	33.6	24.0	10.8	8.6
P50	39.0	27.8	12.3	10.0
P75	44.2	32.4	14.2	11.7
P90	49.6	36.6	16.0	13.5
P95	53.7	40.1	17.2	14.8

Legend: SD: standard deviation, SMA: skeletal muscle mass area, CSMI: cervical skeletal muscle mass index, P: percentile, N: number of patients

CUT-OFF VALUES FOR SMM

Table 3 and 4 shows the mean with corresponding standard deviations (SD) of SMA and CSMI at the level of C3. Gender and BMI specific cut-off values were calculated based on mean -2SD as suggested by the EWGSOP2.[1] For male patients with a BMI <25 kg/m^2, a CSMI ≤6.8 cm^2/m^2 was defined and with a BMI ≥25 kg/m^2 a CSMI ≤8.5 cm^2/m^2 was defined for low SMM. For female patients with a BMI <25 kg/m^2, a CSMI ≤5.3 cm^2/m^2 was defined and with a BMI ≥25 kg/m^2 a CSMI ≤6.4 cm^2/m^2 was defined for low SMM.

Table 3. Cut-off SMA values and gender- and BMI specific cut-off values for low SMA (cm^2)

	Male N = 988	***Cut-off mean -2 SD* (cm^2)**	**Female N = 427**	***Cut-off mean -2 SD* (cm^2)**
BMI < 25 kg/m^2				
N (%)	567 (57.4)		271 (63.5)	
M (SD)	36.6 (7.3)	≤ 22	26.9 (5.9)	≤ 15.1
BMI ≥ 25 kg/m^2				
N (%)	421 (42.6)		156 (36.5)	
M (SD)	43.1 (8.1)	≤ 26.9	31.5 (7.3)	≤ 16.9

Legend: BMI: body mass index, N: number of patients, M: mean, SD: standard deviation
SMA: skeletal muscle mass area

Table 4. Cut-off CSMI values and gender- and BMI-specific cut-off values for low CSMI (cm^2/m^2)

	Male N = 988	***Cut-off mean -2 SD* (cm^2/m^2)**	**Female N = 427**	***Cut-off mean -2 SD* (cm^2/m^2)**
BMI < 25 kg/m^2				
N (%)	567 (57.4)		271 (63.5)	
M (SD)	11.8 (2.5)	≤ 6.8	9.7 (2.2)	≤ 5.3
BMI ≥ 25 kg/m^2				
N (%)	421 (42.6)		156 (36.5)	
M (SD)	13.7 (2.6)	≤ 8.5	11.4 (2.5)	≤ 6.4

Legend: BMI: body mass index, N: number of patients, M: mean, SD: standard deviation
CSMI: skeletal muscle mass index

DISCUSSION

This is the first study describing cut-off values for SMM measured on head and neck CT imaging or MRI at the level of C3 in patients with head and neck cancer. This study provided gender and BMI-specific cut-off values of the mean (SD) quantity of SMM (skeletal muscle area and skeletal muscle mass index). For male patients with a BMI < 25 kg/m^2, a CSMI ≤ 6.8 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤8.5cm^2/m^2 was defined for low SMM. For female patients with a BMI < 25 kg/m^2, a CSMI ≤5.3 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤ 6.4 cm^2/m^2 was defined for low SMM.

Various techniques can be used to quantify muscle mass, however not all of these modalities are routinely used in the clinical setting of HNC patients. Variable costs and sometimes limited availability determine which technique is better suited to the specific setting. In the management of HNC patients, CT and MRI of the head and neck are the most widely used imaging modalities for routine diagnostics and clinical decision making. MRI is considered one of the most accurate methods for analyzing quantitative and qualitative changes in body composition and is associated with an error in quantifying muscle that ranges between 1.1% and 4.4%.[23]

CT, like MRI, is also considered as a highly precise imaging modality in investigating human body composition and has a reported precision error of about 1.4% for tissue areas.[21] Both scanning methods are able to distinguish muscle mass from fat. CT imaging can reveal fat infiltration within muscle by identifying areas in the range of −190 to −30 Hounsfield units. [24] Currently, MRI and CT are considered to be accurate methods for quantifying muscle mass, due to their abilities to separate fat from other soft tissues. Therefore, this study included routinely performed CT and MRI imaging, which makes the results applicable to clinical practice. CT and MRI have already shown to have a significant agreement in measuring SMM and therefore can be used interchangeably in assessing SMM at the level of C3.[22] Using other software programs than the software program used in the current study (slice-O-matic) may give slightly different results, but these differences are not clinically relevant. A previous study showed that the measurement of skeletal muscle area has an excellent inter-software agreement and therefore results of studies using different software programs may reliably be compared.[25]

Reference values for SMM at the level of C3 for a heathy (non-HNC) Caucasian population are lacking, but reference values for SMM analysis at the level of L3 have been reported.[19] Van der Werf et al. included 420 healthy Caucasian kidney donors.[19] They found that SMI was 1.31-fold higher in men than in women. Previous studies also show that men have a significantly higher amount of skeletal muscle mass than women. [26] In our study, we found a significant correlation between SMI and gender and between SMI and BMI. Therefore, gender and BMI-specific cut-off values were provided in this study.

Van der Werf et al. determined cut-off values based on the 5th percentile of SMM in healthy individuals. These 5th percentile cut-off values for low SMM (at L3) corresponded with the cut-off

values presented by Prado et al. for patients with solid tumors in which cut-off values of SMM (at L3) were defined by the use of the optimal stratification method for endpoint mortality.[15] This suggests that the cut-off value for low SMM of 2SD below mean SMM in healthy individuals corresponds with the value of low SMM predictive for mortality in cancer patients.

SMM parameters may differ between ethnicities. Although, we do not collect data on ethnicity in our treatment center, majority of patients has a Caucasian ethnicity. Because the cut-off values in our study are therefore mostly representative for the Western-European population, these cut-off values could probably not be extrapolated to other ethnicities. More research is needed to define cut-off values in other ethnic groups and in respect to treatment outcomes in patients with HNC such as surgical complications and dose-limiting toxicities.

Our study has some limitations. Firstly, EWGSOP recommended the retrieval of SMM reference values in a healthy population. However, in order to avoid unwanted extra radiation exposure at the head and neck region SMM segmentation on MRI is preferred. MRI of the head and neck region in otherwise healthy people is not routinely performed in clinical practice. Secondly, due to heterogeneity of tumor site, tumor characteristics and tumor stages included in this cohort study, no reliable cut-off value of low SMM for mortality could be provided. Further studies are needed to validate the prognostic impact of the cut-off values for low SMM provided in this cohort. Our study also has some strengths. Firstly, this is the first study providing cut-off values for SMM at the level of C3. Although previous studies provided cut-off values for L3, these cut-off values are usually not applied in HNC research due to the unavailability of abdominal imaging in non-advanced stage HNC. Secondly, we included a large sample size with a large proportion of both female and male patients which strengthens the robustness of the cut-off values that were found.

CONCLUSION

In this study, cut-off values for low SMM in patients with HNC were presented in order to provide investigators a tool to further explore the association of low SMM and treatment outcomes in HNC patients. In addition, this tool can also be used for trials investigating interventions to improve SMM in patients with HNC and thereby possibly improve cancer treatment outcomes.

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PART II

The predictive and prognostic impact of low skeletal muscle mass in surgically treated head and neck cancer patients

CHAPTER 6

Low skeletal muscle mass is a strong predictive factor for surgical complications and 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.[5,7,8]

In the last year's 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.[9–12] Sarcopenia has been defined by consensus statements as a syndrome of progressive and generalized loss of skeletal muscle mass and function.[13,14] 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.[11,15–17] 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.[11,15,18–20] 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.[21]

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.[20] Patients were included if they had primary tumor resections without prior treatment and recent (less than 1 month before surgery) imaging (CT or MRI scans) of the head and neck.

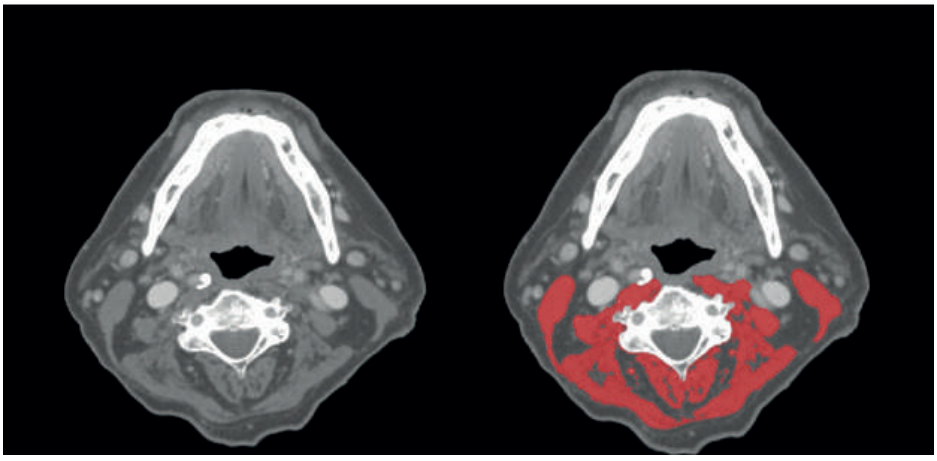
Clinical and demographic data were collected from the medical records. Data collected included age at reconstruction, sex, smoking history, diagnosis, localization of defect, comorbidity as expressed by the Adult Comorbidity Evaluation-27 (ACE-27) score, history of radiation therapy, flap ischemia time, 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.[20] 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.[22] Patients with multiple complications were categorized according to their highest grade of complication. 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 pre-treatment 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 sternocleidomastoid 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 figure 1. CSA at the level of C3 was converted to CSA at the level of L3 using a previously published formula 1.[21] The lumbar skeletal muscle 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.[23]

Figure 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 sternocleidomastoid and paravertebral muscles segmented in red.

Formula 1:

*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)*

Formula 2:

Lumbar SMI (cm^2/m^2) = CSA at L3/length (m^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.

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*
Gender (n, %)				
Female	24 (30.8)	24 (50.0)	-	**0.0001****
Male	54 (69.2)	24 (50.0)	30 (100)	
Age (years) (M, SD)	62.4 (10.2)	63.3 (10.9)	60.9 (8.8)	0.31
Body mass index (kg/m²)(n, %)				
<18.5 kg/m²	20 (25.6)	8 (17.6)	12 (40.0)	**0.004****
18.5-24.9 kg/m²	27 (34.6)	27 (56.3)	-	
25-29.9 kg/m²	26 (33.3)	12 (25.0)	14 (64.7)	
≥ 30 kg/m²	5 (6.4)	1 (2.1)	4 (13.3)	
Smoker (n, %)				
No	32 (41.0)	19 (39.6)	13(43.3)	0.82
Yes	46 (59.0)	29 (60.4)	17 (56.7)	
ACE-27 score (n, %)				
None	28 (35.9)	18 (37.5)	10 (33.3)	0.86
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				
Squamous cell carcinoma	75 (96.1)	46 (95.8)	29 (96.7)	0.29
Osteosarcoma	2 (2.6)	2 (4.2)	-	
Adenoid cystic carcinoma	1 (1.3)	-	1 (3.3)	

Table 1. (Continued)

Variables	All patients N=78	Low SMM N=48	Without low SMM N=30	*p-value*
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, %)				
N0	37 (47.4)	21(43.8)	16(53.3)	0.35
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, %)				
I	1 (1.3)	1(2.1)	-	0.10
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, %)				
Lateral mandible	30 (38.5)	12(25.0)	18(60.0)	0.08
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)

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.

Table 2. All postoperative complications

Postoperative complications	All patients 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)
Wound dehiscence	12		
Wound infection	13		
Pulmonary embolism	1		
Blood transfusion	9		
Pneumonia	1		
CD III - IV	25 (32.1)	19 (39.6)	6 (20.0)
ICU admission	9		
Need for surgical intervention (e.g., necrosectomy, drainage of hematoma)	16		
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)

SURVIVAL ANALYSIS

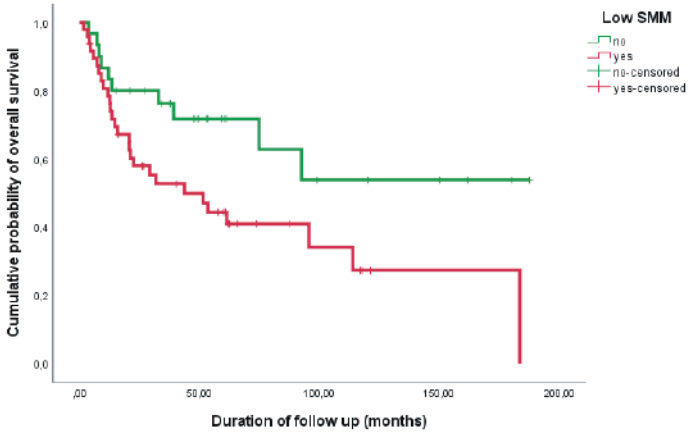
Median follow-up time was 36 months (IQR 13-62 months). At the time of concluding this study, 38 (48.7%) patients of the cohort had died of any cause and 40 (51.3%) were alive. As seen in figure 2, patients with low SMM showed a significant lower median OS (26 months; IQR 10-62) compared to patients without low SMM (48 months; IQR 20-79) (Log rank $\chi 2 = 4.76$; p=0.03). Patients with low SMM had a significantly decreased 5-year OS rate compared to patients without low SMM (41% versus 71%; 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 $\chi 2 = 2.54$; p=0.11) (figure 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 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).

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

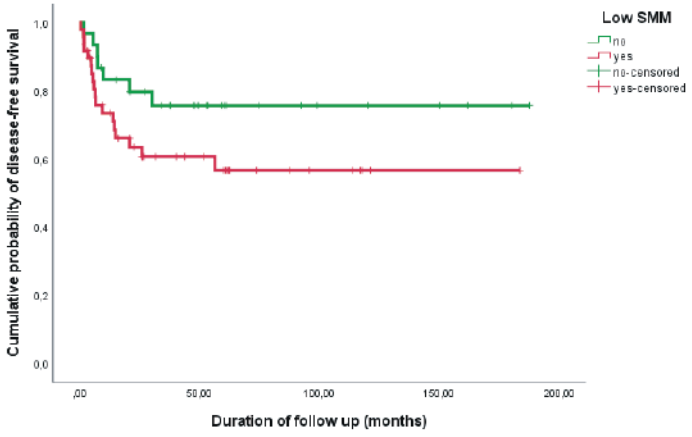
OVERALL SURVIVAL							DISEASE-FREE SURVIVAL					
Variables	**Univariate**			**Multivariate**			**Univariate**			**Multivariate**		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95%CI**	**p-value**	**HR**	**95% CI**	**p-value**
Low SMM	2.2	1.1-4.5	0.03*	2.4	1.1-5.1	**0.02***	2.0	0.8-4.8	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
Adult Comorbidity Evaluation-27												
None	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	
III	1.0	0.0-∞	0.98	-	-	-	-	-	-	-	-	0.73
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

Figure 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	35	25	20	18	14	8	7	5	5	2
Without low SMM	30	26	22	19	14	10	8	7	6	5	5

Figure 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).



	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

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.[11,27,28]

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.[28,29] 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.[30,31] In patients undergoing primary chemoradiotherapy with advanced stage head and neck squamous cell carcinoma it is associated with increased chemotherapy dose-limiting toxicity (CDLT) and decreased OS.[17]

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 microenvironment of inflammation induced by the presence of inflammatory cells, chemokines and cytokines; a phenomenon known as cancer-related inflammation.[32] 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.[33] 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.[34,35] Low SMM may therefore also impair wound healing and increase wound related complications.[36]

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] 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.[31,38] 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.[39,40] These myokines have been shown induce apoptosis in the cells of some tumors.[40,41] 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.[41]

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 loss.[42] 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.[43]

Because of increasing surgical experience and technological advancement, the success rate of microvascular free tissue transfer is reported to be above 95%.[8] 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.[44] 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.[17] 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. Measurement of SMI at the level of C3 is based on a previously published study.[21] We validated the measurement of SMI at the level of C3 with total body muscle area as measured on whole body MRI and found a strong correlation (manuscript in preparation).

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.[12,45] A recent study showed that both methods, CT and MRI, have a strong agreement in measurement of skeletal muscle mass (r^2=0.94, p<0.01).[46]

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. The relatively limited number of cases and events may influence the statistical robustness of the results. 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.

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CHAPTER 7

Association of low skeletal muscle mass and systemic inflammation with surgical complications and survival after microvascular free flap head and neck reconstruction

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Submitted ■

ABSTRACT

Background
Low skeletal muscle mass (SMM) and systematic inflammation are associated with post-operative morbidity and survival.

Materials and methods
Patients undergoing microvascular free flap head and neck (HN) reconstruction were included. SMM was measured on imaging. Inflammation was evaluated by the neutrophil-to-lymphocyte ratio (NLR). Post-operative complications, date of recurrence and death were scored.

Results
616 patients were included. Non-flap and flap-related complications occurred in 39.3% and 12.3%, respectively. Flap-failure rate was 4.7%. For oncological cases, predictors for complications were elevated NLR in all flap surgery (OR 1.5), low SMM in radial forearm flap surgery (OR 2.1) and elevated NLR combined with low SMM in fibula flap surgery (OR 5.2). Patients with solely elevated NLR were at significant risk for flap-related complications (OR 3.0), severe complications (OR 2.2) and when combined with low SMM for increased length of hospital stays (LOS) (+3.9 days).

In early-stage HN squamous cell carcinoma (HNSCC), low SMM (HR 2.3) and combined elevated NLR with low SMM (HR 2.3) were prognostics for overall survival (OS) and age for disease free survival (DFS) (HR 1.1). In advanced-stage HNSCC, hemoglobin (HR 0.99) and body-mass index (HR 0.94) were prognostics for OS and hemoglobin (HR 0.99) for DFS.

Conclusion
SMM and NLR are predictive for complications and increased LOS in microvascular free flap HN reconstruction. Also, SMM and NLR have prognostic impact for OS in early stage HNSCC. SMM and NLR are routinely available and may aid the clinician in the identification of patients at risk of a poor outcome.

INTRODUCTION

Microvascular tissue transfer is the gold standard for reconstruction of complex head and neck defects after extensive resections for head and neck cancer (HNC) or osteoradionecrosis, or traumas.

Reconstructive flap surgery can lead to improved function and aesthetics but is time-consuming and associated with significant postoperative morbidity. Survival rate of flaps depends on various factors, among which are age, comorbidities and many unknown factors.[1–3] Ongoing research is required to identify key predictors for postoperative morbidity, to enable better pre-operative risk-analysis for development of more individualized treatment planning aiming at improving treatment outcomes.

Several studies have demonstrated that poor nutritional status and body composition changes are associated with an increased risk of surgical complications.[4,5] HNC patients often present with inadequate oral intake due to tumor site and treatment-related side effects (e.g., xerostomia, mucositis). This may lead to a decrease of lean body mass of which skeletal muscle mass (SMM) is the largest contributor. The prevalence of low SMM, also referred to as sarcopenia, in patients with HNC is estimated to be approximately 40%.[6] Loss of SMM in patients with cancer is often accompanied with a gain in fat mass, which leads to ''hidden sarcopenia''.[7] Body mass index (BMI) is therefore a poor representative of patient's body composition. It is already known that surgically treated patients with elevated BMI tend to have longer operative times and endure more blood loss.[8,9] However, sometimes elevated BMI may have a protective effect also known as the obesity paradox.[10] Hidden sarcopenia might explain why BMI has shown to have no predictive value for surgical complications in HNC patients who undergo reconstructive surgery.[11,12]

Low SMM has shown to predict surgical complications as well as dose-limiting toxicities and decreased survival.[6,13–16] SMM can be quantified on routinely performed diagnostic imaging using computed tomography (CT) or magnetic resonance imaging (MRI) at the level of the third lumbar vertebrae (L3) or the third cervical vertebrae (C3).[17–19] For head and neck patients, imaging at the level of C3 is routinely performed in the diagnostic workup and for treatment evaluation. Recently, we performed a study in HNC patients undergoing reconstruction by use of free fibular flap (FFF) and found low SMM to be predictive for complications and prognostic for survival.[20] This finding is reinforced by a recently performed study in 168 HNC patients who underwent free flap reconstruction in which low SMM was a predictor for complications.[21] Another recent study in HNC patients undergoing free flap reconstruction showed that low SMM was associated with discharge to post-acute care facilities (instead of home) indicating that patients with low SMM are less tolerant to reconstructive surgery.[22] These studies only included patients who had preoperative abdominal CT scans for SMM measurement at the level of the third lumbar vertebrae (L3). Although SMM measurements at the level of L3 is common in oncological research[23], this may lead to an inclusion bias in HNC patients because only

advanced-stage HNC patients are likely to undergo abdominal imaging as part of screening for distant metastasis with PET-CT.[24]

Another marker receiving increased attention across various cancer types is an elevated neutrophil-to-lymphocyte ratio (NLR), a biomarker for systemic inflammation. An elevated NLR has shown to be prognostic for decreased survival in a variety of cancers such as breast cancer,[25] colorectal cancer,[26] esophageal cancer,[27] and pancreatic cancer[28]. Elevated NLR is also predictive for surgical complications in patients with cancer.[29,30] NLR can be easily quantified by dividing routinely measured neutrophil count by lymphocyte count.

This study aims to investigate the impact of pre-operative low SMM and elevated systemic inflammation (elevated NLR-ratio) on postoperative complications, length of hospital stays, and disease-free survival (DFS) and overall survival (OS) in patients undergoing head and neck microvascular free flap reconstruction.

MATERIAL AND METHODS

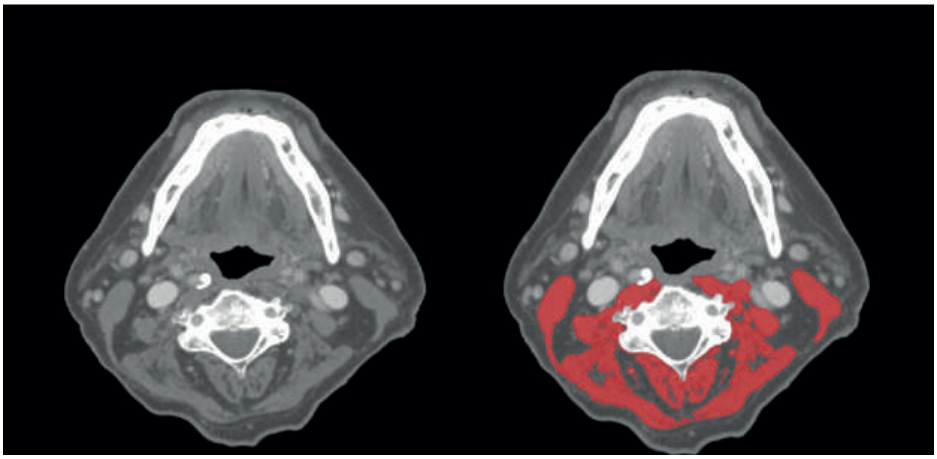
PATIENTS AND STUDY DESIGN

In a retrospective study, all patients who underwent flap reconstructive surgery at the department of Oral and Maxillofacial Surgery of Queen Elizabeth hospital in Birmingham, United Kingdom, between January 2007 and January 2020, were included. All clinical and demographic variables were collected by use of electronic medical records.

SKELETAL MUSCLE MASS

SMM was measured as skeletal muscle area (SMA) on pre-treatment imaging of the head and neck at the level of the third cervical vertebrae (C3). The axial slide which showed both transverse processes and the entire vertebral arc was selected for segmentation of muscle tissue. On CT, muscle area was defined as the pixel area between the muscle-specific radiodensity range of -29 and +150 Hounsfield Units (HU). SMA 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 (N.C). An example of segmentation at the level of C3 is shown in supplemental figure 1. SMA at the level of C3 was converted to SMA at the level of L3 using a previously published formula as shown in formula 1.[17] The lumbar skeletal muscle 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 HNC patients.[13]

Supplemental figure 1. 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 sternocleidomastoid and paravertebral muscles segmented in red



Formula 1:
*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)*

Formula 2:
Lumbar SMI (cm^2/m^2) = CSA at L3/length (m^2)

SYSTEMIC INFLAMMATION

NLR was used to evaluate systemic inflammation. According to literature, an NLR >3 indicates high grade of systemic inflammation.[32]

OUTCOME VARIABLES

Postoperative complications were defined as any adverse development after surgery. Severity of all complications were scored by use of the Clavien-Dindo classification of surgical complications.[31] Complications were also scored by distinction of flap-related complications and non-flap-related complications. Flap-related complications were defined as all complications concerning the flap. Patients with multiple complications were scored according to their highest grade of complication. Length of hospital stay (LOS) was defined as the time between date of operation and date of hospital discharge. Disease-free survival (DFS) was defined as the time between diagnosis date and recurrence date or last follow-up, whichever occurred first. Overall survival (OS) was defined as the time between diagnosis date and date of death or last follow-up, whichever occurred first.

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. Imputation analysis was performed in case of missing clinical variables. Logistic regression was used for univariate and multivariate analysis of surgical complications, only patients with known SMM status were included for analysis. Cox proportional hazard regression model was used for univariate and multivariate analysis of survival, only patients with known SMM status were included for analysis. Covariates used in the multivariate analysis were selected based on clinical significance or selected based on statistical significance ($p < 0.05$) in univariate analysis. Correlation analysis was performed by use of Pearson's correlation analysis for variables with a normal distribution and Spearman's correlation analysis was used for non-normally distributed variables. In case of high multicollinearity of variables in the multivariate analysis, highly correlated predictors were not included to prevent biased estimation.[33] Statistical significance was evaluated at the 0.05 level using two-sided tests. Survival was visualized using Kaplan Meier survival curves.

RESULTS

PATIENT CHARACTERISTICS

Descriptive data are described in table 1. In total, 616 patients were included. Median age at diagnosis was 60.8 years (IQR 51.6-69.5). Of these patients, 554 patients (89.9%) were oncological cases of which 509 patients (91.9%) were diagnosed with head and neck squamous cell carcinoma (HNSCC). Majority of patients were male (60.7%). Most used flap was the radial forearm free flap (RFFF) (n=276, 44.8%). Figure 1. shows the flaps used for reconstruction.

Table 1. Patient characteristics

		All patients N=600	SMM known N= 413			SMM known N=413		
			Without low SMM	Low SMM		NLR ≤ 3	NLR > 3	
Characteristics	Category	n (%)	n (%)	n (%)	*p*	n (%)	n (%)	*p*
Gender	Male	374 (60.7)	168 (88.9)	79 (35.3)	<0.01	83 (41.1)	83 (39.3)	0.8
	Female	242 (39.3)	21 (11.1)	145 (64.7)		119 (58.9)	128 (60.7)	
Age (years)	Median (IQR)	60.8 (51.6 - 69.5)	56.0 (12.4)	63.8 (12.0)	<0.01	58.4 (12.5)	62.0 (12.7)	<0.01
Flap used	Radialis free forearm flap (RFFF)	276 (44.8)	95 (50.3)	104 (46.4)	0.2	110 (54.5)	89 (42.2)	0.1
	Free Fibula flap (FFF)	164 (26.6)	42 (22.2)	54 (24.1)		43 (21.3)	53 (25.1)	
	Anterolateral thigh flap (ALT)	66 (10.7)	26 (13.8)	20 (8.9)		17 (8.4)	29 (13.7)	
	Scapula flap	61 (9.9)	12 (6.3)	27 (12.1)		16 (7.9)	23 (10.9)	
	Others*	49 (8.0)	14 (7.4)	19 (8.5)		16 (7.9)	17 (8.1)	
Reason for reconstructive surgery	Defect after ablative surgery	554 (89.9)	178 (94.2)	209 (93.3)	0.5	191 (94.6)	196 (92.9)	0.4
	Trauma	4 (0.6)	2 (1.1)	0		1 (0.5)	1 (0.5)	
	Osteoradionecrosis	25 (4.1)	3 (1.6)	6 (2.7)		2 (1.0)	7 (3.3)	
	Secondary reconstruction	24 (3.9)	4 (2.1)	7 (3.1)		5 (2.5)	6 (2.8)	
	Odontogenic tumor or cyst	9 (1.5)	2 (1.1)	2 (0.9)		3 (1.5)	1 (0.5)	
Histology Oncology cases	Squamous cell carcinoma	509 (82.6)	157 (88.2)	195 (93.3)	0.1	174 (91.1)	178 (90.8)	0.9
	Other	47 (7.6)	21 (11.8)	14 (6.7)		17 (8.9)	18 (9.2)	
TNM stage (for oncologic SCC patients)	I	76 (12.3)	23 (13.2)	38 (18.8)	0.4	34 (18.2)	27 (14.3)	0.6
	II	88 (14.3)	25 (14.4)	34 (16.8)		32 (17.1)	27 (14.3)	
	III	62 (10.1)	22 (12.6)	20 (9.9)		19 (10.2)	23 (12.2)	
	IV	314 (51.0)	104 (59.8)	110 (54.5)		102 (54.5)	112 (59.3)	

Table 1. (Continued)

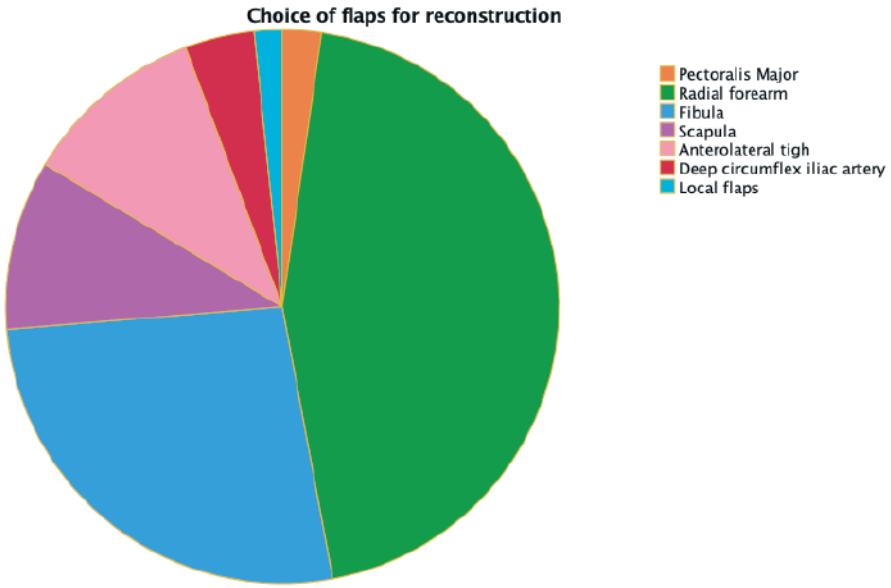
		All patients N=600	SMM known N= 413			SMM known N=413		
Adult Comorbidity Evaluation – 27 score	None	218 (35.4)	75 (39.7)	76 (33.9)	0.4	86 (42.6)	65 (30.8)	0.03
	Mild	258 (41.9)	80 (42.3)	94 (42.0)		78 (38.6)	96 (45.5)	
	Moderate	126 (20.5)	29 (15.3)	48 (21.4)		36 (17.8)	41 (19.4)	
	Severe	14 (2.3)	5 (2.6)	6 (2.7)		2 (1.0)	9 (4.3)	
Performance status	ECOG 0	308 (50.0)	100 (70.4)	104 (71.2)	0.5	108 (76.6)	96 (65.3)	<0.01
	ECOG 1	129 (20.9)	39 (27.5)	35 (24)		31 (22)	43 (29.3)	
	ECOG ≥ 2	19 (3.1)	2 (1.4)	6 (4.1)		0	8 (5.4)	
	Unknown	160 (26.0)	1 (0.7)	1 (0.7)		2 (1.4)	0	
Smoking status	Never	244 (39.6)	76 (40.2)	111 (49.6)	*0.06*	83 (41.1)	104 (49.3)	0.1
	Current/former	171 (27.8)	113 (59.8)	113 (50.4)		119 (58.9)	107 (50.7)	
Alcohol consumption	Never	212 (34.4)	72 (38.1)	105 (46.9)	0.07	85 (42.1)	92 (43.6)	0.8
	Current/former	348 (56.5)	117 (61.9)	119 (53.1)		117 (57.9)	119 (56.4)	
BMI (kg/m²)	Underweight (≤ 18.5)	47 (7.6)	4 (2.1)	28 (12.5)	<0.01	8 (4)	24 (11.4)	<0.05
	Normal weight (18.5 - <25)	271 (44.0)	56 (29.6)	136 (60.7)		96 (47.5)	96 (45.5)	
	Overweight (25 - <30)	204 (33.1)	88 (46.6)	45 (20.1)		69 (34.2)	64 (30.3)	
	Obese (≥ 30)	94 (15.3)	41 (21.7)	15 (6.7)		29 (14.4)	27 (12.8)	
NLR	Median (IQR)	3.1 (2.2 - 4.6)	4.2 (4.9)	4.1 (3.9)	0.8	n.a.	n.a.	
LSMI (cm²/m²)	Median (IQR)	42.5 (36.2 - 48.3)	n.a	n.a		43.5 (9.0)	41.1 (1.3)	<0.01
Low SMM	No	110 (45.3)	n.a	n.a		101 (50)	88 (41.7)	0.1
	Yes	133 (54.7)	n.a	n.a		101 (60)	123 (58.3)	

Table 1. (Continued)

		All patients N=600	SMM known N= 413			SMM known N=413		
NLR > 3	No	305 (49.5)	101 (53.4)	101 (45.1)	0.1	n.a	n.a	
	Yes	311 (50.5)	88 (46.6)	123 (54.9)		n.a	n.a	
Haemoglobin (g/L)	Median (IQR)	135 (122 -146)	137.7 (18.8)	129.1 (17.4)	<0.01	136.6 (15.5)	129.5 (20.4)	<0.01
Haemoglobin ≤100 g/L	No	585 (95)	181 (95.8)	209 (93.3)	0.3	201 (99.5)	189 (89.6)	<0.01
	Yes	31 (5)	8 (4.2)	15 (6.7)		1 (0.5)	22 (10.4)	
White cell count (10^9/L)	Median (IQR)	7.8 (6.4 - 9.4)	8.5 (7.1)	8.0 (2.4)	0.3	7.1 (1.9)	9.2 (6.8)	<0.01
Neutrophils (10^9/L)	Median (IQR)	5.1 (4.0 - 6.6)	5.4 (2.6)	5.5 (2.3)	0.8	4.1 (1.3)	6.6 (2.6)	<0.01
Lymphocytes (10^9/L)	Median (IQR)	1.7 (1.2 - 2.1)	1.7 (0.7)	1.7 (0.7)	0.2	2.1 (0.6)	1.3 (0.5)	<0.01
Eosinophils (10^9/L)	Median (IQR)	0.1 (0.1 - 0.2	0.2 (0.1)	0.2 (0.2)	0.7	0.2 (0.1)	0.1 (0.2)	<0.01
Basophils (10^9/L)	Median (IQR)	0.0 (0.0 - 0.1)	0.03 (0.05)	0.03 (0.07)	0.4	0.03 (0.05)	0.03 (0.07)	0.5
Monocytes (10^9/L)	Median (IQR)	73 (62 - 86)	0.7 (0.3)	0.6 (0.2)	0.2	0.6 (0.3)	0.7 (0.3)	<0.01
Creatinine (µmol/L)	Median (IQR)	73 (62 - 86)	78.9 (17.6)	76.4 (30.5)	0.3	78.6 (18.4)	76.6 (30.7)	
Albumin (g/L)	Median (IQR)	45 (42 - 57)	45.0 (5.3)	44.0 (5.0)	*0.06*	45.2 (4.2)	43.8 (5.8)	<0.01
Albumin ≤ 40 g/L	No	509 (82.6)	161 (85.2)	190 (84.8)	0.9	184 (91.1)	167 (79.1)	<0.01
	Yes	107 (17.4)	28 (14.8)	34 (15.2)		18 (8.9)	44 (20.9)	
Total protein ≤ 70 g/L	Median (IQR)	73 (69 - 77)	72.2 (9.1)	72.2 (8.3)	0.9	73.0 (7.9)	71.5 (9.3)	*0.08*
	No	423 (68.7)	135 (71.4)	156 (69.6)	0.7	148 (73.3)	143 (67.8)	0.2
	Yes	193 (31.3)	54 (28.6)	68 (30.4)		54 (26.7)	68 (32.2)	
C-reactive protein (mg/L)	Median (IQR)	6 (2 - 24)	16.3 (28.5)	26.6 (63.6)	0.3	9.0 (11.9)	30.1 (62.9)	<0.01

*Other flaps used: see figure 1

Figure 1. Choice of flaps for reconstruction



Of the 616 patients, pre-treatment imaging could be retrospectively retrieved for 413 patients (67%). Of these patients, 224 had low SMM (54.2%). All patients had available NLR data, 311 patients (50.5%) were identified with elevated systemic inflammation (NLR >3). SMM and NLR had a low significant correlation (r^2=-0.13, p=0.01). Of the patients with available SMM status (n=413), 101 (24.5%) had no low SMM or elevated NLR, 101 (24.5%) had low SMM without elevated NLR, 88 (21.3%) had no low SMM but had elevated NLR and 123 (29.8%) patients had both low SMM and elevated NLR. Table 1. provides information about the differences in variables between patients with low SMM and without low SMM and between patients with low NLR and elevated NLR. Patients with low SMM were significantly more likely to be female, older of age, to have a BMI ≤18.5 kg/m^2 and to have lower hemoglobin levels, all p<0.01. Patients with elevated NLR were significantly more likely to be older of age, to have a BMI ≤18.5 kg/m^2, more comorbidities, ECOG performance status ≥1, lower hemoglobin levels, lower eosinophil levels, lower monocytes level, lower albumin levels, higher levels of white blood cells, higher levels of c-reactive protein and a lower SMM index (all p<0.01).

POST-OPERATIVE COMPLICATIONS

Table 2. shows the types of flap and non-flap-related complications. All complications were graded by the Clavien-Dindo grading system. Of the 616 patients, 76 (12.3%) experienced a flap-related complication. Flap failure rate was 4.7%. Non-flap-related complications occurred in 243 patients (39.4%). Median time between operation date and complication date was 2 weeks (IQR 0.48-4.8 weeks).

Table 2. Postoperative complications

	All patients N=616		Patients with known SMM N=413	
Type of flap complication	N	%	N	%
None	541	87.8	365	88.4
Flap failure	29	4.7	17	4.1
Venous congestion	14	2.3	11	2.7
Dehiscence	13	2.1	8	1.9
Partial flap failure	5	0.8	3	0.7
Thrombosis	4	0.6	2	0.5
Necrosis	4	0.6	2	0.5
Arterial congestion	3	0.5	3	0.7
Partial skin breakdown	3	0.5	2	0.5
Type of non-flap complication	N	%	N	%
None	374	60.7	251	60.8
Wound infection recipient site	42	6.8	28	6.8
Wound infection donor site	40	6.5	27	6.5
Nerve damage	21	3.4	15	3.6
Wound breakdown	20	3.2	14	3.4
Postoperative bleeding	18	2.9	13	3.1
Dehiscence	14	2.3	7	1.7
Fistula	13	2.1	11	2.7
Pneumonia	13	2.1	4	1.0
Seroma	10	1.6	7	1.7
Hematoma recipient site	7	1.1	5	1.2
Neurological	6	1.0	3	0.7
Plate exposure	6	1.0	6	1.5
Pyrexia e.c.i. treated with antibiotics	5	0.8	2	0.5
Cardiovascular	4	0.6	4	1.0
Chyle leakage	3	0.5	3	0.7
Urinary tract infection	3	0.5	1	0.2
Sialocele	3	0.5	3	0.7
Swelling n.o.s.	2	0.3	3	0.7
Gastrointestinal infection	2	0.3	2	0.5
Pulmonary embolus	1	0.2	1	0.2
Other*	6	1.0	0	0
Clavien-Dindo grade	N	%	N	%
0	320	51.9	219	53
I	14	2.3	11	2.7

Table 2. (Continued)

	All patients N=616		Patients with known SMM N=413	
II	167	27.1	103	24.9
IIIa	12	1.9	10	2.4
IIIb	90	14.6	59	14.3
IVa	7	1.1	7	1.7
IVb	1	0.2	0	0
V	5	0.8	4	1

*other complications: prolonged respiratory wean due to hypodynamic diaphragm, malocclusion due to flap/plate, difficulty swallowing (multiple re-admissions, hypernatremia which prompted ITU admission), elevated liver function tests e.c.i., fractured clavicle

Most common non-flap-related complication was a wound infection at the recipient site (6.8%). Most complications (n=167, 27.1%) were scored as Clavien-Dindo grade 2. Ninety patients (14.6%) had a Clavien-Dindo grade 3b complication which meant that the severity of their complication necessitated intervention under general anesthesia. As shown in Table 3, univariate analysis in oncological patients with surgical complications as dependent variable determined elevated NLR as a significant predictive factor (HR 1.6; 95% CI 1.1-2.3, $p<0.05$). In multivariate analysis elevated NLR remained a significant predictive factor for surgical complications (OR 1.5; 95% CI 1.01-2.3, $p=0.04$), independent of patients' comorbidities and BMI. In order to get more insight in the predictive variables for different types of flap reconstructive surgeries, oncological patients were categorized into 3 subgroups of patients (with available SMM measurement) based on the chosen flap: RFFF, FFF and other flaps (non-RFFF, non-FFF). This yielded a RFFF subgroup with 193 patients, a FFF group with 88 patients and a group of patients with other flaps with 106 patients. Table 3 shows the univariate and multivariate analysis with surgical complications as dependent variable distinguishing predictive factors in the flap-subgroups. For RFFF surgery, multivariate analysis determined low SMM (OR 2.0; 95% CI 1.1-3.8, $p=0.03$) as a predictor, independent of BMI. Gender was not included in multivariate analysis due to multicollinearity between SMM and gender, ($r^2=0.62$; $p<0.001$). For FFF surgery, multivariate analysis distinguished the combination of elevated NLR with low SMM (OR 4.3; 95% CI 1.3-14.2, $p=0.02$) as a predictor for surgical complications, independent of patients' comorbidities. For non-RFF-non-FFF-flap surgery, no predictors for complications could be distinguished.

Table 3. Univariate and multivariate analysis for any surgical complications

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
All oncological patients with known SMM status (n=387)						
Gender						
Female	Ref.					
Male	1.2	0.8-1.8	0.4			
Age (years)	1.0	1.0-1.0	0.3			
Flap used						
Radial forearm	Ref.					
Fibula	0.9	0.5-1.5	0.7			
Others	0.7	0.5-1.2	0.2			
ACE-27						
None	Ref.			Ref.		
Mild	1.1	0.7-1.7	0.8	0.4	0.1-1.6	0.2
Moderate	1.4	0.8-2.4	0.3	0.5	0.1-1.7	0.2
Severe	2.2	0.6-8.0	0.2	0.6	0.1-2.2	0.4
BMI (kg/m²)						
Normal (18.5-24.9)	Ref.			Ref.		
Underweight (≤ 18.5)	0.7	0.3-1.5	0.3	0.6	0.2-1.3	0.2
Overweight (25-29.9)	0.9	0.6-1.5	0.8	0.9	0.6-1.5	0.7
Obese (≥ 30)	1.1	0.6-2.0	0.7	1.1	0.6-2.0	0.8
Smoking status*						
Never	Ref.					
Current/former	0.9	0.6-1.3	0.5			
Alcohol use*						
Never	Ref.					
Current/former	1.0	0.7-1.5	0.9			
Low hemoglobin, ≤ 100 g/L						
No	Ref.					
Yes	2.0	0.8-4.8	0.2			
Elevated NLR, > 3						
No	Ref.			Ref.		
Yes	1.6	1.1-2.3	0.045	1.5	1.01-2.3	0.04
Low albumin, ≤ 40 g/L						
No	Ref.					
Yes	1.1	0.6-2.0	0.7			
Low SMM**						
No	Ref.					
Yes	0.9	0.6-1.3	0.5			
SMM and NLR						
Normal SMM and NLR	Ref.					
Normal NLR, low SMM	1.0	0.6-1.8	1.0			
Normal SMM, NLR > 3	1.8	1.0-3.2	*0.05*			
Low SMM and NLR > 3	1.3	0.8-2.3	0.3			

Table 3. (Continued)

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Oncological patients treated with a radial forearm free flap (n=193)						
Gender						
Female	Ref.					
Male	1.8	1.0-3.2	0.05			
Age (years)	1.0	1.0-1.0	0.8			
ACE-27 score						
None	Ref.					
Mild	0.9					
Moderate	0.9	0.5-1.7	0.7			
Severe	-	0.4-2.0	0.8			
BMI (kg/m^2)						
Normal (18.5 - 24.9)	Ref.			Ref.		
Underweight (≤ 18.5)	0.5	0.2-1.8	0.3	0.6	0.2-2.0	0.4
Overweight (25 - 29.9)	1.0	0.5-1.9	0.9	0.8	0.4-1.5	0.5
Obese (≥ 30)	1.0	0.4-2.3	1.0	0.7	0.3-1.8	0.5
Smoking status						
Never	Ref.					
Current/former	0.8	0.5-1.5	0.5			
Alcohol use						
Never	Ref.					
Current/former	0.9	0.5-1.6	0.7			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes	0.5	0.05-5.7	0.6			
Elevated NLR, > 3						
No	Ref.					
Yes	1.3	0.7-2.3	0.4			
Low albumin, ≤ 40 g/L						
No	Ref.					
Yes	0.8	0.3-2.2	0.6			
Low SMM**						
No	Ref.			Ref.		
Yes	1.9	1.1-3.4	0.03	2.0	1.1-3.8	0.03
SMM and NLR						
Normal SMM and NLR	Ref.					
Normal NLR, low SMM	1.8	0.9-3.3	*0.08*			
Normal SMM, NLR > 3	1.4	0.6-3.2	0.4			
Low SMM and NLR > 3	1.3	0.7-2.5	0.5			
Oncological patients treated with a fibula flap (n=88)						
Gender						
Female	Ref.					
Male	0.9	0.4 - 2.0	0.7			
Age (years)	1.0	1.0 - 1.1	0.3			

Table 3. (Continued)

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
ACE-27 score						
None	Ref.			Ref.		
Mild	1.5	0.6 - 3.8	0.4	1.5	0.5 - 3.9	0.4
Moderate	1.4	0.4 - 5.3	0.6	1.6	0.4 - 6.5	0.5
Severe	1.4	0.1 - 24.7	0.8	1.3	0.1 - 25.1	0.9
BMI (kg/m²)						
Normal (18.5 - 24.9)	Ref.					
Underweight (≤ 18.5)	3.7	0.4 - 38.3	0.3			
Overweight (25 - 29.9)	1.1	0.4 - 2.7	0.9			
Obese (≥ 30)	0.9	0.2 - 3.2	0.8			
Smoking status						
Never	Ref.					
Current/former	0.9	0.4 - 2.1	0.9			
Alcohol use						
Never	Ref.					
Current/former	1.3	0.6 - 3.0	0.5			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes	-					
Elevated NLR, > 3						
No	Ref.					
Yes	3.3	1.3 - 8.0	0.009			
Low albumin, ≤ 40 g/L						
No	Ref.					
Yes	2.2	0.7 - 6.7	0.2			
Low SMM**						
No	Ref.					
Yes	1.7	0.7 - 3.9	0.3			
SMM and NLR						
Normal SMM and NLR	Ref.			Ref.		
Normal NLR, low SMM	1.5	0.4 - 5.7	0.6	1.7	0.4 - 6.8	0.5
Normal SMM, NLR > 3	3.4	0.9 - 13.4	0.08	3.5	0.9 - 13.7	0.07
Low SMM and NLR > 3	4.1	1.3 - 13.2	0.02	4.3	1.3 - 14.2	0.02
Oncological patients treated with non-radialis, non-fibula flap (n=106)						
Gender						
Female	Ref.					
Male	0.8	0.4 - 1.7	0.5			
Age (years)	1.0	1.0-1.1	0.3			
ACE-27 score						
None	Ref.			Ref.		
Mild	1.3	0.5 - 3.3	0.6	1.3	0.5 - 3.4	0.6
Moderate	3.0	1.0 - 9.5	0.06	2.6	0.8 - 8.6	0.1
Severe	1.3	0.2 - 9.2	0.8	1.2	0.2 - 8.7	0.9

Table 3. (Continued)

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
BMI (kg/m²)						
Normal (18.5 - 24.9)	Ref.					
Underweight (≤ 18.5)	0.5	0.1 - 2.0	0.3			
Overweight (25 - 29.9)	0.7	0.3 - 1.8	0.5			
Obese (≥ 30)	1.7	0.5 - 5.7	0.4			
Smoking status						
Never	Ref.					
Current/former	1.0	0.5 - 2.2	1.0			
Alcohol use						
Never	Ref.					
Current/former	0.9	0.4 - 1.9	0.7			
Low hemoglobin, ≤ 100 g/L						
No	Ref.					
Yes	1.8	0.6 - 5.7	0.3			
Elevated NLR, > 3						
No	Ref.					
Yes	1.2	0.5 - 2.6	0.7			
Low albumin, ≤ 40 g/L						
No	Ref.					
Yes	1.1	0.4 - 2.8	0.8			
Low SMM**						
No	Ref.					
Yes	1.4	0.6 - 3.0	0.5			
SMM and NLR						
Normal SMM and NLR	Ref.			Ref.		
Normal NLR, low SMM	2.7	0.8 - 9.2	0.1	2.1	0.6 - 7.7	0.2
Normal SMM, NLR > 3	2.3	0.7 - 7.7	0.2	2.0	0.6 - 7.0	0.3
Low SMM and NLR > 3	1.9	0.6 - 6.0	0.3	1.6	0.5 - 5.2	0.5

*Due to unknown alcohol and smoking status of 40 patients, imputation analysis was performed.
**Low SMM defined as LSMI ≤43.2cm/m²

When performing multivariate analysis to distinguish predictors for flap-related complications in oncological patients, combined elevated NLR with normal SMM was predictive for flap-related complications (OR 3.0; 95% CI 1.2-7.5, p=0.02) independent of hemoglobin levels (OR 1.1; 95%CI 1.0-1.0, p=0.3) and BMI (OR 1.0; 95%CI 0.3-2.8, p=0.5) and for severe complications (Clavien-Dindo grade ≥3b) (OR 2.2; 95%CI 1.1-4.5, p=0.04) independent of hemoglobin levels (OR 1.0, 1.0-1.0, p=0.04) and patients' comorbidities (OR mild 1.3, OR moderate 1.1, OR severe 1.4, all p>0.05).

LENGTH OF HOSPITAL STAY

Median LOS for all included patients was 13 days with an IQR of 11-18 days. When comparing mean LOS between patients with and without low SMM, patients with low SMM had longer

LOS (16.6 days, SD 10.5) compared to patients without low SMM (15.7 days, SD 17.0 days) (mean difference 0.9 days, 95%CI -1.8-3.5, p=0.5). This difference was not statistically significant. Patients with elevated NLR had a significant risk for longer LOS (17.7 days; SD 17.0 days) compared to patients with low NLR (14.5 days; SD 9.2 days) (mean difference 3.2 days, 95%CI 0.5-5.9, p=0.02). Also, patients with elevated NLR and low SMM had a significant longer LOS (17.3 days, SD 10.4) compared to patients without combined elevated NLR and low SMM (13.5 days, SD 7.7) (mean difference 3.9 days, 95% CI 1.4-6.3 days, p=0.002).

SURVIVAL ANALYSIS

Median follow-up time was 39.5 months (IQR 18.0-76.5). At the end of the study, 289 (46.9%) patients died, and 190 (34.2%) oncological patients developed a recurrence.

Figure 2. shows the Kaplan Meier survival curves for DFS and OS for all patients. As shown, elevated NLR (Log rank $\chi2 = 4.4$, p=0.04) was prognostic for decreased DFS and low SMM (Log rank $\chi2 = 4.2$, p=0.04) and elevated NLR (Log rank $\chi2 = 6.0$, p=0.02) were prognostics for decreased OS.

Due to the heterogeneity of reasons for reconstructive surgery and also heterogeneity in tumor histology, we choose to perform survival analysis for the subgroup of patients with HNSCC (n=507). SMM and NLR status was only available in a subgroup of HNSCC patients (n=352), therefore we choose to evaluate the prognostic impact of these variables and other variables in this subgroup. Because TNM stage is a known prognostic factor, we decided to investigate the prognostic impact of low SMM and elevated NLR in patients with early (TNM stage I-II) and advanced stage (TNM stage III-IV) HNSCC. Table 4 shows the univariate and multivariate cox regression analysis of prognostic variables for DFS and OS. For DFS, multivariate analysis determined age to be prognostic in early stage HNSCC (HR 1.04, 1.01-1.1, p<0.05) and in advanced stage HNSCC (HR 0.98; 0.96-0.99, p=0.02). For OS, in patients with early stage HNSCC, multivariate analysis showed low SMM (HR 2.3, 95%CI 1.2-4.4, p=0.01) and combined elevated NLR with low SMM (HR 2.6, 95%CI 1.1-6.0, p=0.03) to be significant prognostics for decreased OS, independent of comorbidity. Age and gender were not included in multivariate analysis due to multicollinearity between SMM and age (r^2=-0.4; p<0.001) and SMM and gender (r^2=0.62; p<0.001). For OS, in patients with advanced stage HNSCC, in multivariate analysis only BMI (HR 0.9; 95%CI 0.9-0.98, p<0.001) and hemoglobin (HR 0.99, 95%CI 0.98-0.99, p=0.03) were prognostic for decreased OS.

Figure 2. Kaplan Meier Survival curves for OS for all patients undergoing head and neck reconstruction according to NLR status (Log rank χ2= 6.0, p=0.02) and SMM status (Log rank χ2= 4.2, p=0.04) and for DFS for all patients undergoing head and neck reconstruction according to NLR status (Log rank χ2= 4.4, p=0.04) and SMM status (Log rank χ2= 1.7, p=0.2)

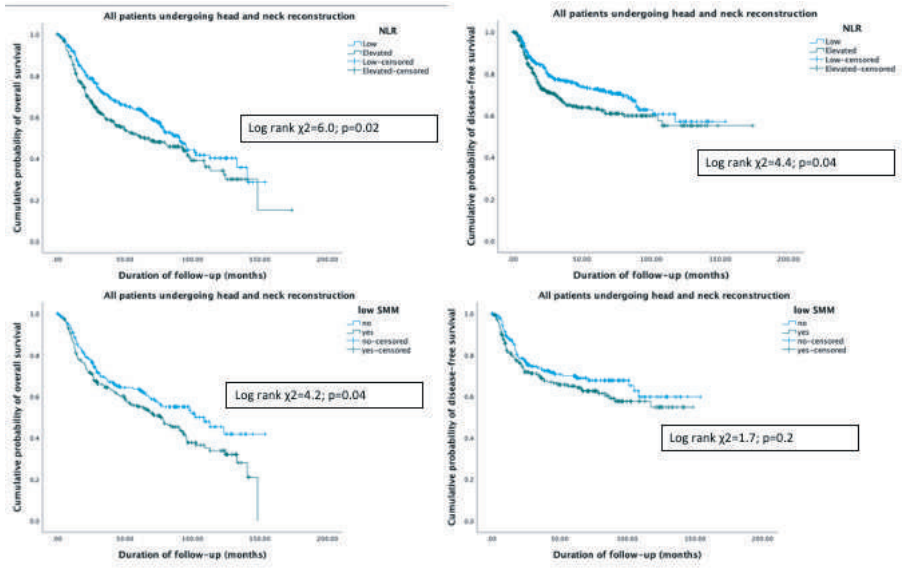


Table 4. Univariate and multivariate cox proportional hazards model for prognostic factors for OS and DFS in early and advanced stage HNSCC

Variable	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Oncological HNSCC patients: TNM stage I=II - OS									
Gender									
Female	Ref.								
Male	0.5	0.3-0.9	0.01						
Age (years)	1.1	1.04-1.1	0.0001						
ACE-27 score									
None	Ref.			Ref.			Ref.		
Mild	1.6	0.8-2.9	0.2	1.6	0.9-3.0	0.1	1.5	0.8-2.9	0.2
Moderate	1.8	0.8-4.2	0.2	1.5	0.7-3.6	0.3	1.7	0.7-4.0	0.2
Severe	1.9	0.4-8.2	0.4	2.2	0.5-9.5	0.3	2.6	0.6-11.5	0.2
BMI (kg/m²)	0.95	0.9-1.0	0.1						
Hemoglobin (g/L)	0.99	0.97-1.0	0.2						
Hemoglobin ≤100 (g/L)									
No	Ref.								
Yes	1.8	0.2-13.2	0.6						

Table 4. (Continued)

Variable	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
NLR									
≤3.0	Ref.								
>3.0	1.3	0.7-2.2	0.4						
Low SMM									
No	Ref.			Ref.					
Yes	2.3	1.2-4.4	0.01	2.3	1.2-4.4	0.01			
SMM and NLR									
Normal SMM and NLR	Ref.						Ref.		
Normal NLR, low SMM	1.6	0.7-2.6	0.3				1.5	0.7-3.5	0.3
Normal SMM, NLR > 3	0.7	0.2-2.3	0.5				0.6	0.2-2.1	0.4
Low SMM and NLR > 3	2.7	1.2-6.3	0.02				2.6	1.1-6.0	0.03
Oncological HNSCC patients: TNM stage III-IV - OS									
Gender									
Female	Ref.								
Male	1.3	0.9-1.9	0.2						
Age (years)	1.0	1.0-1.0	0.7						
ACE-27 score									
None	Ref.								
Mild	1.6	0.8-2.9	0.2						
Moderate	1.8	0.8-4.2	0.2						
Severe	1.9	0.4-8.2	0.4						
BMI (kg/m²)	0.94	0.90-0.98	0.004	0.96	0.93-0.99	0.01	0.94	0.9-0.98	0.008
Hemoglobin (g/L)	0.99	0.98-0.99	0.02				0.99	0.98-0.99	0.03
Hemoglobin ≤100 (g/L)									
No	Ref.								
Yes	1.5	0.8-2.6	0.2						
NLR									
≤ 3.0	Ref.			Ref.					
>3.0	1.2	0.8-2.2	0.4	1.3	0.9-1.7	0.1			
Low SMM									
No	Ref.								
Yes	1.3	0.9-1.8	0.2						
SMM and NLR									
Normal SMM and NLR	Ref.								
Normal NLR, low SMM	1.4	0.8-2.4	0.2						
Normal SMM, NLR > 3	1.3	0.8-2.2	0.3						
Low SMM and NLR > 3	1.5	0.9-2.5	*0.09*						

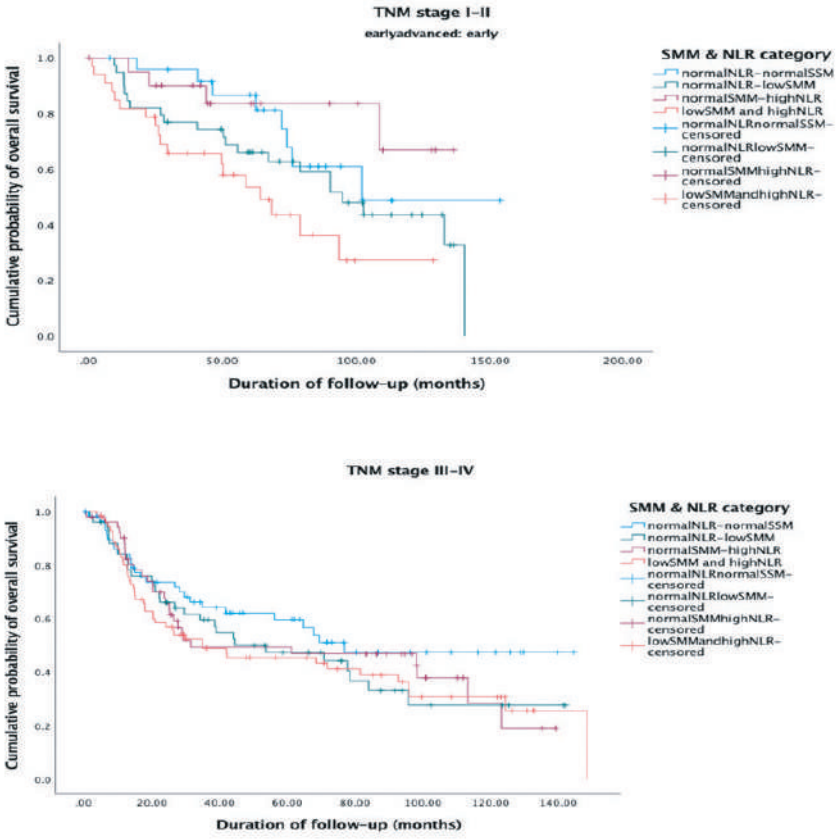
Table 4. (Continued)

Variable	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Oncological HNSCC patients: TNM stage I-II - DFS									
Gender									
Female	Ref.						Ref.		
Male	0.4	0.2-0.8	0.02				0.5	0.2-1.0	*0.06*
Age (years)	1.1	1.01-1.1	0.001				1.04	1.01-1.08	0.007
ACE-27									
None	Ref.			Ref.			Ref.		
Mild	0.8	0.4-1.9	0.7	0.9	0.4-1.9	0.7	0.9	0.4-2.0	0.8
Moderate	2.2	0.9-5.5	0.09	1.9	0.8-4.8	0.2	2.2	0.9-5.6	*0.09*
Severe	1.3	0.2-9.7	0.8	1.4	0.2-10.7	0.7	1.0	0.1-7.8	0.99
BMI (kg/m²)	0.95	0.9-1.0	0.2						
Hemoglobin (g/L)	0.99	0.9-1.0	0.4						
Hemoglobin ≤100 (g/L)									
No	Ref								
Yes	0.05	0-µ	0.7						
NLR									
≤ 3.0	Ref.								
3.0	1.2	0.6-2.4	0.6						
Low SMM									
No	Ref.			Ref.					
Yes	2.2	1.0-5.0	*0.05*	2.0	0.9-4.6	*0.09*			
SMM and NLR									
Normal SMM and NLR	Ref.								
Normal NLR, low SMM	3.4	1.0-11.8	*0.06*						
Normal SMM, NLR>3	2.2	0.5-9.1	0.3						
Low SMM and NLR>3	3.3	0.9-12.1	*0.07*						
Oncological HNSCC patients: TNM stage III-IV - DFS									
Gender									
Female	Ref.								
Male	1.0	0.7-1.5	0.9						
Age (years)	0.98	0.97-1.0	0.05	0.98	0.96-0.99	0.03	0.98	0.96-0.99	0.02
ACE-27									
None	Ref.								
Mild	0.8	0.5-1.2	0.2						
Moderate	1.0	0.6-1.8	1.0						
Severe	0.3	0.04-2.0	0.2						
BMI (kg/m²)	0.9	0.9-1.0	0.2						
Hemoglobin (g/L)	0.9	0.9-1.0	0.1	0.99	0.98-1.0	0.07			

Table 4. (Continued)

Variable	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hemoglobin ≤100 (g/L)									
No	Ref.						Ref.		
Yes	1.5	0.8-2.9	0.3				1.4	0.7-2.9	0.4
NLR									
≤3.0	Ref.								
>3.0	1.1	0.7-1.7	0.5						
Low SMM									
No	Ref.								
Yes	1.3	0.8-2.0	0.2						
SMM and NLR									
Normal SMM and NLR	Ref.						Ref.		
Normal NLR, low SMM	1.1	0.6-2.1	0.8				1.3	0.7-2.4	0.5
Normal SMM, NLR>3	1.0	0.5-1.8	0.9				1.0	0.5-1.9	0.9
Low SMM and NLR>3	1.4	0.8-2.4	0.3				1.6	0.9-2.8	0.1

Figure 3. Kaplan Meier Survival curves for OS for early stage HNSCC patients according to SMM and NLR status shows significant differences in overall survival between patients with low SMM compared to patients without low SMM, especially in those patients with combined low SMM and elevated NLR, (Log rank $\chi 2 = 10.2$, $p=0.02$). Kaplan Meier Survival curves for overall survival of advanced stage HNSCC patients according to SMM and NLR status shows no significant differences in survival (Log rank $\chi 2 = 3.0$, $p=0.4$).



DISCUSSION

This study showed that low SMM and elevated NLR have significant predictive impact for postoperative complications and LOS and prognostic impact for survival in (subgroups of) patients undergoing microvascular free flap head and neck reconstruction. Prognostic impact of these biomarkers was however only seen in patients with early stage HNSCC. It is possible that TNM stage itself is a strong prognostic factor in advanced stage HNSCC and therefore no prognostic impact was seen for SMM and NLR. For advanced stage HNSCC, hemoglobin had significant (but low) prognostic impact for OS. This finding is in accordance with previous literature, which shows that the relative risk of death increased by 75% in anemic patients with head and neck cancer.[34] Also in patients who underwent surgery and adjuvant radiotherapy for locally advanced HNSCC, low hemoglobin appears to be an important prognostic factor.[35]

The prevalence of low SMM and high NLR found in the entire cohort was 54.2% and 50.5%, respectively. For HNSCC patients, the prevalence of low SMM and high NLR was 57.0% and 48.3%, respectively. A previous study performed in colorectal cancer with 2470 patients found similar prevalence of low SMM (44%) and elevated NLR (46%). A significant prognostic value of these markers for decreased overall survival was also found.[36]

SMM and inflammation have been associated with increased risk of postoperative complications and mortality in various types of cancer such as lung cancer, gastrointestinal cancer, pancreatic cancer, hepatobiliary cancer, breast cancer and cancers of the reproductive system.[37–42] Virchow was the first to provide a possible link between inflammation and cancer by observing the presence of leukocytes within tumors in the 19th century. Since then, various studies published about the significant role of inflammation in cancer and only during the last decade clear evidence has been obtained to show the critical role of inflammation in tumorigenesis.[43] It is also known that local inflammation in the microenvironment of the tumor leads to chronic systemic inflammation with significant effects on patient's body weight and amount of lean tissue of which SMM is the largest contributor, also known as cancer cachexia.[44] Also, neutrophils and lymphocytes are host inflammation markers which provide angiogenic, epithelial and stromal growth factors that may cause tumor progression.[45] The role of patients' grade of systemic inflammation in surgically treated patients has been increasingly recognized over the past decade.[42,46–51]

Muscle mass and inflammation also gained increased attention in the field of medical oncology, especially in HNC patients. Low SMM has shown to be predictive for chemotherapy dose-limiting toxicities[13], radiotherapy toxicities, increased risk of pharyngocutaneous fistulas in patients undergoing laryngectomy[52], decreased survival in patients with oral cavity cancers[53] and increased risk of FFF failure and other surgical complications in oral cancer patients.[20] Low SMM has also shown to be prognostic for decreased OS and DFS.[6] Our previous finding showed that low SMM is a significant predictor of surgical complications and prognostic for OS in oral cancer patients undergoing FFF surgery, in this cohort we confirm this and found that the combination of low SMM with elevated NLR (OR 4.3; $p<0.05$) was predictive for surgical complications. Due to the low flap failure rate, especially in patients with FFF surgery (n=7) it was not possible to specifically evaluate the impact of low SM on failure rate, however we assume that the dire effects of low SMM on physical recovery also applies to this flap and that low SMM is a predictive factor for failure rate, as found in our previous study cohort.[20]

In this cohort, we found a significant predictive and prognostic impact of elevated NLR. Previous research also shows the prognostic impact of elevated NLR for decreased survival in patients with HNC.[54] To date, only few articles describe the impact of elevated NLR in surgically treated HNC patients. Kuzucu et al. conducted a study in 145 patients undergoing parotidectomy and 83 healthy persons and found that elevated NLR was significantly higher in patients undergoing surgery for malignant parotid mass.[55] This supports the link between inflammation and cancer. Son et al. performed a retrospective study in 369 patients and found that elevated

NLR was significantly associated with increased risk of surgical site infection in HNC patients undergoing major oncologic resection.[56] This study supports this finding. NLR is not only an index of inflammation, but is also known to reflect nutritional status, as the total lymphocyte count is decreased in cases of malnutrition.[57] The exact underlying mechanism of how low SMM and elevated NLR attributes to surgical complications is not yet elucidated. Inflammation may underline muscle wasting and may also be reinforced by it. Inflammatory mediators promote catabolic metabolism which leads to increased protein degradation and decreased regeneration. Low SMM and high NLR may therefore also interfere with wound healing.

Our study has some limitations. Due to the retrospective design of the study, information was not completely available regarding ischemic time, intra-operative hypotension, operative time and anticoagulant administration. These factors are known to (potentially) have an impact on surgical complications. Besides this limitation, our study has also some strengths. Firstly, we included a large sample size with detailed socio-demographic and clinical factors. Secondly, we measured SMM at the level of C3 instead of L3 which minimizes the risk of only including advanced cases of HNC. Thirdly, this is the first study evaluating the impact of SMM and systemic inflammation in patients undergoing head and neck microvascular reconstruction.

Prevention or treatment of low SMM in head and neck patients remains a challenge due to the high prevalence of malnutrition in these patients. It is however worthwhile to study if interventions aimed at preservation and/or gain of SMM such as pre-operative multimodal rehabilitation programs that include nutritional support, physical therapy and motivational psychotherapy could be effective in preventing adverse outcomes associated with low SMM and elevated NLR. Pharmacological interventions and supplements targeting SMM might also be promising.[58] For example, omega-3-fatty acids may alter body composition by anti-inflammatory effects and thereby contribute to increased anabolism, improve insulin response and glucose transport and reduce triglyceride accumulation in skeletal muscle.[59] Trials are performed where cachexia in patients with cancer are treated with omega-3 fatty acid supplementation and nonsteroidal anti-inflammatory drugs which underlines the interrelationship between inflammation and muscle wasting.[60]

CONCLUSIONS

SMM and NLR are easily evaluated, non-invasive biomarkers which are associated with an increased risk of complications, longer LOS and decreased survival in patients undergoing microvascular free flap reconstruction in the head and neck area.

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CHAPTER 8

Are perioperative complications in patients operated for oral squamous cell carcinoma associated with low skeletal muscle mass?

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Submitted ■

ABSTRACT

Background

Low skeletal muscle mass, also referred to as sarcopenia, is associated with negative outcomes in oncology. The aim of this study was to investigate the predictive impact of sarcopenia on perioperative complication rate in patients with oral squamous cell carcinoma (OSCC).

Material and methods

Patients who had been operated between 2014 and 2017 for OSCC were included. Data were extracted from electronic medical records. The cross-sectional muscle area at the level of the third lumbar vertebra (L3) was estimated from a single CT-slice at the level of the third cervical vertebra (C3) and divided by squared body height to calculate the lumbar skeletal muscle index (LSMI). Sarcopenia was defined as the lowest quartile LSMI of the patient group. Univariate and multivariate analyses were used to test sarcopenia as an independent risk factor for perioperative complication rate.

Results

In total, 226 patients were included of which 51 patients had developed 81 complications. In multivariate analysis, the presence and number of perioperative complications was respectively associated with sarcopenia (OR 2.6, $p<0.05$) (OR 2.4, $p<0.05$), longer operating time (OR 1.4, $p<0.01$) (OR 1.2, $p<0.01$), increased blood loss (OR 1.5, $p<0.01$) (OR 1.6, $p<0.01$) and comorbidity (OR 9.1, $p<0.01$) (OR 6.2, $p<0.01$). Longer hospital stay was associated with longer operating time (OR 1.04, $p<0.01$), decrease in hemoglobin level (OR 1.04, $p<0.01$) and ASA (score 3) (OR 1.1, $p<0.01$)

Conclusion

Sarcopenia is an independent risk factor for perioperative complication rate in OSCC patients undergoing surgical treatment.

INTRODUCTION

Sarcopenia has been defined as the loss of skeletal muscle mass (SMM) and strength that occurs with advancing age.[1,2] In oncology the term cachexia is also used, which is defined as a multifactorial syndrome characterised by an ongoing loss of SMM (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[3]

In bladder, gastrointestinal and liver cancer surgery, sarcopenia has been associated with worse perioperative outcome[3–8] and poor survival rates.[9–12] Patients with head and neck cancer have increased risk of malnutrition.[13] In head and neck cancer surgery, the association between sarcopenia and poor survival has been shown[14–17], but data on the association between sarcopenia and perioperative complications are limited to patients undergoing laryngectomy or fibula flap reconstruction.[18–22] Knowledge on the potential association between sarcopenia and perioperative complications could be helpful for surgeons treating patients with head and neck cancer to minimize the risk of perioperative complications.

Total body SMM can be measured with several imaging methods. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered to be very precise imaging methods that can separate fat from other soft tissues of the body, making these methods gold standards for estimating muscle mass.[2,23] The total body SMM has been shown to correlate strongly with measurements of skeletal muscle mass at the level of axial single abdominal CT slices. These transversal single slices are located 5 cm cranially from the fourth lumbar intervertebral disc (L4-L5)[24] or at the level of the third lumbar vertebra (L3).[25] Abdominal CT scans are not part of the routine diagnostic work-up of head and neck cancer patients, but we have shown previously that there is a strong correlation between the SMM at the third cervical vertebra (C3) and the SMM at L3.[26]

The aims of this study are to determine whether sarcopenia is associated with perioperative complications in OSCC patients undergoing surgical treatment. We hypothesize that sarcopenia is associated with perioperative complications and that sarcopenia is associated with a longer hospital stay.

MATERIAL AND METHODS

ETHICAL CONSIDERATIONS

The local Medical Research Ethics Committee gave approval for this retrospective cohort study (reference number 17-208/C).

PATIENTS AND STUDY DESIGN

Patients who had surgery for OSCC at the University Medical Center Utrecht, the Netherlands, between September 2014 and January 2017 were identified from the departmental database. Inclusion criterion was the presence of a preoperative CT or MRI scan. All patients had been treated according to the national guidelines [27]. The surgical procedures had been performed by surgeons, dedicated to head and neck surgery. Potential risk factors for perioperative complications were collected from the electronic medical records: age, sex, body-mass index (BMI), comorbidity, alcohol intake, tumor, node, metastasis (TNM) stage (7th edition)[27], blood loss measured as decrease in hemoglobin level (mmol/L) following surgery, type of operation and operating time (in hours) (see Table 1 and 2).

The comorbidity was determined using the American Society of Anesthesiologists (ASA) classification system: ASA 1 for normal and healthy patient; ASA 2 for mild, systemic diseases; ASA 3 for severe systemic diseases; ASA 4 for severe systemic disease that is a constant threat to life; ASA 5 for patient not expected to survive without surgery. The overall comorbidity score was also determined with the Adult Comorbidity Evaluation system (ACE-27). The ACE-27 system identifies and grades 27 important ailments and gives an objective overall comorbidity score for the individual patient: 0 (none), 1 (mild), 2 (moderate) or 3 (severe).[28,29] The overall comorbidity score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score is designated Grade 3.

OUTCOME VARIABLES

Perioperative data were obtained from the medical records: myocardial ischemia, acute myocardial infarction, congestive cardiac failure, thrombosis, pulmonary embolism, pneumonia, dysregulated diabetes, fever, postoperative hemorrhage, hematoma, wound dehiscence, wound infection, revision of the anastomosis, flap failure, jaw fracture, nerve damage, seroma, unexpected use of feeding tube, delirium and the length of hospital stay. Perioperative complications were defined according to Patel et al.[30] as any unanticipated adverse event requiring intervention or prolonging length of hospital stay. The perioperative complication rate was measured as presence and number of perioperative complications.

SKELETAL MUSCLE MASS MEASUREMENT

SMM was determined from a single CT-slice at the level of the third cervical vertebra (C3) according to the method described by Swartz et al.[26] When scrolling in caudo-cephalic direction,

the first CT-slice at C3 level to entirely depict the vertebral arc, the transverse and the spinous process(es) was selected. Skeletal muscle was characterized by Hounsfield units (HU) ranging from -29 to +150 HU[23] and identified using Slice-O-Matic software V4.3 (Tomovision, Montreal, Quebec, Canada). By delineating the paravertebral and the sternocleidomastoid muscles at C3 level, the cross-sectional area of the muscles was calculated in cm^2 using Slice-O-Matic software. The cross-sectional muscle area at L3 level was then estimated using Equation (1) as described by Swartz et al.[26] This result was normalized by dividing by the squared body height in m^2 to calculate the lumbar skeletal muscle index (LSMI). Sarcopenia was then defined as the lowest quartile LSMI of the patient group.[31,32]

STATISTICAL METHODS

Statistical analyses were performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A summary of the patient group and tumor description was generated. The perioperative complications were modeled with sarcopenia and the other potential risk factors. Firstly, univariate analysis was performed for potential risk factors to examine the association of potential risk factors with presence of perioperative complications. Potential risk factors with p value <0.25 in the univariate analysis and sarcopenia were then entered in the multivariate analysis using logistic regression for the presence of perioperative complications and negative binomial regression for the number of perioperative complications. Secondly, univariate linear regression was performed for potential risk factors to examine the association of potential risk factors with length of hospital stay. Potential risk factors with p value <0.25 in the univariate analysis and sarcopenia were then entered in the multivariate analysis using normal linear regression for length of hospital stay. For the linear regression, length of hospital stay was transformed using a Log transformation. After the Log transformation, continuity and normality was assumed. All hypotheses in the multivariate analysis were tested two-sided with a statistical level of α=0.05.

RESULTS

PATIENT CHARACTERISTICS

The study group consisted of 259 patients. 33 of these patients were excluded because of unavailable CT/MRI scans or poor image quality. The remaining group of 226 patients consisted of 110 males and 116 females, with median age 67 years. 51 patients had developed one or multiple complications. The patient characteristics are listed in Table 1. Because just one patient had ASA score 4, three ASA groups were made: ASA 1, 2 and 3+. The tumor variables are shown in Table 2.

Table 1. Patient characteristics

Patient characteristics	n = 226
Age, median (sd, range)	67 years (11.65, 35-91)
Gender	
Male	110 (48.7%)
Female	116 (51.3%)
Alcohol	
>3units/day	110 (48.7%)
Sporadic use	44 (19.5%)
ACE-27 [a]	
None (0)	59 (26.1%)
Mild (1)	84 (37.2%)
Moderate (2)	70 (31.0%)
Severe (3)	13 (5.8%)
ASA classification [b]	
1	34 (15.0%)
2	141 (62.4%)
3	50 (22.1%)
4	1 (0.4%)
LSMI [c]**, mean (sd, range)**	38.82 cm^2/m^2 (8.40, 22.20 - 64.38)
Length of hospital stay, mean (sd, range)	8.86 days (5.967, 2 - 43)

a ACE-27 = Adult Comorbidity Evaluation-27, b ASA classification = American Society of Anesthesiologists physical status classification system, c LSMI = lumbar skeletal muscle index

Table 2. Tumor variables

Tumor variables		n = 226
Single tumor		219 (96.9%)
Simultaneous		7 (3.1%)
TNM Stage		
	I	66 (29.2%)
	II	58 (25.7%)
	III	25 (11.1%)
	IV	76 (33.6%)

PERIOPERATIVE COMPLICATIONS

The perioperative complications are listed in Table 3.The univariate logistic regression analysis with potential risk factors for perioperative complications yielded four variables with *p* values less than 0.25: ACE-27 [score 1 (OR = 1.645) and score 3 (OR = 3.740)], ASA [score 3+ (OR = 2.104)], operating time (OR = 1.356) and decrease in hemoglobin level (OR = 2.037) (Table 4). These four variables, and sarcopenia, were entered in the multivariate analysis for perioperative complications.

Table 3. Perioperative complications

Perioperative complications	Number (percentage of total (n=81))
Wound dehiscence	15 (18.1%)
Congestive cardiac failure	8 (9.6%)
Delirium	8 (9.6%)
Wound infection	7 (8.4%)
Dysregulated diabetes	6 (7.2%)
Unexpected use of feeding tube	6 (7.2%)
Hematoma	5 (6.0%)
Pneumonia	4 (4.8%)
Postoperative hemorrhage	4 (4.8%)
Fever	3 (3.6%)
Flap failure	3 (3.6%)
Nerve damage	3 (3.6%)
Thromboembolism	3 (3.6%)
Acute myocardial infarct	1 (1.2%)
Fracture of the jaw	1 (1.2%)
Myocardial ischemia	1 (1.2%)
Pulmonary embolism	1 (1.2%)
Revision of the anastomosis	1 (1.2%)
Seroma	1 (1.2%)

Table 4. Univariate analysis with potential risk factors for presence of perioperative complications

Potential risk factors		Presence of perioperative complications		
		OR (95%-CI)	*p* value	Overall *p* value
Age		1.01 (0.98-1.03)	0.65	-
Gender	Male	Ref.		-
	Female	0.848 (0.467-1.542)	0.59	
ACE-27[a]	0	Ref.		0.23
	1	1.65 (0.73-3.71)	0.23	
	2	1.51 (0.65-3.52)	0.34	
	3	3.74 (1.05-13.35)	**0.04**	

Table 4. (Continued)

Potential risk factors		Presence of perioperative complications		
		OR (95%-CI)	*p* value	Overall *p* value
ASA classification[b]	1	Ref.		0.20
	2	1.18 (0.47-2.95)	0.73	
	3+	2.10 (0.77-5.78)	0.15	
Alcohol use	> 3 U/day	1.44 (0.72-2.87)	0.31	0.52
	Sporadic	1.03 (0.42-2.53)	0.95	
	No	Ref.		
Operating time		1.36 (1.23-1.50)	**<0.001**	-
Decrease in Hb[c] **level**		2.04 (1.58-2.62)	**<0.001**	-
BMI[d]		(0.96-1.07)	0.67	-
Sarcopenia	Yes	1.37 (0.70-2.68)	0.36	-
	No	Ref.		

Variables with p <0.25 were used in the multivariate analysis (indicated in bold)
a ACE-27 = Adult Comorbidity Evaluation-27, b ASA classification = American Society of Anesthesiologists physical status classification system, c Hb = hemoglobin, d BMI = Body Mass Index

LENGTH OF HOSPITAL STAY

The univariate linear regression analysis with potential risk factors for length of hospital stay yielded six variables with *p* values less than 0.25: ACE-27 [score 2 (OR = 1.09)], ASA [score 3+ (OR = 1.10)], alcohol use [>3U/day (OR = 1.06)], operating time (OR = 1.05), decrease in hemoglobin level (OR = 1.106) and BMI (OR=1.0) (Table 5). These six variables, and sarcopenia, were entered in the multivariate analysis for length of hospital stay.

Table 5. Univariate analysis with potential risk factors for longer hospital stay

Potential risk factors		Length of hospital stay		
		ratio (95%-CI)	*p* value	Overall *p* value
Age		1.0 (1.0 - 1.0)	0.59	-
Gender	Male	Ref.		-
	Female	0.97 (0.91 - 1.03)	0.31	
ACE-27[a]	0	Ref.		0.08
	1	0.99 (0.92 - 1.08)	0.99	
	2	1.09 (1.00 - 1.19)	**0.03**	
	3	1.04 (0.90 - 1.20)	0.60	
ASA classification[b]	1	Ref.		0.23
	2	1.04 (0.95 - 1.15)	0.36	
	3+	1.10 (0.99 - 1.22)	**0.09**	
Alcohol use	> 3 U/day	1.06 (0.99 - 1.14)	**0.11**	0.17
	Sporadic	1.0 (0.91 - 1.09)	0.92	
	No	Ref.		
Operating time		1.05 (1.04 - 1.06)	**<0.001**	-
Decrease in Hb[c] **level**		1.11 (1.08 - 1.13)	**<0.001**	-
BMI[d]		1.0 (1.0 - 1.0)	**0.10**	-

Table 5. (Continued)

Potential risk factors		Length of hospital stay		
		ratio (95%-CI)	*p* value	Overall *p* value
Sarcopenia	Yes	1.0 (0.93 - 1.08)	0.93	-
	No	Ref.		

Variables with p <0.25 were used in the multivariate analysis (indicated in bold)
a ACE-27 = Adult Comorbidity Evaluation-27, b ASA classification = American Society of Anesthesiologists physical status classification system, c Hb = hemoglobin, d BMI = Body Mass Index

All tumor variables appeared collinear with the operating time ($p < 0.001$ for all variables). Therefore, the tumor variables were not included in multivariate analysis to prevent biased estimation.

In the multivariate analysis, the presence of perioperative complications was associated with sarcopenia (OR 2.5, p<0.05), longer operating time (OR 1.4, p<0.001), increased blood loss (OR 1.5, p<0.01) and comorbidity (OR 9.1, p<0.05). The number of perioperative complications was associated with sarcopenia (OR 2.4, p<0.05) , longer operating time (OR 1.2, p<0.001), increased blood loss (OR 1.6, p<0.001) and comorbidity (ACE-27 score 3) (OR 6.3, p<0.01). Longer hospital stay was associated with longer operating time, decrease in hemoglobin level, ACE-27 and ASA (score 3). The ratios and *p* values are shown in Table 6 and 7.

Table 6. Multivariate analysis of presence, number and severity (Clavien-Dindo grade) of perioperative complications for patient variables

Patient variables		Presence of perioperative complications		Number of perioperative complications	
		OR (95% CI)	*p* value	Incidence rate (95% CI)	*p* value
ACE-27[b]	0	Ref.	0.11[a]	Ref.	**0.03[a]**
	1	2.52 (0.71-8.94)	0.15	1.89 (0.70-5.08)	0.21
	2	1.95 (0.56-6.82)	0.30	1.64 (0.62-4.36)	0.32
	3	9.08 (1.51-54.54)	0.02	6.21 (1.75-22.0)	**0.005**
ASA[c]	1	Ref.	0.33[a]	Ref.	0.33[a]
	2	0.96 (0.23-4.05)	0.96	0.84 (0.28-2.51)	0.75
	3+	1.93 (0.36-10.28)	0.44	1.39 (0.39-4.93)	0.62
Operating time		1.37 (1.21-1.56)	<0.001	1.21 (1.11-1.32)	**<0.001**
Decrease in Hb[d] level		1.55 (1.14-2.10)	0.005	1.63 (1.31-2.04)	**<0.001**
Sarcopenia	Yes	2.61 (1.12-6.08)	0.03	2.43 (1.24-4.78)	**0.01**
	No	Ref.		Ref.	

Variables with p < 0.05 were considered significant. a Overall p value of the variable for the outcome
b ACE-27 = Adult Comorbidity Evaluation-27, c ASA classification = American Society of Anesthesiologists physical status classification system, d Hb = hemoglobin

Table 7. Multivariate analysis of longer hospital stay for patient variables

Patient variables		Length of hospital stay ratio (95% CI)	*p* value	Overall *p* value
ACE-27 [a]	0	Ref.		0.01
	1	0.97 (0.91-1.04)	0.41	
	2	1.06 (0.99-1.14)	0.09	
	3	1.05 (0.94-1.18)	0.40	
ASA classification [b]	1	Ref.		0.02
	2	1.08 (1.0-1.2)	0.06	
	3+	1.15 (1.0-1.3)	**0.005**	
Alcohol use	> 3 U/day	0.99 (0.935-1.042)	0.63	0.76
	Sporadic	0.98 (0.915-1.042)	0.47	
	No	Ref.		
Operating time		1.04 (1.03-1.05)	**<0.001**	-
Decrease in Hb [c] **level**		1.04 (1.02-1.06)	**0.001**	-
BMI [d]		1.0 (0.99-1.00)	0.08	-
Sarcopenia	Yes	1.04 (0.98-1.10)	0.26	-
	No	Ref.		

Variables with p < 0.05 were considered significant. a ACE-27 = Adult Comorbidity Evaluation-27, b ASA classification, c Hb = hemoglobin, d BMI = Body Mass Index

DISCUSSION

Our first hypothesis was confirmed: we found a significant association between SMM and presence of perioperative complications (OR 2.61) and number (OR 2.43) of perioperative complications, which means that sarcopenia is an independent predictive factor for perioperative complication rate. To the best of our knowledge this is the first study on the relation between sarcopenia and perioperative complications in surgically treated OSCC patients. In recent studies, a similar relation was found for sarcopenia on the occurrence of fistula after laryngectomy and complications after fibula reconstruction in head and region.[18,21,22] Also, a recent study in 125 OSCC patients who underwent curative surgery, found a significant prognostic impact of sarcopenia for decreased disease-free and overall survival. Perioperative complication rate was also associated with longer operating time, increased blood loss and ACE 27. These findings were in concordance with Peters et al.[33]

We evaluated comorbidity using both ASA physical status classification system and ACE-27 index. The ASA physical status classification system is a widely used validated grading system to identify perioperative risk for anesthesiologists.[34] The ACE-27 index is a validated index[28,29,35,36] developed to identify the important medical comorbidities and to grade the

severity. Several studies showed that comorbidities are a reliable predictor for perioperative complications and that the ASA classification and ACE-27 index can both accurately measure comorbidities.[35–39]

We used Slice-O-Matic to identify skeletal muscle from MRI and CT scans. These two different imaging modalities show significant correlation in quantifying SMI when measured by CSA at the level of C3.[19] The excellent inter-observer agreement for SMI measurement at the level of C3 should allow SMI measurements findings to be used globally to select patients for suitable therapy.

We defined sarcopenia as the lowest quartile LSMI of the patient group, because there is no cut-off value for the definition of sarcopenia.[3132] This means that a method to measure sarcopenia in the clinical setting and a clear definition of sarcopenia is needed.

By the European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia is described as a generalized and progressive loss of muscle function and skeletal muscle mass caused by adverse muscle changes that accrue during lifetime.[2] Due to its retrospective design, we could only use the skeletal muscle mass at a single point of time as measured on routinely preformed CT or MRI to define sarcopenia, since skeletal muscle mass of earlier time points could not be measured.

Since the prevalence of perioperative complications was low with 51 patients with perioperative complications out of 226 patients (22.6%), the retrospective cohort design of our study results in more controls than cases. Therefore, a case-controlled setting would be preferred. Also because of the retrospective cohort design, further research is warranted.

Our finding that sarcopenia is associated with perioperative complication rate may help surgeons to anticipate on the risk of perioperative complications. A method to measure sarcopenia in the clinical setting and a clear definition of sarcopenia is needed, as well as studies on the management of sarcopenia in the pre-operative stage.

CONCLUSION

Within the limitations of this study, we may conclude that sarcopenia, among other well-known factors, is associated with perioperative complication rate.

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CHAPTER 9

Arterial calcification and low skeletal muscle mass are independent risk factors for pharyngocutaeneous fistula formation after total laryngectomy

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Submitted ■

ABSTRACT

Background

The occurrence of a pharyngocutaneous fistula after laryngectomy is a common and difficult to treat complication, resulting in significant morbidity and decreased quality of life after laryngectomy. Recent studies showed that arterial calcification is associated with postoperative wound complications in patients with oesophageal cancer.

Material and methods

In this study, we investigated the association between arterial calcification and the occurrence of a pharyngocutaneous fistula. A monocenter retrospective cohort study of patients undergoing laryngectomy between 2008 and 2017. A tertiary referral center for head and neck oncology in the Netherlands.All patients undergoing laryngectomy for any indication were included in this retrospective cohort study. Diagnostic CT-images were scored blinded for the outcome for the presence and severity of arterial calcification on 10 different locations as absent, mild, moderate or severe (cumulative burden maximal 30 points). The association with pharyngocutaneous fistula was investigated using univariable and multivariable logistic regression analysis.

Results

In total 224 patients were included for analysis of whom 62 (27.7%) developed a pharyngocutaneous fistula. Only 1.3% of patients had no arterial calcification and 7.1% had at most mild arterial calcifications present, of whom only 1 experienced a pharyngocutaneous fistula. Moderate to severe arterial calcification of the descending aorta, origo of the brachiocephalic arteries and left carotid siphon were significantly associated with developing a pharyngocutaneous fistula in univariable and multivariable regression analysis (adjusted OR 2.07 - 2.83; all $p<0.05$). A higher cumulative calcification score was significantly associated with pharyngocutaneous fistula formation (adjusted OR 1.06-1.08; $p<0.05$).

Conclusions

The presence of arterial calcification is widespread in patients undergoing laryngectomy and its burden is associated with developing pharyngocutaneous fistula. Extensive arterial calcification on preoperative CT imaging may be taken into consideration as a preoperative risk factor for pharyngocutaneous fistula in patients undergoing laryngectomy.

INTRODUCTION

Total laryngectomy (TL) is a definitive treatment for patients with advanced stage laryngeal or pharyngeal cancer. It is also a salvage treatment option for patients with recurrent disease after initial (chemo)radiotherapy, and can be used to treat patients with a dysfunctional larynx.[1,2] It is an invasive surgical procedure and is associated with frequent postoperative complications resulting in significant morbidity and mortality after surgery, compromising survival and quality of life.[3–5]

Postoperative complications, including wound healing problems and the occurrence of a pharyngocutaneous fistula (PCF), are common and often difficult to treat. Approximately 30% of patients develops a PCF after TL, which often requires additional surgery, flap reconstruction, increased hospital stay and prolonged feeding tube dependency.[6,7] Known risk factors for PCF are prior treatment with radiotherapy with concurrent platin-based chemotherapy, hypopharyngeal cancer, extensive pharyngeal resection and reconstruction, additional neck dissection, and low body mass index (BMI). Recently, radiologically assessed sarcopenia or low skeletal muscle mass has been identified as a novel risk factor for PCF and wound complications in patients undergoing total laryngectomy.[8,9]

In recent years, it has been shown that routinely performed imaging, such as computed tomography (CT) scans, can be used to extract additional information on patient's body composition as a biomarker of functional and biological status, as well as cancer specific features and risk factors.[10–12] The radiological assessment of sarcopenia is an example of this application. Specific for this research, routinely performed CT imaging can be used to measure arterial calcification as a biomarker for generalized cardiovascular disease.[13,14] In head and neck cancer patients, CT imaging of the head and neck area is commonly performed during the diagnostic work-up, on which the carotid arteries and vertebral arteries are shown. Additionally, thoracic CT imaging and/or whole-body PET-CT imaging may be performed, depending on local diagnostic protocols, which provides imaging of the heart and aorta. Smoking, a known etiological factor for atherosclerosis, is common in head and neck cancer patients1[5] as is low-level persistent systemic inflammation, both of which are common in cancer patients.16,[17] For example in patients with esophageal cancer undergoing esophagectomy locoregional and generalized cardiovascular disease as identified on routine CT imaging is predictive of cervical anastomotic leakage.[18,19]

The purpose of this study was to explore the extent of arterial calcifications present in patients undergoing TL, investigate whether the presence and burden of regional and generalized atherosclerotic calcification, as visualized on preoperative CT imaging is a risk factor for PCF in patients undergoing TL.

PATIENTS AND METHODS

This study is a retrospective cohort study. The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (ID 17-365/C). The research was conducted in accordance with the Declaration of Helsinki.

PATIENT AND STUDY DESIGN

All patients who had undergone TL between January 2008 and May 2017 at the University Medical Center Utrecht, Utrecht, the Netherlands, were considered for inclusion. Patients were discussed in the local tumor board meeting, and all patients who were included underwent TL with or without (partial) pharyngectomy and with or without additional lymph node dissection; either as primary treatment, as salvage treatment for new or residual cancerous tissue after prior (chemo)radiotherapy treatment, or as functional treatment for a dysfunctional larynx after prior (chemo)radiotherapy, where no active cancerous tissue was found.

Five dedicated head and neck surgical oncologists performed all TL. Exclusion criteria for this analysis included insufficient quality CT imaging as determined by an experienced radiologist or the absence of CT imaging (e.g., only MRI imaging performed).

Patients' demographic, staging, treatment, and outcome data were collected using electronic patient records. Operating records were checked for details of the surgery, neck dissection, and primary pharyngeal closure or flap reconstruction of the pharynx. The occurrence of PCF was defined as a clinical fistula requiring any form of conservative or surgical treatment. In patients who had surgery for a dysfunctional larynx, the tumor site for which the patient received prior treatment was documented. Follow-up data were retrieved up until August 31, 2017.

The presence of sarcopenia was assessed on preoperative CT imaging using a previously specified protocol. In brief, the cross-sectional skeletal muscle area at the level of C3 was measured on a single transversal CT slice at the level of the third cervical vertebra (C3).8,[12] The cross-sectional muscle area was normalized for height to calculate the skeletal muscle index. A skeletal muscle index of below 43.2cm^2/m^2 was deemed to be sarcopenia.[20]

IMAGE ACQUISITION

All CT imaging was routinely performed at our hospital. Patients underwent contrast-enhanced CT scanning of the head and neck area on a Philips scanner with 64 detector rows or more (Philips Healthcare, Best, The Netherlands) at our institution. All routine diagnostic CT protocols include thin slices (<1-mm) and reconstruction at 3- 5mm.

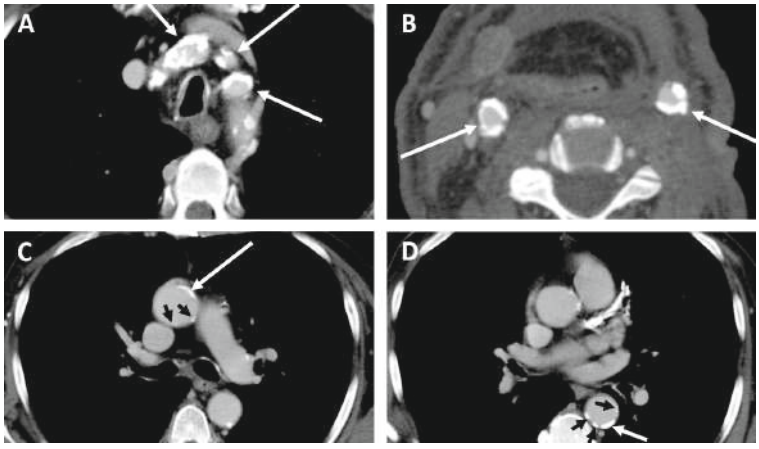
IMAGE EVALUATION

Images were typically analyzed in multiple directions by one reader (P.A.d.J), a radiologist with >10 years of experience in CT evaluation and a specific research interest in arterial calci-

fication. The reader was blinded for patient and treatment related factors, as well as for study outcomes (e.g., formation of PCF).

A visual grading system was used similar to previous studies in order to consistently score CT images on arterial calcification at 10 different anatomical locations.[18,21] The selected locations include large aortic structures (ascending aorta, aortic arch, descending aorta and origo of the brachiocephalic arteries), carotid structures (left and right extracranial carotid artery, left and right carotid siphon), and left and right vertebral arteries. Scores of 0, 1, 2 and 3 were assigned, for all locations except origo of the brachiocephalic arteries corresponding with the absence of calcifications (score 0), mild calcification defined as one or two dots of calcium smaller than 1cm (score 1), moderate calcification defined as one calcification larger than 1cm (score 2), and severe calcification defined as circular calcification or a large calcification combined with smaller dots or >2 dots (score 3), respectively. For the origo of the brachiocephalic arteries, a score of 0 corresponds with no calcification present, a score of 1 with the calcification of one origo of a brachiocephalic artery, a score of 2 with the calcification of two brachiocephalic arteries and a score of 3 with the calcification of all three brachiocephalic arteries. A cumulative calcification score was calculated of arterial calcification scores at all anatomical sites resulting in a score between 0 and 30 for total arterial calcification. Table 1 shows the distribution of arterial calcification at the selected anatomical locations. Examples of arterial calcification on CT imaging are presented in Figure 1.

Figure 1. Examples of preoperative CT images of arterial calcification in patients planned for laryngectomy. A white arrow indicates a severe calcification (score 2 or 3) whereas a black arrow indicates minor calcification (score 1).



A: Calcification of the origo of all three brachiocephalic arteries, resulting in a score of 3 for calcification of the brachiocephalic arteries.
B: Calcification of the left and right external carotid arteries, resulting in a score of 3 for calcification of the external carotid arteries.
C: Calcification of the ascending aorta with two minor specs of calcification and one severe calcification, resulting in a score of 2 for calcification of the ascending aorta.
D: Multiple calcified foci of the descending aorta with several minor specs of calcification and one larger segment, resulting in a score of 2 for calcification of the descending aorta.

STATISTICAL ANALYSIS

Categorical data are represented as a number and percentage of the total. A test for normality (Kolmogorov-Smirnoff test) and histograms were used to assess whether continuous variables were normally distributed. Continuous data are represented as mean ± SD if normally distributed, and median ± interquartile range if skewed. Fisher's exact tests, Pearson Chi square tests, independent sample t tests, and Mann-Whitney U tests were used to assess group differences where appropriate. Univariable and multivariable backward stepwise logistic regression analysis was used to examine the association between vascular calcification and PCF. Parameters entered as covariates in regression analysis were chosen based on known or expected association with a PCF. Not all anatomical locations could be assessed in all patients, most commonly when CT imaging of the thoracic area was not available or because of dental artefacts. The missing data were considered missing at random. Multiple imputation of these missing sites was applied to replace the missing values for logistic regression analysis, using the median of 20 imputated datasets.22,23 All statistical analyses were performed using the IBM SPSS Statistics version 25.0 software package (Chicago, Illinois, USA). All analyses were two-sided and $p \leq 0.05$ was considered significant.

RESULTS

Between January 2008 and June 2017, 245 patients underwent TL at our institution. Of these 245, 17 patients were excluded because there was no CT imaging available, and 4 patients were excluded because of inadequate quality of imaging. Therefore, 224 patients were included in this analysis. Median interval between imaging and TL was 27 days.

PATIENT AND TREATMENT CHARACTERISTICS

The 224 patients that were included for analysis had a mean age of 64.8 years. Patients were predominantly male (82.1%). During the study period, 105 patients (46.9%) underwent primary TL, 108 patients (48.2%) underwent salvage TL, and 11 patients (4.9%) underwent a functional TL.

Prior to total laryngectomy, 99 patients (44.2%) had undergone radiotherapy and 21 patients (9.4%) had undergone chemoradiotherapy.

A PCF occurred in 62 patients (27.7%), which required surgical closure in 40 patients (64.5% of all PCF). Patient, disease and treatment related characteristics, and their relationship with the occurrence of a PCF are presented in Table 2. To summarize, patients who had a PCF more often had hypopharyngeal cancer, a dysfunctional larynx after treatment, sarcopenia, laryngectomy with pharyngectomy and flap closure of the neopharynx. Of note, additional lymph node dissection and prior treatment for head and neck cancer did not appear to be more common in patients with a PCF. Patients with a PCF were not significantly older and did not have a significantly lower BMI.

Table 2. Patient, disease and treatment characteristics

Characteristic	With pharyngocutaneous fistula n = 62 (% of total)	Without pharyngocutaneous fistula n = 162 (% of total)	P value
Gender (male)	48 (77.4)	136 (84.0)	0.25 a
Age at diagnosis (years)	64.0 (SD 9.2)	65.1(SD 9.1)	0.43 b
Body mass index (BMI)	23.4 (SD 4.8)	24.2 (SD 5.1)	0.32 b
Smoking (current)	30 (48.4)	82 (50.6)	0.33 a
Alcohol abuse			
Never	37 (59.7)	111 (68.5)	0.44 c
Former	17 (27.4)	33 (20.4)	
Current	8 (12.9)	18 (11.1)	
ASA classification			
I	28 (45.2)	80 (49.4)	0.84 c
II	18 (29.0)	42 (25.9)	
III	16 (25.8)	40 (24.7)	
Presence of sarcopenia	35 (56.5)	67 (41.4)	**0.04** a
Localization tumor			
Larynx	34 (54.8)	132 (81.5)	**<0.01** a
Hypopharynx	28 (45.2)	30 (18.5)	
AJCC stage			
0	7 (11.3)	4 (2.5)	**0.01** c
I	3 (4.8)	22 (13.6)	
II	11 (17.7)	21 (13.0)	
III	6 (9.7)	28 (17.3)	
IV	35 (56.5)	87 (53.7)	
Indication for TL			
Primary HNC	26 (41.9)	79 (48.8)	**0.02** c
Recurrent HNC	29 (46.7)	79 (48.8)	
Dysfunctional larynx	7 (11.3)	4 (2.5)	
Prior treatment			
None	26 (41.9)	79 (48.8)	0.62 c
Radiotherapy	29 (46.8)	69 (42.6)	
Chemo-radiotherapy	7 (11.3)	14 (8.6)	
Type resection			
Laryngectomy	31(50.0)	120 (74.1)	**<0.01** c
LE + partial pharyngectomy	25 (40.3)	28 (17.3)	
LE + total pharyngectomy	6 (9.7)	14 (8.6)	
Closure of neopharynx			
Vertical	28 (45.2)	110 (67.9)	**<0.01** c
T-closure	5 (8.1)	13 (8.0)	
Flap closure	29 (46.8)	39 (24.1)	
Lymph node dissection			
None	22 (35.5)	73 (45.1)	0.25 c
Unilateral	28 (45.2)	54 (33.3)	
Bilateral	12 (19.4)	35 (21.6)	

a Fisher's exact test, b Independent sample t test, c Pearson Chi squared test.

ARTERIAL CALCIFICATION AND UNIVARIABLE ANALYSIS

Distribution of arterial calcifications is shown in Table 1. Arterial calcifications of the aortic artery and carotid branches were a common finding. In contrast, arterial calcifications in the vertebral arteries were rare. Only 3 patients (1.3%) had no arterial calcifications. In 16 patients (7.1% of total), at most mild calcifications were seen. Of those 16 patients, one patient had a PCF (Pearson Chi square test: p = 0.05). For subsequent analysis calcification scores were divided in two groups: none to mild calcifications, and moderate to severe calcifications.

Table 1. Distribution of arterial calcification on preoperative CT images

Anatomical location	**Calcification scores n (% of total)**				**Missing n (% of total)**
	0 - Absent	**1 - Mild**	**2 - Moderate**	**3 - Severe**	
Ascending aorta	78 (34.8)	49 (21.9)	20 (8.9)	30 (13.4)	47 (21.0)
Aortic arch	37 (16.5)	28 (12.5)	56 (25.0)	78 (34.8)	25 (11.2)
Descending aorta	43 (19.2)	27 (12.1)	27 (12.1)	77 (34.4)	50 (22.3)
Origo of the brachiocephalic arteries	31 (13.8)	30 (13.4)	36 (16.1)	117 (52.2)	10 (4.5)
Left extracranial carotid artery	37 (16.5)	24 (10.7)	46 (20.5)	116 (51.8)	1 (0.4)
Right extracranial carotid artery	39 (17.4)	30 (13.4)	45 (20.1)	109 (48.7)	1 (0.4)
Left vertebral artery	176 (78.6)	18 (8.0)	13 (5.8)	13 (5.8)	4 (1.8)
Right vertebral artery	181 (80.8)	17 (7.6)	13 (5.8)	9 (4.0)	4 (1.8)
Left carotid siphon	33 (14.7)	31 (13.8)	46 (20.5)	104 (46.4)	10 (4.5)
Right carotid siphon	35 (15.6)	32 (14.3)	40 (17.9)	107 (47.6)	10 (4.5)

Distribution of arterial calcification among patients with and without PCF and univariable odds ratios are shown in Table 3. Arterial calcifications in all anatomical locations apart from the vertebral arteries were more frequently observed in patients who had a PCF, which is shown in Table 3.

Arterial calcification of the aorta descendens (OR 2.32 [1.25-4.29], p = 0.01), origo of the brachiocephalic arteries (OR 2.14 [1.05-4.35], p = 0.04), right extracranial carotid artery (OR 2.05 [1.03-4.09], p = 0.04) and left carotid siphon (OR 2.26 [1.12 - 4.59], p = 0.02) were significantly associated with PCF formation. A higher total arterial calcification score was significantly associated with PCF formation (OR 1.06 [1.01-1.11], p = 0.03).

Table 3. Distribution of arterial calcification among patients with and without pharyngocutaneous fistula and univariate odds ratio analysis

Anatomical location of arterial calcification	Score a	With pharyngocutaneous fistula n = 62 (% of total)	Without pharyngocutaneous fistula (n = 162) (% of total)	Unadjusted ORb (95% CI)	P value
Ascending aorta	0	31 (50.0)	101 (63.2)	1.66	0.09
	1	31 (50.0)	61 (37.7)	(0.92 - 2.90)	
Aortic arch	0	20 (32.3)	56 (34.6)	1.11	0.74
	1	42 (67.7)	106 (65.4)	(0.60 - 2.07)	
Descending aorta	0	20 (32.3)	85 (52.5)	2.32	**0.01**
	1	42 (67.7)	77 (47.5)	(1.25 - 4.29)	
Origo of the brachiocephalic arteries	0	12 (19.4)	55 (34.0)	2.14	**0.04**
	1	50 (80.6)	107 (66.0)	(1.05 - 4.35)	
Left extracranial carotid artery	0	16 (25.8)	46 (28.4)	1.14	0.70
	1	46 (74.2)	116 (71.6)	(0.59 - 2.21)	
Right extracranial carotid artery	0	13 (21.0)	57 (35.2)	2.05	**0.04**
	1	49 (79.0)	105 (64.8)	(1.03 - 4.09)	
Left vertebral artery	0	58 (93.5)	136 (84.0)	0.36	0.07
	1	4 (6.5)	26 (16.0)	(0.12 - 1.08)	
Right vertebral artery	0	57 (91.9)	141 (87.0)	0.59	0.31
	1	5 (8.1)	21 (13.0)	(0.21 - 1.64)	
Left carotid siphon	0	12 (19.4)	57 (35.2)	2.26	**0.02**
	1	50 (80.6)	105 (64.8)	(1.12 - 4.59)	
Right carotid siphon	0	15 (24.2)	60 (37.0)	1.84	0.07
	1	47 (75.8)	102 (63.0)	(0.95 - 3.58)	
Total arterial calcification score	Median	18.0	16.0	1.06	**0.03**
	IQRd	12.8 - 22.0	10.0 - 21.0	(1.01 - 1.11)	

Numbers in bold: significant at the level of $p \leq 0.05$, a Score: 0 - none to mild; 1 - moderate to severe, b Univariable logistic regression analysis, c Continuous; score between 0 and 30, d Interquartile range

MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

The calcification scores were entered per location into two multivariable logistic regression models, see Table 4. The first model includes the patient-related variables: age, BMI, sarcopenia, smoking, alcohol abuse, and ASA classification as a surrogate for comorbidities. The second model includes additional known preoperative risk factors for the occurrence of a PCF: localization of tumor (larynx versus hypopharynx), indication for TL (primary, salvage or dysfunctional larynx), additional lymph node dissection, extent of pharyngeal resection and closure method of the neopharynx.

Table 4. Multivariable logistic regression analysis for arterial calcification as a risk factor for pharyngocutaneous fistula

Anatomical location of arterial calcification	Score a	Adjusted OR 1 b (95% CI)	P value	Adjusted OR 2 c (95% CI)	P value
Ascending aorta	0	Ref	0.10	Ref	**0.02**
	1	1.66 (0.91 - 3.02)		2.27 (1.16 - 4.46)	
Aortic arch	0	Ref	0.58	Ref	0.59
	1	1.21 (0.61 - 2.41)		1.21 (0.61 - 2.41)	
Descending aorta	0	Ref	<0.01	Ref	**0.03**
	1	2.80 (1.38 - 5.66)		2.07 (1.07 - 3.99)	
Origo of the brachiocephalic arteries	0	Ref	0.04	Ref	**0.04**
	1	2.09 (1.02 - 4.27)		2.28 (1.05 - 4.92)	
Left extracranial carotid artery	0	Ref	0.64	Ref	0.82
	1	1.19 (0.57 - 2.48)		0.92 (0.45 - 1.89)	
Right extracranial carotid artery	0	Ref	0.03	Ref	0.11
	1	2.17 (1.08 - 4.39)		1.84 (0.87 - 3.89)	
Left vertebral artery	0	Ref	0.05	Ref	0.12
	1	0.33 (0.11 - 1.01)		0.40 (0.13 - 1.25)	
Right vertebral artery	0	Ref	0.28	Ref	0.50
	1	0.56 (0.20 - 1.59)		0.69 (0.23 - 2.03)	
Left carotid siphon	0	Ref	0.01	Ref	**0.04**
	1	2.83 (1.32 - 6.08)		2.21 (1.04 - 4.69)	
Right carotid siphon	0	Ref	0.08	Ref	0.10
	1	1.83 (0.94 - 3.57)		1.82 (0.90 - 3.69)	
Total arterial calcification score	Cont.d	1.08 (1.02 - 1.15)	0.01	1.06 (1.01 - 1.12)	**0.03**

Numbers in bold: significant at the level of $p \leq 0.05$, a Score: 0 - none to mild; 1 - moderate to severe, b Multivariate analysis 1: Corrected for: age at diagnosis, BMI, sarcopenia, smoking, alcohol abuse and ASA classification as a surrogate for comorbidities, c Multivariate analysis 2: Corrected for preoperative risk factors: localization of tumor, indication for total laryngectomy (primary, salvage or dysfunctional larynx), additional lymph node dissection, extent of pharyngeal resection and closing method of neopharynx, d Continuous: score between 0 and 30

In the first model, arterial calcification of the descending aorta (OR 2.80 [1.38 - 5.66], $p < 0.01$), origo of the brachiocephalic arteries (OR 2.09 [1.02 - 4.27], $p = 0.04$), right extracranial carotid artery (OR 2.17 [1.08 - 4.39], $p = 0.03$) and left carotid siphon (OR 2.83 [1.32 - 6.08], $p = 0.01$) remained significantly associated with the occurrence of a pharyngocutaneous fistula. In the second model, arterial calcification of the ascending aorta (OR 2.27 [1.16 - 4.46], $p = 0.02$), descending aorta (OR 2.07 [1.07 - 3.99], $p = 0.03$), origo of the brachiocephalic arteries (OR 2.28 [1.05 - 4.92], $p = 0.04$) and left carotid siphon (OR 2.21 [1.04 - 4.69], $p = 0.04$) were significantly associated with the occurrence of a pharyngocutaneous fistula. A higher total arterial calcification score was significantly associated with PCF formation in the first (OR 1.08 [1.02 - 1.15], $p = 0.01$) and the second (OR 1.06 [1.01 - 1.12], $p = 0.03$) multivariable model.

ARTERIAL CALCIFICATION AND SARCOPENIA

As there may be a shared etiological factor in atherosclerosis and sarcopenia, the occurrence of arterial calcification in patients with and without sarcopenia was explored. Data are shown in Supplementary Data Table 1.

Moderate to severe arterial calcification at the location of the descending aorta was significantly more often present in patients with sarcopenia as compared to patients without sarcopenia (Pearson Chi square test: $p < 0.01$). At the other locations, no significant difference was observed. The association between arterial calcification and sarcopenia as independent risk factors for PCF formation is shown in Supplementary Data Table 2. In multivariable logistic regression analysis, both the total arterial calcification score (adjusted OR 1.05 [1.00 - 1.10], $p = 0.04$) and sarcopenia (adjusted OR 1.86 (1.02 - 3.39), $p = 0.04$) are independently associated with PCF formation.

Supplementary table 1: Presence of arterial calcification and sarcopenia

Anatomical location of arterial calcification	**Score[a]**	**Sarcopenia (n = 103)**	**Normal skeletal muscle mass (n = 121)**	**P value**
Ascending aorta	0	60	72	0.85b
	1	43	49	
Aortic arch	0	32	44	0.40b
	1	71	77	
Descending aorta	0	36	69	**<0.01**b
	1	67	52	
Origo of the brachiocephalic arteries	0	28	39	0.41b
	1	75	82	
Left extracranial carotid artery	0	28	34	0.88b
	1	75	87	
Right extracranial carotid artery	0	35	35	0.42b
	1	68	86	
Left vertebral artery	0	87	107	0.39b
	1	16	14	
Right vertebral artery	0	90	108	0.66b
	1	13	13	
Left carotid siphon	0	30	39	0.62b
	1	73	82	
Right carotid siphon	0	33	42	0.67b
	1	70	79	
Total arterial calcification scored	Mean	16.5	15.1	0.09c
	SD	7.4	6.8	

Numbers in bold: significant at the level of $p \leq 0.05$, a Score: 0 - none to mild; 1 - moderate to severe, b Pearson Chi square test, c Mann-Whitney U test, d Continuous; score between 0 and 30

Table 2. Sarcopenia and arterial calcification as predictors of pharyngocutaneous fistula

	Value	Unadjusted ORb (95% CI)	P value	Adjusted ORc (95% CI)	P value
Total arterial calcification score	Cont.a	1.06 (1.01-1.11)	0.03	1.05 (1.00-1.10)	**0.04**
Sarcopenia	No	Ref		Ref	
	Yes	1.96 (1.9-3.55)	0.03	1.86 (1.02-3.39)	**0.04**

Numbers in bold: significant at the level of $p \leq 0.05$, a Continuous; score between 0 and 30, b Univariable regression analysis, c Multivariable regression analysis using a backward stepwise selection

DISCUSSION

This retrospective cohort study of patients undergoing laryngectomy for any indication shows that generalized arterial calcification is widespread in patients undergoing laryngectomy and is associated with developing a PCF. Moderate to severe arterial calcification of the descending aorta, origo of the brachiocephalic arteries and left carotid siphon were significantly associated with developing a PCF in both univariable and two multivariable regression models. A higher cumulative arterial calcification score (range 0 – 30) was significantly associated with the occurrence of PCF: the relative risk of PCF increased by 6-8% per point increase in total arterial calcification score. Our results are concurrent with recent studies in patients undergoing esophagectomy and colorectal surgery. Recent studies in patients undergoing esophagectomy showed that locoregional and generalized cardiovascular disease as identified by visual grading on preoperative imaging was a risk factor for wound healing problems and anastomotic leakage.[18,19] Another study in patients undergoing colorectal surgery showed that visually graded calcification of the abdominal aorta was associated with increased morbidity after surgery.[24] It is hypothesized that both locoregional and generalized arterial vascular disease may have a detrimental effect on wound and anastomosis healing due to low flow or hypoperfusion of the surgical area, leading to ischemia.[19,25]

The occurrence of a PCF after TL is one of the most severe and most dreaded complications. It is associated with prolonged hospital stay and feeding tube dependency, as well as decreased quality of life, and it negatively affects survival. Recently, radiologically assessed sarcopenia was identified as a preoperative risk factor for PCF and wound complications in head and neck cancer patients.[8,9,26] There may be a link between the presence of arterial calcifications and sarcopenia, due systemic inflammation being a shared etiological factor. The copresence of sarcopenia and arterial calcification was often observed and at the location of the descending aorta arterial calcifications were significantly more often present in patients with sarcopenia. In multivariable regression analysis, the presence of sarcopenia and arterial calcifications were both independent predictors of PCF.

Routinely performed CT imaging may provide more additional information on patients' functional and biological status and may aid in the identification of high-risk patients for the

occurrence of adverse outcomes. Accurate identification of high-risk patients for PCF may provide an opportunity for preoperative interventions to decrease the risk. It seems unlikely to decrease the amount of arterial calcifications in the preoperative period, but preoperative optimization of general cardiovascular status or other risk factors associated with PCF which may co-exist might decrease the risk of a PCF.[27–29] Arterial calcifications as evidence for cardiovascular disease may warrant further examination and medical intervention prior to surgery. A surgical solution in high risk patients may be to use a pectoralis major overlay flap to reinforce the suture line of the neopharynx by covering it with healthy muscle and decrease the risk of PCF.[30] In reconstructive microsurgery, radiological evidence of atherosclerosis may also aid in choosing the optimal flap for recontruction.[31]

There are several limitations that this study needs to address. It is apparent that relevant clinical data such as known cardiovascular disease and diabetes, was missing in our database due to missing information in particular in the earlier years of the study period. Also, some traditional cardiovascular risk factors such as serum cholesterol are missing, because these are not routinely measured at our clinic. Smoking and age was included in analysis, and the ASA classification was used as a surrogate for comorbidities, but we acknowledge that this provides limited information on specific comorbidities.[32] Recent studies do suggest that coronary arterial calcification scores or peripheral arterial calcification scores derived from CT imaging are reliable assessment methods for cardiovascular disease, and can identify patients at high risk that would not have been identified using traditional cardiovascular risk factors.[14,33,34] Second, a visual grading system for arterial calcification as opposed to calcium scores may lead to an observer bias and necessitate a learning curve.

Automatic calcium scoring systems are not yet available using head and neck contrast enhanced CT imaging, but research into automatic arterial calcification scoring on contrast-enhanced CT imaging is ongoing, and this may in the future be available.[35,36] Moreover, machine learning and radiomics using CT features, e.g. skeletal muscle mass (sarcopenia), skeletal muscle quality and arterial calcification, from routinely performed CT imaging of the head and neck area may be helpful to identify patients at high risk for fistula formation after laryngectomy. In this study, all calcification scoring was performed by one observer: an experienced radiologist with a research interest and extensive experience with arterial calcification on CT imaging. The inter- and intraobserver variability was not researched in this study, but previously found to be good in several studies also in less experienced observers.[18,37]

Acknowledging these limitations, we do believe that this study provides a relevant novel application of routinely performed, readily available CT imaging of the head and neck area for optimization of the identification process of patients undergoing TL at high risk of developing a PCF. More research into the method of quantification of arterial calcification in head and neck cancer patients and its clinical application is warranted and clarification of its relevance for fistula prevention is needed.

CONCLUSION

Arterial calcification is widespread in patients undergoing laryngectomy and is associated with pharyngocutaneous fistula formation. Extensive arterial calcification on preoperative CT imaging may be taken into consideration as a preoperative risk factor for pharyngocutaneous fistula in patients undergoing laryngectomy.

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PART III

The predictive and prognostic impact of low skeletal muscle mass in head and neck cancer patients treated with chemo- or bioradiotherapy

CHAPTER 10

Image-based analysis of skeletal muscle mass predicts cisplatin dose-limiting toxicity in patients with locally advanced head and neck cancer

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Submitted ■

ABSTRACT

Background

Evidence suggests that patients' skeletal muscle mass (SMM) can predict the patients at risk for cisplatin dose-limiting toxicities (DLT). Cisplatin is currently dosed on body surface area (BSA). The predictive value of SMM for cisplatin DLT in patients with locally advanced head and neck cancer (LA-HNC) is investigated.

Material and methods

Patients with LA-HNC treated with cisplatin-based chemoradiotherapy (CRT) were included. SMM was measured using pre-treatment scans. Logistic regression analysis was performed to identify the predictive impact of low SMM for DLT.

Results

In total, 343 patients were included of which 199 patients (58.0%) had low SMM and 154 patients (44.9%) experienced cisplatin DLT. In multivariate analysis, low SMM at diagnosis was the only predictive factor for DLT (HR 1.8, 95% CI 1.1-2.9).

Conclusions

Low SMM was associated with an increased risk of DLT. Trials are needed to investigate cisplatin dosing with consideration of SMM rather than solely BSA.

INTRODUCTION

Head and neck cancer accounts worldwide for more than 500.000 cases annually.[1] Locally advanced head and neck cancer (LA-HNC) is the most frequent clinical manifestation of head and neck cancer. Platinum-based chemoradiotherapy is the main treatment option for (technical or functional) irresectable LA-HNC and is also offered in a postoperative setting for resected LA-HNC in which the tumor is resected irradically or in the presence of extracapsular lymph-nodal extension.

Malnutrition is a common problem in LA-HNC in part due to dysphagia caused by the tumor or its treatment.[2] Malnutrition is also a major contributor in the development of low skeletal muscle mass (SMM). Image-based analysis of SMM has shown critical new insights of low SMM as an important predictor and prognosticator in patients with cancer.[3–5] Cisplatin is the preferred platinum agent used in platinum-based chemoradiotherapy in LA-HNC. Cisplatin is dosed based on body surface area. This approach was initially advocated on the assumption that dosing based on body surface area leads to an acceptable degree of toxicities without reducing the therapeutic effect.[6] Cisplatin is highly emetogenic, neurotoxic, nephrotoxic and ototoxic.[7] Clinically, there is a wide interindividual heterogeneity in the ability of LA-HNC patients to tolerate cisplatin-based chemoradiotherapy. Over the last years, emerging evidence suggests a significant negative relationship between low SMM and adverse effects of cytotoxic drugs leading to dose-limiting toxicities (DLTs).[8–11] As such, SMM may (partly) explain the heterogeneity of patient's tolerance for chemotherapy. Cisplatin DLTs lead to frequent hospital readmissions, decreased survival and reduced quality of life.

The mechanism underlying the relationship between low SMM and DLTs of chemotherapeutical drugs is not fully understood. Several hypotheses have been proposed in literature.[12,13] It has been hypothesized that altered fat-to-lean body mass (LBM) influences the pharmacokinetics of anti-cancer drugs and/or may be associated with increased chronic low-grade inflammation, which results in a higher risk of adverse events. The most commonly supported hypothesis is based on the influence of low SMM on the volume of distribution of anti-cancer drugs.[13] Cisplatin is a hydrophilic agent; due to its hydrophilicity it favors distribution to the LBM of which SMM is the largest component. However, SMM is currently not (directly) taken into account in cisplatin dosing. Body surface area is calculated by use of several formulas such as the formula of Du Bois.[6] These formulas incorporate body weight and height. Lower SMM can, however, occurs independently of adiposity, therefore in overweight or obese patients, the loss of SMM may be masked. Hence, dosing according to body surface area leads to substantial variation in drug doses per kilogram of LBM.[8] Higher dose per kilogram LBM has shown to have a significant correlation with higher rates of toxicities in other cancer types.[9] A loss of SMM in patients with head and neck cancer may, consequently, induce drug overdose when dose calculation is based on the conventional body surface area method.

Therefore, the aim of the current study was to investigate the predictive impact of low SMM for cisplatin DLT in a 10-year cohort of patients with LA-HNC treated with cisplatin-based chemoradiotherapy.

MATERIAL AND METHODS

STUDY DESIGN

A retrospective study was conducted in which all patients who were diagnosed with LA-HNC and treated in the UMC Utrecht with cisplatin-based chemoradiotherapy between 2007 and 2018 were screened for inclusion. Inclusion criteria for this study required that patients were treated with curative intent in primary or adjuvant setting and had pre-treatment imaging of the head and neck area within 1 month before the start of chemoradiotherapy and had data available on cisplatin dosages and reported toxicities.

Relevant demographic, clinical, biochemical and anthropometric variables were retrieved from electronic medical records. This study also included the patients who were treated with cisplatin from our previous study.[8]

ETHICAL APPROVAL

The design of this study was approved by the Medical Ethical Research Committee (METC) of the University Medical Center Utrecht, METC ID: 17-365/C. The requirement for informed consent from patients was waived because of its retrospective design.

THERAPY

Chemotherapy regimen consisted of three cycles of intravenous cisplatin-based chemotherapy on days 1, 22 and 43 of treatment. Cisplatin dose was 100 mg per m^2 of body surface area. Chemoradiotherapy was given in primary setting for patients with (technical or functional) irresectable LA-HNC and in postoperative setting for tumors with their aforementioned high-risk features. Radiotherapy was administered in 35 fractions of 2 Gy to a total dose of 70 Gy (primary setting) or in 33 fractions of 2 Gy to a total dose of 66 Gy (postoperative setting).

BODY COMPOSITION MEASUREMENTS- SKELETAL MUSCLE MASS AND LEAN BODY MASS

SMM was segmented as skeletal muscle area using the Slice-O-matic software (version 5.0). At the level of the third cervical vertebrae (C3), a single slice was used for skeletal muscle area segmentation. The first slide to completely show the entire vertebral arc when scrolling through the C3 vertebra from caudal to cephalic direction was selected. For computed tomography (CT) imaging, muscle area was defined as the pixel area between the radiodensity range of -29 and +150 hounsfield units, which is specific for muscle tissue.[14] For magnetic resonance imaging (MRI), muscle area was manually segmented, and fatty tissue was manually excluded. Because the overall intraclass correlation coefficient for the skeletal muscle area obtained by CT and

MRI was previously found to be excellent (ICC 0.97, p<0.01)[15], skeletal muscle area measurements by CT and MRI were analyzed together. The skeletal muscle area was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoideus muscles. SMM is often used interchangeably with LBM, however LBM includes SMM, as well as bones and bodily fluids. Therefore, we also predicted LBM using Mourtzakis formula where the LBM in kilograms by use of the skeletal muscle area obtained by cross-sectional imaging was used.[16] Mourtzakis formula is based on skeletal muscle area measured at the third lumbar vertebrae (L3), not C3. Therefore, skeletal muscle area at the level of C3 was first converted to skeletal muscle area at the level of L3 using a previously published formula.[17] Absolute SMM is strongly correlated with height, therefore SMM must be calculated as an index of relative SMM.[18] This is the same to the use of body mass index (body weight (kg)/height^2 (m^2)) for classifying relative adiposity. Skeletal muscle area at L3 is normalized to stature (using squared height similar to calculating BMI) to obtain the lumbar skeletal muscle mass index (LSMI).

The LSMI cut-off value used in this study was a LSMI of 43.2 cm^2/m^2, as previous established in a separate cohort of LA-HNC patients.[8] This cut-off value was used to categorize patients into patients with low SMM and patients without low SMM. Thus, in further analysis low SMM was defined as LSMI ≤43.2 cm^2/m^2.

DOSE-LIMITING TOXICITY

We defined cisplatin DLT as any toxicity resulting in a cisplatin dose-reduction of ≥ 50%, a treatment delay of ≥ 4 days or a termination of cisplatin-based chemotherapy after the first or second cycle of therapy.

STATISTICAL ANALYSIS

Data analysis was performed using IBM SPSS statistics 25. Demographic, clinical, biochemical and anthropometric data were reported for the total group and according to SMM and DLT status. Baseline measures for these groups were described using descriptive statistics. Normally distributed variables were shown as means ± standard deviation (SD), non-normally distributed variables were shown as medians with an interquartile range (IQR). Normality was investigated using the Kolmogorov-Smirnov test. Categorical variables were described as frequencies with corresponding percentages. Chi-square statistics were used for analyzing differences between the frequencies of each categorical variable with the presence or absence of low SMM and DLT. Wald logistic regression analysis was used for univariate and multivariate analysis of the predictors for cisplatin DLT. Covariates used in the multivariate analysis were selected based on statistical significance in univariate analysis or on clinical relevance. Statistical significance was evaluated at the 0.05 level using 2-tailed tests. The Hosmer-Lemeshow test was performed to test the goodness-of-fit of the multivariate analysis model.

RESULTS

PATIENT CHARACTERISTICS

In total, 343 patients were included between January 2007 and December 2018. Seventeen patients were excluded, six of them did not had evaluable pre-treatment imaging and eleven patients eventually did not receive cisplatin based chemoradiotherapy. Table 1 shows the characteristics of the included patients. Of the included patients, 235 patients (68.5%) were male and the median age at diagnosis was 59.07 years (IQR 53.41-63.70).

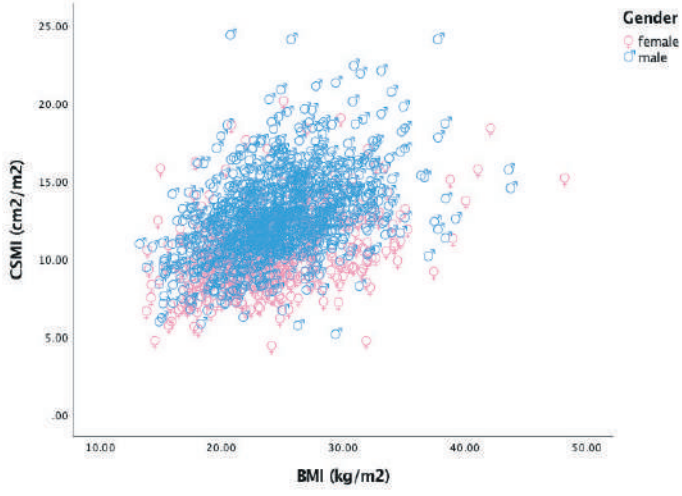
Table 1. Demographic, clinical and biochemical characteristics of patients according to SMM status and DLT status

Characteristic	**Total N=343**	**Without low SMM n=144 41.98%**	**With Low SMM n=199 58.01%**		**Without DLT n=189 55.1%**	**With DLT n=154 44.90%**	
	N, % Mean, SD	**N, % Mean, SD**	**N, % Mean, SD**	**p**	**N, % Mean, SD**	**N, % Mean, SD**	**p**
Gender							
Male	235 (68.5)	139 (59.1)	96 (40.9)		141 (60)	94 (40)	
Female	108 (31.5)	5 (4.6)	103 (95.4)	**<0.01**	48 (44.4)	60 (55.6)	**<0.01**
Age diagnosis	57.7 (8.4)	55.5	59.4	**<0.01**	57.26 (8.6)	58.35 (8.2)	0.23
Smoking							
No	61 (17.8)	35 (57.4)	26 (42.6)		34 (55.7)	27 (44.3)	
Yes	282 (82.2)	109 (38.7)	173 (61.3)	**0.01**	155 (55.0)	127 (45.0)	1.0
Alcohol use							
No	60 (17.5)	26 (43.3)	34 (56.7)		35 (58.3)	25 (41.7)	
Yes	283 (82.5)	118 (41.7)	165 (58.3)	0.89	154 (54.4)	129 (45.6)	0.70
ACE-27							
None	85 (24.8)	37 (43.5)	48 (56.5)		48 (56.5)	37 (43.5)	
Mild	131 (38.2)	56 (42.7)	75 (57.3)		69 (52.7)	62 (47.3)	
Moderate	93 (27.1)	37 (39.8)	56 (60.2)		49 (52.7)	44 (47.3)	
Severe	34 (9.9)	14 (41.2)	20 (58.8)	0.96	23 (67.6)	11 (32.4)	0.43
Performance							
ECOG 0	93 (27.1)	50 (53.8)	43 (46.2)		52 (55.9)	41 (44.1)	
ECOG 1	144 (42)	60 (41.7)	84 (58.3)		77 (53.5)	67 (46.5)	
ECOG ≥2	38 (11.1)	14 (36.8)	24 (63.2)		19 950.0)	10 (50)	
Unknown	68 (19.8)	20 (29.4)	48 (70.6)	**0.02**	41 (60.3)	27 (39.7)	0.73
Albumin (g/L)	40 (4.9)	39.85(4.5)	38.36 (5.2)	**0.04**	38.44 (4.5)	39.50 (5.3)	0.14
Total protein (g/L)	71.2 (7.9)	72.29 (6.04)	70.35 (9.13)	0.41	72.5 (5.90)	68.47 (10.7)	0.10
Hemoglobin (mmol/L)	8.5 (1.1)	8.91 (0.99)	8.23 (1.01)	**<0.01**	8.58 (1.10)	8.44 (0.99)	0.21

Table 1. (Continued)

Characteristic	Total N=343	Without low SMM n=144 41.98%	With Low SMM n=199 58.01%		Without DLT n=189 55.1%	With DLT n=154 44.90%	
	N, % Mean, SD	N, % Mean, SD	N, % Mean, SD	p	N, % Mean, SD	N, % Mean, SD	p
Serum creatinine (mmol/L)	69.9(15.6)	76.77 (14.7)	65.13 (14.5)	**<0.01**	69.97(15.8)	70.0 (15.5)	0.98
Tumor site							
Oral cavity	87 (25.4)	29 (33.3)	58 (66.7)		51 (58.6)	36 (41.4)	
Oropharynx	129 (37.6)	51 (39.5)	78 (60.5)		70 (54.3)	59 (45.7)	
Nasopharynx	45 (13.1)	27 (60.0)	18 (40.0)		24 (53.3)	21 (46.7)	
Hypopharynx	49 (14.3)	22 (15.3)	26 (13.1)		27 (55.1)	22 (44.9)	
Larynx	18 (5.2)	8 (44.4)	10 (55.6)		10 (55.6)	8 (44.4)	
Paranasal sinus	11 (3.2)	5 (45.5)	6 (54.5)	0.12	6 (54.5)	5 (45.5)	0.93
TNM stage							
III	59 (17.2)	26 (44.1)	33 (55.9)		32 (54.2)	27 (45.8)	
IV	284 (82.8)	118 (41.5)	166 (58.5)	0.77	157 (55.3)	127 (44.7)	0.89
CRT							
Primary	274 (79.9)	123 (44.9)	151 (55.1)		154 (56.2)	120 (43.8)	
Postoperative	69 (20.1)	21 (30.4)	48 (69.6)	**0.04**	35 (50.7)	34 (49.3)	0.42
Cisplatin dose (mg/kg LBM) (median, IQR)	8.1 (4.2-11.8)	7.4 (3.6)	9.0 (4.3)	**<0.01**	10.0 (4.4)	6.3 (2.6)	**<0.01**

Figure 1. Boxplot of the amount of LSMI (cm^2/m^2) in patients who have not experienced cisplatin DLT and patients who experienced cisplatin DLT



Known risk factors for HNC are smoking and alcohol use, which is also seen in this study. Majority of patients smoked (n=282, 82.2%) and used alcohol (n=283, 82.5%). In the selection of patients fit for cisplatin treatment, the medical oncologist takes into consideration patients' comorbidities. This is represented by the minority of patients (n=34, 9.9%) who had severe comorbidities, as evaluated by the ACE-27 comorbidity score, in this study. Most patients (n=144, 42%) were symptomatic but completely ambulatory as indicated by the ECOG performance status of 1. Cisplatin-based chemoradiotherapy is most frequently given in a primary treatment setting in patients with LA-HNC.

As previously mentioned, adjuvant chemoradiotherapy is only advised when the tumor is irradically resected or in the presence of extracapsular lymph-nodal extension. In this study, majority of patients were treated in a primary setting (n=274, 79.9%) and had a tumor, node, metastasis (TNM) stage IV tumor according to the 7th edition TNM cancer staging criteria (n=284, 82.8%). Prior to initiation of chemoradiotherapy the mean biochemical values of the patients were as follows: mean hemoglobin of 8.5 mmol/L (SD 1.1), mean serum creatinine of 69.9 mmol/L (SD 15.6), mean serum albumin of 40.0 g/L (SD 4.9) and mean total protein of 71.2 g/L (SD 7.9).

ANTHROPOMETRIC MEASUREMENTS

Table 2 shows the anthropometric measurements of the included patients. Of the 343 included patients, 199 patients (58.0%) had low SMM at diagnosis. The median LSMI was 41.6 cm^2/m^2 (IQR 35.4-45.5). The median LBM was 44.8 kg (IQR 37.1-50.6). Majority of patients (n=191, 55.7%) had ad normal weight as indicated by the body mass index (BMI) of 18.5-24.9 kg/m^2. The median body surface area at diagnosis was 1.9 m^2 (IQR 1.7-2.0).

LOW SKELETAL MUSCLE MAS

Table 1 shows the differences in demographic, clinical and biochemical characteristics between patients with and without low SMM (LSMI ≤ 43.2 cm^2/m^2) at diagnosis. Demographical and clinical characteristics which were significantly more likely to be present in patients with low SMM were being of female gender (n=103, 95.4%; p <0.01), older age at diagnosis (59.4 years; p<0.01), smoking (n=173, 61.3%; p=0.01), an ECOG performance status of ≥ 2 (n=24, 63.2%; p=0.02) and being treated in an adjuvant chemoradiotherapy setting (n=48, 69.6%, p=0.04). In comparison to patients without low SMM, patients with low SMM were more likely to have lower mean albumin levels (38.4 g/L versus 39.9g/L; p<0.05), lower mean hemoglobin levels (8.2 mmol/L versus 8.9 mmol/L; p<0.01) and lower mean serum creatine levels (65.1 mmol/L versus 76.8 mmol/L; p<0.01). Interestingly, patients with low SMM at diagnosis received significantly higher cumulative doses of cisplatin per kilogram of LBM compared to patients without low SMM (9.0mg/kg LBM versus 7.4 mg/kg LBM, p<0.0001).

Table 2 shows the differences in anthropometric measurements between patients with low SMM at diagnosis and patients without low SMM. All underweight patients (BMI < 18.5 kg/m^2) (n=30, 8.7%) had low SMM. Patients without low SMM were more likely to be overweight (65.5%; p<0.01) and obese (73.7%; p<0.01).

Table 2. Anthropometric and clinical measurements according to SMM status and DLT status

	Total N=343 ***Mean, SD***	**Without low SMM** ***n=144 41.98% Mean, SD***	**With Low SMM** ***n=199 58.01% Mean, SD***	**p**	**Without DLT** ***n=189 55.1% Mean, SD***	**With DLT** ***n=154 44.9% Mean, SD***	**p**
Weight (kg)	73.5 (16.1)	82.3 (15.7)	67.2 (13.2)	**<0.01**	74.6 (16.4)	72.3 (15.7)	0.17
Length (m)	1.7 (0.1)	1.8 (0.1)	1.7 (0.1)	**<0.01**	1.8 (0.1)	1.7 (0.1)	0.82
BMI (n, %)							
18.5-24.9 kg/m²	191 (55.7)	61 (31.9)	130 (68.1)	**<0.01**	99 (51.8)	92 (48.2)	**0.03**
<18.5 kg/m²	30 (8.7)	0	30 (100)		12 (40)	18 (60)	
25-29.9 kg/m²	84 (24.5)	55 (65.5)	29 (34.5)		57 (67.9)	27 (32.1)	
≥30 kg/m²	38 (11.1)	28 (73.7)	10 (26.3)		21 (55.3)	17 (44.7)	
Body surface area (m²) Median (IQR)	1.9 (1.7-2.0)	2.0 (0.2)	1.79 (0.2)	**<0.01**	1.89 (0.2)	1.86 (0.2)	0.21
LBM (kg) Median (IQR)	42.0 (37.1-50.6)	51.44 (5.6)	38.59 (6.9)	**<0.01**	45.1 (8.9)	42.7 (8.9)	**0.01**
LSMI cm²/m² (median, IQR)	41.6 (35.43-45.98)	n.a.	n.a.		42.4 (8.3)	39.7 (7.6)	**<0.01**

Cisplatin dose-limiting toxicity

Of the 343 included patients, 154 patients (44.9%) experienced cisplatin DLT. Fig. 1 shows a boxplot of the amount of SMM expressed as LSMI (cm^2/m^2) in patients who have not experienced cisplatin DLT and patients who experienced cisplatin DLT. Table 3 shows the types of cisplatin DLT categorized into patients with low SMM and without low SMM. Of the 154 patients that experienced DLT, in 145 patients (94.2%) this was due to the failure to complete all (n=3) cycles of cisplatin, in 6 patients (3.9%) this was due to a treatment delay of ≥ 4 days and in 3 patients this was due to a cisplatin de-escalation of ≥ 50% (1.9%). The causes of cisplatin DLT were ototoxicity (n= 64, 41.6%), nephrotoxicity (n=41, 26.6%), malaise (n=29, 18.8%), hematopoietic toxicity (n=12, 7.8%), vascular toxicity (n=6, 3.9%) and neurotoxicity (n=1, 0.6%).

Table 3. Cisplatin dose-limiting toxicities according to SMM status

	Total ***n=343*** **n (%)**	**Without low SMM** ***n=144*** ***n (%)***	**Low SMM** ***n=199*** **n (%)**	**p-value**
DLT				
No	189	92 (48.7)	97 (51.3)	**<0.01**
Yes	154	52 (33.8)	102 (66.2)	
< 3 cycles				
No	198	94 (47.5)	50 (34.5)	**0.02**
Yes	145	50 (34.5)	95 (65.5)	
Delay ≥ 4 days				
No	337	142 (42.1)	195 (57.9)	0.71
Yes	6	2 (33.3)	4 (66.7)	
De-escalation ≥ 50%				
No	340	144 (42.4)	196 (57.6)	0.27
Yes	3	0	3 (100)	
Reason DLT				
Ototoxicity				
No	279	123 (44.1)	156 (55.9)	0.12
Yes	64	21 (32.8)	43 (67.2)	
Neurotoxicity				
No	342	144 (42.1)	198 (57.9)	1.00
Yes	1	0	1 (100)	
Hematopoietic toxicity				
No	331	139 (42)	192 (58)	1.00
Yes	12	5 (41.7)	7 (58.3)	
Nephrotoxicity				
No	302	170 (56.3)	132 (43.7)	*0.09*
Yes	41	29 (70.7)	12 (29.3)	
Vascular toxicity				
No	337	140 (41.5)	197 (58.5)	0.41
Yes	6	4 (66.7)	2 (33.3)	
Malaise				
No	314	134 (42.7)	180 (57.3)	0.44
Yes	29	10 (34.5)	19 (65.5)	

Patients with low SMM were more likely to experience cisplatin DLT (n=102, 66.2%) compared to patients without low SMM (n=52, 33.8%) (p<0.01). When comparing the causes of cisplatin DLT with SMM status, patients with low SMM were in particular more likely to not complete all cycles (n=3) of cisplatin (n=95, 65.5%) compared to patients without low SMM (n=50, 34.5%) (p=0.02). Patients who experienced cisplatin DLT were shown to have received significantly higher cisplatin doses per kg of LBM.

Table 1 and table 2 show the differences in demographic, clinical, biochemical and anthropometric characteristic between patients who experienced cisplatin DLT and patients who did not experience cisplatin DLT. The SMM (LSMI) was significantly lower in patients with cisplatin DLT compared to patients without cisplatin DLT (LSMI 39.7 cm^2/m^2 versus 42.4 cm^2/m^2; p<0.01). Female patients were more likely to experience cisplatin DLT (n=60, 55.6%; p<0.01). No significant differences were seen in other demographic, clinical or biochemical characteristics. Interestingly, although cisplatin is currently dosed on body surface area, it was not significantly different between patients who experienced cisplatin DLT (1.9 m^2) and patients whom did not experience cisplatin DLT (1.9 m^2) (p=0.2). However, LBM was significantly different between these patients (p<0.05). Patients who experienced cisplatin DLT had significant lower mean LBM (42.7 kg) compared to patients who did not experience cisplatin DLT (mean LBM 45.1 kg) (p=0.01). Patients who were underweight (n=30, 8.7%) were also more likely to experience cisplatin DLT (n=18, 60%; p=0.03).

PREDICTORS FOR CISPLATIN DOSE-LIMITING TOXICITY

Table 4 shows the univariate and multivariate logistic regression analysis of the predictors for cisplatin DLT. In univariate analysis, significant predictors for increased risk of cisplatin DLT were female gender (OR 1.88; 95% CI 1.18-2.97; p<0.01), LBM (OR 0.97; 95% CI 0.95-0.99; p=0.01) and low SMM at diagnosis (OR 1.20; 95% CI 1.20-2.89, p<0.01). Patients' body surface area was not predictive for cisplatin DLT (HR 0.7, 95% CI 0.4-1.4; p=0.4). Subsequently, low SMM was included in the multivariate analysis with the clinically relevant variables, age at diagnosis and BMI. Female gender was not included in the multivariate analysis because 95.4% of patients with low SMM were female patients. The LBM was not included because LBM is calculated by use of SMA in the Mourtzakis formula, SMA is already represented in SMM. In multivariate analysis, low SMM at diagnosis (OR 1.75; 95% CI 1.06-2.90, p=0.03) remained the only significant predictive factor for cisplatin DLT. The Hosmer and LemesHow test showed that the multivariate analysis model had a high goodness-of-fit (Chi-square 8.11, p=0.42).

Table 4. Univariate and multivariate predictors of cisplatin dose-limiting toxicity

	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Gender				
Male	Ref.			
Female	1.88 (1.18-2.97)	**0.007**		
Age (years)	1.02 (0.99-1.04)	0.23	1.01 (0.98-1.04)	0.53
BMI (kg/m²)	0.97 (0.92-1.02)	0.18	0.99 (0.94-1.05)	0.80
Perfomance				
ECOG 0	Ref.			
ECOG 1	1.10 (0.65-1.86)	0.71		
ECOG ≥2	1.27 (0.60-2.70)	0.54		
Unknown	0.84 (0.44-1.58)	0.58		
ACE-27 score				
None	Ref.			
Mild	1.17 (0.67-2.02)	0.58		
Moderate	1.17 (0.65-2.10)	0.61		
Severe	0.62 (0.27-1.43)	0.26		
Albumin (g/L)	0.96 (0.90-1.01)	0.14		
Total protein (g/L)	0.94 (0.86-1.02)	0.12		
Hemoglobin (mmol/L)	0.88 (0.72-1.08)	0.21		
Creatinine (mmol/L)	1.00 (0.99-1.01)	0.98		
LBM (kg)	0.97 (0.95-0.99)	0.01		
Body surface area (m²)	0.58 (0.22-1.55)	0.28		
Low SMM				
No	Ref.			
Yes	1.86 (1.20-2.89)	**0.006**	1.75 (1.06-2.90)	**0.03**

DISCUSSION

In this large retrospective study, we evaluated the association between low SMM prior to treatment with cisplatin-based chemoradiotherapy and the occurrence of cisplatin DLTs. We found that patients with low SMM at diagnosis were at significant risk for experiencing cisplatin DLTs compared to patients without low SMM. Cisplatin DLTs lead to failure of the intended treatment plan in 44.9% of patients. Our findings are in line with previous studies in patients with LA-HNC.[8,19] Our previous study in a smaller cohort of LA-HNC patients treated with either cisplatin or carboplatin showed a threefold increase in DLT frequency in patients with low SMM.[8] An association between low SMM and DLT has also been found in patients with non-small cell lung cancer, breast cancer, colorectal cancer, esophagogastric cancer and pancreatic cancer.[10,11,20,21] The scale of increased risk for DLTs found in these studies varies, mainly depending on type of cytotoxic agent used and the cut-off points used to define low SMM.

Several hypotheses have been proposed in literature to explain the underlying mechanism of this important finding in several types of cancers.[22,23] The most accepted hypothesis is based on the influence of low SMM on the volume of distribution of anti-cancer drugs and assumes that dosing of anti-cancer drugs on body surface area is insufficient to capture body composition differences. Dosing cytotoxic agents on body surface area was initially derived from observations that basal metabolic rates non-linearly differed between species (humans, animals) according to weight.[6] These observations also showed that the maximum tolerated dose expressed as mg/m^2 was similar in different species.[6] Therefore, in the 1950's, body surface area (m^2) calculated with patient's body weight and body height was used as an estimate for safe starting doses in phase 1 human trials based on preclinical animal toxicology studies.[6] However, the use of body surface area for predicting a safe starting dose was extended as a dosing tool for cytotoxic agents. Prado et al. showed that LBM has a poor association with body surface area (r^2= 0.37) in patients with solid tumors of the respiratory or gastro-intestinal tract.[24] Prado et al. estimated that the individual variation in LBM could account for up to a threefold variation in volume distribution for anticancer drugs dosed per unit body surface area.

Currently, the best tool used to predict who will benefit from chemotherapy is the performance status of the patient, which can be measured by the Eastern Cooperative Oncology group (ECOG) or the Karnofsky performance status. Besides the performance status, patients' comorbidities such as renal conditions and otologic conditions are taken into consideration as objective measures to classify a cisplatin-fit patient. However, the assessment of performance status by the clinician may be a subjective measure. In our study, also partly because unfit patients do not receive cisplatin, the performance status was, as expected, not an independent predictor for DLT. Besides performance status, BMI is mostly used as surrogate measure of patients' physical fitness or nutritional status in clinical oncology practice. We found that low BMI at diagnosis was not associated with an increased risk of DLTs. BMI is not an appropriate measurement tool to identify patient at risk for DLTs and may unjustly reassure oncologists about patients' nutritional status and risk for experiencing adverse treatment effects. Ideally in the future, the body composition rather than the body weight should be taken into account during the diagnostic, treatment and surveillance stages of phases in oncology. A need for a more objective and integrated measurement tool, such as SMM assessment, is needed. This enables an individualized patient approach, as wide variations in body composition, especially SMM, are reported in many populations.[25] SMM can be determined on routinely performed diagnostic imaging and therefore may be useful in clinical practice to identify patients at risk for DLTs without additional patient burden.

Our study had some limitations. First, due to the retrospective design of this study no information was available on nutritional status and physical exercise, which may influence the relationship between SMM and DLT. Second, due to the observative nature of this study no causal relationship between cisplatin pharmacokinetics and body surface area or SMM could be drawn from this study and further prospective studies are needed to elucidate this relationship.

Early screening to identify patients with occult low SMM combined with multimodal interventions may offer an improvement in treatment tolerance. In order to improve treatment tolerance to chemoradiotherapy in patients with LA-HNC two possible solutions are worth investigating: I. A new concept of cisplatin drug dosing schedules per kilogram of LBM using C3 muscle area measured on CT or MRI and II. SMM improvement by a multimodal approach including physical exercise (aerobic and resistance training), nutritional supplements (high protein) and pharmacological agents (anti-inflammatory, detoxifying agents).

In conclusion, the current method of dosing cisplatin in patients with LA-HNC leads to observed high frequency of DLT which may impair tumor treatment and definitely impairs quality of life. Low SMM at diagnosis is highly predictive for DLT. Cisplatin dosing based taking SMM into account may be a promising new concept in HNC in order to improve treatment tolerance.

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CHAPTER 11

Pre-treatment low skeletal muscle mass is associated with chemotherapy dose-limiting toxicity in head and neck cancer patients undergoing primary chemoradiotherapy with high dose cisplatin

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Submitted ■

ABSTRACT

Objectives

Low skeletal muscle mass (SMM) is an adverse predictive factor for chemotherapy dose-limiting toxicity (CDLT) in cancer patients. In patients with locally-advanced-head-and-neck-squamous-cell-carcinoma (LA-HNSCC) undergoing primary chemoradiotherapy (CRT), low SMM is a predictor for CDLT. We aimed to validate these findings.

Materials and methods

Consecutive LA-HNSCC patients treated with primary CRT with high-dose cisplatin were retrospectively included. SMM was measured on pre-treatment CT-imaging. A cumulative cisplatin dose below 200mg/m^2 was defined as CDLT.

Results

153 patients were included; 37 (24.2%) experienced CDLT and 84 had low SMM (54.9%). Patients with low SMM experienced more CDLT than patients with normal SMM (35.7% vs 10.1%, p<0.01). Low SMM (OR 3.99 [95%CI 1.56–10.23], p=0.01) and an eGFR of 60-70 mL/min (OR 5.40 [95%CI 1.57–18.65], p<0.01) were predictors for CDLT.

Conclusion

Pre-treatment low SMM is associated with CDLT in LA-HNSCC patients treated with primary CRT. Routine SMM assessment may allow for CDLT risk assessment and treatment optimalization.

INTRODUCTION

Locally advanced head and neck squamous cell carcinoma (LA-HNSCC) is preferably treated with concomitant chemoradiotherapy (CRT) with cisplatin, with or without prior surgery.[1] The standard-of-care cisplatin regimen consists of three three-weekly courses of high dose cisplatin at a dose of 100mg/m^2 body surface area (BSA), with a cumulative dose of 300mg/m^2 BSA cisplatin.[2] The addition of high dose cisplatin chemotherapy to radiotherapy treatment improves locoregional disease control and results in a 6.5% increase in 5-year overall survival.[3] Large prospective trials and retrospective studies show that a higher cumulative dose is associated with better survival rates.[4–7]

The addition of cisplatin also results in a significant increase in the toxicity of treatment, such as acute nephrotoxicity, bone marrow depression or severe nausea and vomiting, which cause treatment delay, dose reduction and treatment cessation as well as decreased quality of life.[2,8] Approximately 30% of patients experience chemotherapy dose-limiting toxicity (CDLT) and are unable to complete full treatment.[9] There are several contraindications for the use of high dose cisplatin, such as a decreased renal function, severe hearing loss and poor WHO functional status. Nevertheless, even in absence of these contra-indications, still 30% of patients experience CDLT in daily clinically practice which currently cannot be identified in advance. Therefore, there is a clinical need for additional predictive characteristics or biomarkers to accurately identify LA-HNSCC patients at high risk for CDLT from cisplatin.

In recent years, radiologically identified sarcopenia or low skeletal muscle mass (SMM) has been identified as a novel predictive and prognostic factor in cancer patients. Pre-treatment low SMM is associated with chemotherapy toxicity and CDLT in patients with a variety of cancer types, including lung, renal cell, colorectal and breast cancer.[10,11] Several risk factors for low SMM are known, including malnutrition, immobilization and chronic illness including cancer.[12] In HNSCC, malnutrition at diagnosis is highly common, and several retrospective studies report an incidence of approximately 50% of low SMM in HNSCC patients.[9,13–15] Recent retrospective studies in LA-HNSCC patients also concluded that pre-treatment low SMM was a significant predictor of CDLT in patients treated with CRT with platinum-based chemotherapy.[9,16] The purpose of this study was to investigate and validate the predictive value of low SMM on CDLT in a larger cohort of LA-HNSCC patients, treated with standard-of-care treatment with primary CRT with high dose cisplatin.

MATERIAL AND METHODS

This study was performed as a secondary analysis of a prior retrospective study.[6] All data were used in an coded fashion. Because of the retrospective nature of this study, formal informed consent or medical ethical approval was waived at the time of the inception of this study. This research was conducted in accordance with the Declaration of Helsinki and all subsequent legislation.

PATIENT AND STUDY DESIGN

All patients were treated at the Netherlands Cancer Institute in Amsterdam, The Netherlands, with curative intent. Between January 2008 and December 2015, all 279 consecutive patients with histologically proven squamous cell carcinoma of the oropharynx, hypopharynx, or larynx who were eligible for concomitant primary chemoradiotherapy with three three-weekly courses of high dose cisplatin courses at 100mg/m^2 BSA were identified. Patients who were not treated with cisplatin for any reason, and patients who received cisplatin in another regimen such as weekly cisplatin or carboplatin were excluded. Patients without recent CT or MRI scans (less than 3 months) of the head and neck area prior to TL were excluded. Patients who had severe dental artifacts at the level of C3 that impeded accurate assessment of SMM were also excluded. Relevant clinical information such as weight, stature, body mass index (BMI), smoking, AJCC stage according to the 7th AJCC staging manual and outcome data were retrieved from medical records.

The Adult Comorbidity Evaluation index (ACE-27) was used to measure comorbidities.[17] In oropharyngeal cancer, HPV status was assessed by p16 staining, followed by high-risk HPV PCR for confirmation. Survival data were collected until February 2017. Because of a known vastly better prognosis of HPV-related oropharyngeal cancer, those patients were excluded from survival analysis.

CHEMOTHERAPY DOSE-LIMITING TOXICITY

Chemotherapy dose-limiting toxicity was defined as any toxicity resulting in a cumulative cisplatin dose of less than 200mg/m^2. This could be because of a chemotherapy dose-reduction of ≥50% (e.g. due to neutropenia or nephrotoxicity) after the first cycle of treatment, a postponement of treatment of ≥4 days (e.g. in the case of bone marrow suppression) resulting in the termination of a cycle combined with a dose-reduction, or a definite termination of chemotherapy after the first cycle of therapy. The aim was to complete all three cycles, but if treatment tolerance was perceived to be low, two full cycles of high dose cisplatin was accepted as adequate treatment.

CT IMAGE ACQUISITION

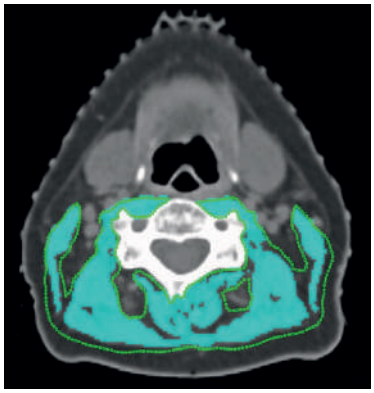
As part of radiotherapy planning, pre-treatment head and neck CT-imaging in radiation mould was performed in all patients. Patients were immobilized in supine treatment position in a custom-made head-and-neck mask. For planning, contrast-enhanced 3-mm slides CT-scan

simulation was performed in all patients. All patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulate arc therapy (VMAT). The radiation treatment consisted of 46 Gy of elective irradiation to both sides of the neck (level II-IV in case of node-negative neck and level II-V in case of cervical lymph node metastases), followed by a boost of 24 Gy in 12 fractions to the primary tumor and the involved nodes in case of node-positive disease, to a total dose 70 Gy.

IMAGE EVALUATION

Measurement of SMM was performed at the level of C3 according to a method previously described by Swartz et al.[18] In brief, a single axial CT-slide at level C3 was selected using a standard procedure: the first slide to completely show the entire vertebral arc when scrolling through the C3 vertebra from caudal to cephalic direction was selected. Skeletal muscle tissue was identified using Hounsfield unit (HU) ranges settings from -29 to +150 HU, to avoid overestimation of skeletal muscle area and to exclude fatty tissue (which has a HU value below -30).[19] The outer contours of the sternocleidomastoid and paravertebral muscles were traced manually (figure 1) using the Worldmatch Research Software Package, an in-house software package designed for image evaluation, registration and delineation for radiotherapy. The cross-sectional muscle area (CSMA) at the level of C3 was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoid muscles within HU ranges of -29 to +150 in cm^2. All CT slides were analyzed by a single researcher (S.B.). The CSMA at the level of C3 was then normalized for stature to calculate a cervical skeletal muscle index (CSMI).[20]

Figure 1. Skeletal muscle area segmentation at the level of C3.



STATISTICAL ANALYSIS

All analyses were performed using SPSS version 23.0 (SPSS Inc. Chicago IL, USA). Continuous data are represented as mean ± standard deviation (SD). Categorical data are represented as the number and percentage of total. The optimum SMM cut-off value based on CDLT was obtained using the optimal point in a receiver optimum stratification for binary outcomes (in this

study, the occurrence of CDLT). The Fisher's exact test, Pearson Chi square test, independent sample t-test and Mann-Whitney U test were used for comparisons between groups where appropriate. The predictive effect of low SMM on CDLT was evaluated using univariate and multivariate logistic regression analysis. Variables with a p-value lower than 0.05 in univariate analysis were selected for inclusion in multivariate analysis. Cox proportional hazard regression analysis was used to evaluate the relationship between low SMM and overall survival (OS). Kaplan Meier curves were used to visualize overall survival.

RESULTS

Of all 279 patients predefined as having an indication for high dose cisplatin, 39 patients did not receive any cisplatin and 73 patients were treated with daily cisplatin as part of a clinical study and were thus excluded. Six patients were treated with induction TPF (docetaxel, cisplatin, fluorouracil), and 4 with weekly cisplatin, and were also excluded. In 4 patients, imaging quality was deemed insufficient. In total, 153 patients who were treated with three-weekly high dose cisplatin were included for analysis. For the overall survival analysis, 41 patients with HPV-positive oropharyngeal cancer were excluded and 112 patients with HPV-negative or unknown status were included.

PATIENT CHARACTERISTICS

Patient, disease and outcome characteristics are presented in Table 1. All patients received at least 1 cycle of high dose cisplatin. Patients were predominantly male, current smokers and presented with AJCC stage III or IV disease. Of note, almost 50% of all patients with oropharyngeal cancer had HPV-related oropharyngeal cancer. Approximately half of all patients completed 3 cycles of high dose cisplatin (52.9%). Two cycles of cisplatin were completed in 22.9% of patients. In 24.2% of patients, only 1 cycle of chemotherapy could be completed. CDLT occurred in 24.2% of patients. The most frequent reason for chemotherapy treatment termination was grade 3 toxicity, being a significant decrease in renal function in 52%, severe nausea in 9% and infectious disease such as sepsis in 9% of patients. There were no significant differences in patients' characteristics between patients with and without CDLT, apart from a mild renal function impairment prior to start of treatment with an eGFR between 60 and 70 ($p = 0.02$).

Table 1. Patient, disease and outcome characteristics.

Characteristic	Total patients n = 153 (%)	Patients with CDLT n = 37 (%)	Without CDLT n = 116 (%)	P value
Gender				
Men	112 (73.2)	28 (75.7)	84 (72.4)	0.70*
Women	41 (26.8)	9 (24.3)	32 (27.6)	
Age at diagnosis (years)				
Mean (SD)	59.9 (6.7)	61.1 (5.9)	59.5 (7.0)	0.20$
Smoking				
Never	25 (16.3)	5 (13.5)	20 (17.2)	0.40#
Former	16 (10.5)	6 (16.2)	10 (8.6)	
Active	112 (73.2)	26 (70.3)	86 (74.1)	
Body mass index (kg/m²)				
Mean (SD)	23.7 (4.1)	23.6 (3.8)	23.8 (4.2)	0.82$
ACE-27 score				
0	115 (75.2)	28 (75.7)	87 (75.0)	0.20#
1	37 (24.2)	8 (21.6)	29 (25.0)	
2	1 (0.7)	1 (2.7)	0 (0)	
Renal function				
eGFR >70	130 (85.0)	27 (79.4)	103 (93.6)	**0.01***
eGFR 60-70	14 (9.2)	7 (20.6)	7 (6.4)	
Tumor site				
Oropharynx,HPV+	41 (26.8)	9 (24.3)	32 (27.6)	0.40#
Oropharynx, HPV- or unknown	51 (33.3)	12 (32.4)	39 (33.6)	
Hypopharynx	50 (32.7)	11 (29.7)	39 (33.6)	
Larynx	11 (7.2)	5 (13.5)	6 (5.2)	
T stage				
1	15 (9.8)	4 (10.8)	11 (9.5)	0.23#
2	46 (30.1)	10 (27.0)	36 (31.0)	
3	48 (31.4)	12 (32.4)	36 (31.0)	
4	44 (28.8)	11 (29.7)	33 (28.4)	
N stage				
0	19 (12.4)	3 (8.1)	16 (13.8)	0.53#
1	17 (11.1)	5 (13.5)	12 (10.3)	
2a	9 (5.9)	4 (10.8)	5 (4.3)	
2b	66 (43.1)	13 (35.1)	53 (45.7)	
2c	35 (22.9)	10 (27.0)	25 (21.6)	
3	7 (4.6)	2 (5.4)	5 (4.3)	
AJCC stage				
II	4 (2.6)	0 (0)	4 (3.4)	0.34#

Table 1. (Continued)

Characteristic	Total patients n = 153 (%)	Patients with CDLT n = 37 (%)	Without CDLT n = 116 (%)	P value
III	66 (43.1)	14 (37.8)	52 (44.8)	
IV	83 (54.2)	23 (62.2)	60 (51.7)	
Extracapsular extension				
No	109 (71.2)	29 (78.4)	80 (69.0)	0.27*
Yes	44 (28.8)	8 (21.6)	36 (31.0)	
Number of cisplatin cycles				
1	37 (24.2)	37 (100)	-	n/a
2	35 (22.9)	-	35 (30.2)	
3	81 (52.9)	-	81 (69.8)	
CDLT				
Absent	116 (75.8)	-	116 (100)	n/a
Present	37 (24.2)	37 (100)		
Survival status				
Alive	99 (64.7)	21 (56.8)	78 (67.2)	0.25*
Deceased	54 (35.3)	16 (43.2)	38 (32.8)	

* Fisher's exact test, # Pearson Chi square test, $ Independent student's T test

LOW SMM AS A PREDICTOR FOR CDLT

A sex-specific cut-off point for low SMM as a predictor for CDLT was formulated using a ROC curve. The AUC of the ROC curve was 0.72 for women (Mann-Whitney U test: $p = 0.05$) and 0.58 for men (Mann-Whitney U test: $p = 0.11$). The optimal cut-off value for low SMM was 10.7 cm^2 for women and 13.1 cm^2 for men. Using this cut-off, 54.9% of patients had low SMM.

UNIVARIATE AND MULTIVARIATE ANALYSIS FOR CDLT

Table 2 shows patient and disease characteristics of patients with low SMM and normal SMM. Patients with low SMM had a significantly lower BMI ($p < 0.01$) and a higher T stage ($p = 0.05$) and showed a trend towards a higher N stage ($p = 0.09$). There were no significant differences in terms of gender or age of patients with and without low SMM. Patients with low SMM experienced CDLT significantly more often than patients with normal SMM (35.7% versus 10.1%; $p < 0.01$).

In table 3, the univariate and multivariate analysis for the occurrence of CDLT are shown. In univariate analysis, only low SMM (OR 3.75 [95% CI 1.58 – 8.90], $p < 0.01$) and a mild renal function impairment with an eGFR of 60 – 70 (OR 3.82 [95% CI 1.23 – 11.81], $p = 0.02$) were associated with the occurrence of CDLT. In multivariate analysis, both low SMM (OR 3.99 [95% CI 1.56 – 10.23], $p = 0.01$) and a mild renal function impairment (OR 5.40 [95% CI 1.57 – 18.65], $p < 0.01$) remained associated with the occurrence of CDLT.

Table 2. Patient characteristics in patients with low and normal SMM

All patients Characteristic	Patients with low SMM n = 84 (%)	Patients with normal SMM n = 69 (%)	P value
Gender			
Men	64 (76.2)	48 (69.6)	0.37*
Women	20 (23.8)	21 (30.4)	
Age at diagnosis (years)			
Mean (SD)	59.9 (6.3)	59.8 (7.3)	0.95$
Smoking			
Never	14 (16.7)	11 (15.9)	0.92#
Former	8 (9.5)	8 (11.6)	
Active	62 (73.8)	50 (72.5)	
Body mass index (kg/m²)			
Mean (SD)	22.1 (3.6)	25.6 (3.9)	**<0.01$**
ACE-27 score			
0	62 (73.8)	53 (76.8)	0.60#
1	21 (25.0)	16 (23.2)	
2	1 (1.2)	0 (0)	
Renal function			
eGFR >70	73 (92.4)	57 (87.7)	0.40*
eGFR 60-70	6 (7.6)	8 (12.3)	
Tumor site			
Oropharynx,HPV+	16 (19.0)	25 (36.2)	0.12#
Oropharynx, HPV- or unknown	31 (36.9)	20 (29.0)	
Hypopharynx	30 (35.7)	20 (29.0)	
Larynx	7 (8.3)	4 (5.8)	
T stage			
1	10 (11.9)	5 (7.2)	**0.05#**
2	18 (21.4)	28 (40.6)	
3	27 (32.1)	21 (30.4)	
4	29 (34.5)	15 (21.7)	
N stage			
0	10 (11.9)	9 (13.0)	*0.09#*
1	11 (13.1)	6 (8.7)	
2a	4 (4.8)	5 (7.2)	
2b	29 (34.5)	37 (53.6)	
2c	24 (28.6)	11 (15.9)	
3	6 (7.1)	1 (1.4)	
AJCC stage			
II	2 (2.4)	2 (2.9)	0.11#
III	30 (35.7)	36 (52.2)	
IV	52 (61.9)	31 (44.9)	
CDLT			
No	54 (64.3)	62 (89.9)	**<0.01***
Yes	30 (35.7)	7 (10.1)	

Bold p-value indicates a significant difference between groups. Cursive indicates a p value < 0.10
* Fisher's exact test, # Pearson Chi square test, $ Independent student's T test

Table 3. Univariate and multivariate logistic regression analysis for prediction of CDLT

	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Gender				
Male	Ref			
Female	0.84 (0.36 - 1.98)	0.70		
Age at diagnosis				
(years)	1.04 (0.98 – 1.10)	0.20		
BMI at diagnosis				
(kg/m^2)	0.99 (0.90 – 1.08)	0.82		
Tumor site				
Oropharynx HPV+	Ref			
Oropharynx HPV-/unknown	1.09 (0.41 – 2.92)	0.86		
Hypopharynx	2.96 (0.72 - 12.00)	0.13		
Larynx	1.00 (0.37 - 2.72)	1.00		
AJCC stage				
II-III	Ref			
IV	1.53 (0.72 - 3.27)	0.27		
Renal function				
eGFR >70	Ref		Ref	
eGFR 60-70	3.82 (1.23 - 11.81)	**0.02**	5.40 (1.57 - 18.65)	**< 0.01**
Low SMM				
No	Ref		**Ref**	
Yes	3.75 (1.58 - 8.90)	**< 0.01**	**3.99 (1.56 - 10.23)**	**0.01**
ACE-27 score				
0	Ref			
1 or 2	0.96 (0.41 - 2.28)	0.94		
Smoking				
No	Ref			
Former	2.40 (0.59 - 9.82)	0.22		
Active	1.21 (0.41 - 3.54)	0.73		

Bold p-value indicates a significant difference between groups.

Table 4. Univariate and multivariate analysis for overall survival

	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Gender				
Male	Ref			
Female	1.06 (0.57 - 1.98)	0.86		
Age at diagnosis				
(years)	1.02 (0.97 – 1.06)	0.58		
BMI at diagnosis				
(kg/m^2)	0.93 (0.87 – 0.99)	0.03	0.94 (0.88 - 1.00)	0.07
Tumor site				
Oropharynx HPV+	*Excluded**			
Oropharynx HPV-/unknown	Ref			
Hypopharynx	1.86 (0.74 - 4.69)	0.19		
Larynx	1.46 (0.81 - 2.61)	0.21		
AJCC stage				
2 and 3	Ref		Ref	
4	3.57 (1.79 - 7.14)	**<0.01**	3.40 (1.69 - 6.81)	**<0.01**
CDLT				
No	Ref		Ref	
Yes	2.11 (1.15 - 3.89)	**0.02**	2.10 (1.13 - 3.90)	**0.02**
Low SMM				
No	Ref			
Yes	1.23 (0.71 - 2.16)	0.46		
ECE				
No	Ref			
Yes	1.10 (0.55 - 2.19)	0.80		
ACE-27 score				
0	Ref			
1 or 2	0.79 (0.41 - 1.53)	0.48		

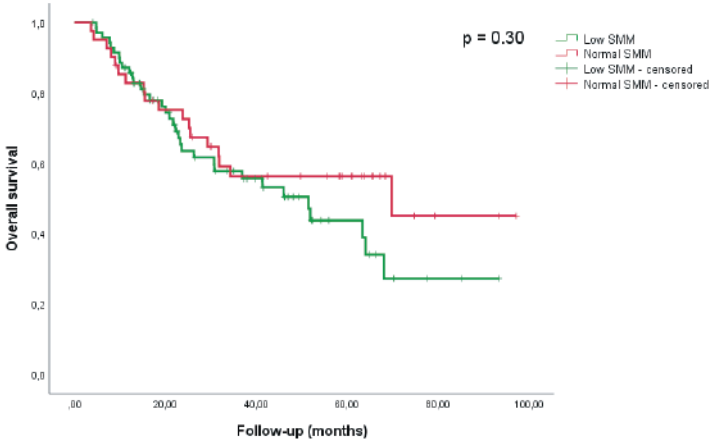
Bold indicates a significant difference between groups. * HPV-related oropharyngeal cancer: HR 0.07 (95% CI 0.02 - 0.31], p < 0.01.

SURVIVAL ANALYSIS

Table 4 shows univariate and multivariate Cox regression analysis for OS in HPV-negative patients or patients with unknown HPV-status (n=112). In univariate Cox regression analysis, by far the most important prognosticator was HPV-status of the tumor; with patients with HPV-related oropharyngeal cancer having a better prognosis than other patients in this cohort (HR 0.07 [95% CI 0.02 - 0.31], p < 0.01). In univariate Cox regression analysis, low SMM was not a significant prognosticator (HR 1.23 [95% CI 0.71 - 2.16], p = 0.46) for OS, as visualized in figure 2. In contrast, the occurrence of CDLT was significantly associated with a decreased OS (HR 2.11 [95% CI 1.15 - 3.89], p = 0.02), as visualized in figure 3. Other significant prognosticators for OS were AJCC stage IV disease (HR 3.57 [95% CI 1.79 - 7.14), p < 0.01) and BMI (HR 0.93 [95% CI 0.87 - 0.99], p = 0.03), with a higher BMI being associated with significantly better OS. In

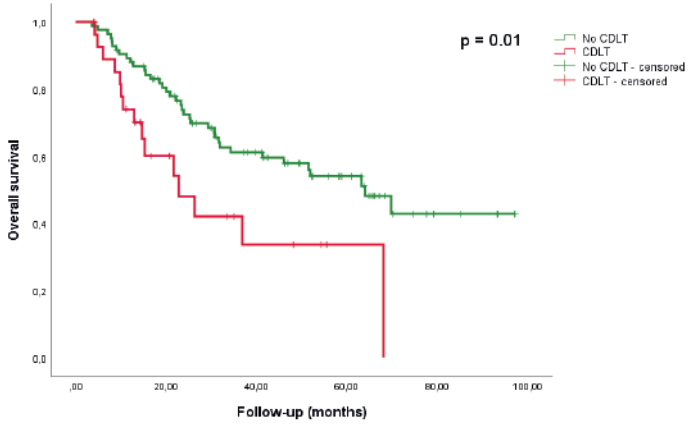
multivariate regression analysis only AJCC stage IV disease and CDLT remained significantly associated with decreased OS.

Figure 2. Kaplan Meier survival curve for low SMM in HPV negative patients



	At 20 months	At 40 months	At 60 months	At 80 months
Number of events	26	44	48	52
Remaining cases	73	43	23	4

Figure 3. Kaplan Meier survival curve for CDLT in HPV negative patients



	At 20 months	At 40 months	At 60 months	At 80 months
Cumulative number of events	26	44	48	52
Remaining cases	73	43	23	4

DISCUSSION

Low SMM is associated with an increase in chemotherapy related toxicity and CDLT in a variety of cancer types. Our study also shows this relationship in HNSCC patients treated with primary CRT with high-dose cisplatin. Patients with low SMM had a trifold risk of experiencing CDLT compared to patients with normal SMM in this study. Although patients with low SMM did not have a decreased OS, patients who experienced CDLT did have a significantly decreased OS. This study adds to the mounting evidence that there is a clear relationship between low SMM and the occurrence of CDLT in HNSCC patients treated with high dose cisplatin.[9,16,21,22]

Platinum-based chemotherapy is routinely used in the curative treatment of LA-HNSCC to enhance the antitumor effect of radiation. Several treatment schemes and dosing levels are available for platinum-based chemotherapy in HNSCC. Level 1 evidence is available for the improvement of locoregional control and overall survival with concurrent CRT with three three-weekly cycles of high dose cisplatin at a dose level of 100mg/m^2 BSA.[2] Despite irrefutable efficacy, the toxicity of treatment with high dose cisplatin is a well-known problem in daily clinical practice. Early chemotherapy termination due to unacceptable toxicity occurs in approximately 30% of patients and is associated with a marked decrease in overall survival (52% versus 72% in 3-year survival) as well as increase in long-term morbidity of treatment. In recent years, several large clinical trials have investigated de-escalation strategies with weekly low-dose cisplatin or cetuximab as radiosensitizer in HNSCC, but these trials concluded that concurrent CRT with high-dose cisplatin remains the preferred treatment option with the highest survival benefit.[23–25]

There is an evident clinical need for improved risk assessment in patients planned for high-dose cisplatin treatment. Several risk factors for cisplatin toxicity are already established absolute contra-indications, such as a decreased renal function with an eGFR <60, severe hearing loss or poor functional WHO-status. Better knowledge on relative contraindications is needed to identify patients who may benefit from modified treatments. Low SMM is a radiological biomarker that may aid in the identification of those patients at high risk of cisplatin related toxicity that would otherwise not have been identified.[26]

Over the last decade, the body composition of cancer patients has been researched extensively using diagnostic computer tomography (CT) imaging.[27] Recent retrospective studies in a variety of cancer types have shown an association between low SMM, sometimes termed sarcopenia, and the occurrence of chemotherapeutic toxicity and CDLT.[10] Several hypothesis have been proffered. One hypothesis behind this relationship is that most (hydrophilic) chemotherapy, including cisplatin, mainly distributes into the fat-free body mass, of which skeletal muscle mass is the largest contributor.[11,28] Patients with low SMM and normal or high fat mass may receive a relatively higher dose of chemotherapy than is anticipated using a standard dosing regimen based on BSA. Previous research has shown that drug dosing based on BSA

poorly predicts plasma drug concentrations of most cytotoxic drugs in individual patients, including cisplatin.[29,30]

Currently, a prospective study investigating this relationship in HNSCC patients is ongoing.

It may also be that low SMM reflects an overall poorer physical functioning in patients, which is not as distinctly found as using other routinely used risk stratification methods. In recent years, there has been increased interest in the supportive care of cancer patients undergoing chemotherapy, including increased interest in guided exercise and nutritional support during cancer treatment. A randomized controlled trial in breast cancer patients undergoing several physical activity programs showed a positive effect on treatment tolerance and fatigue.[31] A recently published randomized controlled trial in rectal cancer patients undergoing neoadjuvant CRT showed a significant increase in SMM in patients who followed an exercise program during neoadjuvant chemotherapy, compared to patients who did not.[32] A recent study in breast cancer patients undergoing adjuvant chemotherapy did not show a difference in chemotherapy completion in patients participating in an exercise intervention, but it did show a significant decrease in hospitalization during treatment.[33] Besides exercise and nutritional support during cancer treatment, 'prehabilitation' with exercise and nutritional support prior to start of treatment are likely to increase treatment tolerance. However, limited time between diagnosis and start of treatment may decrease the ability to effectively implement a prehabilitation program in patients undergoing primary CRT.

Feasibility studies in patients with HNSCC have shown that muscle resistance training programs in patients undergoing chemoradiotherapy or radiotherapy are feasible and show high patient satisfaction.[34,35] Whether such interventions also provide benefit in terms of overall survival is unknown, but low SMM prior to start of treatment may be an indicator that a patient may benefit from intensified supportive care in terms of physical exercise and nutritional support. Pre-treatment low SMM may also be used as an argument for an intended treatment de-escalation choice, such as weekly low-dose cisplatin, to maximize treatment adherence and cumulative cisplatin dose administered.

Several limitations to this study need to be addressed. Due to the retrospective nature of the research, not all relevant research parameters for body composition or nutritional status were measured or documented during normal clinical practice. Because of the academic nature of the tertiary referral center this study was conducted in, a relatively large percentage of patients was excluded because of a trial-based treatment regimen (weekly or daily cisplatin).

In the present study CDLT was defined as any toxicity resulting in a cumulative cisplatin dose of less than 200mg/m^2; it is generally accepted that at least a dose of 200mg/m^2 should be administered to be sufficiently effective.[3,4] In the previous study of Wendrich et al, CDLT was defined as any toxicity resulting in any chemotherapy dose-reduction of ≥50% (e.g. due to neutropenia or nephrotoxicity), a postponement of treatment of ≥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. Despite slightly different definitions of CDLT, the conclusions of both studies were comparable: a threefold significant higher incidence of CDLT in SMM patients (35.7% vs. 10.1% and 44.3% vs. 13.7%). In both studies patients experiencing CDLT had a significantly lower overall survival than patients who did not.

In the current study, we decided not to use a previously published multivariate formula to calculate CSMA at the level of L3, but rather use CSMA at the level of C3 directly to assess SMM. This better allowed us to formulate a sex-specific cut-off point for low SMM, as is commonly done in other areas of oncological research, rather than use a single cut-off point. It is known that women have less SMM than men.[36]. Sex is part of the previously published prediction formula for translation of CSMA at level of C3 to CSMA at level of L3 as such sex is implicitly already accounted for using this method. This choice does hinder direct comparison to our previous results. It should be noted that the incidence of low SMM as well as the trifold risk of CDLT in patients with low SMM is equal in both our previous (9) and this current study and compares to results in other studies.

CONCLUSION

This study validates the previous findings that pre-treatment low SMM is significantly associated with CDLT in LA-HNSCC patients treated with primary CRT with high dose cisplatin. Pre-treatment low SMM alone was not a prognostic factor for OS, but CDLT was. Routine SMM assessment may allow for CDLT risk assessment and identification of those patients who may benefit from treatment modifications and from interventions to increase SMM.

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CHAPTER 12

The predictive and prognostic value of low skeletal muscle mass for dose-limiting toxicity and survival in head and neck cancer patients receiving concomitant cetuximab and radiotherapy

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ABSTRACT

Background

This study aims to investigate the predictive value of low skeletal muscle mass (SMM) for cetuximab dose-limiting toxicity (DLT) and its prognostic value in head and neck squamous cell carcinoma (HNSCC) patients treated with concomitant cetuximab and radiotherapy.

Material and methods

Patients diagnosed with HNSCC and treated with primary or adjuvant concomitant cetuximab and radiotherapy were included. Clinical and demographic variables were retrospectively retrieved and SMM was measured at the level of the third cervical vertebra using pre-treatment diagnostic computed tomography or magnetic resonance imaging. An optimal cut-off value for low SMM was determined based on the lowest log likelihood associated with cetuximab DLT. A multivariate linear regression model was used to determine predictive factors for cetuximab DLT. The prognostic value of low SMM for disease-free and overall survival was analyzed using Kaplan-Meier curves.

Results

The optimal cut-off value for low SMM as a predictor of cetuximab DLT was an LSMI ≤ 45.2 cm^2/m^2. Of the 91 included patients, 74.7% had low SMM and 30.8% experienced cetuximab DLT. At multivariate analysis, low SMM had no predictive value for DLT (OR 0.83; 95% CI 0.27-2.56; p=0.74). The Kaplan-Meier curve demonstrated that patients with low SMM had significantly lower overall survival (Log Rank $\chi 2 = 5.87$; p=0.02).

Conclusion

Low SMM is highly prevalent in HNSCC patients treated with concomitant cetuximab and radiotherapy. Low SMM has no predictive value for cetuximab DLT in HNSCC patients. Low SMM is probably not a prognostic factor for overall survival in highly selected HNSCC patients treated with concomitant cetuximab and radiotherapy and unfit for platin-based chemotherapy.

INTRODUCTION

Head and neck cancer is the sixth most common cancer, with over 600,000 new cases annually worldwide.[1] At diagnosis, locoregionally advanced disease is present in up to 60% of patients.[1] Locoregionally advanced stage head and neck squamous cell carcinoma (HNSCC) is generally treated with surgery plus adjuvant radiotherapy with or without cisplatin chemotherapy or, as primary treatment, concomitant cisplatin chemotherapy and radiotherapy with salvage surgery in reserve for residual disease or recurrence.[1] The addition of chemotherapy to radiotherapy improves disease control and survival but also results in increased toxicity and can, therefore, influence adherence to the treatment.[2] Cisplatin dose-limiting toxicity (DLT) includes, among others, bone marrow depression, ototoxicity, and nephrotoxicity.[3] This can cause treatment delay, dose reduction, and possible failure to complete treatment as well as decreased quality of life.[3]

To improve treatment adherence and reduce toxicity, predictive factors should be identified that indicate the risk of a patient to experience DLT. Currently, patients are evaluated by their oncologist to determine whether they are medically fit to undergo cisplatin treatment. This takes into consideration age, comorbidities, and the presence of contraindications for cisplatin, such as impaired renal function, poor general health, bone marrow suppression, and impaired hearing. If patients are considered unfit for cisplatin alternative options to increase the anti-tumor effect of radiotherapy include the addition of cetuximab.[4] However, patients treated with cetuximab in combination with radiotherapy may also experience considerable amounts of toxicity, specifically leucopenia, neutropenia, and mucositis.[5] Therefore, to improve treatment adherence and reduce toxicity, predictive factors should be identified that indicate the risk of DLT. Low skeletal muscle mass (SMM) is a possible predictive factor to estimate whether a patient will experience chemotherapy DLT. Moreover, low SMM may also be a prognostic factor. Low SMM has a high prevalence in adults with cancer; in HNSCC prevalence as high as 55% has been reported.[3] SMM can be measured on a routinely performed computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck.[6–8] Low SMM has previously been linked to an increased prevalence of chemotherapy DLT for several types of cancer such as breast[9], colorectal[10], renal[11], lung[12], and oesophago-gastric cancer[13]. Specifically, for HNSCC, Wendrich *et al.* demonstrated that low SMM is a predictive factor for platin DLT (occurring in 30.4%) in patients treated with platin-based chemotherapy and radiotherapy.[3]

Based on previous evidence supporting the predictive value of low SMM for chemotherapy DLT in several types of cancer, it is logical to question whether low SMM is also predictive for DLT in treatment of HNSCC using cetuximab. This study focusses on investigating the possible predictive value of low SMM for DLT during concomitant cetuximab and radiotherapy treatment of locally advanced HNSCC. Also, the prognostic value of low SMM for overall survival (OS) and the disease-free survival (DFS) in HNSCC patients treated with concurrent cetuximab and radiotherapy is investigated.

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

We conducted a retrospective study of HNSCC patients treated with primary or adjuvant concomitant cetuximab and radiotherapy in the University Medical Center Utrecht between January 2007 and December 2018. The included patients were unfit for cisplatin treatment. HNSCC patients were included if they had a pre-treatment (≤ 3 months prior) diagnostic imaging scan (CT or MRI) of the third cervical vertebra (C3) level which was suitable for muscle segmentation. Patients were excluded if treatment was provided with palliative intent. Relevant demographic and clinical variable such as age at diagnosis, sex, weight, length, body mass index (BMI), alcohol consumption, alcohol abuse as identified by the treating physician, comorbidity as expressed by the Adult Comorbidity Evaluation-27 (ACE-27), tumor, lymph nodes, and metastasis (TNM) staging, treatment regimen, cetuximab DLT data, date of last follow up, and eventually, the date of recurrent disease or death were obtained from patients' records.

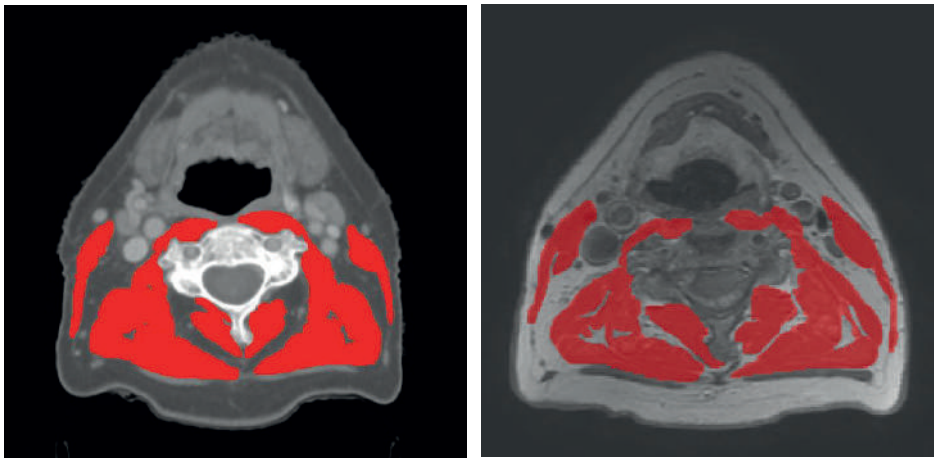
IMAGE ANALYSIS AND MEASUREMENTS

The cross-sectional area (CSA) of skeletal muscles was measured on pre-treatment diagnostic CT or MRI imaging that included the C3 vertebra. Segmentation of the muscle was performed using the commercially available SliceOmatic (Tomovision, Canada) by a single researcher (L.H.) on the axial slide which showed the entire vertebral arc as well as both transverse processes. The CT scans used were 3-mm axial slices with or without contrast made using Philips (16-slice or 64-slice) or Siemen's scanners (40-slice) and the MRI scans were axial T1 weighted sequence without fat suppression made using Philips's scanners (1.5T or 3T). CSA was calculated as the sum of the measured area of both sternocleidomastoid muscles (SCM) and the paravertebral muscles. If tumor growth interfered with the measurement of either the left or right SCM, the area of the contralateral SCM was used to replace it. Patients were excluded, if, the CSA could not be measured reliably due to a CT or MRI artifacts, a too small field of view, or tumor growth in both SCM.

In the case of CT imaging, muscle area was measured semi-automatic using a combination of manual segmentation in a predefined radiodensity range of -29 to +150 Hounsfield units (HU).[14] In the case of MRI imaging, muscle area was measured manually. Figure 1 shows an example of muscle delineation at the C3 level. The CSA at C3 level was converted to the CSA at third

lumbar vertebra L3 level using the formula previously published by Swartz *et al*.[6] The CSA at L3 level was corrected for squared height to create the lumbar skeletal muscle index (LSMI).

Figure 1. Example of delineation on 3 mm axial slide of CT (Siemens 40-slice) (left) and axial T1 weighted sequence MRI (Philips 1.5T) (right) at the level of C3 using SliceOmatic. The left and right SCM as well as the paravertebral muscles are delineated excluding the trapezius muscle. Please note that the muscles in the anterior neck are not included in the delineation as previously described



DOSE-LIMITING TOXICITY

DLT was defined as any toxicity that resulted in a treatment postponement of ≥ 4 days, dose reduction of ≥ 50%, dose omission, or termination of cetuximab treatment before completing the predetermined cetuximab regimen (most commonly consisting of eight cycles, none extending beyond last radiotherapy fraction).

SURVIVAL

OS was defined as the time between the date of diagnosis and the date of death or the date of the last follow up. DFS was defined as the time between the date of diagnosis and the date of recurrence or the date of the last follow up.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using IBM SPSS statistics 25. Descriptive statistics for categorical variables were presented as frequencies and percentages. Continuous variables with normal distribution were presented as mean with standard deviation (SD), while those with skewed distribution were presented as median with interquartile range (IQR).

The means of the continuous variables with the presence or absence of low SMM were computed using the independent sample t-tests. The percentages of the categorical variables with the presence or absence of low SMM were analyzed using the Pearson's or Mantel-Haenszel

chi-square test. The risk parameters were calculated and presented with corresponding 95% confidence intervals (95% CI) and p-values.

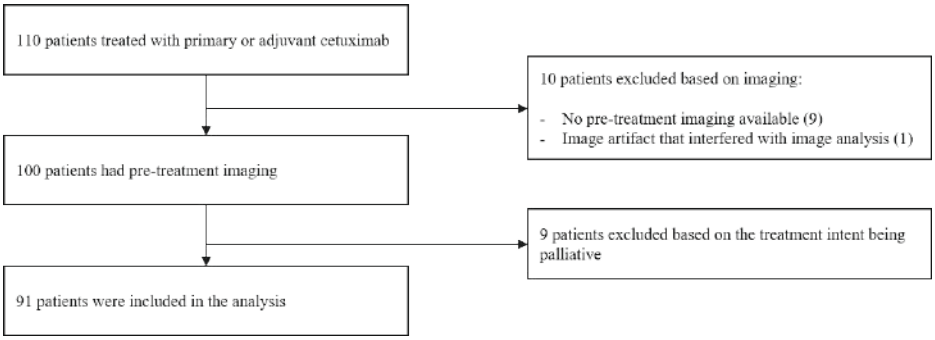
The predictive value of low SMM on cetuximab DLT was evaluated using univariate and multivariate logistic regression. A Cox proportional hazard regression model was used for univariate and multivariate analysis of OS and DFS. Covariates used in the multivariate analysis were selected based on clinical significance or statistical significance ($p < 0.05$) in univariate cox or logistic regression analysis. Statistical significance was evaluated at the 0.05 level using 2-sides tests. OS and DFS were visualized using Kaplan Meier survival curves and number at risk tables.

RESULTS

STUDY POPULATION

Between 2007 and 2018, 110 HNSCC patients were treated with primary or adjuvant cetuximab and radiation for oropharynx, hypopharynx, or larynx tumor. Of these patients, 100 had pre-treatment imaging of the C3 vertebra which is necessary for the determination of SMM. Additionally, patients receiving cetuximab with palliative intent were excluded. As can be seen in Figure 2, 91 patients were included in the analysis, 28 patients (30.8 %) experienced cetuximab DLT and 63 (69.2%) experienced no cetuximab DLT.

Figure 2. Flowchart of patient inclusion



Determining the optimal cut-off value for low SMM

The cut-off value for low SMM was determined by calculating the log likelihood using a technique previously described by Williams *et al.*[15] The cut-off value best associated with the presence of cetuximab DLT (lowest Log-Likelihood value) was LSMI ≤ 45.2 cm^2/m^2. Using this cut-off value for the study population, 68 (74.7%) were identified with low SMM and 23 (25.3%) were identified without low SMM.

CHARACTERISTICS OF STUDY POPULATION

Table 1 shows the general characteristics of the study population according to the presence or absence of low SMM. Significant differences were observed for the occurrence of low SMM in the presence of weight loss six months prior to diagnosis, sex, and body mass index. Patients with low SMM were more likely to be female (35.3% versus 4.3%; $\chi^2 = 8.26$; p = 0.002), more likely to have experienced weight loss in the six months prior to diagnosis (50.0% versus 17.4%; MH $\chi^2 = 9.32$; p = 0.01) and were less likely to be overweight (BMI 25-29.9) (16.2% versus 39.1%; MH $\chi 2 = 45.88$; p < 0.001) or obese (BMI ≥ 30) (2.9% versus 52.2%; MH $\chi 2 = 45.88$; p < 0.001).

Table 1. General characteristics of the study population according to presence or absence of low SMM

	Low SMM	**Without low SMM**	
n	**68 (74.7%)**	**23 (25.3%)**	
	***n*(%) or mean(±SD)**	***n*(%) or mean(±SD)**	**p-value[a]**
Gender			
Female	24 (35.3%)	1 (4.3%)	**0.002****
Male	44 (64.7%)	22 (95.7%)	
Age at diagnosis	62.18 (±7.22)	63.33 (±7.78)	0.52
Weight loss 6 months prior			
None	34 (50.0%)	19 (82.6%)	**0.008***
≤ 10%	17 (25.0%)	4 (17.4%)	
> 10%	17 (25.0%)	0 (0.0%)	
Body Mass Index (kg/m²)			
< 20	29 (42.6%)	0 (0%)	**<0.001****
20-24.9	26 (38.2%)	2 (8.7%)	
25-29.9	11 (16.2%)	9 (39.1%)	
≥ 30	2 (2.9%)	12 (52.2%)	
Smoking status			
Non-smoker	2 (2.9%)	3 (13.0%)	0.19
Former-Smoker	23 (33.8%)	8 (34.8%)	
Smoker	43 (63.2%)	12 (52.2%)	
Pack-Years			
0	2 (3.4%)	3 (14.3%)	0.62
1-15	8 (13.6%)	2 (9.5%)	
16-25	9 (15.3%)	5 (23.8%)	
26-40	17 (28.8%)	6 (28.6%)	
≥ 41	23 (39.0%)	5 (23.8%)	
Alcohol use			
No	5 (8.5%)	5 (15.6%)	0.21
Former	11 (18.6%)	2 6.3%)	
Yes	43 (72.9%)	25 (78.1%)	
Alcohol(U/day)	4.25 (±4.19)	2.38 (±1.69)	0.05

Table 1. (Continued)

	Low SMM	Without low SMM	
n	**68 (74.7%)**	**23 (25.3%)**	
	***n*(%) or mean(±SD)**	***n*(%) or mean(±SD)**	**p-value[a]**
Alcohol abuse			
No	40 (58.8%)	17 (73.9%)	0.44
Yes, current	6 (8.8%)	1 (4.3%)	
Yes, former	22 (81.5%)	5 (21.7%)	
ACE-27 Score[b]			
None	6 (8.8%)	2 (8.7%)	1.0
Mild	17 (25.0%)	6 (26.1%)	
Moderate	25 (36.8%)	8 (34.8%)	
Severe	20 (29.4%)	7 (30.4%)	
Tumor Site			
Oropharynx	48 (70.6%)	17 (73.9%)	0.73
Hypopharynx	8 (11.8%)	1 (4.3%)	
Larynx	2 (2.9%)	2 (8.7%)	
Other	10 (14.7%)	3 (13.1%)	
TNM-stage			
Stage 1	1 (1.5%)	0 (0.0%)	0.62
Stage 2	2 (2.9%)	1 (4.3%)	
Stage 3	8 (11.8%)	5 (21.7%)	
Stage 4	57 (83.8%)	17 (73.9%)	
Surgery			
No	64 (94.1%)	22 (95.7%)	0.63
Yes	4 (5.9%)	1 (4.3%)	
Recurrence			
No	46 (67.6%)	20 (87.0%)	0.06
Yes	22 (32.4%)	3 (13.0%)	
Synchronous tumor			
No	56 (82.4%)	20 (87.0%)	0.75
Yes	12 (17.6%)	3(13.0%)	
HPV status[c]			
Negative	44 (64.7%)	12 (52.2%)	0.21
Positive	7 (10.3%)	6 (26.1%)	
Missing	17 (25.0%)	5 (21.7%)	

a Chi-square test or Independent sample t-test, b ACE-27 = Adult Comorbidity Evaluation
c HPV = Human Papillomavirus, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

UNIVARIATE AND MULTIVARIATE ANALYSIS

Table 2 shows the univariate and multivariate logistic regression analysis for the association with cetuximab DLT. In the univariate analysis, weight loss six months prior to diagnosis and ACE-27 score had statistically significant predictive value for cetuximab DLT. Low SMM did not show significant predictive value for cetuximab DLT (OR = 0.60; 95%CI 0.22-1.63; p = 0.31). The

multivariate Cox regression analysis for the association with cetuximab DLT included weight loss, ACE- 27 score, and low SMM. These variables were chosen because of their clinical significance or statistical significance in the univariate analysis. Both weight loss six months prior to diagnosis and ACE-27 score showed statistically significant predictive value for cetuximab DLT in this multivariate analysis. Low SMM remained non-significant in multivariate analysis (OR 0.83; 95% CI 0.27-2.56; p = 0.74).

Table 2. Univariate and multivariate analysis of predictive factors for cetuximab dose-limiting toxicity

Variable	Cetuximab dose-limiting toxicity					
	Univariate analysis[a]			Multivariate analysis[b]		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender	0.44	0.17-1.18	0.1			
Age	1.02	0.96-1.08	0.55			
Weight loss 6 months prior						
None	Ref.			Ref.		
≤ 10%	0.24	0.06–0.90	**0.03***	0.20	0.05-0.87	**0.03***
> 10%	0.30	0.08-1.18	0.09	0.31	0.07-1.41	0.13
Body Mass Index (kg/m²)						
20-24.9	Ref.					
< 20	1.35	0.44-4.32	0.61			
25-29.9	2.50	0.72-8.38	0.15			
≥ 30	0.82	0.18-3.80	0.80			
Smoking status						
Non-smoker	Ref.					
Smoker	0.56	0.09-3.71	0.56			
Former-Smoker	0.83	0.12-5.71	0.85			
Alcohol use						
No	Ref.					
Yes	1.04	0.25-4.43	1.0			
Former	1.04	0.17-6.23	1.0			
Alcohol(U/day)	0.93	0.80-1.07	0.3			
ACE-27 score [c]						
None	Ref.			Ref.		
Mild	0.19	0.02-0.75	**0.02***	0.09	0.01-0.67	**0.02***
Moderate	0.13	0.02-0.74	**0.02***	0.09	0.01-0.64	**0.02***
Severe	0.12	0.02-0.72	**0.02***	0.10	0.02-0.74	**0.02***
HPV-status [d]	0.90	0.22-3.74	0.89			
Low SMM	0.60	0.22-1.63	0.32	0.83	0.27-2.56	0.74

a Logistic regression analysis, b Multivariate logistic regression (Backward Wald model, c ACE-27 = Adult Comorbidity Evaluation, d HPV = Human Papillomavirus, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

Table 3 shows the univariate and multivariate Cox regression analysis for the association with OS. The univariate analysis showed that weight loss six months prior to diagnosis, HPV status,

alcohol units per day, and low SMM are statistically significant prognostic factors for OS. These statistically significant prognostic factors of the univariate analysis were used in the multivariate analysis. BMI was close to statistically significant (HR 0.43; 95% CI 0.18-1.01; p = 0.05), therefore, BMI was added into the multivariate analysis. With weight loss, BMI, HPV status, alcohol units per day, and low SMM entered into the multivariate analysis, the two statistically significant prognostic factors were weight loss of more than 10% prior to diagnosis (HR 3.66; 95%CI 1.66-8.09; p = 0.001) and positive HPV status (HR 0.24; 95%CI 0.07-0.85; p = 0.03). Low SMM showed no statistically significant prognostic value in the multivariate analysis (HR 1.48; 95% CI 0.48-4.58; p = 0.50).

Table 3. Univariate and multivariate analysis of prognostic factors for overall survival

Variable	Overall Survival					
	Univariate analysis [a]			Multivariate analysis [b]		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender	0.10	0.88-3.20	0.11			
Age	0.97	0.94-1.01	0.14			
Weight loss 6 months prior						
None	Ref.			Ref.		
≤ 10%	1.68	0.87-3.24	0.12	1.60	0.78-3.27	0.20
> 10%	3.41	1.79-6.50	**0.001****	3.66	1.66-8.09	**0.001****
Body Mass Index (kg/m²)						
20-24.9	Ref.			Ref.		
< 20	1.56	0.85-2.88	0.15	0.96	0.49-1.98	0.96
25-29.9	0.43	0.18-1.01	0.05	0.70	0.34-2.06	0.70
≥ 30	0.59	0.24-1.49	0.27	0.70	0.31-5.63	0.70
Smoking status						
Non-smoker	Ref.					
Smoker	6.59	0.90-48.41	0.06			
Former-Smoker	2.78	0.36-21.32	0.33			
Alcohol(U/day)	1.08	1.02	**0.013***	1.04	0.97-1.11	0.30
ACE-27 score [c]						
None	Ref.					
Mild	1.78	0.5-6.39	0.38			
Moderate	2.74	0.82-9.19	0.10			
Severe	2.32	0.66-8.18	0.19			
TNM-stage						
Stage 1	Ref.					
Stage 2	0.60	0.05-6.73	0.70			
Stage 3	0.42	0.05-3.62	0.43			
Stage 4	0.99	0.14-7.20	0.99			
HPV status [d]	0.14	0.03-0.58	**0.007****	0.24	0.07-0.85	**0.03***
Low SMM	2.45	1.16-5.19	**0.019***	1.48	0.48-4.58	0.50

a Cox regression analysis, b Multivariate cox regression (Backward Wald model), c ACE-27 = Adult Comorbidity Evaluation, d HPV = Human Papillomavirus, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

Table 4 shows the univariate and multivariate Cox regression analysis for the association with DFS. The univariate analysis showed that none of the clinically relevant variables had significant prognostic value for DFS. However, BMI (HR 0.22; 95% CI 0.05-1.00; p = 0.05) and weight loss six months prior to diagnosis (HR 2.56; 95% CI 0.99-6.57; p = 0.05) did demonstrate a p-value close to statistically significant. Low SMM, BMI, and weight loss six months prior to diagnosis were entered into the multivariate analysis. In the multivariate analysis, none of the entered variables demonstrated a statistically significant prognostic value for DFS.

Table 4. Univariate and multivariate analysis of prognostic factors for disease-free survival

Variable	Disease-free survival					
	Univariate analysis[a]			Multivariate analysis[b]		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender	1.39	0.55-3.48	0.49			
Age	0.98	0.93-1.03	0.39			
Weight loss 6 months prior						
None	Ref.			Ref.		
≤ 10%	1.537	0.58-4.10	0.39	1.49	0.55-4.08	0.43
> 10%	2.556	0.99-6.57	0.05	2.04	0.72-5.78	0.18
Body Mass Index (kg/m²)						
20-24.9	Ref.					
< 20	0.90	0.36-2.26	0.83	0.74	0.28-1.94	0.54
25-29.9	0.22	0.05-1.00	0.05	0.31	0.07-1.44	0.14
≥ 30	0.75	0.24-2.36	0.62	2.21	0.47-10.57	0.32
ACE-27 score [c]						
None	Ref.					
Mild	0.95	0.19-4.71	0.95			
Moderate	1.12	0.24-5.22	0.88			
Severe	1.15	0.24-5.46	0.86			
TNM-stage						
Stage 1	Ref.					
Stage 2	0.45	0.03-7.16	0.57			
Stage 3	0.18	0.02-2.01	0.16			
Stage 4	0.45	0.06-3.35	0.43			
HPV status [d]	0.39	0.07-1.28	0.10			
Low SMM	2.42	0.72-8.11	0.15	3.79	0.71-20.12	0.12

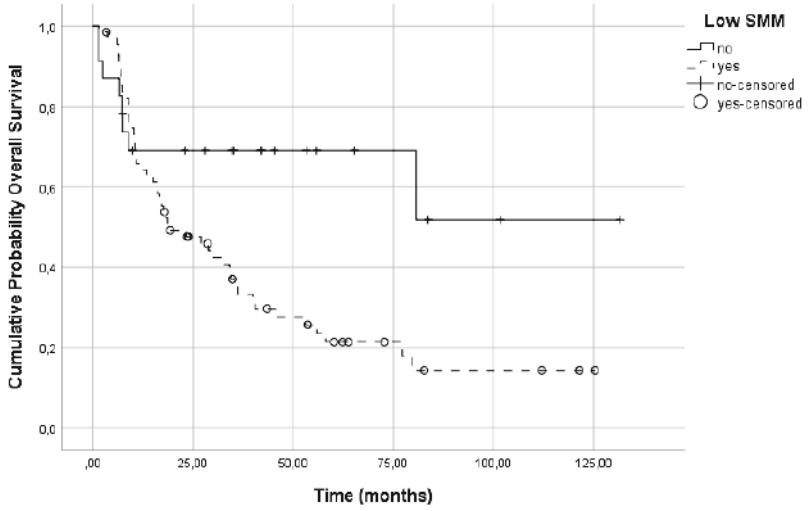
a Cox regression analysis, b Multivariate cox regression (Backward Wald model), c ACE-27 = Adult Comorbidity Evaluation, d HPV = Human Papillomavirus, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL

Figures 3 and 4 show the Kaplan Meier Survival curves and number at risk tables for patients with and without low SMM. As can be seen in figure 3, patients with low SMM have a lower median OS (18.48 months; IQR 9.04-40.26) compared to patients without low SMM (34.66

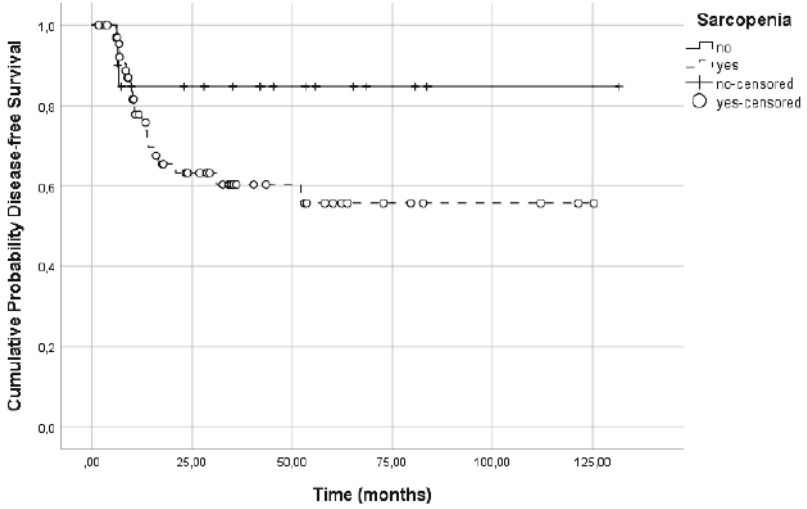
months; IQR 7.39-55.85) (Log Rank $\chi^2 = 5.87$; p = 0.02). As shown in **figure 4**, patients with low SMM did not show a significantly different mean DFS rate (14.83 months; IQR 8.80-35.17) compared to patients without low SMM (28.02 months; IQR 6.51-55.85) (Log Rank $\chi^2 = 2.19$; p = 0.14).

Figure 3. Kaplan Meier curve and number at risk table for patients with and without low SMM for overall survival (Log Rank χ2 = 5.8730; p = 0.015)



	T = 0	T = 12	T = 24	T = 36	T = 48	T = 60
With low SMM	68	43	28	19	14	10
Without low SMM	23	14	13	10	7	5

Figure 4. Kaplan Meier curve and number at risk table for patients with and without low SMM for disease-free survival (Log Rank $\chi 2 = 2.191$; $p = 0.139$)



	T = 0	T = 12	T = 24	T = 36	T = 48	T = 60
With low SMM	68	39	26	16	13	9
Without low SMM	23	13	12	10	7	5

DISCUSSION

This study demonstrated that low SMM has a high prevalence in HNSCC patients with 74.7% of the patients included in this study. Additionally, roughly a third of the patients (30.8%) experienced cetuximab DLT. This study showed that weight loss of more than 10% in the six months prior to diagnosis as well as comorbidities as measured by the ACE-27 have predictive value for cetuximab DLT. However, no significant predictive value of low SMM was observed for cetuximab DLT in HNSCC patients treated with cetuximab and radiotherapy. Furthermore, this study shows that low SMM may be of prognostic value in these patients for overall survival.

The most commonly used method for the measurement of SMM in cancer patients is based on measurement of the CSA of skeletal muscles on a single transversal slice at the level of the third lumbar vertebra (L3).[6] Swartz et al. found a correlation between the CSA of skeletal muscles at C3 and L3 ($r = 0.785$).[6] Using a multivariate prediction equation, the correlation between measured the CSA at L3 and estimated CSA at L3 from C3 was even stronger ($r = 0.895$). Therefore, the CSA of skeletal muscles at the level of C3 can be used as an alternative to that of L3 to assess total SMM in patients who only received imaging of the head and neck area.[10] Moreover, an excellent inter-observer agreement for measurement of skeletal muscle CSA was found.[7] Additionally, a recent study demonstrated a strong correlation ($r^2 = 0.94$, $p < 0.01$) between

the measurement of CSA on CT imaging and MRI imaging.[8] Measurement of skeletal muscle CSA at the level of L3 can, therefore, be assessed using skeletal muscle CSA measurement at the level of C3 on CT or MRI.

Several studies show that low SMM is a prognostic factor in HNSCC patients.[16–18] In the present study, low SMM showed no significant prognostic value in the multivariate cox regression analysis. The populations in studies showing low SMM as prognostic factor consisted of elderly[16], cisplatin fit[17] and advanced stage disease patients[18]. Some reasons for this difference in prognostic value of the present study with highly selected patients compared to other studies can be hypothesized. First, this study consists of a limited number of patients. Secondly, these patients were unfit for cisplatin-based chemotherapy, mainly because of comorbidity which can affect overall survival as well. The poor condition of these selected patients is illustrated by the very high prevalence of low SMM. Finally, in our study only patients with locoregional advanced stage disease with generally already a poor prognosis were included.

This is the first study on the predictive value of low SMM for cetuximab DLT in HNSCC patients. There is only one study that previously looked at the predictive value of low SMM for DLT in cancer patients treated with cetuximab.[10] In this study, Barret et al. showed that in metastatic colorectal cancer patients treated with cetuximab low SMM was a significant predictive factor for grade 3-4 toxicity. This is in contradiction with our results, which show that low SMM is not a predictive factor for cetuximab DLT. However, the patients in the study by Barret *et al.* received cetuximab in combination with another chemotherapeutic agent, most commonly oxaliplatin. This makes it difficult to determine whether the predictive value of low SMM applies to cetuximab treatment or the chemotherapeutic treatment it was combined with. Both studies differ substantially in patient, tumor and treatment characteristics. In our study patients received concomitant radiotherapy which may also affect toxicity. Patients in the colorectal cancer study had metastatic disease and patients in our head and neck cancer study were unfit for cisplatin chemotherapy. These differences could be responsible for the fact that Barret *et al*., contrary to our study, concluded that low SMM was a predictive factor for DLT.[10] There are several hypotheses explaining the influence of low SMM on the occurrence of chemotherapy toxicity. Some hypothesize that the altered fat-to-lean body composition may influence the pharmacokinetics of chemotherapeuticals.[19] In HNSCC patients, low SMM appears to be independently associated with frailty[20], which describes a general state of increased vulnerability to stressors, such as cancer and anticancer treatment, and a higher risk of adverse events.[13,19,20] However, the hypothesis most supported in literature is based on the influence of low SMM on the drug distribution. The body is comprised of two major compartments, fat mass (FM) and lean body mass (LBM). Distribution of hydrophilic drugs, e.g., cisplatin, occurs mostly in the LBM, of which muscle mass is a large contributor.[19,21] Therefore, a decrease in LBM due to low SMM may result in increased plasma levels and thereby increased risk of toxicity.[17,19,21–23]Low SMM has been demonstrated to have different predictive value for a variety of chemotherapeutical agents. This difference in predictive value could be explained by the mechanism of action by which low SMM causes an increased risk for toxicity. Platinum-based chemotherapies, such

as cisplatin, carboplatin, and oxaliplatin, mostly distribute to the LBM and are therefore affected by the decrease in LBM in patients with low SMM.[3] Although cetuximab is also hydrophilic it has a very high molecular weight, and therefore, cetuximab distributes less towards the LBM and is mostly present in the plasma levels.[24] In the case of a patient with low SMM, it is possible that the decrease in LBM will not affect the plasma levels of cetuximab and therefore not increase the risk of toxicity. To be able to confirm this hypothesis additional research is needed. Currently, it is unknown what the underlying pathophysiology of decreased SMM is, although there is a range of theories. Firstly, it is hypothesized that age plays an important role in the mechanism of sarcopenia and decreasing SMM. This could be explained by the decrease of physical activity, the decrease of food intake, or the hormonal changes which are associated with aging.[25] Secondly, intracellular oxidative stress is speculated to be of influence on the occurrence of sarcopenia, specifically the increased concentration of inflammatory cytokines.[12,25] Lastly, there are theories about genetic components that could cause a decrease in SMM or muscle function.[25] Additional research into the mechanisms causing loss of muscle mass could progress the strategies for improving muscle mass and function, thereby improving overall survival. Further knowledge regarding drug distribution of chemotherapeutic agents could provide a better understanding of the process by which low SMM could cause an increased risk of toxicity. If there is a link between the distribution of a drug and the predictive value of low SMM for DLT, it would be possible to select a chemotherapeutic agent with less distribution towards the LBM or adapt the dose for patients with low SMM. This could result in less toxicity for patients with low SMM, however, it should not reduce the efficacy of the treatment. In order to ensure that efficacy is not reduced further research is required. To accurately determine whether patients with low SMM would profit more from treatment with cetuximab as opposed to cisplatin, a randomized controlled trial with endpoints toxicity and survival would be required.

CONCLUSION

In conclusion, in contrast with cisplatin dose-limiting toxicity, low SMM has no predictive value for cetuximab dose-limiting toxicity in HNSCC patients treated with cetuximab and radiotherapy, probably attributable to the difference in lean body mass distribution of these chemotherapeutical agents. This study showed no significant prognostic value of low SMM for overall survival in HNSCC patients treated with cetuximab and radiotherapy unfit for platin-based chemotherapy.

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CHAPTER 13

The predictive value of low skeletal muscle mass assessed on cross-sectional imaging for anti-cancer drug toxicity: a systematic review and meta-analysis

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ABSTRACT

Background

Low skeletal muscle mass (SMM) is increasingly recognized for its predictive value for adverse events in cancer patients. In specific, the predictive value of low SMM has been demonstrated for anti-cancer drug toxicity in a variety of cancer types and anti-cancer drugs. However, due to the limited sample size and study populations focused on a single cancer type, an overall predictive value of low SMM for anti-cancer drug toxicity remains unknown. Therefore, this review aims to provide a comprehensive overview of the predictive value of low SMM and perform a meta-analysis to analyse the overall effect.

Material and methods

A systematic search was conducted of MEDLINE, Scopus, EMBASE, and Cochrane. Inclusion criteria were skeletal muscle mass (SMM) evaluated with computed tomography (CT) or magnetic resonance imaging (MRI), articles published in English, SMM studied in humans, SMM measurement normalized for height, and patients did not receive an intervention to treat or prevent low SMM. A meta-analysis was performed using a random-effects model and expressed in odds ratio (OR) with 95% confidence interval (CI). Heterogeneity was assessed using $\chi 2$ and I2 statistics.

Results

The search yielded 907 studies. 31 studies were included in the systematic review. Sample sizes ranged from 21 to 414 patients. The occurrence of low SMM ranged from 12.2% to 89.0%. The most frequently studied cancer types were oesophageal, renal, colorectal, breast, and head and neck cancer. Patients with low SMM had a higher risk of severe toxicity (OR 4.08; 95% CI 2.48–6.70; $p < 0.001$) and dose-limiting toxicity (OR 2.24; 95% CI 1.28–3.92; $p < 0.001$) compared to patients without low SMM.

Conclusion

To conclude, the predictive value of low SMM for anti-cancer drug toxicity can be observed across cancer types. This information increases the need for further research into interventions that could treat low SMM as well as the possibility to adapt treatment regimens based on the presence of low SMM.

INTRODUCTION

There is a high prevalence of low skeletal muscle mass (SMM), sometimes referred to as sarcopenia, in cancer patients. Moreover, in advanced stages of cancer, the majority of patients exhibit low SMM.[1,2] A large number of studies has been performed to investigate the predictive value of low SMM. Especially, the association between low SMM and survival has been thoroughly investigated.[2–4] This prognostic value of low SMM has been demonstrated in a variety of cancer types including lung[3], colorectal[5], breast[6], renal[7], and head and neck cancer[8]. Low SMM has also been investigated as a predictive factor for adverse events such as chemotherapy toxicity, surgical complications, and radiotherapy toxicity.[5–7,9,10]

There are several techniques for the measurement of skeletal muscle mass (SMM). This includes dual-energy X-ray absorptiometry (DXA), which uses x-rays that will reduce in energy based on the composition and thickness of the material that it passes through, and bioelectric impedance analysis (BIA), which measures body composition using an electrical current that experiences more resistance through adipose tissue as opposed to electrolyte-rich fluids.[7,11] The most commonly used technique utilizes computed tomography (CT) as it is part of routine care in the majority of cancer patients, and it has a proven high accuracy in measuring SMM.[3,8,12] Most studies quantify SMM using CT scans of the third lumbar (L3) vertebrae, although other levels have also been used. The cross-sectional area (CSA) of skeletal muscle mass is measured on a single cross-sectional image and normalized for height resulting in the skeletal muscle mass index (SMI). The SMI correlates strongly with total-body skeletal muscle mass.[12,13] Recently, magnetic resonance imaging (MRI) has been proven to have a strong correlation (r^2=0.94, $p<0.01$) with CT for the measurement of the CSA of SMM.[14]

Although the predictive value of low SMM has been investigated frequently, the underlying mechanism is only hypothesized. There are theories about the underlying pathophysiology of low SMM such as the influence of age, intracellular oxidative stress, and genetic components.[3,15] In cancer patients, there is also a high possibility of developing cachexia which could also result in low SMM.[3,15] There are several theories for the mechanism by which low SMM influences toxicity. Some theorize that the altered ratio of fat-to-lean body mass can influence the pharmacokinetics of anti-cancer drugs.[11] Others theorize that low SMM is independently associated with frailty, which can result in a higher risk of adverse events.[4,11,16] The most commonly supported hypothesis is based on the influence of low SMM on drug distribution. The body consists of two major compartments, fat mass (FM) and lean body mass (LBM); drugs can be inclined to distribute towards one of these compartments. Patients with low SMM have a decreased LBM and, as muscle mass is the largest contributor to LBM, this may result in increased drug levels in the plasma and thereby a higher risk of toxicity.[6,8,11,17]

Although there have been many studies devoted to the predictive value of low SMM for anti-cancer drug toxicity, these studies have several limitations, such as small sample sizes. Additionally, the majority of studies focus on a single cancer type or disease stage which limits

its ability to draw conclusions for a large population of cancer patients[4,5,7] To conclude whether this predictive value of low SMM is present across cancer types and treatments, studies have to be performed in a larger and wider population.

This systematic review aims to provide a comprehensive overview of the literature and data regarding the predictive value of low SMM for anti-cancer drug toxicity and analyze the overall effect in a meta-analysis. Specifically, this review will investigate whether this predictive value is universal across cancer types. Additionally, this review will study if there is a relationship between drug distribution and the predictive value of low SMM for anti-cancer drug toxicity.

METHODS

SEARCH STRATEGY

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.[18] A systematic search was performed in four electronic databases, which are MEDLINE, EMBASE, Cochrane, and Scopus, from inception through 17 February 2020. The search terms included toxicity, sarcopenia, chemotherapy, cancer, and synonyms for each of these terms detailed in Appendix A. The references of each included article were also screened to identify additional records.

STUDY SELECTION

The studies obtained from the systematic search were assessed by screening titles and abstracts, by a single researcher (L.F.J.H.) Subsequently, the potentially included articles were assessed using the full text. Studies were included in the analysis when they met the following inclusion criteria: (1) examine the association of low SMM and anti-cancer drug toxicity, (2) evaluate skeletal muscle mass by measuring cross-sectional area on CT or MRI, (3) are published in English, and (4) describe studies in humans only. Studies were excluded from the analysis when they met the following exclusion criteria: (1) do not normalize SMM for height; (2) are a systematic review, conference paper, or study protocol; or (3) only describe an intervention and its effects on SMM or toxicity.

DATA EXTRACTION

The data were extracted and collected from each included study. This consisted of (1) author and publication year, (2) population size and cancer type, (3) occurrence and definition of low SMM, (4) technique used for the evaluation of SMM (such as scan type, software for image analysis, and vertebrae level analyzed), (5) treatment specifications (anti-cancer drug, curative or palliative intent, primary or adjuvant, and combination with radiotherapy), (6) time between scan and treatment, (7) measure and occurrence of toxicity. Only published data was included.

ASSESSMENT OF RISK OF BIAS

The risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool.[19] The QUIPS tool assesses the risk of bias based on six domains each with multiple sub-domains. Each sub-domain is rated with "yes", "no", "partial", or "unsure" after which each domain is rated low, moderate, or high based on the ratings of the sub-domains. The six domains are (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting.[19] A study was scored as low risk of bias when at least four domains were rated as low, and a maximum of two domains was rated moderate (of which prognostic factor measurement and outcome measurement must be rated low), with no domains rated as high. A study was scored as high risk of bias if more than two domains were rated high, or four domains were rated moderate. All remaining studies were scored as a moderate risk of bias.

DATA ANALYSIS

A meta-analysis was performed using Review Manager (Revman v5.3, The Nordic Cochrane Collaboration, Copenhagen, Denmark, 2014). A random-effects model was used because of the assumed heterogeneity between the studies. Studies were excluded from the meta-analysis if (1) there was insufficient data to calculate an odds ratio (OR); (2) low SMM was not defined with a cut-off value, and SMI was instead used as a continuous variable; or (3) the endpoint for toxicity did not match any other studies, hampering combination with other studies for meta-analysis.

The results were visualized using forest plots expressed in OR with 95% confidence interval (CI). The results were stratified for toxicity definition, namely, toxicity ≥ grade 3 according to Common Terminology Criteria for Adverse Events (CTCAE) and dose-limiting toxicity (DLT). Further stratification was based on cut-off values, measurement technique, and vertebrae level analysed. Heterogeneity was assessed with the $\chi 2$ and I2 statistic tests. I2 values between 25% and 50% were considered to demonstrate low heterogeneity, 50% to 75% demonstrates moderate heterogeneity, and >75% was considered to demonstrate high heterogeneity. Subgroup analysis was performed for any monotherapy which was used in the populations of more than one study. p-values < 0.05 were considered statistically significant.

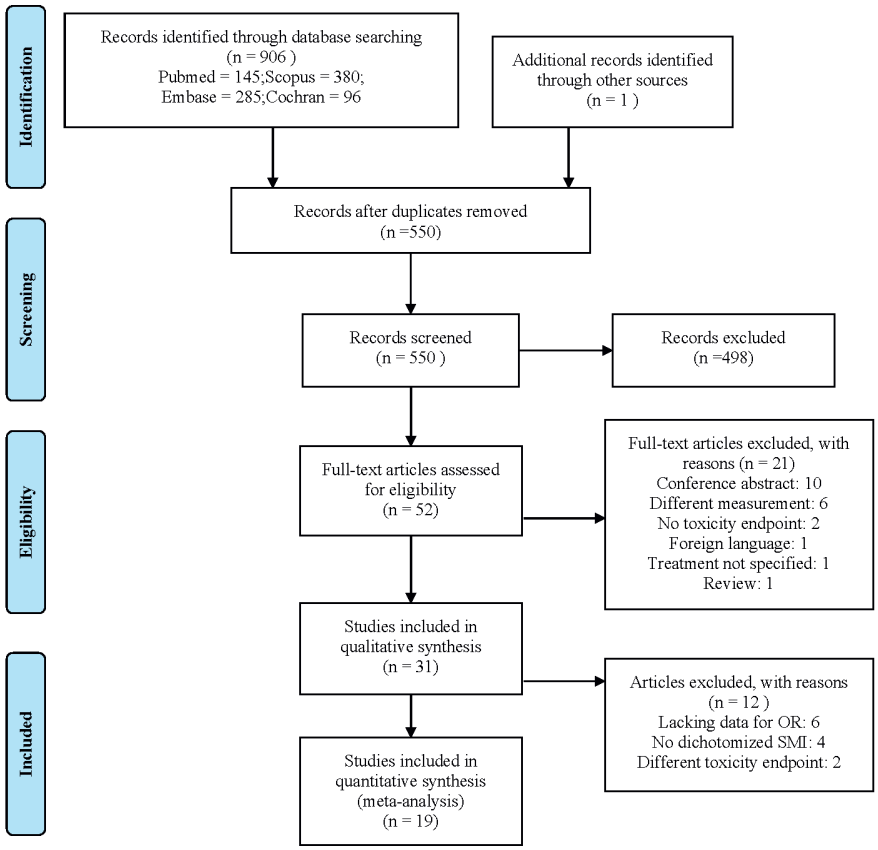
RESULTS

SEARCH RESULTS

The search yielded 906 hits. One additional study was included after the screening of all included articles reference lists. After the removal of 357 duplicates, the titles and abstracts of 550 studies were screened. The screening of abstracts and titles yielded 52 studies for full-text screening. After the full-text screening, 31 met all inclusion criteria and were included in this review.[5–8,16,20–45] The selection process with exclusion reasons is shown in Figure 1. A total of 19 studies were included in the meta-analysis. Studies were excluded from the meta-analysis because the study did not

include sufficient data to calculate odds ratios (n = 6),[22,26,32,37,39,41] did not dichotomize low SMM (n = 4),[28,29,34,36] or featured a toxicity endpoint that did not match with any other studies (n = 2).[6,38]

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flowchart detailing the study selection process.



STUDY CHARACTERISTICS

Table 1 shows the characteristics of the included studies. Samples sizes ranged from 21 to 414 patients with a total sample size of 2918 patients. The study populations existed of patients with a variety of cancer types. The most frequent were esophageal, renal, colorectal, breast, and head and neck cancer. The occurrence of low SMM ranged from 12.2% to 89.0%. The endpoint used to measure toxicity varied between studies. Most studies used DLT, defined as toxicity leading to dose reduction, treatment delay, or treatment discontinuation. Another common measurement of toxicity was according to the CTCAE grading system. The occurrence of toxicity ranged from 21.8% to 77.4%. Supplementary Table S1 shows additional information regarding the treatment specificities of the included studies, such as treatment intent, primary or adjuvant treatment, and the addition of radiotherapy.

Table 1. Characteristics of included studies

Author and Date	*n*	Type of Cancer	Measure low SMM	Occurrence low SMM *n* (%) or Mean (SD)	Location Analyzed	Anti-Cancer Drug	Measure of Toxicity	Occurrence Toxicity *n* (%)
Anandavadivelan et al. 2016 [41]	72	Oesophageal	1	31 (43.0%)	CT-L3	Cisplatin + 5-FU	DLT [a]	Not given
Antoun et al. 2010 [42]	55	Renal cell	1	30 (54.5%)	CT-L3	Sorafenib	DLT [a]	12 (21.8%)
Barret et al. 2014 [5]	51	Metastatic colorectal	1	36 (70.6%)	CT-L3	FP with/without oxaliplatin or irinotecan with/without cetuximab	≥grade 3 toxicity	14 (27.5%)
Chemama et al. 2016 [43]	97	Peritoneal carcinomatosis and colorectal	2	39 (40.0%)	CT-L3	HIPEC oxaliplatin + irinotecan	≥grade 3 toxicity	33 (39.0%)
Cushen et al. 2016 [44]	63	Metastatic castrate resistant prostate	2	30 (47.6%)	CT-L3	Docetaxel-based	DLT [a]	22 (34.9%)
Cushen et al. 2017 [45]	55	Clear cell renal cell	3	13 (23.6%)	CT-L3	Sunitinib	DLT [a]	40 (73.0%)
Daly et al. 2017 [21]	84	Metastatic melanoma	2	20 (23.8%)	CT-L3	Ipilimumab	≥grade 3 toxicity	35 (41.7%)
Da Rocha et al. 2019 [20]	60	Gastro-intestinal	2	14 (23.3%)	CT-L3	5-FU+ leucovorin, FOLFOX, or paclitaxel + carboplatin	DLT [a] during first cycle	14 (23.3%)
Dijksterhuis et al. 2019 [22]	88	Esophago-gastric	2	43 (48.9%)	CT-L3	CAPOX	≥grade 3 toxicity during first cycle	32 (36.4%)
Freckelton et al. 2019 [23]	52	Metastatic pancreatic ductal adenocarcinoma	1	30 (57.7%)	CT-L3	Gemcitabine + nab-paclitaxel	≥grade 3 toxicity during first cycle	14 (27.0%)
Ganju et al. 2019 [24]	246	Head and neck	2	143 (58.0%)	CT-C3	Cisplatin, cetuximab, or carboplatin	DLT [a]	91 (37.0%)
Huillard et al. 2013 [7]	61	Metastatic renal cell	1	32 (52.5%)	CT-L3	Sunitinib	DLT [a] during first cycle	18 (29.5%)
Huiskamp et al. 2020 [25]	91	Head and neck	≤45.2 cm^2/m^2	68 (74.7%)	CT-C3 MRI-C3	Cetuximab	DLT [a]	28 (30.8%)
Kobayashi et al. 2019 [26]	23	Inoperable soft tissue sarcoma	<39 cm^2/m^2	11 (47.8%)	CT-L3	Eribulin	≥grade 3 toxicity	16 (69.6%)
Kurk et al. 2019 [27]	414	Metastatic colorectal	2	198 (47.8%)	CT-L3	CAPOX-B or CAP-B	DLT [a]	130 (56.0%) 111 (61.0%)[b]
Looijaard et al. 2019 [28]	53	Colorectal	Continuous SMI	46.3 (8.9)	CT-L3	Capecitabine, CAPOX, 5-FU+leucovorin, or FOLFOX	DLT [a]	41 (77.4%)
Mazzuca et al. 2018 [29]	21	Stage 1–3 breastcancer	≤38.5 cm^2/m^2	8 (38.1%)	CT-L3	A combination of 2–3: adriamycin, paclitaxel, docetaxel, epirubicin, trastuzumab, 5-FU, or cyclophosphamide	≥grade 3 toxicity	Not given

Table 1. (Continued)

Author and Date	*n*	Type of Cancer	Measure low SMM	Occurrence low SMM *n* (%) or Mean (SD)	Location Analyzed	Anti-Cancer Drug	Measure of Toxicity	Occurrence Toxicity *n* (%)
Palmela et al. 2017 [30]	47	Stomach or gastroesophageal junction	2	11 (23%)	CT-L3	A combination of 2–3: epirubicin, cisplatin, 5-FU, oxaliplatin, docetaxel, leucovorin, or capecitabine	DLT [a]	21 (44.7%)
Panje et al. 2019 [31]	61	Locally advanced esophageal	2	18 (29.5%)	CT-L3	Docetaxel + cisplatin with/ without cetuximab	≥grade 3 toxicity	37 (60.7%)
Parsons et al. 2012 [16]	48	Liver metastasis	1	20 (42.0%)	CT-L3	HAI oxaliplatin + leucovorin + 5-FU + bevacizumab	≥grade 3 toxicity	Not given
Prado et al. 2009 [6]	55	Metastatic breastcancer	1	14 (25.5%)	CT-L3	Capecitabine	≥grade 2 toxicity	15 (27.3%)
Sawada et al. 2019 [33]	82	Hepatocellular	4	16 (19.5%)	CT-L3	Sorafenib	DLT [a]	27 (32.9%)
Sealy et al. 2020 [34]	213	Head and neck cancer	Continuous SMI	L3: 51.62 (10.16) T4: 65.53 (12.60)	CT-L3 or CT-T4	Cisplatin or carboplatin	DLT [a]	61 (29.0%)
Shachar et al. 2017a [35]	40	Metastatic breast	≤41 cm^2/m^2	23 (58%)	CT-L3	Paclitaxel, docetaxel, or nab-paclitaxel combined with trastuzumab, pertuzumab, or bevacizumab	DLT [a]	23 (58.0%)
Shachar et al. 2017b [36]	151	Early breast cancer	Continuous SMI	44.72 (6.86)	CT-L3	Adraimycin + cyclophosphamide	≥grade 3 toxicity	50 (33.1%)
Srdic et al. 2016 [37]	100	Non-small cell lung cancer	1	47 (47%)	CT-L3	Platinum based chemotherapy with gemcitabine, paclitaxel or etoposide	≥grade 2 toxicity during first cycle	57 (57.0%)
Staley et al. 2019 [38]	134	Epithelial ovarian	≤41 cm^2/m^2	73 (54.5%)	CT-L3	Platinum and taxan-based chemotherapy	Dose delay or reduction	51 (38.1%) 50 (37.3%)[c]
Sugiyama et al. 2018 [39]	118	Metastatic gastric	1	105 (89.0%)	CT-L3	FP with cisplatin or oxaliplatin	≥grade 3 toxicity	Not given
Tan et al. 2015 [16]	89	Esophago-gastric	1	44 (49.4%)	CT-L3	Cisplatin + 5-FU or epirubicin + cisplatin + capecitabine	DLT [a]	37 (41.6%)
Ueno et al. 2020 [40]	82	Breast cancer	5	10 (12.2%)	CT-L3	Epirubicin + cyclophosphamide	≥grade 3 laboratory toxicity	23 (28.0%)
Wendrich et al. 2017 [8]	112	Squamous cell head and neck cancer	≤43.2 cm^2/m^2	61 (54.5%)	CT- C3	Cisplatin or carboplatin	DLT [a]	34 (30.4%)

5-FU: 5-Fluorouracil; BMI: body mass index; CAP-B: capecitabine and bevacizumab; CAPOX: Capecitabine and oxaliplatin; CAPOX-B: Capecitabine, oxaliplatin, and bevacizumab; C3: cervical vertebrae 3; CT: computed tomography; FOLFOX: oxaliplatin, leucovorin, 5-fluorouracil; FP: fluoropyrimidine; HAI: hepatic arterial infusion; HIPEC: hyperthermic intraperitoneal chemotherapy; L3: Lumbar vertebrae 3; Low SMM: low skeletal muscle mass; MRI: magnetic resonance imaging; NS: not significant; SMI: skeletal muscle index (skeletal muscle area/height2); T4: thoracic vertebrae 4.

a. DLT (dose-limiting toxicity): toxicity leading to dose reduction, treatment delay, or discontinuation
b. Occurrence of DLT for CAPOX-B and CAP-B respectively
c. Occurrence of dose delay and dose reduction respectively

Definitions of low SMM

1. Prado et al. 2008 [46]: <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women
2. Martin et al. 2013 [47]: <43 cm^2/m^2 for men if BMI ≤24.9 kg/m^2 or <53cm^2/m2 for men if BMI >25kg/m^2 and <41 cm^2/m^2 for women[48]
3. 25th percentile < 44.8cm^2/m^2 vs 75th percentile >63.2cm^2/m^2
4. Fujiwara et al. 2015 [48] : ≤36.2 cm^2/m^2 for men and ≤29.6 cm^2/m^2 for women 5.Caan et al. 2018 [49]: <40 cm^2/m^2

SKELETAL MUSCLE MASS ASSESSMENT

There were several differences between the studies in the method used to measure SMM. All included studies used CT to evaluate SMM with one study also using MRI.[50] However, there was a difference in the selected vertebrae used for the SMM assessment as shown in Table 1. Most studies used lumbar level 3 (L3); other vertebrae that were used were cervical level 3 (C3) and thoracic level 4 (T4). Supplementary Table S1 shows other differences between studies such as the time between CT and treatment start, as well as the software used to measure SMM. The included studies also used different cut-off values for low SMM; this can be seen in Table 1. Most studies used cut-off values cited from previous articles. The most commonly used cut-off values were established by Prado et al., 2008 [46] (<52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women), followed by Martin et al., 2013 [47] (<43 cm^2/m^2 for men if body mass index (BMI) ≤ 24.9 kg/m^2 or <53 cm^2/m^2 for men if BMI > 25 kg/m^2 and <41 cm^2/m^2 for women), Fujiwara et al., 2015 [48] (≤36.2 cm^2/m^2 for men and ≤29.6 cm^2/m^2 for women), and Caan et al., 2018 [51] (<40 cm^2/m^2). It is noteworthy that five studies cited the cut-off values of Prado et al. [46] but used other cut-off values in their analysis than those published by Prado et al.[5,7,37,39] Four studies did not use cut-off values for low SMM and instead used continuous SMI during analysis.[28,29,34,36]

STUDY QUALITY ASSESSMENT

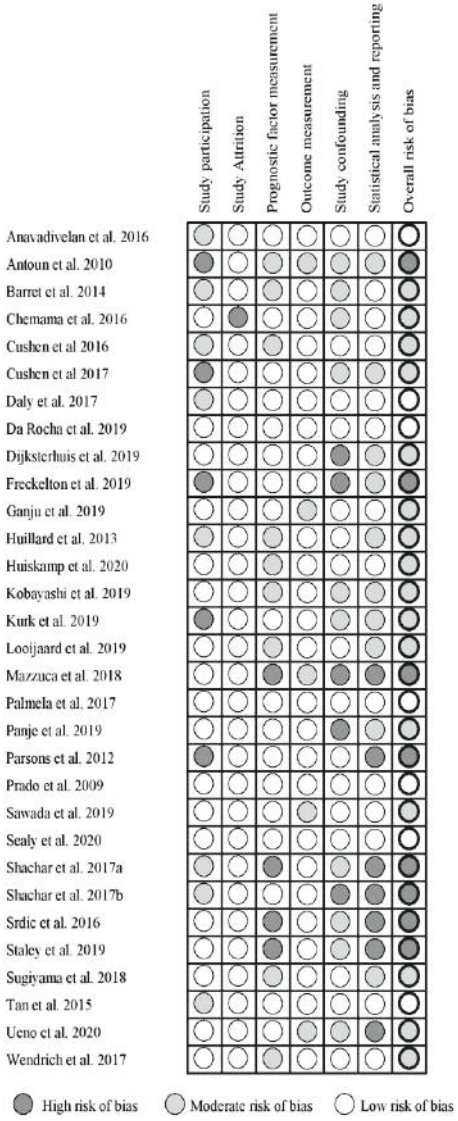
The results of the QUIPS assessment of all included studies are summarized in Figure 2. Out of the 31 included studies, seven studies had a low risk of bias,[6,16,20,21,30,34,41] 16 studies had a moderate risk of bias, [5,7,8,22,24,26,28,31,33,39,40,43–45,50,52] and eight had a high risk of.[23,29,31,36–38,42] The domains study participation, study confounding, and statistical analysis and reporting were most frequently assessed as having a high risk of bias. Whereas the domains study attrition, prognostic factor measurement, and outcome measurement were most frequently assessed as having a low risk of bias.

ASSOCIATION BETWEEN LOW SMM AND TOXICITY

Figure 3A shows the forest plot for the OR of 13 studies that used DLT as the measure of toxicity. Kurk et al., 2019 [27] performed two separate analyses in the same patient population receiving sequential treatments, 232 patients treated with Capox-B and 182 patients treated with Cap-B. These results were entered into the forest plot separately. Patients with low SMM had a significantly higher risk for DLT compared to patients without low SMM (OR 2.24; 95% CI 1.28–3.92, $p < 0.001$). Heterogeneity across studies was high ($\chi 2 = 60.97$ and $I2 = 79\%$). Figures 3B,C show a selection of the 13 studies that used DLT as an endpoint. To create an analysis with less heterogeneity, studies were matched together based on identical cut-off values, measurement techniques, and vertebrae level analyzed. The studies included in Figure 3B all used the cut-off values established by Martin et al., 2013 [47] and measured SMM at L3 using CT.

There was no association between low SMM and DLT (OR 1.98; 95% CI 0.76–5.22, $p = 0.16$). Heterogeneity across studies was high ($\chi 2 = 24.48$ and $I2 = 84\%$). The studies included in Figure 3C all used cut-off values established by Prado et al., 2008 [46] as well as the same measurement technique at L3 using CT. There was no associated between low SMM and DLT (OR 1.87; 95% CI 0.32–10.93, $p = 0.49$). Heterogeneity across studies was high ($\chi 2 = 60.97$ and $I2 = 79\%$).

■ **Figure 2.** Quality in Prognostic Studies (QUIPS) for the included studies.

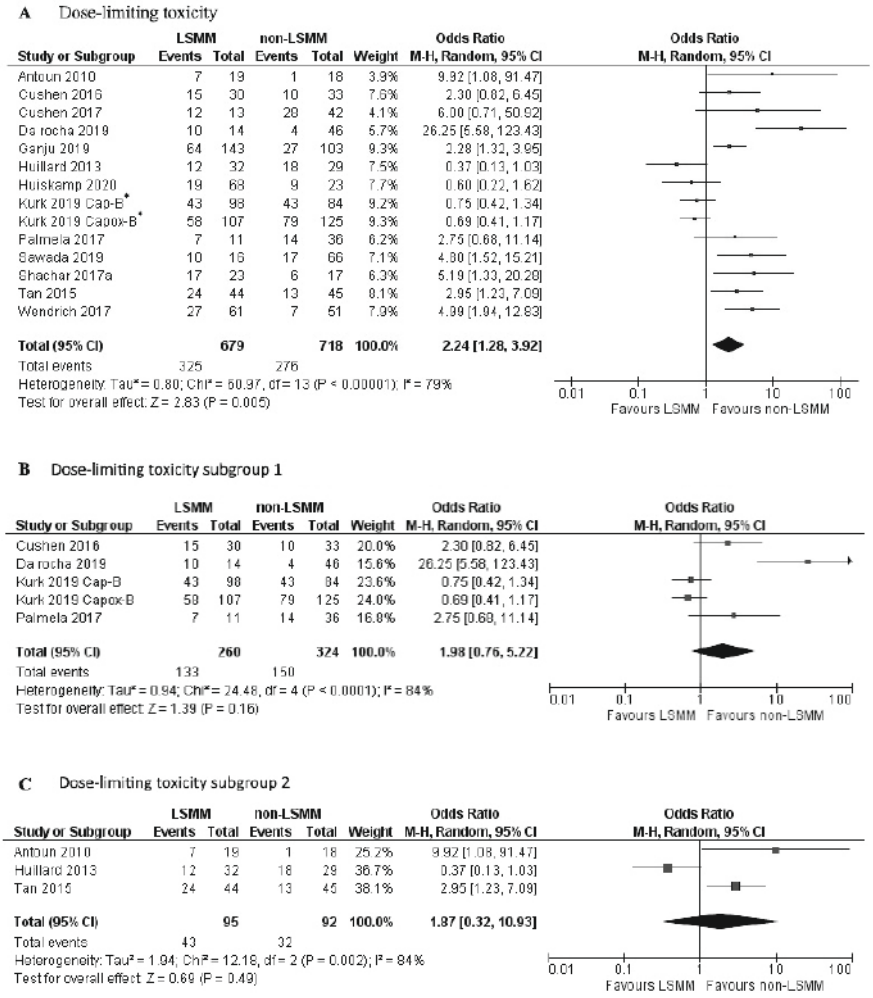


a. DLT (dose-limiting toxicity): toxicity leading to dose reduction, treatment delay, or discontinuation.
b. Occurrence of DLT for CAPOX-B and CAP-B respectively.
c. Occurrence of dose delay and dose reduction respectively.
Definitions of low SMM
1. Prado et al. 2008 [46]: <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women
2. Martin et al. 2013 [47]: <43 cm^2/m^2 for men if BMI ≤24.9 kg/m^2 or <53cm^2/m2 for men if BMI >25kg/m^2 and <41 cm^2/m^2 for women[48]
3. 25th percentile < 44.8cm^2/m^2 vs 75th percentile >63.2cm^2/m^2
4. Fujiwara et al. 2015 [48] : ≤36.2 cm^2/m^2 for men and ≤29.6 cm^2/m^2 for women
5. Caan et al. 2018 [49]: <40 cm^2/m^2

Figure 4A shows the forest plot for the OR of 6 studies that used toxicity ≥ grade 3 according to the CTCAE as the measure for toxicity. Patients with low SMM had a significantly higher risk of ≥grade 3 toxicity compared to patients without low SMM (OR 4.08; 95% CI 2.48–6.70; $p < 0.01$). Heterogeneity across studies was low ($\chi 2$ of 1.14 and I2 of 0%). Figure 4B shows the forest plot for the OR of 3 studies that besides using the same toxicity description also used the same cut-off value, namely that established by Martin et al., 2013 [47], as well as the same measurement technique on CT at the L3 vertebrae. Patients with low SMM had a significantly higher risk of ≥grade 3 toxicity compared to patients without low SMM (OR 3.81; 95% CI 2.07-6.98; $p < 0.001$). Heterogeneity across studies was low ($\chi 2$ of 0.13 and I2 of 0%).

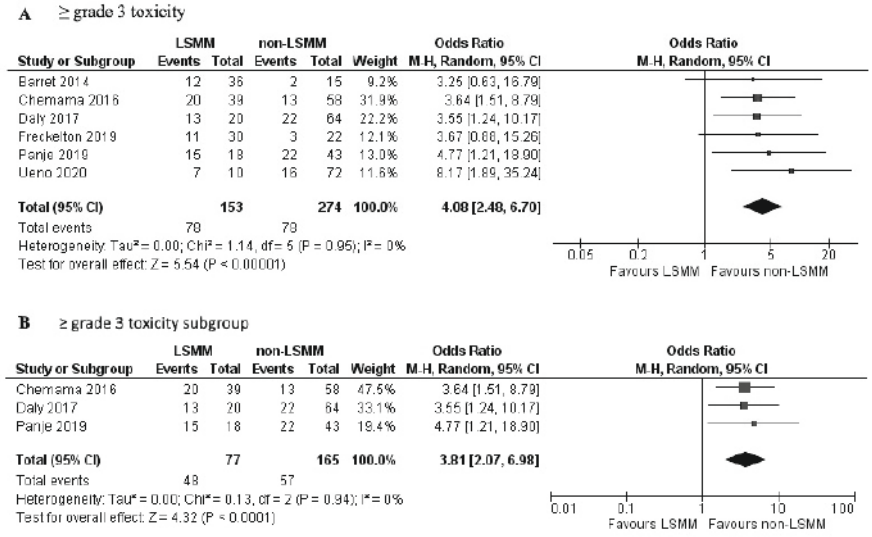
Of the 31 studies included in this review, 19 were included in the meta-analysis. Six studies were excluded because there was not sufficient statistical data published to determine an OR. [22,26,32,37,39,41] Of these six, five concluded that there was no association between SMI and toxicity[22,26,32,37,39] and one concluded that a lower SMI was related to a higher risk of toxicity.[41] Four studies were excluded because they did not dichotomize SMI and instead performed the analysis with SMI as a continuous variable.[28,29,34,36] Of these four, one concluded no association[28], and three concluded that low SMI was related to increased toxicity occurrence.[29,34,36] Two studies were excluded from the meta-analysis because the toxicity endpoint did not match any of the other studies.[6,38] Of these two, one showed a negative association between toxicity occurrence and SMI[6], and one showed no association[38]. Of the seven studies excluded that demonstrated no association between sarcopenia, several provided a theory as to why this association was not demonstrated. Some of these studies hypothesized that the distribution of the anti-cancer drug investigated was not influenced by low SMM, because of the hydrophilic characteristics of the drug or because of the route of administration.[22,26,32] Other studies mentioned the variety of cut-off values used for low SMM, which originated in populations that differ from the investigated population and can be observed in the varying prevalence of low SMM between studies.[28,37] Although these studies did not find an association between low SMM and toxicity, some did observe other associations related to low SMM and toxicity. These associations include the association between sarcopenic obesity and toxicity[22]; muscle quality and toxicity[26]; muscle loss during treatment and toxicity[39]; and low SMM and survival[38].

Figure 3. Forest plots for the association between low skeletal muscle mass (LOW SMM) and the odds to develop anti-cancer drug toxicity, specifically dose-limiting toxicity (DLT).



(A) shows the odds to develop toxicity for all included studies with DLT as the toxicity endpoint. (B) shows the odds to develop DLT for a selected group of studies that besides the same toxicity endpoint also share the same cut-off value established by Martin et al., 2013 47, as well as the same measurement technique using CT at the L3 vertebrae. (C) shows the odds to develop DLT for a second selected group of studies that share the same cut-off value established by Prado et al., 2008 46, as well as the same measurement technique using CT at the L3 vertebrae. For each forest plot, the combined effect of the studies is plotted with a black diamond. * The patient population in the study by Kurk et al., 2019, received sequential treatments. The odds ratio was determined for each treatment separately and therefore entered separately into the forest plot.

Figure 4. Forest plots for the association between low skeletal muscle mass (SMM) and the odds to develop anti-cancer drug toxicity, specifically.

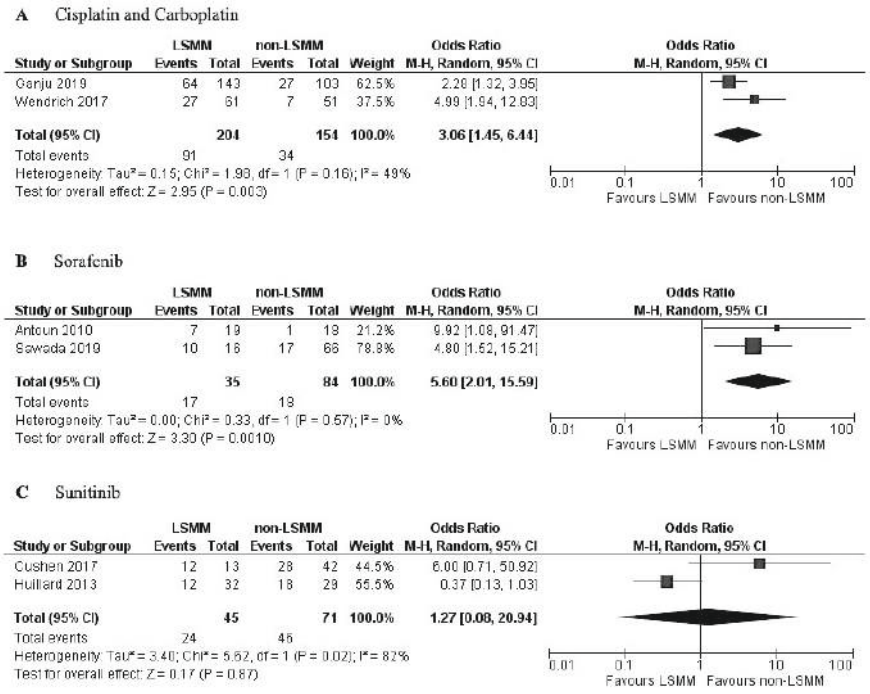


(A) toxicity ≥ grade 3 which was used as the toxicity endpoint in 6 studies. (B) shows a selection of studies that besides the same toxicity endpoint also used the same cut-off values established by Martin et al., 2013 [47], as well as the same measurement techniques using CT at the L3 vertebrae. For each forest plot, the combined effect of the studies is plotted with a black diamond.

SUBGROUP ANALYSIS

The studies that investigated the influence of a monotherapy were used for a subgroup analysis. Three different drugs used in monotherapy were the topic of more than one study. Figure 5A shows the forest plot for the OR of toxicity in low SMM and non-low SMM patients treated with cisplatin or carboplatin. Cisplatin and carboplatin have an apparent volume of distribution which approximately equals total body water (40–60 L).[53,54] These drugs were used as monotherapy in two studies[8,24] and showed an association between low SMM and toxicity (OR 3.06; 95% CI 1.45–6.44, p = 0.003) with moderate heterogeneity ($\chi 2 = 1.98$; I2 = 49%). Figure 5B shows the forest plot for low SMM and non-low SMM patients treated with sorafenib as a monotherapy, which has an apparent volume of distribution of 213 L[55]. These two studies[33,42] demonstrated an association between low SMM and toxicity (OR 5.60; 95% CI 2.01–15.59; p = 0.001) with low heterogeneity ($\chi 2 = 0.33$; I2 = 0%). Figure 5C shows the forest plot for low SMM and non-low SMM patients treated with sunitinib as a monotherapy, which has an apparent volume of distribution of 2230 L[56]. These two studies[7,45] showed no association between low SMM and toxicity (OR 1.27; 95% CI 0.08–20.94; p = 0.87) with high heterogeneity ($\chi 2 = 5.62$; I2 = 82%).

Figure 5. Forest plots for association between low skeletal muscle mass (SMM) and toxicity specifically for monotherapies used in multiple studies.



DISCUSSION

In this review, 31 studies were evaluated, of which 19 were used in the meta-analysis. The meta-analysis showed that low SMM has predictive value for toxicity (DLT OR = 2.24 and ≥grade 3 toxicity OR = 4.08). Heterogeneity across studies using DLT as the outcome was very high, which can be explained by the differences in the definition of DLT. The general definition of DLT is any toxicity leading to dose reduction, treatment delay, or discontinuation. However, studies differed in the level of detail of this definition, for example, some studies included any dose reduction[20,41], others applied a minimum of 50% reduction[8,42], some studies also included toxicity leading to hospitalization[35], some studies included any treatment delay[20,41], and others included delays over 4 days[8] or 7 days[24]. Even when creating subgroups by matching cut-off values, measurement techniques, and vertebrae level analyzed, the heterogeneity remained high because of the difference in the definition of DLT and could not provide accurate evidence of the association between low SMM and DLT. The results presented in Figure 4 for the association of low SMM with toxicity ≥ grade 3 were much more reliable because of the low level of heterogeneity with an I2 of 0%. This can be explained by the clear definition of grade 3 toxicity according to CTCAE. Therefore, the meta-analysis for the association between low

SMM and toxicity ≥ grade 3 should be seen as more accurate and trustworthy compared to the meta-analysis for DLT.

A limitation of this study is the differences in measurement of SMM and diagnosis of low SMM. All included studies used CT which is the most commonly used and validated technique for SMM measurement[3,8,12], one study also included MRI measurements[50]. However, studies did measure SMM on different vertebrae levels. Most commonly L3 was used, which is also the most conventionally applied method in literature[12,13]. Several studies in this review used alternative vertebrae levels C3 or T4. The methods using these other vertebrae levels have been researched in recent publications but are less frequently used as L3 and some lack validation. The forest plot in Figure 4B shows studies that all used the same measurement technique although there was still a difference in the software used, as well as the time between scan and treatment start. This could influence the results, but it is difficult to estimate this influence as there is no previous research on these topics. Especially, the time between scan and treatment start is difficult to interpret as many studies do not report the used time frame. Future research should take this into account for their study design and the results they report.

Furthermore, the definition of low SMM varies between studies. Although some studies use SMI as a continuous variable, most determine a cut-off value to define the presence of low SMM. Most studies use cut-off values from previous publications in similar populations with larger sample sizes. Within this review, the most frequently used cut-offs were those determined by previous studies performed by Prado et al.[46] and Martin et al. [47]. Additional confusion in the already complex field of cut-off values is caused by the incorrect citation of these cut-off values. In this review, five studies cited the cut-off values of Prado et al.[46] but used cut-off values that deviate from those published in the original study. This variation in cut-off values could explain the large range in the occurrence of low SMM, which can be observed in literature as well as in this review (12.2–89.0%). For the optimal diagnosis of low SMM, a universal cut-off value would be preferable. This could be done in a large population of healthy individuals where two standard deviations below average SMI could be seen as a cut-off for low SMM.

The leading theory behind the association between low SMM and increased risk of toxicity relates to the influence of low SMM on drug distribution. Patients with low SMM have a decreased LBM, as muscle mass is a large contributor to LBM. This could cause increased drug levels in the plasma of patients with low SMM and thereby increase the risk of toxicity[6,8,11,17]. Many studies in this review consisted of populations treated with a combination of anti-cancer drugs using different dosing regimens, which makes it challenging to compare the drug distribution. Therefore, we specifically focused on studies focused on monotherapy. There was a trend showing increased OR with an increased volume of distribution. This can be seen in the forest plots, as sorafenib has a higher OR for toxicity occurrence when compared to cisplatin and carboplatin, and this correlates with the higher volume of distribution of sorafenib (Figure 5A,B). However, no definitive conclusions can be drawn yet since the sample size in these studies was too low.

Besides the distribution of anti-cancer drugs, many other treatment characteristics could be influenced by changes in SMM. To further investigate this, studies would be needed that observe similar populations treated with different anti-cancer drugs, preferably as monotherapy. However, this might be challenging to accomplish as many treatment regimens consist of combined anti-cancer drugs and the possible addition of radiotherapy or surgical procedures. This review showed a large variety of treatment details such as concomitant radiotherapy, treatment intent, and the possibility to use chemotherapy as an adjuvant treatment. There is previous research on the influence of treatment details such as the research by Ganju et al.[24], which showed that low SMM is associated with prolonged radiation breaks in head and neck cancer patients who underwent chemoradiotherapy. However, to fully investigate this association a meta-analysis should be focused on specifically chemoradiotherapy or adjuvant chemotherapy. This review is not designed to draw conclusions on those topics, and therefore, future research is needed. Another option is to further research the mechanism that causes this decrease of SMM and by that identify how low SMM influence adverse events.

The studies included in this review all investigated the association between pre-treatment low SMM and the occurrence of toxicity. Several studies also investigated the relationship between the change in SMM during treatment and increased toxicity. However, reverse causality could not be excluded from these observational studies. Randomized intervention studies are needed to elucidate whether diet, exercise, or supplements could reverse or prevent a decrease in SMM during systemic treatment and whether this leads to a lower risk of toxicity. Another strategy to produce better treatment outcomes is to adapt treatment regimens based on the presence or absence of low SMM, although this would require a universal cut-off value. Alternatively, the dosing of anti-cancer drugs could be adapted to be based on SMI as opposed to weight or body surface area. This would also require randomized trials to demonstrate the superiority of SMI dosing above current dosing methods.

CONCLUSIONS

Based on the association between low SMM and toxicity ≥ grade 3 according to the CTCAE, it can be concluded that the predictive value of low SMM for toxicity of anti-cancer drugs can be observed across cancer types and patient populations. This information increases the need for further research into interventions that could treat low SMM as well as the possibility to adapt treatment regimens based on the presence of low SMM. Additional research should also be done to validate measurement methods, create universal cut-off values, monitor changes in SMM during treatment, and investigate the influence of concurrent treatments.

Appendix A (dose-limiting toxicity OR CDLT OR toxicity OR adverse effect OR side effect) AND
(sarcopenia OR skeletal muscle mass OR SMM OR body composition) AND
(chemother * OR immunotherapy OR biotherapy OR chemoradiotherapy OR radiochemotherapy OR CRT OR bioradiotherapy OR immunoradiotherapy) AND
(cancer * OR tumor OR tumour)

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56. CHMP. *ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS*.

CHAPTER 14

The association of cisplatin pharmacokinetics and skeletal muscle mass in head and neck cancer: the prospective PLATISMA study

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**Contributed equally*

Submitted ■

ABSTRACT

Background

Locally advanced head and neck squamous cell carcinoma (HNSCC) is commonly treated with cisplatin-based chemoradiotherapy (CRT). Cisplatin is associated with severe toxicity, which negatively affects survival. In recent years, a relationship between low skeletal muscle mass (SMM) and toxicity has been described. This increased toxicity may be related to altered cisplatin distribution and binding in the fat-free body mass of which SMM is the largest contributor. This study aims to investigate the association between cisplatin pharmacokinetics and SMM in HNSCC patients.

Material and methods

We performed a prospective observational study in HNSCC patients treated with CRT. Patients received standard-of-care chemotherapy with three cycles of cisplatin at a dose of 100 mg/m^2 per cycle. Quantitative data on SMM, measured on computed tomography scans and cisplatin pharmacokinetics (total and ultrafiltrable plasma concentrations) were collected, as well as data on toxicity.

Results

In total, 45 evaluable patients were included in the study. A large proportion of the study population had a low SMM (46.7%). The majority of patients (57.8%) experienced cisplatin dose limiting toxicities. Pharmacokinetic analysis showed a relationship between cisplatin pharmacokinetics and SMM (p<0.005). In a simulation, patients with a low SMM (<25.8 kg) were predicted to reach higher bound cisplatin concentrations.

Conclusion

We found an association between cisplatin pharmacokinetics and SMM, however this relationship was also seen between cisplatin pharmacokinetics and other body composition descriptors.

INTRODUCTION

Head and neck squamous cell carcinomas (HNSCCs) are among the most frequent tumors worldwide.[1] Two-thirds of HNSCC patients present with advanced disease which is treated with cisplatin-based chemoradiotherapy (CRT).[2] Acute toxicity of cisplatin, such as nephrotoxicity and ototoxicity, results in dose-reductions, treatment delay or treatment cessation (chemotherapy dose limiting toxicity, CDLT) in at least 30% of patients.[3–5] CDLTs negatively affect survival because patients receive a suboptimal treatment.[5] In recent years, a relationship between radiologically assessed low skeletal muscle mass (SMM) and CDLT has been described for HNSCC.[6–8] A retrospective study in HNSCC patients undergoing CRT showed that patients with low SMM had a 3-fold higher risk of experiencing CDLT (44.3% vs. 13.7%), which resulted in a significantly shorter overall survival than for patients who were able to complete CRT.[7]

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.[9] Cisplatin is a highly reactive drug and upon administration the drug will bind to tumor DNA causing its anti-cancer effect, but also to tissue causing side effects and lastly to tissue without any pharmacodynamic effect.[10] We hypothesized that this latter compartment is highly related to SMM. In patients with a low SMM less tissue is available to which cisplatin can bind relatively harmless, but more reactive cisplatin is available to bind to tissue related to toxicity. This might lead to increased CDLTs negatively affecting outcome. The aim of this prospective observational study was to investigate the relationship between SMM and pharmacokinetic (PK) parameters of cisplatin in HNSCC patients. We hypothesized that an altered distribution of cisplatin could explain why patients with low SMM are more prone to experience cisplatin toxicity.

MATERIALS AND METHODS

ETHICAL CONSIDERATIONS

The Medical Research Ethics Committee (METC) of the University Medical Center Utrecht has reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations and has approved this study in June 2018 (METC 18-225/D). The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to inclusion in the study.

STUDY POPULATION, STUDY DESIGN AND SAMPLE SIZE

This study was designed as a monocenter prospective observational cohort study in HNSCC patients receiving three-weekly high-dose (100 mg/m^2) primary or adjuvant CRT. To estimate the sample size a clinical trial simulation (n = 200) was performed based on a previously published PK model on ultrafilterable cisplatin.[14] An allometric relationship between SMM and cisplatin clearance was assumed. Patient characteristics (SMM and body surface area (BSA)) were simulated in accordance with clinical practice. It was estimated that data from 45 patients was sufficient to find a significant relationship between cisplatin clearance and SMM with a power of >80%. As PK models with SMM and BSA are non-hierarchical, the difference between the two models cannot be statistically tested. However, in approximately 70% of the trials, this relationship showed better goodness-of-fit than a BSA-based relationship. Finally, the allometric exponent could be estimated with acceptable precision (approximately 28% relative standard error) with a sample size of 45 patients.

SKELETAL MUSCLE MASS MEASUREMENT

Segmentation of SMM was manually performed using the SliceOmatic software (Tomovision, Canada). Skeletal muscle area (SMA) was measured on pre-treatment computed tomography (CT) imaging at the level of the third lumbar vertebrae (L3) by a validated method.[15] If no pre-treatment imaging was available at the level of L3, SMA was measured at the level of the third cervical vertebrae (C3) and then converted to SMA at the level of L3 by use of an earlier defined formula.[15] To correct for height, SMA was divided by squared height to yield the skeletal muscle mass index (SMI). Low SMM was defined as a lumbar SMI (LSMI) ≤ 43.2 cm^2/m^2.[16] For PK analysis, the absolute volume of the muscle compartment was used by converting SMA to SMM with use of the following equations [17,18]:

$$Skeletal\ muscle\ volume\ (L) = 0.166\ L/cm^2 \times skeletal\ muscle\ area\ in\ cm^2 + 2.142\ L \quad (1)$$

$$SMM\ (kg) = skeletal\ muscle\ volume\ in\ L \times 1.06\ g/cm^3 \quad (2)$$

For simulation purposes, the threshold value of low LSMI was converted to a threshold value for SMM in kilograms. Using the median height in our patient population, the threshold for low SMM was defined to be ≤ 25.8 kg. SMM was compared with the calculated fat-free mass (FFM), which is another way to estimate body composition. For calculation of FFM the equations of Janmahasatian *et al.* were used [19]:

$$FFM\ (in\ males) = \frac{9.27 \times 10^3 \times weight}{6.68 \times 10^3 + 216 \times BMI} \quad (3)$$

$$FFM\ (in\ females) = \frac{9.27 \times 10^3 \times weight}{8.78 \times 10^3 + 244 \times BMI} \quad (4)$$

In these equations BMI is the body mass index (weight/height^2; weight in kg and height in m).

CISPLATIN BIOANALYSIS

Plasma and ultrafiltrable (using a filter of 30 kDa) samples were collected from patients at different time points (pre-dose, end of infusion and 1 hour, 3 hours, 7 hours and 20 hours after end of infusion) during the first cycle of cisplatin. Both total and ultrafiltrable plasma concentrations of platinum were measured by inductively coupled plasma-mass spectrometry (ICP-MS) by a previously described method.[20] For simplification, the terms free and bound cisplatin are used throughout to denote ultrafilterable and non-ultrafilterable platinum species, respectively.

CISPLATIN RELATED TOXICITY

Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines, version 4.03.[21] CDLT was defined as any toxicity resulting in cisplatin dose-reduction of ≥50%, a treatment delay of ≥4 days or cessation of cisplatin after the first or second cycle of therapy.

PHARMACOKINETIC ANALYSIS

For description of cisplatin PK a two-compartment model for free cisplatin, followed by one compartment for protein-bound cisplatin was used, as previously described by Urien *et al*.[14] Clearance of free cisplatin was considered negligible compared to binding to proteins and, therefore, not included in the model. More detailed information about the PK model can be found in the Supplementary materials.

The body composition descriptors weight, SMM, FFM, and BSA were separately evaluated as covariates on clearance of free cisplatin (CL_{free}), volume of distribution of free cisplatin (V_{free}), intercompartmental clearance (Q), and volume of distribution of the peripheral compartment (V_p) of free cisplatin, clearance of bound cisplatin (CL_{bound}) and volume of distribution of bound cisplatin (V_{bound}). The body composition descriptors were evaluated using equation 5:

$$\theta_i = \theta_{pop} \times \left(\frac{body\ composition}{median\ body\ composition}\right)^k \quad (5)$$

Where θ_i represents the parameter estimate for individual *i*, θ_{pop} represents the typical parameter estimate for the population, and k represents the exponent.

Based on the theory of allometric scaling the exponent was fixed to 0.75 for evaluation of clearance, and to 1 for volume of distribution [22]. For both clearance and volume of distribution the exponent was also estimated. The glomerular filtration rate (GFR; calculated using

the creatinine-based Cockcroft-Gault formula, or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation and capped on a maximum value of 130 mL/min), and albumin were examined as additional relevant covariates, as described in the Supplementary materials.

In case that addition of the GFR and/or albumin resulted in a better fit of the baseline model (based on the objective function value (OFV), a drop in inter-individual variability (IIV) and a difference in effect size between the 25% and 75% quartile), body composition was also evaluated in combination with these covariates. Lastly, the final model was used to simulate the effects of different SMMs on the population predicted cisplatin concentrations. In this simulation the effects of different SMMs around the threshold of 25.8 kg for low SMM were predicted. For the chosen SMMs, the corresponding BSAs were extracted from the data to calculate the given dose for the virtual patients.

STATISTICAL ANALYSIS

Formal statistical testing for the PK model was performed using the likelihood ratio test (by means of the OFV which is minus twice the log likelihood) for the models without fixed coefficients, a *p*-value of 0.005 was used to take into account multiple testing [23] and the degrees of freedom were equal to the number of included relationships. For the models with fixed coefficients, the drop in OFV was used as a guidance. Other statistical analyses were performed using R (version 3.6.3).

RESULTS

PATIENTS' CHARACTERISTICS

In total, 50 patients were included between July 2018 and September 2020. Five patients eventually did not participate in the study, 3 due to withdrawal of informed consent and 2 did not undergo CRT. Table 1 shows the characteristics of the included patients, 21 patients (46.7%) had low SMI. Median LSMI was 44.06 cm^2/m^2 (interquartile range (IQR) 37.7-50.9). Patients without low SMM were more likely to be overweight (58.3% versus 19%; $p<0.01$) and obese (25.0% versus 4.8%; $p<0.01$) compared to patients with low SMM. Majority of patients were treated in a primary setting (n=40, 88.9%) and had a tumor, node, metastasis (TNM) stage IV tumor according to the 8th edition TNM cancer staging criteria (n=25, 55.5%). One patient received a weekly low-dose cisplatin schedule (40 mg/m^2 weekly) due to comorbidity.

Table 1. Demographic and anthropometric measurements according to SMM status and DLT status

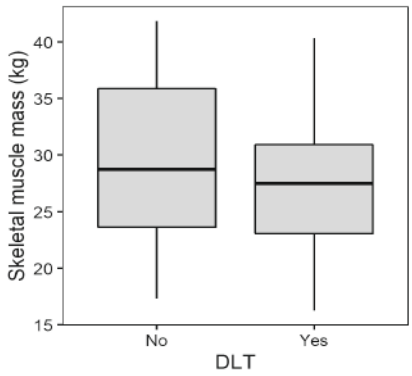
	Total N=45 N (%) or Mean, SD	Without low SMM* n= 24 (53.3) Mean, SD	With Low SMM n=21 (46.7) Mean, SD	p	Without DLT n= 19 (42.2) Mean, SD	With DLT n= 26 (57.8) Mean, SD	p
Gender				<0.01			0.7
Male	32 (71.1)	23 (95.8)	9 (42.9)		12 (66.7)	20 (74.1)	
Female	13 (28.9)	1 (4.2)	12 (57.1)		6 (33.3)	7 (25.9)	
Age	59.1 (6)	58 (5.2)	60.3 (6.6)	0.2	57.8 (4.6)	59.9 (6.7)	0.3
Weight (kg)	79.9 (18.8)	90.4 (17.4)	67.9(12.16)	<0.01	79.7 (18.9)	80.0 (19.2)	1.0
Length (m)	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)	0.3	1.8 (0.1)	1.8 (0.1)	0.8
BMI kg/m²							
18.5-24.9	16 (35.6)	4 (16.7)	12 (57.1)	<0.01	4 (22.2)	12 (44.4)	*0.07*
<18.5	4 (8.9)	0 (0)	4 (19.0)		2 (11.1)	2 (7.4)	
25-29.9	18 (40.0)	14 (58.3)	4 (19.0)		11 (61.1)	7 (25.9)	
≥30	7 (15.6)	6 (25.0)	1 (4.8)		1 (5.6)	6 (22.2)	
LSMI cm²/m² (median, IQR)	44.1 (37.7-50.9)	50.6 (5.2)	36.9 (4.1)	<0.01	45.0 (8.6)	43.7 (8.3)	0.6

*Low SMM is defined as an LSMI ≤ 43.2 cm/m2

CISPLATIN DOSE-LIMITING TOXICITY

Of the 45 included patients, 26 patients (57.8%) did not complete 3 cycles of cisplatin. All were due to CDLT and consisted of: creatinine increase grade 2 (n=11) and grade 3 (n=2), nausea grade 3 (n=3), hearing impairment grade 2 (n=6), neutropenia grade 3 (n=1), heart failure grade 3 and increased creatinine grade 3 (n=1), creatinine increase grade 2, hypomagnesaemia grade 3 and hyponatremia grade 3 (n=1), hearing impaired grade 2 and neutropenia grade 4 (n=1). In our dataset no correlation was found between CDLTs and SMM (unpaired T-test, *p*=0.39), as illustrated in figure 1.

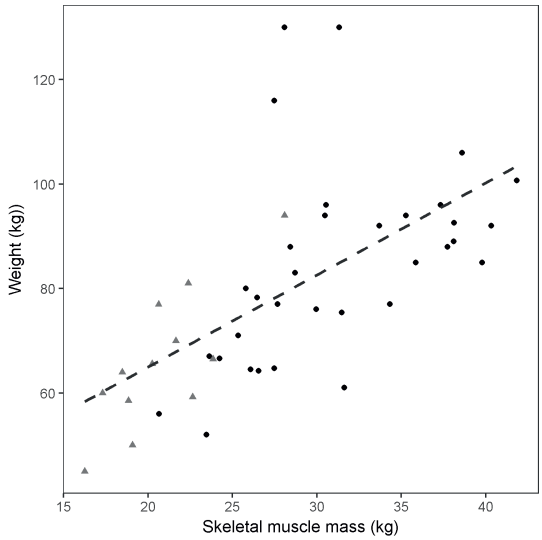
Figure 1. Correlation between dose limiting toxicities (DLTs) of cisplatin and skeletal muscle mass (unpaired T-test; p=0.39)



PHARMACOKINETIC RESULTS

SMM and weight were significantly correlated with a Pearson correlation coefficient of 0.6, as shown in figure 2. Based on goodness-of-fit plots the data were well described by the used PK model. For 5 patients no SMA at the L3 slice was available, therefore SMA at the C3 slice was used. To examine whether other relevant covariates had influence on the PK model of cisplatin, and thereby could influence the effect of SMM, albumin and GFR were first tested as covariates on the baseline model. No effect of albumin on the PK model was found. Addition of the GFR as a covariate on CL_{bound} resulted in a drop in OFV of 28 and 33 points, for the GFR calculated based on creatinine and cystatin C, respectively (nonhierarchical models). Also, a drop in IIV and a relevant difference in effect size were encountered. Therefore, GFR was also evaluated in combination with SMM. The PK model was extended with SMM, weight, and FFM as covariates on the PK parameters CL_{free}, V_{free}, Q, V_p, CL_{bound}, and V_{bound} of cisplatin. Using estimated exponents, compared to fixed exponents based on the theory of allometric scaling, led to a substantially better description of the data, as indicated by the OFV. The exponent was unidentifiable for V_{free} and Q. Addition of GFR, next to SMM, had no effect on the PK model (additional dOFV -5 and -4, for creatinine and cystatin C, respectively), which could be explained by a relationship between weight and GFR (weight is even used to calculate creatinine clearance in the Cockcroft-Gault formula).Therefore, SMM, weight, and FFM were added as potential covariates on CL_{free}, CL_{bound}, and V_{bound} of cisplatin while estimating the exponents. The OFV was significantly decreased by addition of SMM (dOFV -64, p<0.005), weight (dOFV -77, p<0.005), and FFM (dOFV -70, p<0.005). Since cisplatin is dosed based on BSA, BSA was also tested as covariate in the final model, which resulted in a significant drop in OFV (dOFV -86, p<0.005). The parameter estimates and estimated exponents for the model with SMM are shown in Supplementary materials S2.

Figure 2. Correlation between weight and skeletal muscle mass. Males are displayed by black circles and females by grey triangles. R= 0.63, p<0.005



For the final model a simulation was performed in which the effects of different SMMs on the PK of cisplatin were predicted. Plots of the population predicted cisplatin concentrations vs time derived from this simulation are shown in figure 4, which shows that patients with a lower SMM are predicted to reach higher concentrations of bound cisplatin.

Figure 3. Population predicted cisplatin concentrations versus time. The left panel shows predicted free cisplatin concentrations, and the right panel shows predicted bound cisplatin concentrations. Simulations were performed using the model in which skeletal muscle mass was added as covariate on clearance of free cisplatin, and on clearance and volume of distribution of bound cisplatin. Skeletal muscle mass was simulated around the threshold of 25.8 kg for a low skeletal muscle mass, with corresponding body surface area and thus dose given.

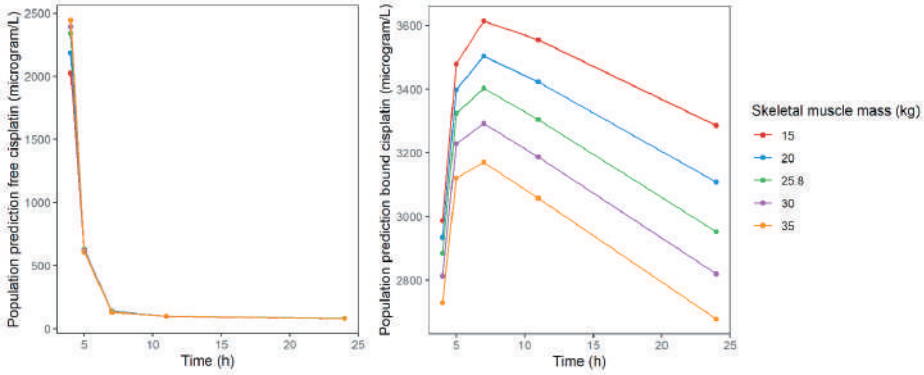
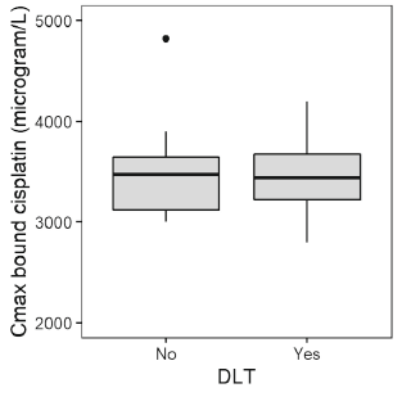


Figure 4. Correlation between dose limiting toxicities (DLTs) of cisplatin and the maximum plasma concentration (Cmax) of bound cisplatin (Wilcoxon rank sum test; p=0.85)



Lastly, the correlation between CDLTs and the maximum plasma concentration (C_{max}) of bound cisplatin was examined. One subject was excluded in this analysis, because this subject received a lower dose of cisplatin compared to the other patients. No correlation between CDLTs and the C_{max} of bound cisplatin was found (Wilcoxon rank sum test; p=0.85), which is illustrated by the boxplots in figure 6.

DISCUSSION

In this prospective observational study, we investigated the relationship between cisplatin PK and SMM. As expected, we found an association between cisplatin PK, especially bound cisplatin, and SMM. A pharmacokinetic simulation showed that patients with low SMM reached higher concentrations of bound cisplatin, which could be an explanation for the higher toxicity in this patient group. 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 cisplatin can distribute to and bind with, without inducing toxicity. In this study no data was available on the concentration of bound cisplatin in tissue. We expected that patients experiencing CDLTs would have higher maximum concentrations of bound cisplatin in plasma, however we did not find a correlation between these two parameters. No relationship was found between DLTs and a low LSMI, which was seen in previous studies, most likely explained by the low number of patients to study this association.[7,24]

Although we found a relationship between cisplatin PK and SMM, there was also a significant relationship between cisplatin PK and the other body composition descriptors. Based on the findings in this study, both SMM and the other body composition descriptors predict cisplatin pharmacokinetics. We also found SMM to be correlated with weight, which might explain why cisplatin pharmacokinetics is also related to weight and FFM.

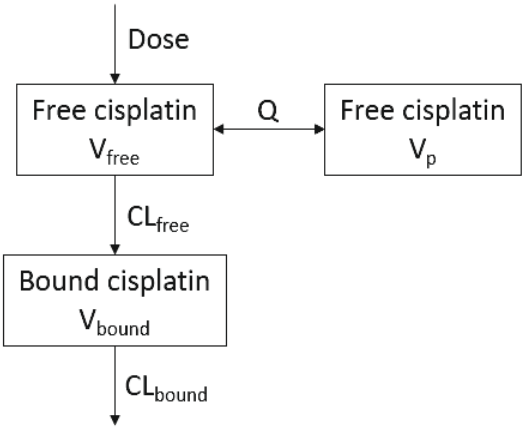
CONCLUSION

HNSCC patients with low SMM reach higher bound cisplatin concentrations, although no correlation was seen between cisplatin DLT and low SMM. Further studies which examine the level of bound cisplatin at the end organs are needed to further clarify the relationship between low SMM and cisplatin DLTs in HNSCC patients.

SUPPLEMENTARY MATERIALS

S1. **Details** of the pharmacokinetic model of cisplatin

A schematic overview of the pharmacokinetic model of free and bound cisplatin is shown in the following figure:



Vfree, volume of distribution of free cisplatin; CLfree, clearance of free cisplatin; Vp, volume of distribution of the peripheral volume of free cisplatin; Q, intercompartmental clearance; Vbound, volume of distribution of protein-bound cisplatin; CLbound, clearance of protein-bound cisplatin

The interindividual variability (IIV) was described with an exponential model according to equation S1:

$$\theta_i = \theta_{pop} \times \exp(\eta_i) \quad \text{(S1)}$$

Where θ_i represents the parameter estimate for individual *i*, θ_{pop} represents the typical parameter estimate for the population, and η_i represents the IIV for individual *i*.

The residual unexplained variability was described by a proportional model for free cisplatin and protein-bound cisplatin separately, according to equation 2:

$$C_{obs,ij} = C_{pred,ij} \times (1 + \varepsilon_{prop}) \quad \text{(S2)}$$

Where $C_{obs,ij}$ represents the observed concentration for individual *i* and observation *j*, $C_{pred,ij}$ represents the predicted concentration for individual *i* and observation *j*, and ε_{prop} represents the proportional error which was assumed to be normally distributed with a mean of zero and a variance of σ^2.

In order to further investigate the effects of SMM on PK of cisplatin, glomerular filtration rate (GFR), and albumin were examined as additional relevant covariates. These potential covariates were first tested as covariates on the baseline model. GFR was evaluated on clearance of protein-bound cisplatin as follows:

$$L_{bound} = \left(CL_{non-renal} + CL_{renal} \times \frac{GFR}{6}\right) \times \left(\frac{weight}{70}\right)^{0.75} \quad \text{(S3)}$$

Where CL_{bound} represents the total clearance of protein-bound cisplatin, $CL_{non\text{-}renal}$ represents the non-renal clearance, CL_{renal} represents the renal clearance, and GFR represents the glomerular filtration rate as calculated by the Cockcroft-Gault formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C formula, which is divided by 6 L/hour as 'normal' glomerular filtration rate, the clearance is standardized for a 70 kg person [25].

In case body composition was evaluated in combination with GFR the part in equation S3 which standardizes for a 70 kg person, was replaced by the body composition description part of equation 5.

Albumin was evaluated on CL of free cisplatin and V of protein-bound cisplatin, according to equation S4:

$$\theta_i = \theta_{pop} \times (1 + \theta_{albumin} \times (albumin - median\ albumin)) \quad \text{(S4)}$$

Where θ_i represents the parameter estimate for individual *i*, θ_{pop} represents the typical parameter estimate for the population with a median albumin, and $\theta_{albumin}$ represents the fractional increase per unit albumin.

MODEL EVALUATION

The fit of the baseline model was evaluated using goodness-of-fit (GOF) plots. Addition of the covariates GFR, albumin and body composition descriptors was evaluated by GOF plots, a drop in the objective function value (OFV; minus twice the log likelihood), successful minimization, parameter precision ($COVARIANCE option of NONMEM) and a drop in inter-individual variability (IIV).

SOFTWARE

Nonlinear mixed-effects modeling was performed using NONMEM (version 7.3, ICON Development Solutions, Ellicott City, USA) and Perl-speaks-NONMEM (PsN, version 4.7.0)[23]. In order to obtain parameter estimates the first-order conditional estimation with interaction (FOCE-I) method was used. Model management was performed using Pirana (version 2.9.9)[26]. R (version 3.6.3) was used for data management and graphical diagnostics [27].

S2. Parameter estimates of cisplatin in the pharmacokinetic model with skeletal muscle mass imputed as covariate on CLfree, CLbound, and Vbound

Parameter	Estimate (RSE %)
CL_{free} (L/h) Effect of SMM	12.2 (4.2) 0.313 (23.8)
V_{free} (L)	14.4 (5.7)
Q (L/h)	8.99 (9.1)
V_p (L)	307 (11.3)
CL_{bound} (L/h) Effect of SMM	0.644 (4.6) 0.842 (17.1)
V_{bound} (L) Effect of SMM	32 (4.8) 0.67 (14)
Inter-individual variability	%CV (RSE %)
CL_{free} (L/h)	12.7 (18.8)
V_{free} (L)	27.3 (18)
CL_{bound} (L/h)	15.9 (30.6)
V_{bound} (L)	16.5 (9.9)
Proportional residual unexplained variability	%CV (RSE %)
Free cisplatin	17.1 (9.4)
Bound cisplatin	6.1 (10.8)

CLfree, clearance of free cisplatin; Vfree, volume of distribution of free cisplatin; Q, intercompartmental clearance; Vp, volume of distribution of the peripheral compartment of free cisplatin; CLbound, clearance of bound cisplatin; Vbound, volume of distribution of bound cisplatin; RSE, relative standard error; %CV, percentage coefficient of variation

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CHAPTER 15

Patterns, predictors and prognostic value of skeletal muscle mass loss in patients with locally advanced head and neck cancer undergoing cisplatin-based chemoradiotherapy

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Submitted ■

ABSTRACT

Background

Low skeletal muscle mass (SMM) is associated with toxicities and decreased survival in head and neck cancer (HNC). Chemoradiotherapy (CRT) may exaggerate loss of SMM. We investigated the changes in SMM, their predictors and prognostic impact of SMM in patients treated with CRT between 2012 and 2018.

Material and methods

Skeletal muscle area (SMA) segmentation was performed on pre- and post-CRT imaging. Observed changes in SMM were categorized into: (I) stable (II) moderate gain (III) moderate loss (IV) large gain and (V) large loss.

Results

In total, 235 HNC patients were included of which 39% had stable SMM, 55% moderate loss, 13% moderate gain, 0.4% large loss and 0.4% large gain of SMM. After CRT, SMA decreased compared to pre-CRT (31.6 cm^2 versus 33.3 cm^2, $p<0.01$). Key predictors were a body-mass index (BMI) of ≥25 or ≥30kg/m^2 (HR 2.4, $p<0.01$ and HR 3.1, $p<0.05$, respectively), oropharynx tumor (HR 2.4, $p< 0.05$), albumin level (HR 1.1, $p<0.01$) and postoperative CRT (HR 0.39, $p<0.01$).

Conclusion

Low SMM and SMM changes were not prognostic for survival. Loss of SMM is highly prevalent after CRT and the aforementioned variables may aid in identifying patients at risk.

INTRODUCTION

Head and neck cancer (HNC) accounts worldwide for approximately 550.000 cases annually.[1] Locally advanced HNC (LA-HNC) is the most prevailing clinical manifestation of HNC and has poor prognosis with a 5-year disease-free survival (DFS) of approximately 40-50%. Although the addition of the cytotoxic compound cisplatin to radiotherapy (RT) improved 5-years PFS from 36% to 47% and 5-years overall survival (OS) from 40% to 53%, it also caused a significant increase in severe functional mucosal adverse effects from 21% to 40%.[2] Due to the increased risk of side-effects, full compliance of chemoradiotherapy (CRT) is seen in only about two thirds of the initially eligible patients.[3–5] Ongoing research evaluates and compares different systemic treatment regimens and novel therapeutic approaches with consideration of potential patient-related (i.e., HPV-status) and treatment-related factors (i.e., dose regimen) in order to improve treatment tolerance and survival in LA-HNC patients.

An emerging patient-related predictive and prognostic factor in the management of HNC is patients' skeletal muscle mass (SMM). SMM quantification can be easily performed with the use of computed tomography (CT) or magnetic resonance imaging (MRI) images, which are routinely performed in the diagnostic work-up prior to treatment. Low SMM is common in HNC and especially in LA-HNC patients.[6] Patients with LA-HNC frequently experience dysphagia due to tumor site and adverse effects caused by CRT. This leads to weight loss and nutritional deficiencies which are the major contributors to low SMM. Low SMM has shown to be a significant predictive factor for failure of the treatment plan due to toxicities in various types of cancer.[7,8,9,10] Also in LA-HNC patients, low SMM at diagnosis has shown to be predictive for platinum dose-limiting toxicities.[11,12] Moreover, previous studies suggest that chemotherapy itself may induce SMM loss, also referred to as muscle wasting, in patients with cancer by increasing lipolysis and fatty acid B-oxidation.[13] It has also been suggested that patients with low SMM have higher blood levels of cytotoxic agents compared to patients without low SMM, which together with the previous mentioned mechanism may cause a vicious circle of muscle wasting.[12] In addition, various studies in other types of cancers have shown that loss of SMM during systemic chemotherapy is prognostic for decreased survival in patients with several types of cancer including colorectal and pancreatic cancer[14–17].

For HNC, several studies have shown that low SMM at diagnosis is prognostic for decreased survival.[18,19,20,21] However, little is known about the patterns and prognostic impact of changes in SMM after cisplatin-based CRT in LA-HNC patients. In HNC, one previous study investigated the prognostic impact of changes in SMM after (C)RT in patients with nasopharyngeal carcinoma and showed that loss of SMM was associated with decreased OS[22]. Nasopharyngeal carcinoma is, however, a distinctive entity in HNC. Furthermore, patients were treated with different treatment strategies (induction CRT as well as concurrent CRT) and SMM segmentation was performed on CT scans with a wide time interval (median: 110 days, range 41-1083 days). As regards to squamous cell carcinomas of other anatomical head and neck subsites, no evidence is published yet. If loss of SMM after CRT is indeed a prognostic factor, it can be

used as an objective measurement tool for decision making and it may offer the opportunity for timely therapeutic intervention to potentially reverse muscle wasting.

Therefore, this study will evaluate the patterns and predictors of changes in SMM in LA-HNC patients treated with cisplatin-based CRT. In addition, this study will determine if low SMM before CRT or loss of SMM after CRT have a prognostic impact on OS and DFS in LA-HNC patients.

MATERIAL & METHODS

ETHICAL APPROVAL

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht, METC ID: 17-365/C. The requirement for informed consent from patients was waived because of its retrospective design.

STUDY DESIGN

A retrospective cohort study was conducted. All patients diagnosed with LA-HNC and treated with cisplatin-based CRT in primary or postoperative setting between 2012 and 2018 in our tertiary referral center were screened for inclusion. Inclusion criteria for this study required that patients had CT or MRI imaging of the head and neck area within 1 month before CRT and follow-up CT or MRI imaging within 1 year after completion of CRT. Relevant demographic and clinical variables were retrieved from patients' electronic medical records.

THERAPY

Chemotherapy regimen consisted of three cycles of intravenous cisplatin-based chemotherapy on days 1, 22 and 43 of CRT. Chemotherapy dose was 100 mg/m^2. CRT was given in a primary setting for patients with (technical or functional) irresectable LA-HNC and in a postoperative setting in case of positive resection margins and/or in the presence of extranodal tumor extension in resected lymph node metastases. Radiotherapy was administered in 35 fractions of 2 Gy to make a total dose of 70 Gy (primary setting) and in 33 fractions of 2 Gy to make a total dose of 66 Gy (postoperative setting).

SKELETAL MUSCLE MEASUREMENTS

Skeletal muscle area (SMA) was segmented using the Slice-O-matic software. Patients' SMA was segmented on pre-CRT imaging and post-CRT imaging. At the level of the third cervical vertebra (C3), a single slice was used for SMA segmentation. The first slide to completely show the entire vertebral arc when scrolling through the C3 vertebra in caudal to cephalic direction was selected. 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.[23] For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. The overall intraclass correlation coefficient (ICC) for the muscle SMA obtained by CT and MRI has shown to be excellent (ICC 0.9, $p<0.01$)[24], and can therefore be used interchangeably for

measuring CSA at the level of C3. The SMA was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoid muscles. When measurement of SMA of one sternocleidomastoid was not possible, due to e.g., lymph node invasion or radical neck dissection, we calculated the SMA of the other sternocleidomastoid and multiplied this by two. SMA at the level of C3 was first converted to SMA at the level of L3 using a previously published formula.[25] The SMA at the level of L3 was corrected for patients' squared height to obtain the lumbar skeletal muscle mass index (LSMI).

The LSMI cut-off value for the diagnosis of low SMM chosen in this study was a LSMI of 43.2 cm^2/m^2, as previous calculated in a separate cohort of LA-HNC patients.[12] This cut-off value was used to categorize patients into patients with low SMM and patients without low SMM. Thus, in further analyses low SMM was defined as LSMI ≤ 43.2 cm^2/m^2.

SKELETAL MUSCLE MASS CHANGES

Relative changes of SMM were calculated by using the following formula:

Relative change of SMM = (SMA after CRT – SMA before CRT) / (SMA before CRT) x 100%.

Hereafter, the standard deviation (SD) of the relative changes in SMM were calculated as previously described by Brown et al.[26] in order to derive five categories of changes in SMM in the 5^{th} to 95^{th} percentiles:

Stable changes in SMM: no change ± 1 SD from baseline
Moderate gain in SMM: ≥ 1SD to < 2 SD of gain from baseline
Moderate loss in SMM: ≥ 1SD to <2 SD of loss from baseline
Large gain in SMM: ≥2 SD from baseline
Large loss in SMM: ≥2 SD from baseline

SURVIVAL

OS was defined as the time between the date of histologic diagnosis of LA-HNC and death, or date of last follow-up. DFS was defined as the time between the date of histologic diagnosis of LA-HNC and the date of pathologic confirmed recurrence or date of last follow-up, whichever occurred first.

STATISTICAL ANALYSIS

Data analysis was performed using IBM SPSS statistics 25. Demographic and clinical data were reported for the included patients. Baseline measures for these groups were described using descriptive statistics. Normally distributed variables were shown as means ± standard deviation (SD), non-normally distributed variables were shown as medians with an interquartile range (IQR). Normality was investigated using the Kolmogorov-Smirnov test. Independent sample student's *t*-tests were used to compare the means of normally distributed continuous variables with regard to presence or absence of low SMM. Categorical variables were described

as frequencies with corresponding percentages. Chi-square statistics were used for analyzing differences between the frequencies of each categorical variable with regard to the presence or absence of low SMM and of muscle changes.

A Cox proportional hazard model was used for univariate and multivariate analysis of the predictors for loss of SMM (including patients from the groups of moderate and large loss of SMM) and for the prognostic impact of low SMM at baseline and a loss of SMM (including patients from the groups of moderate and large loss of SMM) after CRT on OS and DFS. The time interval chosen in the Cox proportional hazard model was the time between pre-CRT and follow-up imaging for estimating the predictors for loss of SMM and the time interval between diagnosis and the date of the event (death, recurrence) for estimating the prognostic impact of SMM on OS and DFS. Covariates used in the multivariate analysis were selected based on clinical relevance. Clinical relevance was determined based on literature and expert-opinion. Backward elimination was used to exclude potential predictors with a p-value of more than 0.05. Furthermore, the relationship between survival and SMM and change in SMM was visualized using Kaplan-Meier survival curves, including Log-rank tests. Statistical significance was evaluated at the 0.05 level using 2-tailed test

RESULTS

PATIENTS' CHARACTERISTICS

In total, 235 LA-HNC patients were identified who received cisplatin-based CRT between 2012 and 2018 and had evaluable pre-CRT and follow-up imaging of the head and neck area within 1 year. The median time between follow-up imaging and pre-CRT imaging was 6 months (IQR 5-9). The follow-up period of the included patients ranged from November 2012 till May 2019.

The clinical and demographic characteristics of the study population prior to initiation of CRT are presented in table 1. The majority of patients was male (70%). Mean age at diagnosis was 59 years (SD 8) and the mean body mass index (BMI) was 24.5 kg/m^2. Nearly half of the patients (49%) had mild comorbidities as evaluated by the Adult Comorbidity Evaluation 27 (ACE-27) score. Most patients were current/former smokers (82%) and/or consumed alcohol (83%), 75% of patients had combined tobacco and alcohol use. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (47%). The mean serum albumin levels of the included patients at diagnosis were 39.8 g/L (SD 4.6). Most patients had either a tumor located in the oral cavity (35%) or oropharynx (31%) of which the majority (60%) was not associated with human papillomavirus. A majority of the patients (83%) was diagnosed with a tumor, node, metastasis (TNM) stage IV tumor and underwent CRT in a primary setting (71%).

At pre-CRT imaging, 141 patients (60%) had low SMM. As is shown in table 1, patients with low SMM were significantly more likely to be female, older of age, to be (current/former) smokers, to have combined tobacco and alcohol use, and to have a BMI <18.5 kg/m^2.

At follow-up imaging, 149 patients (63%) were diagnosed with low SMM. Mean SMA at follow-up imaging (31.62 cm^2, SD 8.69) was significantly lower than mean SMA at pre-CRT imaging (33.34 cm^2, SD 9.11) (p<0.01). Table 2 shows the SMM changes that occurred in the study population. Only 91 patients (39%) had stable SMM compared to pre-CRT. A rather large proportion of the study population (n=129, 55%) had moderate loss in SMM compared to pre-CRT SMM and only 13 (6%) patients showed moderate gain in SMM compared to pre-CRT SMM. A minority of patients experienced large loss in SMM (n=1, 0.4%) or large gain in SMM (n=1, 0.4%).

Table 1. Study population characteristics

Characteristic	Total (n=235)	Low SMM (n=141, 60%)	Without low SMM (n=94, 40%)	*p*-value
	N (%)	N (%)	N (%)	
Gender				
Male	164 (69.8)	73 (51.8)	91 (96.8)	**<0.01**
Female	71 (30.2)	68 (48.2)	3 (3.2)	
Age diagnosis (years) (mean, SD)	58.6 (8.0)	59.9 (7.3)	56.7 (8.8)	**<0.01**
BMI (kg/m^2)				
<18.5	21 (8.9)	21 (14.9)	0	**<0.01**
18.5-24.9	117 (49.8)	83 (58.9)	34 (36.2)	
25.0-29.9	65 (27.7)	26 (18.4)	39 (41.5)	
≥ 30	32 (13.6)	11 (7.8)	21 (22.3)	
ACE-27 score				
None	50 (21.3)	31 (22)	19 (20.2)	0.95
Mild	115 (48.9)	67 (47.5)	48 (51.1)	
Moderate	53 (22.6)	33 (23.4)	20 (21.3)	
Severe	17 (7.2)	10 (7.1)	7 (7.4)	
Performance status				
ECOG 0	63 (26.8)	35 (24.8)	28 (29.8)	0.56
ECOG 1	111 (47.2)	68 (48.2)	43 (45.7)	
ECOG 2	26 (11.1)	16 (11.3)	10 (10.6)	
ECOG 3	1 (0.4)	0	1 (1.1)	
Missing	34 (14.4)	22 (15.6)	12 (12.8)	
Smoker				
No	43 (18.3)	20 (14.2)	23 (24.5)	0.05
Current/former	192 (81.7)	121 (85.8)	71 (75.5)	
Alcohol use				
No	40 (17)	23 (16.3)	17 (18.1)	0.73
Yes	195 (83)	118 (83.7)	77 (81.9)	

Table 1. (Continued)

Characteristic	Total (n=235)	Low SMM (n=141, 60%)	Without low SMM (n=94, 40%)	*p*-value
	N (%)	N (%)	N (%)	
Smoker & Alcohol use				
No	60 (25.5)	28 (19.9)	32 (34.0)	**0.02**
Yes	175 (74.5)	113 (80.1)	62 (66.0)	
Albumin (g/L) (mean, SD)	39.8 (4.6)	39.7 (4.8)	40.0 (4.3)	0.70
Tumor site				
Oral cavity	83 (35.3)	55 (39)	28 (29.8)	0.49
Oropharynx	73 (31.1)	39 (27.7)	34 (36.2)	
HPV –	*44 (60.3)*	*26 (66.7)*	*18 (52.9)*	
HPV +	*21 (28.8)*	*6 (15.4)*	*15 (44.1)*	
HPV unknown	*8 (11.0)*	*7 (17.9)*	*1 (2.9)*	
Nasopharynx	19 (8.1)	9 (6.4)	10 (10.6)	
Hypopharynx	32 (13.6)	22 (15.6)	10 (10.6)	
Larynx	10 (4.3)	5 (3.5)	5 (5.3)	
Paranasal sinus	10 (4.3)	6 (4.3)	4 (4.3)	
Unknown primary	8 (3.4)	5 (3.5)	3 (3.2)	
TNM stage				
III	40 (17.0)	22 (15.6)	18 (19.1)	0.48
IV	195 (83.0)	119 (84.4)	76 (80.9)	
CRT setting				
Primary	166 (70.6)	93 (66)	73 (77.7)	*0.05*
Adjuvant	69 (29.4)	48 (34)	21 (22.3)	

Legend table 1: p-values printed in bold were significant at a 0.05 level. p-values printed in italics were near statistical significance at a 0.05 level Abbreviations: SMM: skeletal muscle mass, BMI: body-mass index, ACE-27: Adult-Comorbidity Evaluation 27, ECOG: Easter Cooperative Oncology Group HPV: human papilloma virus, TNM: tumor, node, metastasis, CRT: chemoradiotherapy

Table 2. Changes in SMM after CRT

	Stable	Moderate Loss	Moderate Gain	Large Loss	Large gain
Change in SD	**± 1SD**	**≥ 1SD to < 2SD**	**≥ 1SD to < 2SD**	**≥ 2SD**	**≥ 2SD**
SMA range (cm^2)	>24.33 to <42.45	≤24.33 to >18.22	≥42.45 to <51.56	≤18.22	≥51.56
N (%)	91 (38.7)	129 (54.9)	13 (5.5)	1 (0.4)	1 (0.4)

Legend table 2: Abbreviations: SMM: skeletal muscle mass, CRT: chemoradiotherapy, SD: standard deviation, SMA: skeletal muscle area

Table 3 shows the characteristics of patients with stable SMM versus patients with loss in SMM (moderate and large loss) and gain in SMM (moderate and large gain). Patients with loss in SMM were more likely to have a BMI ≥25kg/m^2 compared to patients with stable SMM (p<0.01).

Table 3. Characteristics of patients with stable SMM versus patients with loss and gain of SMM

Characteristic	Stable n=91 41.2%	Muscle Loss N=130 90.3%	Muscle Gain N=14 9.7%	p
	N (%)	N (%)	N (%)	
Gender				
Male	63 (69.2)	89 (68.5)	12 (85.7)	0.4
Female	28 (30.8)	41 (31.5)	2 (14.3)	
Age >60 years				
No	45 (49.5)	72 (55.4)	7 (50)	0.7
Yes	46 (50.5)	58 (44.6)	7 (50)	
BMI (kg/m²)				
<18.5	14 (15.4)	6 (4.6)	7 (50)	**0.01**
18.5-24.9	50 (54.9)	60 (46.2)	1 (7.1)	
25.0-29.9	19 (20.9)	40 (30.8)	6 (42.9)	
≥ 30	8 (8.8)	24 (18.5)	0 (0)	
ACE-27 score				
None	18 (19.8)	29 (22.3)	3 (21.4)	0.7
Mild	48 (52.7)	64 (49.2)	3 (21.4)	
Moderate	19 (20.9)	30 (23.1)	4 (28.6)	
Severe	6 (6.6)	7 (5.4)	4 (28.6)	
Performance				
ECOG 0	24 (26.4)	37 (28.5)	2 (14.3)	0.2
ECOG 1	48 (52.7)	53 (40.8)	10 (71.4)	
ECOG ≥2	8 (8.8)	19 (14.6)	0 (0)	
Unknown	11 (12.1)	21 (16.2)	2 (14.3)	
Smoking				
No	18 (19.8)	24 (18.5)	1 (7.1)	0.7
Former	25 (27.5)	37 (28.5)	3 (21.4)	
Current	48 (52.7)	69 (53.1)	10 (71.4)	
Alcohol use				
No	18 (19.8)	2 (14.3)	20 (15.4)	0.7
Current/former	73 (80.2)	12 (85.7)	110 (84.6)	
Tumor site				
Oral cavity	30 (33)	46 (35.4)	7 (50)	0.2
Oropharynx	22 (24.2)	46 (35.4)	5 (35.7)	
Nasopharynx	9 (9.9)	10 (7.7)	0 (0)	
Hypopharynx	16 (17.6)	14 (10.8)	2 (14.3)	
Larynx	4 (4.4)	6 (4.6)	0 (0)	
Paranasal sinus	3 (3.3)	7 (5.4)	0 (0)	
Unknown primary	7 (7.7)	1 (0.8)	0 (0)	
TNM-stage				
III	14 (15.4)	26 (20)	0 (0)	0.3
IV	77 (84.6)	104 (80)	14 (100)	

Legend table 3: p-values printed in bold were significant at a 0.05 level. Abbreviations: SMM: skeletal muscle mass, BMI: body-mass index, ACE-27: adult comorbidity evaluation-27, ECOG: Easter Cooperative Oncology Group, HPV: human papilloma virus, TNM: tumor, node, metastasis

PREDICTORS OF LOSS IN SKELETAL MUSCLE MASS

Table 4 shows the Cox regression analysis of the predictors for loss of SMM. In univariate regression analysis, significant predictors for loss of SMM were a BMI ≥25kg/m^2 (hazard ratio (HR) 1.7, 95% confidence interval (CI) 1.1-2.6), blood albumin levels (HR 1.1, 95% CI 1.0-1.2), a tumor located in the oropharynx (HR 2.6, 95% CI 1.7-4.0), nasopharynx (HR 2.5, 95% CI 1.3-5.0) or larynx (HR 2.9; 95% CI 1.2-6.9). Having an ECOG performance status of 1 was associated with a lower risk of loss of SMM (HR 0.5, 95% CI 0.3-0.7) compared to patients with ECOG 0. Undergoing CRT in a postoperative setting was also associated with a lower risk of loss in SMM (HR 0.5; 95% CI 0.3-0.7). Patients able to receive an absolute cumulative cisplatin dose of ≥300mg were also less likely to experience loss of SMM (HR 0.6, 95% CI 0.4-0.97). In multivariate Cox regression analysis including the variables BMI, albumin levels, tumor site, treatment setting and received cisplatin dose; a BMI ≥25kg/m^2 or BMI ≥30kg/m^2 (HR 2.4, 95% CI 1.3-4.6 and HR 3.1, 95% CI 1.3-7.3, respectively), albumin level (HR 1.1, 95% CI 1.1-1.2), a tumor located in the oropharynx (HR 2.4, 95% CI 1.2-4.8), receiving CRT in an adjuvant setting (HR 0.4, 95% CI 0.2-0.8) remained significant predictors for loss of SMM after CRT.

Table 4. Proportional Cox regression analysis: predictors for SMM loss

	Univariate analysis		**Multivariate analysis**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years) (mean, SD)	0.98 (0.96-1.0)	0.09		
Gender				
Male	Ref.			
Female	0.75 (0.51-1.09)	0.13		
BMI (kg/m^2)				
18.5-24.9	Ref.		Ref.	
≤18.5	0.77 (0.33-1.79)	0.55	0.82 (0.19-3.67)	0.79
25-29.9	1.69 (1.12-2.55)	**0.01**	2.43 (1.27-4.64)	**<0.01**
≥30	1.40 (0.87-2.26)	0.17	3.06 (1.28-7.28)	**0.01**
Smoking				
No	Ref.			
Yes	1.06 (0.68-1.67)	0.79		
Alcohol use				
No	Ref.			
Yes	1.17 (0.72-1.92)	0.52		
Performance status				
ECOG 0	Ref.			
ECOG 1	0.48 (0.31-0.74)	**<0.01**		
ECOG ≥2	0.93 (0.53-1.62)	0.80		
Unknown	0.57 (0.33-0.97)	**0.04**		
Albumin (mmol/L)	1.1 (1.03-1.2)	**<0.01**	1.14 (1.06-1.23)	**<0.01**
ACE-27 score				
None	Ref.			
Mild	1.04 (0.66-1.63)	0.87		
Moderate	0.79 (0.47-1.34)	0.38		
Severe	0.52 (0.22-1.19)	0.12		

Table 4. (Continued)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Tumor localization				
Oral cavity	Ref.		Ref.	
Oropharynx	2.64 (1.72-4.04)	**<0.01**	2.36 (1.16-4.8)	**0.02**
Nasopharynx	2.52 (1.26-5.04)	**<0.01**	3.6 (0.9-14.1)	0.07
Hypopharynx	0.72 (0.39-1.31)	0.28	0.55 (0.21-1.46)	0.23
Larynx	2.88 (1.21-6.85)	**0.02**	1.81 (0.37-8.9)	0.47
Paranasal sinus	1.36 (0.60-3.09)	0.46	0.82 (0.2-3.47)	0.79
Unknown primary	0.71 (0.10-5.21)	0.74	0 (0-9.999)	0.98
HPV-status				
Negative	Ref.			
Positive	1.25 (0.62-2.49)	0.53		
Unknown	1.45 (0.59-3.55)	0.42		
CRT setting				
Primary	Ref.		Ref.	
Adjuvant	0.46 (0.32-0.68)	**<0.01**	0.39 (0.2-0.77)	**<0.01**
Dose-limiting toxicity				
No	Ref.			
Yes	1.04 (0.73-1.47)	0.84		
Cumulative chemotherapy dose				
<300mg	Ref.		Ref.	
≥300mg	0.63 (0.42-0.97)	**0.03**	0.57 (0.29-1.1)	0.09
Weight loss during CRT				
None	Ref.			
< 10%	1.45 (0.94-2.23)	*0.09*		
≥ 10%	1.76 (0.91-3.42O)	*0.09*		

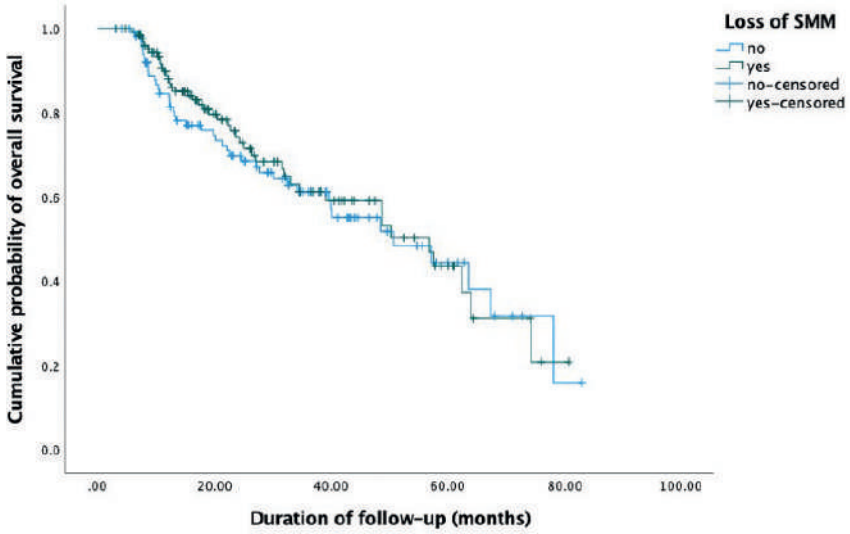
Legend table 4: Abbreviations: SMM: skeletal muscle mass, HR: hazard ratio, SD: standard deviation BMI: body-mass index, ACE-27: adult comorbidity evaluation-27, ECOG: Easter Cooperative Oncology Group, HPV: human papilloma virus, TNM: tumor, node, metastasis, CRT: chemoradiotherapy

SURVIVAL: OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL

During the follow-up period from November 2011 till May 2019, 86 (37%) patients died, and 72 (31%) patients developed a recurrence. The median OS was 22 months (IQR 12-39) and the median DFS was 19 months (IQR 9-35). Of the patients that died, 43 (50%) patients experienced a loss in SMM, 36 (42%) patients had stable SMM changes, and 7 (8%) patients gained SMM after treatment. Of the patients that developed a recurrence during follow up, 36 (50%) patients had a loss in SMM, 31 (43%) patients had stable SMM changes, and 5 (7%) patients gained SMM. Although half of the patients who died or had a recurrence during follow-up experienced a loss in SMM, in univariate Cox regression analysis no prognostic value of loss in SMM for OS nor DFS were found. Using stable or gain in SMM changes as the reference group, HRs for SMM loss were 0.9 (95% CI 0.6-1.4) and 0.8 (95% CI 0.5-1.3) respectively. Figure 1 shows the Kaplan-Meier OS and DFS curves for patients with loss in SMM versus no loss in SMM (stable

SMM and muscle gain (moderate and large). In univariate Cox regression analysis, low SMM prior to initiation of CRT showed no prognostic value for decreased OS (HR 1.5; 95% CI 0.9-2.3). No significant prognostic impact of low SMM for DFS was seen (HR 1.4; 95% CI 0.9-2.3). Low SMM after treatment showed no prognostic value for OS (HR 1.4; 95% CI 0.9-2.2) nor DFS (HR 1.3; 95% CI 0.8-2.2). Figure 2 shows the Kaplan-Meier OS and DFS curves for patients with low SMM before CRT.

Figure 1. Kaplan-Meier OS and DFS curves of patients with stable SMM versus muscle changes (muscle loss and muscle gain) showed no significant differences in OS (Log-rank Chi-square 0.1, p=0.8) nor DFS (Log-rank Chi-square 0.5, p=0.5).



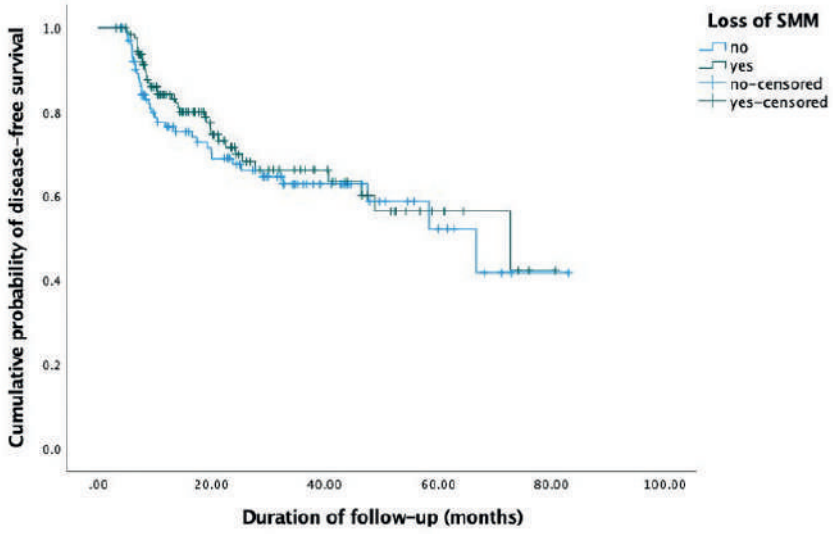
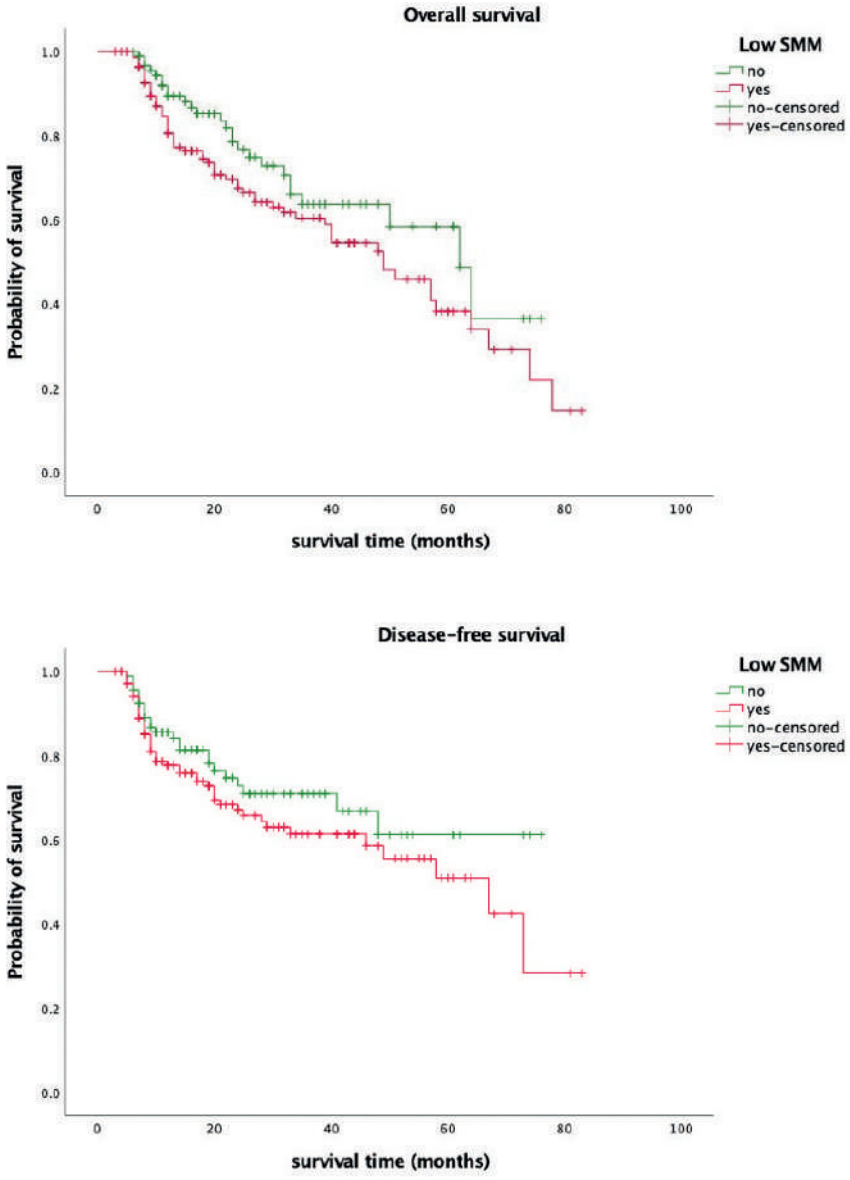


Figure 2. Kaplan-Meier OS and DFS curves of patients with low SMM at diagnosis decreased OS (Log-rank Chi-square 2.80, p=0.09) and DFS (Log-rank Chi-square 1.85, p=0.17) compared to patients without low SMM, although this finding was not statistically significant.



DISCUSSION

This study is the first to evaluate the patterns of changes in SMM in LA-HNC patients treated with cisplatin-based CRT. After CRT, the majority of the patients (n=129, 55%) had moderate loss of SMM and one patient (0.4%) had large loss of SMM after CRT. A minority of the patients (n=13, 6%) had moderate gain of SMM after CRT and one patient (0.4%) had large gain of SMM after CRT. Of the 235 LA-HNC patients who underwent CRT only 91 patients (39%) had stable SMM. Mean SMA at follow-up (31.62 cm^2, SD 8.69) was significantly lower than mean SMA at initiation of CRT (33.34 cm^2, SD 9.11). The prevalence of low SMM increased after CRT from 60% of the study population to 63%.

As reported in many studies, low SMM prior to initiation of CRT seemed to have a negative prognostic impact on overall survival, but this finding was not statistically significant. Previous research has shown that low SMM is a significant negative prognostic factor for survival.[19,21] Because we also included patients who were treated as recently as in 2018, right-censoring of these cases might explain why we did not find a prognostic impact of low SMM for survival. Another explanation for this finding might be that tumor stage itself as a prognostic factor outweighs the prognostic impact of low SMM. In a previous study in elderly HNC patients we also showed that low SMM had prognostic impact in patients with stage I-III HNC, but lost its prognostic impact in patients with stage IV HNC.[21] In this study we included patients with LA-HNC, stage III-IV, and it is possible that low SMM does not have a prognostic impact in this group of patients. The mechanism underlying the relation between low SMM and decreased survival is yet to be elucidated. Low SMM may impact survival by causing treatment-related toxicities, which may lead to ineffective cancer treatment. In a previous study, although low SMM was not prognostic for the whole group of HNC patients treated with primary CRT, patients who experienced cisplatin dose limiting toxicity, significantly more frequently observed in patients with low SMM, had a worse prognosis.[12] Moreover, malignancies also cause a state of hyper catabolism and inflammation which negatively impacts SMM causing a negative vicious circle.[27]

The loss of SMM after treatment, also referred to as muscle wasting, is the net result of a combination of an imbalance between protein synthesis and protein degradation, cell death of muscle cells and a decrease in the muscle's capability of regenerating news muscle cells. Previous research also underlines the role of oxidative stress and inflammation in the development of muscle wasting.[28]

In this study, patients with an oropharyngeal carcinoma had a significantly higher risk of a loss of SMM after CRT. Patients with oropharyngeal carcinoma are especially prone to malnutrition due to the localization of the tumor impairing oral intake. This may explain the higher risk of a loss in SMM and may advocate for early nutritional support for these patients at high-risk for loss in SMM. Being overweight or obese at diagnosis also showed to be a significant predictive factor for loss of SMM in our study population. Although this may feel counterintuitive, BMI

may mask an underlying unfavorable body composition, i.e., a patient may be overweight by a surplus of fatty tissue and still have low SMM. This combination of low SMM and a surplus of fatty tissue is also referred to in the literature as sarcopenic obesity. Sarcopenic obesity has shown to carry the cumulative risk of low SMM and high fat mass.[29] In clinical practice, the start of nutritional support in cancer patients is mainly guided by their body weight at presentation and loss of body weight prior to treatment rather than body composition, i.e., the amount of SMM and fat mass. This approach may result in underdiagnosis of patients in need for nutritional support.

Although previous studies have shown that loss of SMM in patients whom received cancer treatment [30,15,16,31]had significant prognostic impact on survival, in this study a loss in SMM showed no prognostic impact for OS nor DFS. This difference may be explained by the heterogeneity in the definition of muscle mass changes, the timing of the follow-up imaging and the type and stage of cancer and its type of treatment. Another explanation might be that in HNC dietician guidance is incorporated earlier into standard care practice than in non-HNC due to the high risk of malnutrition in patients with HNC.

The median time between follow-up imaging and pre-CRT imaging in our study was 6 months (range 5-9]. In previous studies conducted in non-HNC cancer patients in which loss of SMM showed to have prognostic value, this interval ranged between 9-27 months[26] and 9-18 weeks.[15] Besides the difference in time interval between this study and previous studies, there is also a difference in the investigated study population. In this study we included patients who received cisplatin-based CRT in a curative setting. In a previous study a prognostic impact of loss of SMM after CRT for decreased survival was also demonstrated in the palliative setting .[14] Timing of baseline and follow-up SMM assessment may influence the prognostic value of loss of SMM. Nevertheless, this study and the previous studies conducted on muscle wasting in cancer patients all underline the finding of significant SMM changes, which itself is an interesting finding which needs more standardized and prospective research to evaluate its value for treatment outcomes and prognosis in patients with cancer.

For patients with HNC, the frequent use of CT and MRI imaging for staging, evaluation and surveillance provides the opportunity to measure SMM without additional patient burden or costs. SMM assessments can serve as an objective and clinical measure of patient nutritional status and physical vulnerability and can be used to predict treatment outcomes in patients with cancer. SMM can be objectively and reliably measured and is a potentially modifiable risk factor. An increased understanding of the underlying mechanisms of the negative prognostic effects of low SMM in patients with cancer is crucial in order to innovate and to improve current treatment strategies and eventually treatment outcomes. Commonly proposed strategies include combination of high-protein nutritional support, exercise and pharmacological interventions. Use of an intervention program, which includes nutrition support and high-intensity exercise is probably an ideal option for patients with low SMM.[3233]

Our study has some limitations. Firstly, due to the retrospective design of the study not all information on potential confounding variables could be retrieved, such as life-style measures including nutritional support and physical exercise. Nutritional support during CRT may influence the observed changes in SMM and their prognostic value. Secondly, we used routinely performed baseline and follow-up imaging and the time between the baseline and follow-up imaging therefore varied between patients, this may inherently lead to bias of the results. Thirdly, muscle function and muscle strength were not measured in this study. However, these measures are also important in functional depletion and should be investigated further.

Concluding, this study is the first to evaluate longitudinal SMM changes in patients with LA-HNC treated with cisplatin-based CRT and the first to identify risk factors for loss of SMM. Loss of SMM after CRT occurs in majority of LA-HNC patients. Overweight/obese patients and patients with oropharyngeal carcinoma are at increased risk for experiencing loss of SMM. Decreased risk of loss of SMM was seen in patients who received CRT in a postoperative setting or who were able to withstand higher cumulative cisplatin doses.

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CHAPTER 16

Skeletal muscle mass is an imaging biomarker for decreased survival in patients with oropharyngeal squamous cell carcinoma

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ABSTRACT

Objectives

Low skeletal muscle mass (SMM) and sarcopenic obesity (co-presence of low SMM and obesity) are emerging prognosticators in oncology, but the prevalence and prognostic value in oropharyngeal squamous cell carcinoma (OPSCC) is not yet known.

Materials and methods

Patients with OPSCC, curative treatment intention and pre-treatment diagnostic imaging of the head and neck area were included. Patients with unknown HPV-status, palliative treatment intention or unavailable imaging were excluded. Relevant demographic and clinical characteristics were collected between 2009-2016. Patients were stratified into a low-, intermediate-, and high-risk group according to HPV-status, number of pack-years, tumor and nodal stage. SMM was radiologically measured, and cutoff values were determined by optimal stratification. The prognostic value of low SMM and sarcopenic obesity for overall survival (OS) and disease-free survival (DFS) was determined by Cox regression analysis and Kaplan Meier survival curves.

Results

In 216 patients, low SMM and sarcopenic obesity were present in 140 (64.8%) and 13 (6.0%) patients, respectively. On multivariate analysis, stratification into a high-risk group (HPV-negative status with ≥ 10-pack-years or T4-stage) was a prognostic factor for OS and DFS (HR 2.93, $p<0.01$) (HR 4.66, $p<0.01$). Of specific interest, sarcopenic obesity was a strong negative prognostic factor for OS and DFS (HR 4.42, $p<0.01$) and (HR 3.90, $p<0.05$), independent from other well-known prognostic factors such as HPV-status.

Conclusion

Low skeletal muscle mass is highly prevalent in OPSCC patients. Sarcopenic obesity is a novel pretreatment prognosticator for OS and DFS in OPSCC and should therefore be considered in clinical decision making.

INTRODUCTION

Head and neck cancers (HNCs) are among the most frequent tumors in the world with an estimated 835.000 new cases and 428.000 deaths in 2018.[1] The vast majority of HNCs are head and neck squamous cell carcinomas (HNSCCs), and most are related to alcohol consumption and/or smoking.[2, 3] There has been a rise in the incidence of HNSCC over the past decade, in particular, the incidence of oropharyngeal squamous cell carcinoma (OPSCC). This is largely due to a specific increase in incidence of a particular subset of OPSCC, which is driven by high-risk Human Papilloma Virus (HPV) infection.[4,5] In general, HPV-positive OPSCC has a better prognosis than HPV-negative OPSCC.[6] Other known prognostic factors in OPSCC include age, tumor stage, nodal stage, and comorbidities.[7, 8] For HPV-related OPSCC, several risk models have been published in medical literature in order to gain more precise prognostic information for this specific subset of HNSCCs patients, which may allow for development of treatment de-intensification approaches for HPV-associated OPSCC. [9-12] Ang et al. were the first to propose a risk stratification model for OPSCC, which stratified patients according to HPV-status, smoking status, tumor and nodal stage into a low, intermediate and high risk of death.[9] Although previously reported risk models included a variety of known prognostic factors in OPSCC, none included body composition as a possible interacting variable.

Over the last decade, the radiological assessment of individual body composition has increasingly gained interest in oncological patients.[13] Sarcopenia, sometimes also termed low skeletal muscle mass (SMM) or low lean body mass, is traditionally described as a geriatric syndrome consisting of both the specific loss of SMM and the decrease of skeletal muscle function.[14] Sarcopenia is a multifactorial syndrome; risk factors include malnutrition, immobility and illness.[14] In oncological studies, sarcopenia is often defined as low SMM only, because skeletal muscle function tests are not commonly performed in routine clinical practice. Sarcopenic obesity is described as the co-presence of both low SMM and obesity.[15,16]

In several retrospective studies, low SMM and sarcopenic obesity have been associated with increased rates of postoperative complications, chemotherapy-related toxicity, and decreased survival rates in colon cancer, breast cancer, lung cancer, and pancreatic cancer, amongst others.[17,18,19] Research on the prevalence, predictive value and prognostic impact of low SMM and sarcopenic obesity in HNC patients has more recently been initiated. In patients with locally advanced HNSCC undergoing chemoradiotherapy, sarcopenia was associated with a trifold risk of chemotherapy dose-limiting toxicity.[20] Pre-treatment low SMM was associated with an increased incidence of pharyngocutaneous fistula and decreased overall survival in HNSCC patients undergoing a total laryngectomy. [21,22]

A recent study in OPSCC patients showed an association between low SMM and decreased overall survival, independent of HPV-status.[23] In this study, only patients with advanced OPSCC were included and SMM was assessed on a pre-treatment PET-CT scan of the abdomen. Even though measurement of SMM on a CT scan of the abdomen at the level of the third lumbar

vertebra (L3) is very common in oncological research[17] , this may lead to an inclusion bias in HNC patients because not all patients will undergo a PET-CT during the diagnostic work-up.[24] Recently, a novel SMM assessment method at the level of the third cervical vertebra (C3) was published. [25,26] Imaging at the level of C3 is almost always available in HNC patients because diagnostic imaging of the head and the neck area is used for staging, which allows the routine assessment of SMM.

In this study, we aim to investigate the prevalence and prognostic value of pre-treatment low SMM and sarcopenic obesity as measured at the level of C3 in a large cohort of OPSCC patients corrected for known prognostic factors including age, weight loss 6 months prior to diagnosis, comorbidities, HPV-status, and TNM-stage.

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. All data were handled according to general data protection regulation (GDPR).

PATIENTS AND STUDY DESIGN

A retrospective cohort study was conducted in 241 OPSCC patients diagnosed and treated with curative intent at the University Medical Center Utrecht, Utrecht, The Netherlands, between 2009 and 2016. Patients with OPSCC were included if they had recent (≤ 1 months prior) pre-treatment imaging scans (CT or MRI) of the head and neck at the level of the third cervical vertebrae (C3). The median time between imaging and treatment was 0.79 month (IQR 0.56-1.12). Patients were excluded if they had a palliative treatment intent (n=17) or if diagnostic imaging was of poor quality which impaired measurements of SMM (n=8). In total, 216 OPSCC patients were included. Relevant demographic and clinical variables were collected from patients' medical record. Demographic variables included sex and age at diagnosis. Clinical variables included; length and weight at diagnosis, body-mass-index (BMI), percentage of weight loss in the six months prior to diagnosis, smoking status, amount of pack-years, alcohol intake, comorbidities as expressed by the Adult Comorbidity Evaluation-27 (ACE-27) score, tumor localization, date of histologic diagnosis, HPV-status, tumor staging according to the tumor-node-metastasis (TNM) 7th Edition IUCC manual, treatment modality (chemotherapy, radiotherapy, surgery or a combination) and survival data. HPV-status was determined using the algorithm described by Smeets et al: a p16 staining was performed. In case of a positive result this was followed by a PCR on HPV. [27] Patients with known HPV-status were stratified into risk groups as described by Ang et al: HPV-positive patients with less than 10 pack-years or with more than 10-pack-years but a N0-N2a nodal stage were considered to be at low risk,

whereas HPV-positive patients with more than 10 pack-years and a N2b-N3 nodal stage and HPV-negative patients with less than 10 pack-years and a T1-3 tumor stage were considered to be at a intermediate risk, HPV-negative patients with more than 10 pack-years or with less than 10 pack-years but a T4 tumor stage were considered to be at high risk. [9] Overall survival (OS) was defined as the time between the date of histologic diagnosis and death, or date of last follow-up. Disease-free survival (DFS) was defined as the time between the date of histologic diagnosis and the date of pathologic confirmed recurrence or date of last follow-up, whichever occurred first. Whenever possible, 5-year OS and DFS rates were calculated.

BODY COMPOSITION MEASUREMENT

SMM was measured as muscle cross-sectional muscle area (CSA) on pre-treatment 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. [28] For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. The overall intraclass correlation coefficient for the muscle CSA obtained by CT and MRI is excellent (0.97, $p<0.01$) (unpublished data). The CSA was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoideus muscles. An example of segmentation at the level of C3 is shown in figure 1.

Figure 1. Example of segmentation of skeletal muscle tissue at the level of the third cervical vertebra (C3)

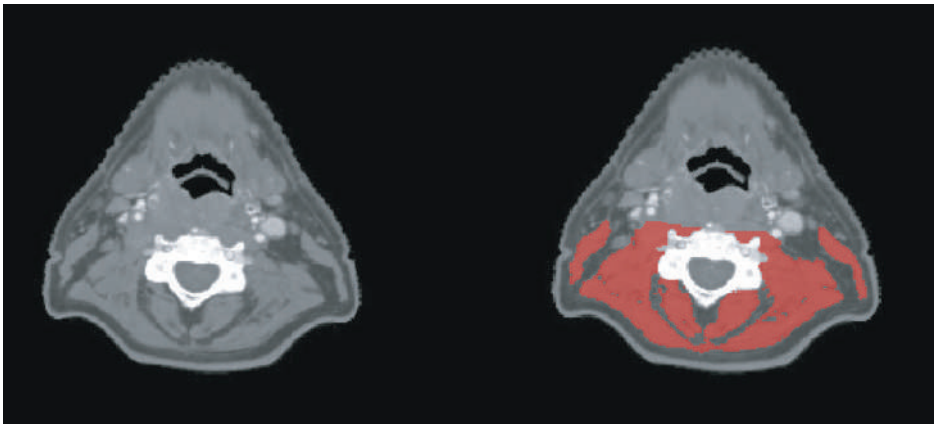


Figure shows two identical axial CT-slides at the level of C3; left shows the muscle tissue unsegmented, right shows both sternocleidomastoideus and paravertebral muscles segmented in red.

Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (Tomovision, Canada) by a single researcher (N.C). CSA at the level of C3 was converted to CSA at the level of L3 using a previously published formula, as shown in formula 1.[25] The lumbar skeletal muscle index (LSMI) was calculated by correcting SMM at

the level of L3 for squared height, as shown in formula 2. Sarcopenic obesity was defined as the combination of low SMM in combination with a BMI ≥ 27 kg/m^2.

Formula 1:
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)

Formula 2:
Lumbar SMI (cm^2/m^2) = CSA at L3/length (m^2)

STATISTICAL METHODS

The optimal stratification method was used to determine cohort specific cutoff values of the SMM. This method is the preferred method in literature and is based on log rank statistics to find the most significant cutoff value for SMM with respect to overall and disease-free survival.[29] Endpoints (OS and DFS) specific cutoff values were determined for the lumbar SMM index and these were used to categorize patients into patients with low SMM and without low SMM for each endpoint. Data analysis was performed using IBM SPSS statistics 25. Descriptive statistics for continuous variables with a normal distribution were presented as mean with standard deviation (SD). Normality was investigated using the Kolmogorov-Smirnov test. The variables age at diagnosis and units of alcohol intake per day were not normally distributed. Variables with a skewed distribution were presented as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Chi-square statistics were used for analyzing differences between the frequencies of each categorical variable with the presence or absence of low SMM. Independent sample student's t-tests were used for comparing the means of the normally distributed continuous variables with the presence or absence of low SMM. Statistical significance was evaluated at the 0.05 level using 2-tailed tests. Survival was visualized using Kaplan Meier survival curves and number at risk tables. Survival analysis was performed for the subset of patients with known HPV-status, patients with missing HPV-status (n=42) were excluded.

A Cox proportional hazard regression model was used for univariate and multivariate analysis of overall and disease-free survival. Covariates used in the univariate analysis were selected based on clinical relevance based on literature. Covariates used in the multivariate analysis were selected based on statistical significance ($p<0.05$) in univariate cox regression analysis. In multivariate Cox regression analysis, two models were constructed, each examining the role of low SMM and sarcopenic obesity separately. Statistical significance was evaluated at the 0.05 level using 2-tailed tests.

RESULTS

A total of 216 OPSCC patients with curative treatment intent and adequate pre-treatment imaging of the head and neck area at the level of C3 were included. Of these patients, 174 patients were identified with known HPV-status.

RISK-STRATIFICATION ACCORDING TO HPV-STATUS

Patients within the high-risk group had a statistically significant worse median OS and DFS (27 months; IQR 12-50 and 20 months; IQR 9-46 respectively) compared to patients within an intermediate risk group (47 months; IQR 38-63 and 47 months; IQR 26-63 respectively) and low risk group (45 months; IQR 22-62 and 44 months; IQR 16-62 respectively) (high versus intermediate risk: Log Rank $\chi 2$= 20.02; p<0.01 and high versus low risk: Log Rank $\chi 2$= 16.61; p<0.01). Patients within a high-risk group had a significantly worse 5-year OS and DFS rate (32% and 50%, respectively) compared to patients within an intermediate risk group (74% and 80%, respectively) (p<0.01) and low risk group (72% and 87%, respectively) (p<0.01).

As shown in table 2 and 3; univariate Cox regression analysis showed that stratification into a high-risk group was statistically significant associated with a decreased OS (HR 3.11; 95% CI 1.61-6.01, p<0.01) and DFS (HR 4.85; 95% CI 1.89-12.42, p<0.01). When corrected for multiple, potentially interacting variables by multivariate Cox regression analysis; stratification into a high-risk group remained of significant negative prognostic value for OS (HR 2.31; 95% CI 1.14-4.68, p<0.05) and DFS (HR 4.06; 95% CI 1.52-10.84, p<0.01).

BODY COMPOSITION

Endpoint-specific cutoff values for L3 muscle mass indices were determined at 43.0 cm^2/m^2 for OS and 43.2 cm^2/m^2 for DFS. These cut-off values are comparably with previous cutoff values established in a separate cohort of head and neck cancer patients. 20 Using these cutoff values, 140 patients (64.8%) were identified with low SMM and 13 patients (6%) were identified with sarcopenic obesity.

Clinical and demographic characteristics of patients with and without low SMM are listed in table 1. Statistically significant differences between patients with and without low SMM were seen in sex, age at diagnosis, percentage of weight loss within six months prior to diagnosis, body-mass-index, number of pack-years, HPV-status and HPV risk group. Patients with low SMM were more likely to be female (50.7% versus 2.6%; p<0.01), to be older of age at diagnosis (mean 63.6 years versus 60.3 years; p<0.05), to have 10% or more weight loss in the six months prior to diagnosis (15% versus 7.9%, p<0.05), to have a BMI that is less than 20kg/m^2 (28.6% versus 2.6%; p<0.01), to have smoked for more than 41 pack-years (40.3% versus 22.2%; p<0.05), to have a HPV-negative related tumor (55% versus 36.8%; p<0.01) and to be stratified within a high-risk group (39.1% versus 13.8%; p<0.01).

Table 1. Demographic and clinical characteristics of patients with and without low SMM

Variables	Low SMM N=140		Without low SMM N=76		χ^2	*p-value*
HPV-status (n, %)						
Positive	33	23.6	36	47.4	12.88	**0.001****
Negative	77	55	28	36.8		
Unknown	30	21.4	12	15.8		
HPV risk group (n,%)						
Low	23	13.2	28	16.1	11.68	**0.001****
Intermediate	19	10.9	12	6.9		
High	68	39.1	24	13.8		
Gender (n, %)						
Female	71	50.7	2	2.6	50.90	**0.0001****
Male	69	49.3	74	97.4		
Age (years) (M, SD)	63.6	9.6	60.3	9.7	NA	**0.02***
BMI (kg/m²) (n, %)						
<20	40	28.6	2	2.6	67.23	**0.001****
20-24.9	76	54.3	20	26.3		
25-29.9	19	13.6	34	44.7		
≥ 30	5	3.6	20	26.3		
Weight loss 6 months prior to diagnosis (n, %)						
Non	86	61.4	61	80.3	8.04	**0.02***
<10%	33	23.6	9	11.8		
≥ 10%	21	15	6	7.9		
Smoker (n, %)						
No	13	9.3	15	19.7	4.86	0.09
Former	45	32.1	23	30.3		
Current	82	58.6	38	50		
Pack-years (n, %)						
0	13	9.4	15	20.8	10.11	**0.04***
1-15	25	18	13	18.1		
16-25	15	10.8	11	15.3		
26-40	30	21.6	17	23.6		
≥41	56	40.3	16	22.2		
Alcohol use (n, %)						
No	19	13.6	13	17.1	2.13	0.36
Yes	100	71.4	47	61.8		
Former	21	15	16	21.1		
Alcohol units/day (M, SD)	3.3	2.7	4.4	3.9	NA	0.11
ACE-27 score (n, %)						
None	38	27.1	19	25	1.35	0.72
Mild	34	24.3	19	25		
Moderate	41	29.3	27	35.5		
Severe	27	19.3	11	14.5		

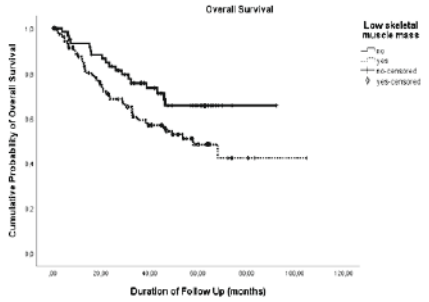
Table 1. (Continued)

Variables	Low SMM N=140		Without low SMM N=76		χ^2	*p-value*
Localization (n, %)						
Tonsil	33	23.6	24	31.6	2.02	0.57
Base of tongue	6	11.4	6	7.9		
Soft palate	7	5	3	3.9		
Oropharynx n.o.s	84	60	43	56.6		
Tumor stage (n, %)						
T1	30	21.4	16	21.1	2.03	0.74
T2	52	37.1	31	40.8		
T3	26	18.6	15	19.7		
T4a	25	17.9	13	17.1		
T4b	7	5	1	1.3		
Nodal stage (n, %)						
N0	66	47.1	24	31.6	9.73	0.08
N1	23	16.4	15	19.7		
N2a	4	2.9	6	7.9		
N2b	28	20	23	30.3		
N2c	16	11.4	8	10.5		
N3	3	2.1	0	0		
TNM stage (n, %)						
I	20	14.3	7	9.2	2.38	0.51
II	29	20.7	14	18.4		
III	26	18.6	12	15.8		
IV	65	46.4	43	56.6		
Chemotherapy (n, %)						
No	95	67.9	41	53.9	4.86	0.09
Primary	40	28.6	33	43.4		
Adjuvant	5	3.6	2	2.6		
Radiotherapy (n, %)						
No	18	12.9	5	6.6	2.41	0.29
Primary	113	80.7	64	84.2		
Adjuvant	9	6.4	7	9.2		
Surgery (n, %)						
No	110	78.6	61	80.3	0.06	0.86
Yes	30	21.4	15	19.7		

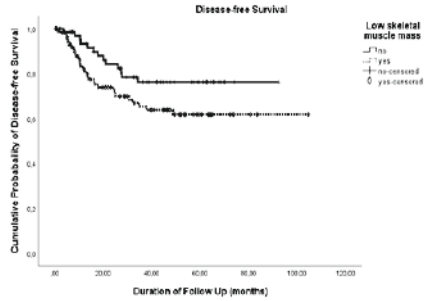
Legend: **. Correlation is significant at the 0.01 level (2-tailed), *. Correlation is significant at the 0.05 level (2-tailed), NA. Not applicable

Figure 1. shows the Kaplan Meier survival curves and number at risk tables of overall and disease-free survival for OPSCC patients with and without low SMM. Patients with low SMM had a significant lower median OS (32.74; IQR 12.72-53.70) compared to patients without low SMM (42.05; IQR 23.61-62.32) (Log rank $\chi 2$= 4.30; p=0.04) with a 5-year OS rate of 43% versus 66%. Patients with low SMM showed a statistical trend towards lower median DFS rate (24.72 months; IQR 9.42-51.78) compared to patients without low SMM (35.25 months; IQR 15.93-62.10) (Log rank $\chi 2$=3.35, p=0.07) with a 5-year DFS rate of 61% versus 76%.

Figure 1. Kaplan Meier curves and number at risk tables for overall survival (top) and disease-free survival (bottom) in OPSCC patients with and without low SMM shows significant difference in OS (Log Rank $\chi 2 = 4.30$, $p = 0.04$) and a statistical trend towards decreased DFS (Log Rank $\chi 2 = 3.35$, $p = 0.07$)



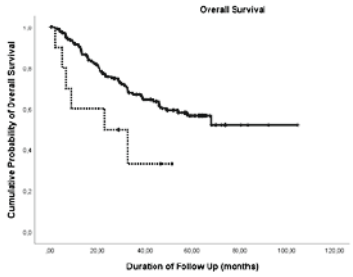
OS	T= 0	T= 12	T= 24	T= 36	T= 48	T= 60
Low SMM	110	85	63	51	37	17
Without low SMM	64	55	48	37	24	19



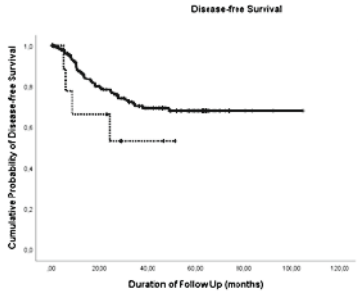
DFS	T= 0	T= 12	T= 24	T= 36	T= 48	T= 60
Low SMM	106	73	55	43	31	15
Without low SMM	68	54	45	34	24	19

Figure 2. shows the Kaplan Meier survival curves and number at risk tables of overall and disease-free survival for OPSCC patients with and without sarcopenic obesity. Patients with sarcopenic obesity had a significant lower median OS (23.03; IQR 4.90-32.82) compared to patients without sarcopenic obesity (38.74; IQR 16.00-57.92) (Log rank $\chi 2 = 4.60$; $p=0.03$) with a 3-years OS rate of 39% versus 60%. Patients with sarcopenic obesity showed lower median DFS rate (23.66 months; IQR 5.48-33.35) compared to patients without sarcopenic obesity (32.35 months; IQR 10.60-57.08) (Log rank $\chi 2 = 1.90$, $p = 0.17$) with a 3-year DFS rate of 51% versus 70%.

Figure 2. Kaplan Meier curves and number at risk tables for overall survival (top) and disease-free survival (bottom) in OPSCC patients with and without sarcopenic obesity shows significant difference in OS (Log Rank $\chi 2 = 4.60$, $p = 0.03$), but not for DFS (Log Rank $\chi 2 = 1.90$, $p = 0.17$)



OS	T= 0	T= 12	T= 24	T= 36	T= 48	T= 60
Sarcopenic obesity	11	5	6	2	1	-
Without sarcopenic obesity	163	134	106	86	60	36



DFS	T= 0	T= 12	T= 24	T= 36	T= 48	T= 60
Sarcopenic obesity	10	6	5	2	1	-
Without sarcopenic obesity	164	121	95	75	54	34

As shown in table 2 and 3. univariate Cox regression analysis showed that low SMM and sarcopenic obesity were statistically significant associated with a decreased OS (HR 1.76; 95% CI 1.02-3.04, p=0.04 and HR 2.44; 95% CI 1.05-5.69, p=0.04, respectively), but not with a decreased DFS (HR 1.81; 95% CI 0.95-3.45, p=0.07 and HR 2.03; 95% CI 0.73-5.68, p=0.18, respectively). In multivariate Cox regression analysis, sarcopenic obesity remained a significant negative prognostic factor for OS (HR 3.16; 95% CI 1.31-7.63, p<0.05) and became a significant negative prognostic for DFS (HR 3.49; 95% CI 1.08-11.27, p<0.05). For OS, this result was independent of HPV-related risk group, percentage of weight loss 6 months prior to diagnosis and comorbidity as assessed by the ACE-27 score and for DFS this result was independent of HPV-related risk group and BMI.

Table 2. Univariate and multivariate Cox regression analysis for analyzing variables associated with overall survival in OPSCC patients

Variable	Univariate analysis			Multivariate analysis (*)					
				Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Low SMM	1.76	1.02-3.04	**0.04***	1.28	0.68-2.22	0.50	-	-	-
Sarcopenic obesity	2.44	1.05-5.69	**0.04***	-	-	-	3.16	1.31-7.63	**0.01***
Risk group									
Low	Ref.			Ref.					
Intermediate	0.90	0.35-2.31	0.82	0.81	0.31-2.11	0.66	Ref.	0.34-2.30	0.79
High	3.11	1.61-6.01	**0.001****	2.31	1.14-4.68	**0.02***	0.882.56	1.30-5.06	**0.007****
Age (years)	1.02	0.99-1.04	0.17						
BMI (kg/m²)									
20-24.9	Ref.								
<20	1.36	0.73-2.54	0.33						
25-30	0.56	0.29-1.09	0.09						
≥30	0.77	0.35-1.68	0.51						
Weight loss 6 months prior to diagnosis (%)									
0	Ref.			Ref.			Ref.		
<10%	1.56	0.85-2.85	0.15	1.43	0.76-2.69	0.27	1.62	0.86-3.05	0.14
≥10%	3.28	1.76-6.11	**0.0001****	2.62	1.38-4.98	**0.003****	3.05	1.61-5.78	**0.001****
ACE-27 score									
Non	Ref.			Ref.			Ref.		
Mild	2.08	0.93-4.68	0.08	1.97	0.87-4.45	0.10	1.95	0.86-4.41	0.11
Moderate	2.97	1.38-6.36	**0.005****	2.43	1.12-5.29	**0.03***	2.27	1,04-4.92	**0.04***
Severe	4.74	2.05-10.98	**0.0001****	4.08	1.75-9.52	**0.001****	3.86	1.65-9.06	**0.002****
TNM stage									
I	Ref.								
II	0.94	0.28-3.21	0.92						
III	2.39	0.79-7.25	0.13						
IV	2.10	0.75-5.86	0.16						

Legend: **. Correlation is significant at the 0.01 level (2-tailed), *. Correlation is significant at the 0.05 level (2-tailed), (*) Model 1 includes the variables; low SMM (SMM), HPV-related risk group, age, BMI, percentage weight loss 6 months prior to diagnosis, ACE-27 score and TNM-stage. Model 2 includes sarcopenic obesity, HPV-related risk group, age, BMI, percentage weight 6 months prior to diagnosis, ACE-27 score and TNM-stage.

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

Variable	Univariate analysis			Multivariate analysis (*)					
				Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Low SMM	1.81	0.95-3.45	0.07	1.41	0.60-3.33	0.44	-	-	-
Sarcopenic obesity	2.03	0.73-5.68	0.18	-	-	-	3.49	1.08-11.27	**0.037***
HPV risk group									
Low	Ref.			Ref.			Ref.		
Intermediate	1.76	0.54-5.77	0.35	1.71	0.51-5.72	0.38	1.93	0.59-6.36	0.28
High	4.85	1.89-12.42	**0.001****	4.06	1.52-10.84	**0.005****	4.32	1.64-11.38	**0.003****
Age (years)	0.99	0.96-1.02	0.57						
BMI (kg/m²)									
20-24.9	Ref.						Ref.		
<20	1.05	0.48-2.29	0.90	Ref.	0.34-1.64	0.75	0.78	0.36-1.72	0.54
25-30	0.36	0.14-0.88	**0.03***	0.75	0.21-1.42	0.21	0.39	0.14-1.05	0.06
≥30	0.96	0.43-2.15	0.92	0.541.30	0.47-3.56	0.62	0.80	0.33-1.94	0.62
Weight loss 6 months prior to diagnosis (%)									
0	Ref.								
≤10%	1.46	0.73-2.91	0.29						
>10%	1.33	0.52-3.45	0.55						
ACE-27 score									
Non	Ref.								
Mild	1.02	0.45-2.31	0.97						
Moderate	1.42	0.68-2.97	0.36						
Severe	1.14	0.40-3.25	0.80						
TNM stage									
I	Ref.								
II	0.70	0.21-2.28	0.55						
III	1.19	0.39-3.64	0.76						
IV	1.13	0.43-2.94	0.81						

Legend: **. Correlation is significant at the 0.01 level (2-tailed),*. Correlation is significant at the 0.05 level (2-tailed), (*) Model 1 includes the variables; low SMM, HPV-related risk group, age, BMI, percentage weight loss 6 months prior to diagnosis , ACE-27 score and TNM-stage. Model 2 includes sarcopenic obesity, HPV-related risk group, age, BMI, percentage weight loss6 months prior to diagnosis, ACE-27 score and TNM-stage.

DISCUSSION

The worldwide incidence of OPSCC is increasing, as is the prevalence of HPV-positive status in OPSCC. The most important prognostic factor in OPSCC is HPV-status; patients with HPV-positive OPSCC have a vastly better prognosis than patients with HPV-negative disease. Over the last decade, low SMM and sarcopenic obesity have emerged as negative prognostic factors in a variety of cancer types and stages.[17,15,30]

This study shows that low SMM, sarcopenic obesity and stratification into a high-risk group are associated with impaired survival rates in patients with OPSCC; sarcopenic obesity especially is a negative prognostic factor for overall and disease-free survival in OPSCC, independent from HPV-status and other factors such as age, BMI, percentage of weight loss 6 months prior to diagnosis, comorbidities and TNM-stage. Pre-treatment low SMM is highly prevalent in patients with OPSCC with an incidence of 64.8%. In contrast, sarcopenic obesity is rare, and occurs in only 6.0% of patients with OPSCC. The individual body composition of cancer patients is increasingly recognized as an important predictive factor for treatment tolerance and for survival after treatment. Specifically, an abnormal body composition with a deficit of SMM with or without a surplus of fat mass (sarcopenia and sarcopenic obesity), is associated with adverse outcomes in oncological patients[31]. Studies in patients with gastrointestinal cancer[32], lung cancer[33], breast cancer[34] and pancreatic cancer have shown that patients with sarcopenia or sarcopenic obesity appear to be more prone to experience toxicity of chemotherapeutical treatment and to suffer from complications after surgery.In head and neck cancer patients, recent studies have shown that there is an association between pre-treatment low SMM and chemotherapy dose-limiting toxicity[20], complications and pharyngocutaneous fistula after total laryngectomy[21,22], and decreased overall survival.[35]Regarding chemotherapy related toxicity, a hypothesis for this relationship is that patients with low SMM and sarcopenic obesity have a different distribution of chemotherapeutical agents in the body. In terms of complications after surgery, it is hypothesized that patients with sarcopenia may have a decreased capability for recovery, for instance due to an altered protein metabolism or a decreased physiological reserve to deal with surgical stress.

In a recent study in advanced oropharyngeal cancer patients, pre-treatment low SMM as a negative prognostic factor in patients with HPV-positive and HPV-negative oropharyngeal cancer showed a trend towards statistical significance.[23] Our study in a larger unselected cohort of OPSCC patients concurs with these results and adds information on the prevalence and prognostic value of sarcopenic obesity in relation to a previous published HPV-related risk stratification model in OPSCC patients. It shows that sarcopenia is highly prevalent in OPSCC patients prior to start of treatment, possibly because oropharyngeal tumors have a high risk of causing dysphagia.[30]

The exact mechanisms of sarcopenia and its relationship with adverse outcomes are currently unknown. It is also unknown to which extent the negative effect of sarcopenia can be over-

turned by improving a patient's physical condition and nutritional status before and during treatment. Future research is needed to clarify these mechanisms. Treatment strategies may be personalized to the patient's specific body composition to decrease the risk of severe toxicity and adverse outcomes, while still maintaining optimal efficacy.

A limitation of this study is the retrospective design which increases the risk of systemic errors and missing data. For example, HPV-status was not available in all patients in this cohort; thus, for survival analysis, patients without a known HPV-status were excluded. Another limitation is that low SMM was not defined according to sex-specific cut-offs, which may result in an over-representation of women in the low SMM group. When more data of female HNSCC patients is available, we aim to define sex-specific cut-offs for low SMM in HNSCC patients. Another limitation is that survival was not measured by treatment modality due to heterogeneity and variations between- and within treatment modalities. Further research is needed to investigate the role of low SMM on survival in patients treated with different treatment modalities. Our recently published measurement method for SMM at the level of C3 allows for the routine evaluation of sarcopenia in almost all head and neck cancer patients. In the future, this tool may be used as a screening tool for patients at risk of severe toxicity or complications from treatment.

This study has examined the prevalence and prognostic value of low SMM and sarcopenic obesity, while adjusting for a variety of known confounders (e.g., comorbidity, weight loss, BMI, HPV-status, TNM-stage), in a large cohort of OPSCC patients. The findings in this study highlight the potential usefulness of determining pre-treatment SMM in HNC patients and contributes to a growing knowledge of low SMM and sarcopenic obesity in HNSCC patients. This knowledge can be used for the development of new interventions, patient management and treatment decision making. In addition, this information can be used for the development of improved risk stratification models in OPSCC patients and de-intensification approaches in HPV-related OPSCC.

CONCLUSION

Pre-treatment low skeletal muscle mass is highly prevalent in patients with oropharyngeal squamous cell carcinoma. The simultaneous presence of low skeletal muscle mass and obesity, sarcopenic obesity, has a statistically significant association with decreased overall and disease-free survival, independent from other well-known prognostic factors such as HPV-status. Therefore, skeletal muscle mass should be considered as a pre-treatment prognostic factor in clinical decision making.

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CHAPTER 17

Dysphagia, trismus and speech impairment following radiation-based treatment for advanced stage oropharyngeal carcinoma: a one-year prospective evaluation

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Article in press ■

ABSTRACT

Background

The objective was to assess swallowing, mouth opening and speech function during the first year after radiation-based treatment (RT (+)) combined with a dedicated preventive rehabilitation program for stage III-IV oropharyngeal carcinoma (OPC).

Material and Methods

Swallowing, mouth opening, and speech function were collected before and at six- and twelve-month follow-up after RT (+) for OPC as part of ongoing prospective assessments by speech-language pathologists.

Results

Objective and patient-perceived function deteriorated until six months and improved until twelve months after treatment, but did not return to baseline levels with 25%, 20% and 58% of the patients with objective dysphagia, trismus and speech problems, respectively. Feeding tube dependency and pneumonia prevalence was low.

Conclusion

A substantial proportion of patients experience functional limitations after RT (+) for OPC, suggesting room for improvement of the current rehabilitation program. Pretreatment sarcopenia seems to be associated with worse functional outcomes and might be a relevant target for rehabilitation strategies.

INTRODUCTION

The incidence of oropharyngeal cancer (OPC) has risen over the past decades, partially due to the rising incidence of human papilloma virus (HPV) associated cases.[1] In early stage OPC, surgery as well as radiotherapy (RT) are curative treatment options.[1,2] In more advanced stages, especially when the disease is technically and functionally irresectable organ preserving concurrent radiotherapy and systemic therapy (RT(+)) has become the common treatment modality.

Despite advancement in treatment, e.g., Intensity Modulated RT (IMRT) and Volumetric Modulated Arc Therapy (VMAT), and rehabilitation, e.g., the addition of prophylactic swallowing exercises to ameliorate functional sequelae related to the tumor and its treatment, negative side effects still do occur. Multiple studies have shown that RT(+) for OPC, although organ preserving, is accompanied with serious functional impairment and a decreased quality of life in the short- and long-term.[3–7] Apart from xerostomia, swallowing impairment (dysphagia), is the most important side effect, which can worsen over time or even develop years after treatmen.[4,7–10] Impaired mouth opening (trismus), also commonly occurs after radiation-based treatment for OPC. Incidence rates of trismus vary across studies including patients with all head and neck cancer sites treated with surgery and/or RT(+), but oropharyngeal localization of the tumor consistently seems a significant risk factor.[11–16] Besides, RT(+) of the oropharynx also may affect articulation and speech.[17] Finally, a potential increased risk of carotid stenosis and cerebrovascular accidents has also been documented after RT(+).[18] These negative side effects and the prolonged survival achieved with the improved treatment technologies over the last decades demand an increased awareness of functionality and quality of life after OPC treatment.

Most functional results at one-year post treatment stay stable up until five years posttreatment, which makes functional status at one year posttreatment predictive of the four year thereafter.[19] Thorough knowledge on the course of functional limitations during the first year after RT (+) for OPC will thus aid in adequate pretreatment patient counseling, and the development and optimization of targeted and patient specific (preventive) rehabilitation protocols. Moreover, identification of risk factors might aid in the development of individualized rehabilitation programs. For example, the correlation of HPV status with functional outcome has never been studied but might be a factor. Also, pretreatment sarcopenia, i.e., low skeletal muscle mass, is associated with unfavorable outcomes after treatment for head and neck cancer, including decreased survival and increased long-term feeding tube dependency, and might also be related to other posttreatment functional impairments[20,21]

The objective of this study was to present OPC patients' objective and subjective swallowing function, mouth opening and speech data before and at six and twelve months after RT(+) (IMRT) combined with a dedicated preventive rehabilitation program, with special attention for the possible role of HPV and pretreatment sarcopenia. These data are relevant for the optimization of current rehabilitation protocols.

METHODS

ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Board of the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AVL) (IRBd19044).

PATIENT SELECTION

All patients diagnosed with head and neck cancer in the NKI-AVL, a tertiary cancer center, are followed up in ongoing prospective assessments by speech-language pathologists, who intensively monitor functional limitations before, during and after treatment and start (additional) targeted rehabilitation. For this analysis, Dutch speaking patients were included who were curatively treated with primary RT or RT+ (RT with cisplatin or cetuximab) for a stage III-IV squamous cell carcinoma of the oropharynx between January 2013 and September 2018. Patients were excluded in case of distant metastases, a synchronous primary tumor elsewhere, prior treatment of the head and neck area (except neck dissection or skin lesions), missing pre-treatment assessment data or if only pretreatment assessment data were available. Patients were excluded from follow-up of this study when additional oncological treatment was given due to residual or recurrent disease.

RADIOTHERAPY BASED TREATMENT

According to protocol, the treatment consisted of radiotherapy given with 6 MV photons up to 70 Gy in 35 fractions in six weeks in case of RT alone and seven weeks in case of RT+ using sequential of simultaneous integrated boost (SIB) according to the IMRT technique (either step and shoot or VMAT). Patients receiving sequential integrated boost were given an elective dosage of 46 Gy (23 fractions of 2 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy). Patients receiving simultaneous integrated boost were given an elective dosage of 54.25 Gy (35 fractions of 1.55 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy). Concurrent systemic treatment (which was indicated in case of stage N2b or higher or extranodal spread) consisted of cisplatin or cetuximab. Cisplatin was administered intravenously either in high-dose (100mg/m^2 at day 1, 22 and 43 of radiotherapy), intermediate-dose (40mg/m^2 every week), or low-dose (6mg/m^2 daily during the first 5 weeks of radiotherapy). Cetuximab was given when patients were unfit for cisplatin. One week before the start of RT, a loading dose of 400 mg/m^2 was administered, followed by 250 mg/m^2 weekly for 7 weeks.

PREVENTIVE REHABILITATION PROTOCOL

Since studies have suggested benefit of preventive rehabilitation during RT (+), in April 2008 a preventive rehabilitation protocol was introduced in the NKI-AVL.[22] All RT+ patients and all RT patients, from the start of 2016, were instructed to perform preventive swallowing and mouth opening exercises daily from the start of treatment up until at least three months afterwards.[23]

DATA COLLECTION

Baseline characteristics collected included gender, age at start treatment, comorbidity according to the Adult Comorbidity Evaluation-27 (ACE-27) index, body mass index (BMI), tumor site, T and N classification (AJCC 7th edition, used at time of diagnosis), AJCC stage, HPV-status and treatment modality. HPV status was determined using immunohistochemistry for p16 and p53. In case immunohistochemistry did not provide a definite result, polymerase chain reaction was used. Skeletal muscle mass was assessed at baseline. This was performed by measuring the total cross-sectional muscle areas (SMA) of the bilateral paravertebral and sternocleidomastoid muscles on a single CT slice at the level of C3 using the software tool SliceOmatic, as described previously.[20,24,25] Routine pretreatment CT- of PET/CT scans were used for this purpose. The transformation formula of Swartz et al. was used to estimate SMA at L3 level.[24] The lumbar skeletal muscle mass (LSMI) was calculated by normalizing the SMA for squared height, from here called the skeletal mass index (LSMI). Lower values of the LSMI indicate lower skeletal muscle mass with values below 43.2 cm^2/m^2 indicating sarcopenia.[25]

Furthermore, swallowing, mouth opening, and speech outcomes were collected from the speech-language pathologists' records. For each domain an observer- as well as patient-rated outcome measure was collected before (*t*0) and six (*t*1) and twelve months (*t*2) post RT (+) as described below.

SWALLOWING OUTCOMES

The primary observer-rated swallowing outcome was the functional oral intake scale (FOIS) which is a validated seven-point ordinal scale with lower scores indicating more intake problems.[26] As primary patient-rated swallowing outcome, the SWAL-QOL was used. This is a validated 44-item questionnaire on dysphagia and its influence on daily life. It includes ten domains: burden*, food selection*, eating duration*, eating desire*, fear*, sleep, fatigue, communication, mental health*, social functioning*, and symptom frequency. The total SWAL-QOL score is calculated from the subscales marked with an asterisk. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems.[2728] Secondary swallowing outcomes included feeding tube dependence and pneumonia during the past six months.

MOUTH OPENING OUTCOMES

The primary observer-rated trismus outcome was the mouth opening (maximum central inter-incisal opening) measured in millimeters using the TheraBite® Jaw Range of Motion Scale (Atos Medical AB, Hörby, Sweden). When a patient was missing the central incisors, 19mm was subtracted from the score.[29] The patient-rated outcome was whether the patient experienced the mouth opening as limited.

VOICE AND SPEECH OUTCOMES

In order to assess observer-rated voice and speech outcomes, audio recordings were made of patients performing a set of speech tasks which included respectively reading aloud a 149 word long Dutch reading text called ''Tachtig dappere fietsers'' (Eighty brave cyclists),

a word list, and sustained vowels (/a/, /i/, and /u/). All recordings were analyzes using the PRAAT program.[30]

The primary observer-rated speech outcome was the vowel space area, a measure of articulation, for which the read text was used, or the word list if the text was not available. It was calculated as a percentage of the maximum total area of the vowel triangle.[31] In this study, values below 80% were used to indicate abnormal articulation. The primary patient-rated speech outcome was the Speech Handicap Index (SHI). This is a thirty-item speech-related quality of life questionnaire on which a patient indicates the frequency of problems experienced on a five-point scale: never (=0), almost never (=1), sometimes (=2), almost always (=3), and always (=4). The score can range from 0–120 with higher scores indicating more speech-related problems. A psychosocial and a speech function subscale can be calculated from these thirty questions. The SHI also includes one global question indication the overall speech quality (excellent (=0), good (=30), average (=70), and bad (=100)).[32,33] Secondary speech outcomes were the articulation rate in syllables per second, which was measured from the reading text using a script in PRAAT.[34] The voice outcome measure was the acoustic voice quality index (AVQI), which was determined using a combination of 3 seconds of the sustained /a/ and 4 seconds of the read text.[35,36] If no 3 seconds of /a/ was available, a combination of the sustained vowel records was used. If the read text was not present, 4 seconds of the word list was used. This outcome ranges from 1 to 10, with 1 being most equal to normal and 10 least equal to normal. A value of the AVQI less than 2.95 was considered a good voice quality.[37]

STATISTICAL ANALYSIS

Analyses were performed using IBM® SPSS® Statistics 25.0. Baseline characteristics were presented using descriptive statistics. To test whether patient and tumor characteristics of the patients at *t*0, *t*1 and *t*2 were different, the Kruskall-Wallis test was used for continuous data and the linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided *p*-value) for dichotomous and ordinal data. To test differences in baseline characteristics of included patients and patients who were excluded because they either had only data at *t*0 available or did not have data at *t*0 available, the Mann Whitney U test for continuous data was used, the linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided significance) for ordinal data and the Fisher's exact test for dichotomous data. Proportions and percentages were used to describe dichotomous outcomes and the median and range were used to describe all continuous outcomes. Differences between three timepoints were statistically analyzed by means of paired tests (i.e., Friedman test for continuous or ordinal data and a Cochran's Q for dichotomous data) as well as the differences between two timepoints (i.e. Wilcoxon signed rank test for continuous or ordinal data and the McNemar test for dichotomous data). Univariable logistic regression analysis was used to explore factors related to dysphagia (FOIS < 7), trismus (mouth opening < 36 mm) and abnormal articulation (vowel space area > 80%) at *t*2. Differences in outcomes between HPV positive and negative patients and patients with and without pretreatment sarcopenia were assessed. Differences in baseline characteristics were assessed by means of the Mann-Whitney U test for continuous data, the

linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided *p*-value) for ordinal data and the Fisher's exact test for dichotomous data. *P* values were adjusted for tumor and treatment characteristics (T and N classification, treatment and modified diet at *t*0 for differences in HPV classification and AJCC stage and modified diet at t0 for sarcopenia) by means of multivariable logistic or linear regression analyses. Results were considered statistically significant when the *p* value was less than .05. For all post-hoc pairwise comparisons, a *p* value less than .01 was considered statistically significant.

RESULTS

Between January 2013 and September 2018, 248 patients with stage III-IV oropharyngeal squamous cell carcinomas were curatively treated with RT (+) at our institute of whom 106 patients were excluded from these analyses. Twenty-two patients were excluded because of previous treatment in the head and neck area (*n* = 7), a second primary tumor elsewhere (*n* = 14) or not speaking Dutch (*n* = 1). Eighty-four patients were eligible, but were excluded because of unavailable outcome data, due to several reasons: patient canceled pretreatment appointment (*n* = 4), appointment was not made (*n* = 40) or appointment was made, but assessments were not obtained (*n* = 40). Baseline characteristics of these 84 patients are shown in table 1 and showed no significant differences with the included patients. Percentages of patients not included in the data assessment per accrual year are presented in figure 1. This figure also shows that the accrual increased from 19% in 2013 to 85% in 2018, with a slight decrease to 79% in 2019. Prevalence of functional impairment was comparable between patients included in 2013-2014 and 2017-2018 (appendix 1).

Appendix 1. Functional outcomes at t1 and t2 stratified by inclusion year. P values shown for multivariable regression adjusted for AJCC stage and modified diet at t0.

		***t*1**		***t*2**	
		2013/2014 n = 14	**2017/2018 n = 40**	**2013/2014 n = 14**	**2017/2018 n = 29**
Swallowing outcomes					
Modified diet (FOIS < 7)	*No*	9 (64)	26 (67)	13 (93)	20 (69)
	Yes	5 (36)	13 (33)	1 (7)	9 (31)
	Unknown	0	1	0	0
SWAL-QOL total score (0–100) *Median (range)*		21 (0-37)	20 (0-77)	10 (0-26)	6 (0-37)
SWAL-QOL ≥ 14	*No*	3 (43)	10 (42)	9 (75)	17 (77)
	Yes	4 (57)	14 (58)	3 (25)	5 (23)
	Unknown	7	16	2	7
Trismus outcomes					
Mouth opening in mm *Median (range)*		46 (30-59)	44 (27-52)	44 (10-58)	43 (25-52)

Appendix 1. (Continued).

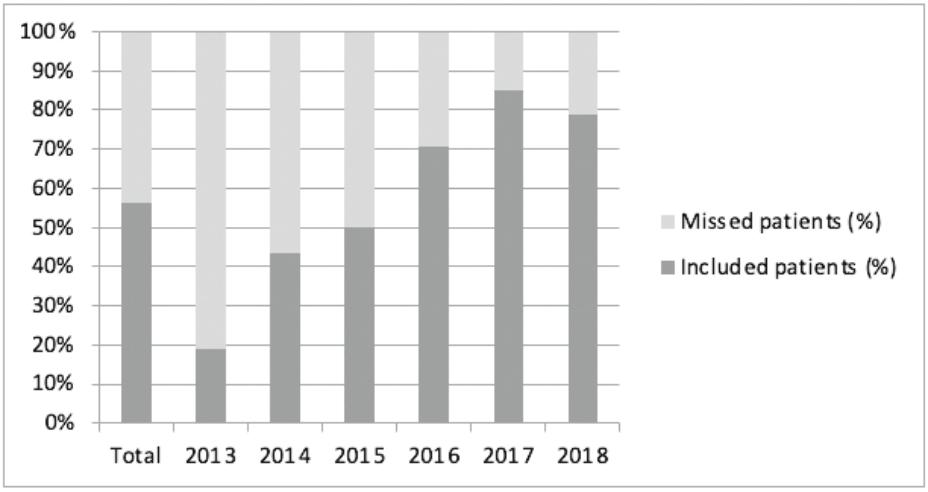
		*t*1		*t*2	
		2013/2014 n = 14	**2017/2018 n = 40**	**2013/2014 n = 14**	**2017/2018 n = 29**
Trismus	*No*	11 (85)	28 (76)	11 (79)	24 (83)
	Yes	2 (15)	9 (24)	3 (21)	5 (17)
	Unknown	1	3	0	1
Perceived trismus	*No*	9 (82)	28 (78)	11 (85)	27 (93)
	Yes	2 (18)	8 (22)	2 (15)	2 (7)
	Unknown	3	4	1	0
Speech and voice outcomes					
Vowel Space Area (%) *Median (range)*		81 (59-99)	75 (49-100)	86 (58-96)	71 (51-102)
Vowel Space Area < 80%	*No*	5 (50)	14 (39)	7 (58)	6 (24)
	Yes	5 (50)	22 (61)	5 (42)	19 (76)
	Unknown	4	4	2	4
SHI total score (0–120) *Median (range)*		0 (0-7)	4 (0-60)	0 (0-22)	0 (0-40)
SHI ≥ 6	*No*	6 (86)	9 (56)	9 (82)	12 (92)
	Yes	1 (14)	71 (44)	2 (18)	1 (8)
	Unknown	7	24	3	16

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, t1 = six months after treatment, t2 = twelve months after treatment.

In total, pretreatment data was assessed of 142 patients curatively treated with primary RT (+) for OPC. A further 34 patients had to be excluded due to missing follow-up data (11 patients withdrew, 3 patients did not receive a follow-up appointment, 15 had recurrent/residual disease, 1 developed second primary in the lung within the first six months post treatment, and 5 died (due to aspiration pneumonia, abdominal sepsis, sudden death, peritonitis or bleeding during alcohol abuse).

This left 108 patients for inclusion in the current analysis. Ninety-nine patients (92%) were present at *t*1 and 71 patients (66%) at *t*2 with 62 patients (57%) present at all three assessments. In figure 2 the reasons for loss to follow-up are presented. Median follow-up time at *t*1 was 6 months (range 2 months to 9 months) and 12 months (range 8 to 18 months) at *t*2.

Figure 1 Percentages of 'missed' patients per accrual year. 'Missed' patients are defined as patients who were eligible and willing to participate but data at t0 was not collected.



BASELINE CHARACTERISTICS

Baseline characteristics are presented in table 1. Of the 108 included patients, 73 (67%) were male, 53 patients (49%) had an ACE-27 score > 0 indicating comorbidity, 49 patients (45%) had sarcopenia, 35 patients (32%) had a tumor located in the base of tongue, 80 (74%) had stage IV disease and 70 (68%) were HPV positive. There were no significant differences regarding these characteristics between the patients present at the different assessments. Patients who were excluded because only *t*0 data was available (*n* = 34), had higher tumor stages, and had more often a modified diet pretreatment (FOIS < 7) and trismus. Patients who were eligible but not included in the study (*n* = 84) were comparable to the included patients with regard to patient, tumor and treatment characteristics. However, baseline BMI, SMM, presence of sarcopenia, FOIS and mouth opening were not available for these patients. Of the 108 included patients, 42 were treated with RT only (39 by tumor indication and 3 because they were unfit for systemic therapy), and 66 with RT+ (49 with cisplatin and 17 with cetuximab). Patients treated with RT+ more often had pretreatment sarcopenia, obviously had higher tumor stages, and more often had HPV negative tumors. All baseline characteristics categorized by treatment modality are presented in appendix 2.

■ **Figure 2.** Follow-up flowchart

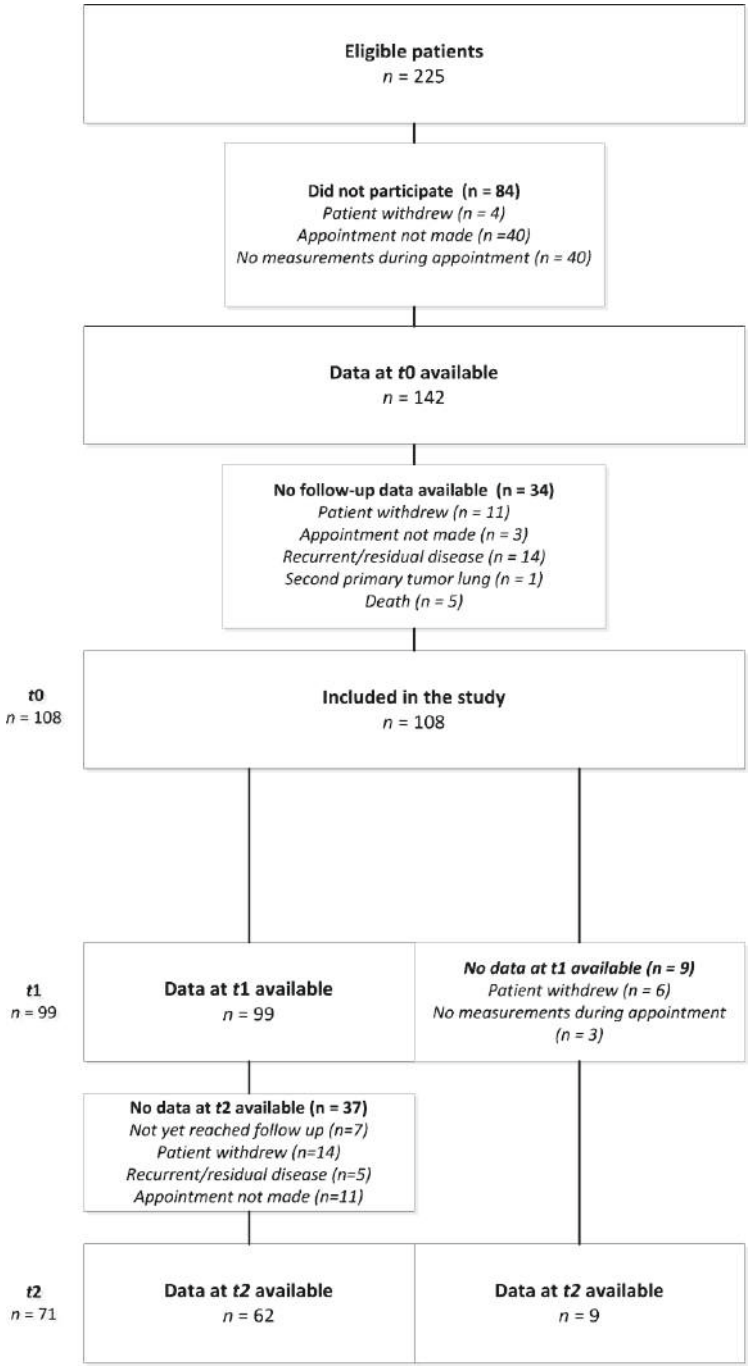


Table 1. Baseline characteristics of patients at t0, t1 and t2. P values shown for Kruskal-Wallis Testa, linear-by-linear approximation of the Pearson's Chi-square Testb, Mann Whitney U testc or Fisher's exact testd.

		***t*0** ***n* = 108**	***t*1** ***n* = 99**	***t*2** ***n* = 71**	***P* value** ***t*0, *t*1, *t*2**	**Only *t*0 available** ***n* = 34**	***P* value** ***t*0, only *t*0**	**Not included because no t0 available** ***n* = 84**	***P* value** ***t*0, no *t*0**
Gender	*Male*	73 (68)	68 (69)	52 (73)	.461[b]	24 (71)	.834[d]	54 (64)	.648[d]
	Female	35 (32)	31 (31)	19 (27)		10 (29)		30 (36)	
Age at baseline *Median (range)*		63 (39–81)	63 (39–81)	60 (39–77)	.499[a]	65 (49–78)	.316[c]	62 (47-83)	.530[c]
ACE-27	*0*	53 (49)	46 (47)	39 (55)	.357[b]	14 (41)	.248[b]	37 (44)	.442[b]
	1	37 (34)	35 (35)	26 (37)		10 (29)		30 (36)	
	2	14 (13)	14 (14)	3 (4)		9 (27)		13 (16)	
	3	4 (4)	4 (4)	3 (4)		1 (3)		4 (5)	
BMI Median (range)		25 (17-44)	25 (17-44)	26 (17-44)	.791[a]	24 (49-78)	.127[d]		
SMM Median (range)		44 (22-64)	44 (22-64)	45 (22-64)	.506[a]				
Sarcopenia	*No*	59 (55)	53 (54)	44 (62)	.402[b]				
	Yes	49 (45)	46 (47)	27 (38)					
Oropharyngeal tumor site	*Base of tongue*	35 (32)	33 (33)	25 (35)	.819[b]	13 (38)	.888[b]	31 (37)	.685[b]
	Tonsil	57 (53)	54 (55)	35 (49)		13 (38)		33 (39)	
	Other	16 (15)	12 (12)	11 (16)		8 (24)		20 (24)	
T classification	*T1*	27 (25)	23 (23)	19 (27)	.832[b]	4 (12)	.006[b]	22 (26)	.791[b]
	T2	30 (28)	30 (30)	19 (27)		8 (24)		28 (33)	
	T3	29 (27)	25 (25)	20 (28)		5 (15)		14 (17)	
	T4	22 (20)	21 (21)	13 (18)		17 (50)		20 (24)	
N classification	*N0*	12 (11)	11 (11)	8 (11)	.794[b]	3 (9)	.589[b]	6 (7)	.205[b]
	N1	24 (22)	22 (22)	13 (18)		7 (21)		14 (17)	
	N2	69 (64)	63 (64)	48 (68)		22 (65)		62 (74)	
	N3	3 (3)	3 (3)	2 (3)		2 (6)		2 (2)	
AJCC stage	*III*	28 (26)	25 (25)	18 (25)	.931[b]	4 (12)	.102[d]	17 (20)	.394[d]
	IV	80 (74)	74 (75)	53 (75)		30 (88)		67 (80)	
HPV status	*Negative*	33 (32)	31 (31)	18 (26)	.454[b]	14 (47)	.192[d]	29 (40)	.267[d]
	Positive	70 (68)	64 (67)	51 (74)		16 (53)		43 (60)	

Table 1. (Continued)

		*t*0 *n* = 108	*t*1 *n* = 99	*t*2 *n* = 71	*P* value *t*0, *t*1, *t*2	Only *t*0 available *n* = 34	*P* value *t*0, only *t*0	Not included because no t0 available *n* = 84	*P* value *t*0, no *t*0
	Unknown	5	4	2		4		12	
Treatment modality	*RT*	39 (36)	36 (36)	26 (37)	.973[b]	9 (27)	.384[b]	33 (39)	.481[b]
	RT unfit for chemo	3 (3)	3 (3)	2 (3)		2 (6)		6 (7)	
	CRT (cetuximab)	17 (16)	17 (17)	11 (16)		7 (21)		12 (14)	
	CRT (cisplatin)	49 (45)	43 (43)	32 (45)		16 (47)		33 (39)	
Modified diet at *t*0 (FOIS < 7)	*No*	89 (82)	81 (82)	66 (93)	.090[b]	23 (72)	.212[d]	NA	
	Yes	19 (18)	18 (18)	5 (7)		9 (28)			
	Unknown	0	0	0		2			
Trismus at *t*0	*No*	98 (94)	91 (96)	64 (94)	1.000[b]	21 (66)	<.001[d]	NA	
	Yes	6 (6)	4 (4)	4 (6)		11 (34)			
	Unknown	4	4	3		2			

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: BMI = body mass index, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, FOIS = functional oral intake scale, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, SMM = skeletal muscle mass, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment, sarcopenia = SMM below 43.2 cm^2/m^2.

Appendix 2. Baseline characteristics stratified by treatment modality.

		Number of patients (%)			Total
		RT ***n*** **= 42**	**CRT cetuximab** ***n*** **= 17**	**CRT cisplatin** ***n*** **= 49**	***n*** **= 108**
Gender	*Male*	29 (69)	14 (82)	30 (61)	73 (68)
	Female	13 (31)	3 (18)	19 (39)	35 (32)
Age at baseline Median (range)		61 (39–81)	64 (56–79)	62 (42–72)	63 (39–81)
ACE-27	*0*	19 (45)	4 (24)	30 (61)	53 (49)
	1	14 (33)	7 (41)	16 (33)	37 (34)
	2	7 (17)	5 (29)	2 (4)	14 (13)
	3	2 (5)	1 (6)	1 (2)	4 (4)
BMI Median (range)		26 (17-44)	25 (18-33)	24 (17-32)	25 (17-44)
SMM Median (range)		45 (22-64)	45 (28-54)	42 (27-54)	44 (22-64)
Sarcopenia	No	27 (64)	9 (53)	23 (47)	59 (55)
	Yes	15 (36)	8 (47)	26 (53)	49 (45)
Oropharyngeal tumor site	*Base of tongue*	16 (38)	3 (18)	16 (33)	35 (32)
	Tonsil	21 (50)	12 (71)	24 (49)	57 (53)
	Other	5 (12)	2 (12)	9 (18)	16 (15)
T classification	*T1*	19 (45)	1 (6)	7 (14)	27 (25)
	T2	19 (45)	6 (35)	5 (10)	30 (28)
	T3	3 (7)	5 (29)	21 (43)	29 (27)
	T4	1 (2)	5 (29)	16 (33)	22 (20)
N classification	*N0*	1 (2)	5 (29)	6 (12)	12 (11)
	N1	13 (31)	2 (12)	9 (18)	24 (22)
	N2	27 (64)	10 (59)	32 (65)	69 (64)
	N3	1 (2)	0 (0)	2 (4)	3 (3)
AJCC stage	*III*	14 (33)	5 (29)	9 (18)	28 (26)
	IV	28 (68)	12 (71)	40 (82)	80 (74)
HPV status	*Negative*	7 (18)	8 (53)	18 (38)	33 (32)
	Positive	33 (83)	7 (47)	30 (62)	70 (68)
	Unknown	2	2	1	5
Treatment modality	*RT*	39 (93)	0 (0)	0 (0)	39 (36)
	RT unfit for chemo	3 (7)	0 (0)	0 (0)	3 (3)
	CRT (cetuximab)	0 (0)	17 (100)	0 (0)	17 (16)
	CRT (cisplatin)	0 (0)	0 (0)	49 (100)	49 (45)
Modified diet at *t*0 (FOIS < 7)	*No*	36 (86)	16 (94)	37 (76)	89 (82)
	Yes	6 (14)	1 (6)	12 (24)	19 (18)
Trismus at *t*0	*No*	39 (93)	16 (94)	43 (96)	98 (94)
	Yes	3 (7)	1 (6)	2 (4)	6 (6)
	Unknown	0	0	4	4

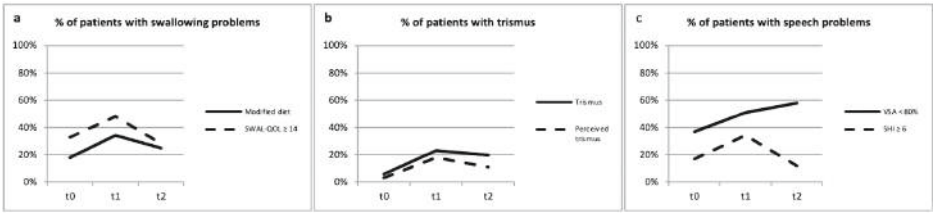
NB: Not all percentages sum up exactly to 100% due to rounding.Abbreviations: BMI = body mass index, CRT = chemoradiotherapy (cisplatin or cetuximab based), FOIS = functional oral intake scale, HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, SMM = skeletal muscle mass.

SWALLOWING OUTCOMES

Swallowing outcomes are presented in figure 3a and table 2. Swallowing problems increased significantly from *t*0 to *t*1 and decreased afterwards although not returning to baseline. This was also true for the percentage of patients who needed a modified diet (FOIS < 7), the median total SWAL-QOL score, as well as for most subscales of the SWAL-QOL. Respectively 2 (2%), 6 (6%) and 0 patients (0%) were feeding tube dependent at *t*0, *t*1 and *t*2. At *t*0, 4 patients (4%) had suffered from a pneumonia in the six months prior to the assessment. At *t*1, this concerned 3 patients (3%), of whom one also had a pneumonia before *t*0. At *t*2, this concerned 3 patients (4%), none of whom had suffered from a pneumonia before *t*0 or *t*1.

Swallowing outcomes stratified by treatment modality are presented in figure 4a and appendix 3. Patients treated with cisplatin-based RT+ more often had a modified diet (FOIS < 7) at *t*0, *t*1 and *t*2 compared to patients treated with RT only. In patients treated with RT+ (cisplatin and cetuximab), post-treatment SWAL-QOL scores were higher than in patients treated with RT only, indicating more swallowing related problems.

Figure 3. Percentage of patients with subjective and objective functional limitations at t0, t1 and t.



Abbreviations: SHI = speech handicap index, VSA = vowel space area.

Table 2. Swallowing outcomes at t0, t1 and t2. P values shown for Friedman testa, Cochran's Q testb, Wilcoxon signed rank testc or McNemar testd, ↑ indicating more problems and ↓ indicating less problems.

		Total			*P* value	*P* value	*P* value	*P* value
		*t*0 *n* = 108	*t*1 *n* = 99	*t*2 *n* = 71	*t*0, *t*1, *t*2	*t*0 to *t*1	*t*1 to *t*2	*t*0 to *t*2
Observer-rated outcome								
FOIS	*7*	89 (82)	65 (66)	53 (75)	.012[a]	.195[c]	.499[c]	**.043[c]↑**
	6	8 (7)	24 (25)	14 (20)				
	5	7 (7)	4 (4)	3 (4)				
	4	2 (2)	1 (1)	1 (1)				
	3	2 (2)	4 (4)	0 (0)				
	2	0 (0)	0 (0)	0 (0)				
	1	0 (0)	0 (0)	0 (0)				
	Unknown	0	1	0				

Table 2. (Continued)

		Total			*P* value *t*0, *t*1, *t*2	*P* value *t*0 to *t*1	*P* value *t*1 to *t*2	*P* value *t*0 to *t*2
		***t*0** ***n* = 108**	***t*1** ***n* = 99**	***t*2** ***n* = 71**				
Modified diet (FOIS < 7)	*No*	89 (82)	65 (66)	53 (75)	.005[b]	.012[d] ↑	.832[d]	**.004[d] ↑**
	Yes	19 (18)	33 (34)	18 (25)				
	Unknown	0	1	0				
Patient-rated outcome								
SWAL-QOL (0–100) Median (range)								
General burden		0 (0-88)	0 (0-100)	0 (0-50)	**.004[a]**	.001[c] ↑	.620[c]	**.010[c] ↑**
Food selection		0 (0-88)	25 (0-100)	0 (0-50)	**<.001[a]**	<.001[c] ↑	.031[c] ↓	**.001[c] ↑**
Eating duration		13 (0-88)	38 (0-100)	38 (0-100)	**<.001[a]**	<.001[c] ↑	.431[c]	**<.001[c] ↑**
Eating desire		8 (0-92)	17 (0-83)	8 (0-67)	**.003[a]**	.001[c] ↑	.245[c]	**.002[c] ↑**
Fear		0 (0-69)	0 (0-69)	0 (0-38)	.066[a]	.002[c] ↑	.490[c]	**.031[c] ↑**
Sleep		38 (0-75)	38 (0-75)	25 (0-88)	.044[a]	.307[c]	.003[c] ↓	.372[c]
Fatigue		25 (0-67)	29 (0-75)	17 (0-83)	**.001[a]**	.001[c] ↑	.177[c]	.055[c]
Communication		0 (0-75)	0 (0-75)	0 (0-63)	.087[a]	.008[c] ↑	.780[c]	.065[c]
Mental health		0 (0-75)	0 (0-100)	0 (0-45)	.138[a]	.002[c] ↑	.391[c]	.182[c]
Social functioning		0 (0-70)	0 (0-60)	0 (0-30)	.215[a]	.002[c] ↑	.349[c]	.233[c]
Symptoms		7 (0-79)	16 (0-52)	13 (0-41)	**.003[a]**	<.001[c] ↑	.032[c]	**.003[c] ↑**
Total score		5 (0-69)	14 (0-77)	9 (0-43)	**<.001[a]**	<.001[c] ↑	.342[c]	**<.001[c] ↑**
SWAL-QOL ≥ 14	*No*	52 (67)	35 (52)	38 (72)	.307[b]	.057[d]	.754[d]	.388[d]
	Yes	26 (33)	32 (48)	15 (28)				
	Unknown	30	32	18				
Secondary outcomes								
Feeding tube	*No*	106 (98)	93 (94)	71 (100)	**.018[b]**	.289[d]	.125[d]	1.000[d]
	Yes	2 (2)	6 (6)	0 (0)				
Pneumonia	*No*	98 (96)	90 (97)	67 (96)	.050[b]	1.000[d]	.250[d]	1.000[d]
	Yes	4 (4)	3 (3)	3 (4)				
	Unknown	6	6	1				

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment.

■ **Appendix 3.** Swallowing outcomes at t0, t1 and t2 stratified by treatment modality. P values shown for Friedman testa or Cochran's Q testb.

		RT			CRT (cetuximab)			CRT (cisplatin)		
		*t*0 *n* = 42	*t*1 *n* = 39	*t*2 *n* = 28	*t*0 *n* = 17	*t*1 *n* = 17	*t*2 *n* = 11	*t*0 *n* = 49	*t*1 *n* = 43	*t*2 *n* = 32
Observer-rated outcome										
FOIS	*7*	36 (86)	25 (64)	23 (82)	16 (94)	14 (82)	7 (64)	37 (76)	26 (62)	23 (72)
	6	2 (5)	12 (31)	5 (18)	1 (6)	1 (6)	3 (27)	6 (12)	11 (26)	6 (19)
	5	2 (5)	2 (5)	0 (0)	0 (0)	1 (6)	1 (9)	5 (10)	1 (2)	2 (6)
	4	1 (2)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	1 (2)	1 (2)	1 (3)
	3	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Unknown	0	0	0	0	0	0	0	0	0
FOIS < 7	*No*	36 (86)	25 (64)	23 (82)	16 (94)	14 (82)	7 (64)	37 (76)	26 (62)	23 (72)
	Yes	6 (14)	14 (36)	5 (18)	1 (6)	3 (18)	4 (36)	12 (25)	16 (38)	9 (28)
	Unknown	0	0	0	0	0	0	0	1	0
Patient-rated outcome										
SWAL-QOL (0–100) Median (range)										
General burden		0 (0-88)	0 (0-50)	0 (0-38)	0 (0-50)	0 (0-100)	25 (0-50)	0 (0-75)	13 (0-63)	0 (0-50)
Food selection		0 (0-88)	0 (0-50)	0 (0-38)	0 (0-25)	25 (0-100)	25 (0-50)	7 (0-75)	19 (0-75)	0 (0-50)
Eating duration		0 (0-88)	32 (0-100)	13 (0-100)	0 (0-63)	38 (0-88)	38 (0-88)	19 (0-75)	50 (0-100)	38 (0-75)
Eating desire		0 (0-92)	17 (0-42)	8 (0-38)	9 (0-50)	25 (0-50)	34 (0-58)	13 (0-83)	25 (0-83)	17 (0-67)
Fear		0 (0-69)	0 (0-38)	0 (0-38)	0 (0-38)	25 (0-69)	16 (0-25)	0 (0-50)	19 (0-69)	16 (0-38)
Sleep		38 (0-100)	38 (0-75)	25 (0-88)	38 (0-88)	50 (0-75)	13 (0-63)	44 (0-88)	38 (0-75)	25 (0-50)
Fatigue		25 (0-67)	25 (0-58)	17 (0-83)	17 (0-50)	25 (0-75)	21 (0-50)	21 (0-67)	42 (0-75)	25 (0-83)

Appendix 3. (Continued).

		RT			CRT (cetuximab)			CRT (cisplatin)		
		***t*0** ***n* = 42**	***t*1** ***n* = 39**	***t*2** ***n* = 28**	***t*0** ***n* = 17**	***t*1** ***n* = 17**	***t*2** ***n* = 11**	***t*0** ***n* = 49**	***t*1** ***n* = 43**	***t*2** ***n* = 32**
Communication		0 (0-50)	0 (0-38)	0 (0-25)	0 (0-50)	25 (0-75)	7 (0-25)	0 (0-75)	0 (0-63)	0 (0-63)
Mental health		0 (0-69)	0 (0-25)	0 (0-30)	0 (0-25)	25 (0-100)	20 (0-25)	0 (0-75)	3 (0-60)	0 (0-45)
Social functioning		0 (0-40)	0 (0-40)	0 (0-30)	0 (0-25)	25 (0-60)	0 (0-25)	0 (0-70)	0 (0-50)	0 (0-30)
Symptoms		11 (0-79)	15 (0-36)	13 (0-27)	5 (0-21)	14 (5-52)	15 (0-23)	7 (0-48)	20 (0-48)	14 (0-41)
Total score		1 (0-67)	6 (0-41)	2 (0-31)	3 (0-28)	21 (0-77)	25 (0-32)	10 (0-69)	18 (0-57)	10 (0-43)
SWAL-QOL ≥ 14	*No*	19 (68)	15 (68)	21 (91)	12 (86)	5 (39)	3 (38)	21 (58)	15 (47)	14 (64)
	Yes	9 (32)	7 (32)	2 (9)	2 (14)	8 (62)	5 (63)	15 (42)	17 (53)	8 (36)
	Unknown	14	17	5	3	4	3	12	11	10
Secondary outcomes										
Feeding tube	*No*	41 (98)	39 (100)	28 (100)	17 (100)	15 (88)	11 (100)	48 (98)	39 (91)	32 (100)
	Yes NGT	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Yes PRG	0 (0)	0 (0)	0 (0)	0 (0)	2 (12)	0 (0)	1 (2)	4 (9)	0 (0)
	Unknown	0	0	0	0	0	0	0	0	0
Pneumonia	*No*	40 (95)	34 (97)	27 (96)	16 (94)	16 (94)	10 (91)	42 (98)	40 (98)	30 (97)
	Yes	2 (5)	1 (3)	1 (4)	1 (6)	1 (6)	1 (9)	1 (2)	1 (2)	1 (3)
	Unknown	0	4	0	0	0	0	6	2	1

NB: Not all percentages sum up exactly to 100% due to rounding.Abbreviations: FOIS = functional oral intake scale, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment.

TRISMUS OUTCOMES

Trismus outcomes are presented in figure 3b and table 3. The percentage of patients with trismus significantly worsened from *t*0 to *t*1 and improved from *t*1 to *t*2, however, not to baseline levels. Perceived trismus followed the same trend, however, not all patients with objective trismus (mouth opening < 36 mm) perceived their mouth opening as impaired (figure 3b). Trismus outcomes stratified by treatment modality are presented in figure 4b and appendix 4. Patients treated with RT+ had and perceived more post treatment trismus compared to patients treated with RT only.

Table 3. Trismus outcomes at t0, t1 and t2. P values shown for Friedman testa, Cochran's Q testb, Wilcoxon signed rank testc or McNemar testd. ↑ indicating more problems and ↓ indicating less problems.

		Total			***P* value *t*0, *t*1, *t*2**	***P* value *t*0 to *t*1**	***P* value *t*1 to *t*2**	***P* value *t*0 to *t*2**
		***t*0 *n* = 108**	***t*1 *n* = 99**	***t*2 *n* = 71**				
Observer-rated outcomes								
Mouth opening in mm Median (range)		48 (18-65)	45 (16-63)	43 (10-64)	**<.001[a]**	**<.001[c] ↑**	.497[c]	**<.001[c] ↑**
Trismus	*No*	98 (94)	68 (77)	55 (80)	**.006[b]**	**<.001[d] ↑**	1.000[d]	**.039[d] ↑**
	Yes	6 (6)	20 (23)	14 (20)				
	Unknown	4	11	2				
Patient-rated outcomes								
Perceived trismus	No	87 (97)	67 (82)	56 (89)	.082[b]	**.022[d] ↑**	.065[d]	.453[d]
	Yes	3 (3)	15 (18)	7 (11)				
	Unknown	18	17	8				

NB: Not all percentages sum up exactly to 100% due to rounding.Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment

Table 4. Speech and voice outcomes at t0, t1 and t2. P values shown for Friedman testa, Cochran's Q testb, Wilcoxon signed rank testc or McNemar testd. ↑ indicating more problems and ↓ indicating less problems.

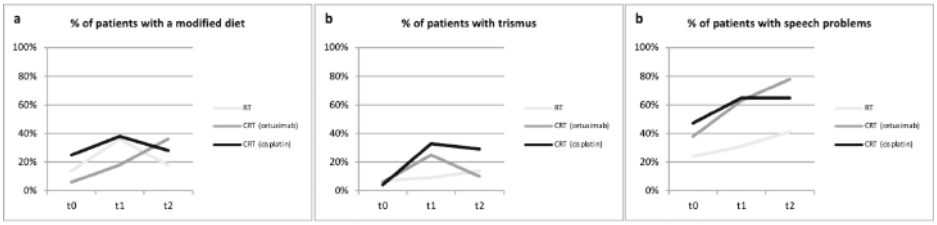
		Total			***P* value *t*0, *t*1, *t*2**	***P* value *t*0 to *t*1**	***P* value *t*1 to *t*2**	***P* value *t*0 to *t*2**
		***t*0 *n* = 108**	***t*1 *n* = 99**	***t*2 *n* = 71**				
Observer-rated outcomes								
Vowel Space Area (%) Median (range)		85 (51-129)	79 (49-107)	77 (51-112)	**.014[a]**	**.015[c]↑**	.137[c]	**.002[c]↑**
Vowel Space Area < 80%	*No*	59 (63)	37 (49)	24 (42)	.050[b]	.210[d]	.344[d]	**.019[d]↑**
	Yes	35 (37)	39 (51)	33 (58)				
	Unknown	14	23	14				
Patient-rated outcomes								
SHI Median (range)								

Table 4. (Continued)

		Total			*P* value *t*0, *t*1, *t*2	*P* value *t*0 to *t*1	*P* value *t*1 to *t*2	*P* value *t*0 to *t*2
		***t*0** ***n* = 108**	***t*1** ***n* = 99**	***t*2** ***n* = 71**				
Speech domain (0–56)		0 (0-42)	2 (0-32)	0 (0-31)	.076[a]	**.005[c]** ↑	**.045[c]** ↓	.580[c]
Psychosocial domain (0–56)		0 (0-39)	0 (0-34)	0 (0-15)	.326[a]	.476[c]	.236[c]	.281[c]
Total score (0–120)		0 (0-83)	3 (0-61)	0 (0-40)	.190[a]	**.001[c]** ↑	.073[c]	.640[c]
SHI ≥ 6	*No*	65 (83)	39 (66)	36 (88)	.074[b]	**.006[d]** ↑	.453[d]	.500[d]
	Yes	13 (17)	20 (34)	5 (12)				
	Unknown	30	40	30				
Secondary outcomes								
Articulation rate (syllables/s) Median (range)		2.3 (0.2-7.7)	2.6 (0.6-6.1)	2.7 (0.1-6.1)	.739[a]	.302[c]	.626[c]	.698[c]
AVQI Median (range)		4.5 (3.3-5.3)	4.5 (3.4-5.5)	4.5 (3.6-5.5)	.901[a]	.905[c]	.723[c]	.473[c]

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: AVQI = acoustic voice quality index, FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, SHI = speech handicap index, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment

Figure 4. Percentage of patients with a modified diet (FOIS < 7) (a), trismus (b) or speech problems (vowel space area < 80%) (c) at t0, t1 and t2 stratified by treatment modality.



■ **Appendix 4.** Trismus outcomes at t0, t1 and t2 stratified by treatment modality.

		RT			CRT (cetuximab)			CRT (cisplatin)		
		***t*0 *n* = 42**	***t*1 *n* = 39**	***t*2 *n* = 28**	***t*0 *n* = 17**	***t*1 *n* = 17**	***t*2 *n* = 11**	***t*0 *n* = 49**	***t*1 *n* = 43**	***t*2 *n* = 32**
Observer-rated outcomes										
Mouth opening in mm Median (range)		49 (25-65)	47 (31-63)	48 (27-64)	48 (30-60)	42 (27-55)	43 (32-50)	47 (18-64)	40 (16-59)	41 (10-58)
Trismus	*No*	39 (93)	29 (91)	24 (86)	16 (94)	12 (75)	9 (90)	43 (96)	27 (68)	22 (71)
	Yes	3 (7)	3 (9)	4 (14)	1 (6)	4 (25)	1 (10)	2 (4)	13 (33)	9 (29)
	Unknown	0	7	0	0	1	1	4	3	1
Patient-rated outcomes										
Perceived trismus	*No*	34 (100)	26 (90)	25 (93)	16 (94)	13 (81)	8 (100)	37 (93)	28 (76)	23 (82)
	Yes	0 (0)	3 (10)	2 (7)	1 (6)	3 (19)	0 (0)	3 (8)	9 (24)	5 (18)
	Unknown	8	10	1	0	1	3	9	6	4

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment

Appendix 5. Speech outcomes at t0, t1 and t2 stratified by treatment modality.

		RT			CRT (cetuximab)			CRT (cisplatin)		
		***t*0** ***n* = 42**	***t*1** ***n* = 39**	***t*2** ***n* = 28**	***t*0** ***n* = 17**	***t*1** ***n* = 17**	***t*2** ***n* = 11**	***t*0** ***n* = 49**	***t*1** ***n* = 43**	***t*2** ***n* = 32**
Observer-rated outcomes										
Vowel Space Area (%) Median (range)		92 (61-128)	86 (56-107)	83 (53-112)	86 (68-129)	74 (59-97)	69 (53-96)	81 (51-114)	76 (49-102)	76 (51-97)
Vowel Space Area < 80%	*No*	25 (76)	20 (69)	13 (59)	10 (63)	6 (38)	2 (22)	24 (53)	11 (36)	9 (35)
	Yes	8 (24)	9 (31)	9 (41)	6 (38)	10 (63)	7 (78)	21 (47)	20 (65)	17 (65)
	Unknown	9	10	6	1	1	2	4	12	6
Patient-rated outcomes										
SHI Median (range)										
Speech domain (0–56)		1 (0-18)	2 (0-21)	0 (0-14)	0 (0-25)	2 (0-27)	0 (0-6)	0 (0-42)	2 (0-32)	1 (0-31)
Psychosocial domain (0–56)		0 (0-5)	0 (0-10)	0 (0-7)	0 (0-32)	0 (0-34)	0 (0-1)	0 (0-39)	0 (0-19)	0 (0-15)
Total score (0–120)		1 (0-23)	2 (0-36)	0 (0-23)	0 (0-57)	2 (0-61)	0 (0-6)	0 (0-83)	3 (0-52)	1 (0-40)
SHI ≥ 6	*No*	23 (82)	13 (65)	16 (94)	12 (86)	10 (77)	6 (86)	30 (83)	16 (62)	14 (82)
	Yes	5 (18)	7 (35)	1 (6)	2 (14)	3 (23)	1 (14)	6 (17)	10 (39)	3 (18)
	Unknown	14	19	11	3	4	4	13	17	15
Secondary outcomes										
Articulation rate (syllables/s) Median (range)		2.2 (0.9-7.7)	2.8 (1.4-4.2)	2.9 (0.1-5.0)	2.7 (1.0-4.3)	2.6 (0.6-4.6)	2.7 (1.6-5.1)	2.2 (0.2-5.8)	2.6 (0.6-6.1)	2.4 (0.6-6.1)
AVQI Median (range)		4.7 (3.7-5.3)	4.5 (3.4-5.5)	4.7 (4.1-5.3)	4.4 (3.7-5.1)	4.4 (3.6-5.1)	4.5 (4.1-5.2)	4.5 (3.3-5.2)	4.5 (3.5-5.3)	4.5 (3.6-5.5)

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: AVQI = acoustic voice quality index, FOIS = functional oral intake scale, SHI = speech handicap index, t0 = pretreatment, t1 = six months after treatment, t2 = twelve months after treatment

SPEECH AND VOICE OUTCOMES

Speech and voice outcomes are presented in figure 3c and table 4. Vowel space area decreased significantly from *t*0 to *t*1, and not significantly from *t*1 to *t*2, indicating worsening articulation. Articulation rate and voice quality (AVQI) did not change significantly over time. Significantly more patients had speech related problems in daily life, as assessed with the SHI, at *t*1 compared to *t*0.

Speech and voice outcomes stratified by treatment modality are presented in figure 4c and appendix 5. Patients treated with RT+ more often had a vowel space below 80%, indicating abnormal articulation, at *t*0, *t*1 and *t*2. SHI scores were comparable for patients treated with RT and RT+.

FACTORS ASSOCIATED WITH FUNCTIONAL LIMITATIONS

Appendix 6 shows the baseline characteristics stratified by patients who did or did not have a modified diet (FOIS < 7) at *t*2. A modified diet at *t*2 was univariably associated with pretreatment lower BMI, lower SMI, sarcopenia, and a T4 tumor. Appendix 7 shows the baseline characteristics stratified by patients who had trismus (mouth opening < 36 mm) at *t*2. Trismus at *t*2 was univariably associated with tumor site other than base of tongue and tonsil (i.e., soft palate, uvula, pharyngeal wall, vallecula, and pharyngeal arches). Appendix 8 shows the baseline characteristics stratified by patients who had a vowel space below 80%, indicating abnormal articulation, at *t*2. A vowel space below 80% at *t*2 was univariably associated with a pretreatment vowel space area below 80% only.

Appendix 6. Baseline characteristics by modified diet (FOIS < 7) at t2 and univariable analysis.

		Normal diet (FOIS 7) at *t1* *n* = 53	Modified diet (FOIS < 7) at *t1* *n* = 18	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	40 (76)	12 (67)	1.0	
	Female	13 (25)	6 (33)	1.5 (0.5-4.9)	.468
Age at baseline Median (range)		62 (39-81)	63 (47-75)	1.0 (1.0-1.1)	.477
ACE-27					.963
	0	28 (53)	11 (61)	1.0	
	1	20 (38)	6 (33)	0.8 (0.2-2.4)	.645
	2	2 (4)	1 (6)	1.3 (0.1-15.5)	.850
	3	3 (6)	0 (0)	NA	NA
BMI Median (range)		25 (17-44)	23 (18-30)	0.8 (0.7-1.0)	**.020**
SMM Median (range)		45 (27-64)	41 (30-54)	0.9 (0.8-1.0)	**.034**
Sarcopenia					
	No	36 (68)	8 (44)	1.0	
	Yes	17 (32)	10 (56)	2.6 (0.9-7.9)	.081
Tumor site					.588
	Base of tongue	20 (38)	5 (28)	1.0	
	Tonsil	26 (49)	9 (50)	1.4 (0.4-4.8)	.607
	Other	7 (13)	4 (22)	2.3 (0.5-11.0)	.303
T classification					.222
	T1	18 (34)	1 (6)	1.0	
	T2	13 (25)	6 (33)	8.3 (0.9-77.6)	.063
	T3	14 (26)	6 (33)	7.7 (0.8-71.7)	.072

■ **Appendix 6.** (Continued).

		Normal diet (FOIS 7) at *t*1 *n* = 53	Modified diet (FOIS < 7) at *t*1 *n* = 18	Univariable logistic regression analysis	
				OR (95%CI)	***P* value**
	T4	8 (15)	5 (28)	11.3 (1.1-112.5)	**.039**
HPV status					
	Negative	13 (25)	5 (29)	1.0	
	Positive	39 (75)	12 (71)	0.8 (0.2-2.7)	.719
	Unknown	1	1		
Treatment modality					.444
	RT	23 (43)	5 (28)	1.0	
	CRT (cetuximab)	7 (13)	4 (22)	2.6 (0.6-12.6)	.226
	CRT (cisplatin)	23 (43)	9 (50)	1.8 (0.5-6.2)	.352
Pretreatment modified diet (FOIS < 7)					
	No	50 (94)	16 (89)	1.0	
	Yes	3 (6)	2 (11)	2.1 (0.3-13.6)	.443

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: BMI = body mass index, CI = confidence interval, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 7. Baseline characteristics by trismus at t2 and univariable analysis.

		No trismus at *t1* *n* = 55	Trismus at *t1* *n* = 14	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	39 (71)	12 (86)	1.0	
	Female	16 (29)	2 (14)	0.4 (0.1-2.0)	.272
Age at baseline Median (range)		60 (39-77)	64 (42-73)	1.1 (1.0-1.1)	.154
ACE-27					.886
	0	31 (56)	7 (50)	1.0	
	1	19 (35)	7 (50)	1.6 (0.5-5.4)	.421
	2	2 (4)	0 (0)	NA	NA
	3	3 (6)	0 (0)	NA	NA
BMI Median (range)		26 (17-44)	24 (18-30)	0.9 (0.7-1.0)	.073
SMM Median (range)		45 (22-64)	44 (34-50)	1.0 (0.9-1.1)	.617
Sarcopenia					
	No	35 (64)	8 (57)	1.0	
	Yes	20 (36)	6 (43)	1.3 (0.4-4.3)	.655
Tumor site					.142
	Base of tongue	23 (42)	2 (14)	1.0	
	Tonsil	25 (46)	8 (57)	3.7 (0.7-19.2)	.122
	Other	7 (13)	4 (29)	6.6 (1.0-43.8)	.052
T classification					.164
	T1	17 (31)	2 (14)	1.0	
	T2	17 (31)	2 (14)	1.0 (0.1-7.9)	1.000
	T3	12 (22)	7 (50)	5.0 (0.9-28.2)	.071

■ **Appendix 7.** (Continued).

		No trismus at *t*1 *n* = 55	Trismus at *t*1 *n* = 14	Univariable logistic regression analysis	
				OR (95%CI)	***P* value**
	T4	9 (16)	3 (21)	2.8 (0.4-10.2)	.298
HPV status					
	Negative	15 (28)	2 (14)	1.0	
	Positive	38 (72)	12 (86)	2.4 (0.5-11.9)	.294
	Unknown	2	0		
Treatment modality					.272
	RT	24 (44)	4 (29)	1.0	
	CRT (cetuximab)	9 (16)	1 (7)	0.7 (0.1-6.8)	.732
	CRT (cisplatin)	22 (40)	9 (64)	2.5 (0.7-9.1)	.180
Pretreatment trismus					
	No	52 (96)	10 (83)		
	Yes	2 (4)	2 (17)	5.2 (0.7-41.4)	.119
	Unknown	1	2		

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: BMI = body mass index, CI = confidence interval, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 8. Baseline characteristics by vowel space area below 80% at t1 and univariable analysis.

		VSA > 80% at *t1* *n* = 24	VSA < 80% *t1* *n* = 33	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	20 (83)	24 (73)	1.0	
	Female	4 (17)	9 (27)	1.9 (0.5-7.0)	.350
Age at baseline Median (range)		61 (44-75)	60 (39-75)	1.0 (1.0-1.1)	.756
ACE-27					.501
	0	12 (50)	21 (64)	1.0	
	1	11 (46)	8 (24)	0.4 (0.1-1.3)	.136
	2	0 (0)	2 (6)	NA	
	3	1 (4)	2 (6)	1.1 (0.1-14.0)	.917
BMI Median (range)		26 (20-44)	25 (18-33)	1.0 (0.8-1.1)	.473
SMM Median (range)		46 (32-64)	45 (30-54)	1.0 (0.9-1.0)	.345
Sarcopenia					
	No	18 (75)	20 (61)	1.0	
	Yes	6 (25)	13 (39)	2.0 (0.6-6.2)	.258
Tumor site					.756
	Base of tongue	8 (33)	14 (42)	1.0	
	Tonsil	12 (50)	15 (46)	0.7 (0.2-2.3)	.568
	Other	4 (17)	4 (12)	0.6 (0.1-2.9)	.502
T classification					.963
	T1	7 (29)	8 (24)	1.0	
	T2	7 (29)	10 (30)	1.3 (0.3-5.1)	.755
	T3	6 (25)	8 (24)	1.2 (0.3-5.1)	.837

■ **Appendix 8.** (Continued).

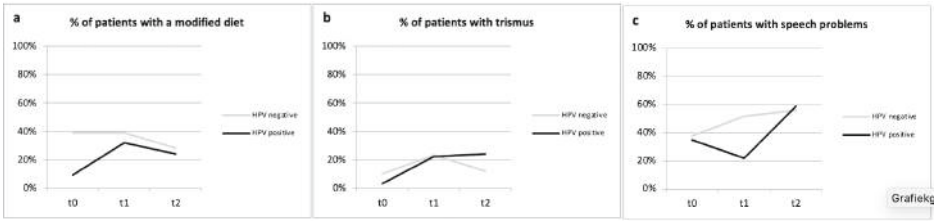
		VSA > 80% at *t*1 *n* = 24	VSA < 80% *t*1 *n* = 33	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
	T4	4 (17)	7 (21)	1.5 (0.3-7.5)	.600
HPV status					
	Negative	7 (30)	9 (28)	1.0	
	Positive	16 (70)	23 (72)	1.1 (0.3-3.6)	.852
	Unknown	1	1		
Treatment modality					.108
	RT	13 (54)	9 (27)	1.0	
	CRT (cetuximab)	2 (8)	7 (21)	5.1 (0.8-30.2)	.075
	CRT (cisplatin)	9 (38)	17 (52)	2.7 (0.8-8.8)	.093
Pretreatment VSA < 80%					
	No	17 (77)	14 (48)	1.0	
	Yes	4 (24)	15 (52)	4.6 (1.2-16.9)	.023
	Unknown	3	4		

NB: Not all percentages sum up exactly to 100% due to rounding.Abbreviations: BMI = body mass index, CI = confidence interval, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass, VSA = vowel space area.

HPV STATUS

Appendix 9 shows the baseline characteristics stratified by HPV status. Compared to patients with an HPV negative tumor, patients with an HPV associated tumor had a higher BMI, higher SMI, lower T classifications, higher N classification, were more often treated with RT only, and had less often a modified diet at baseline. Functional outcomes at *t*0, *t*1 and *t*2 stratified by HPV status are presented in figure 5 and appendix 10. As presented in figure 5a, at *t*1 and *t*2, patients with an HPV negative tumor more often had a modified diet compared to patients with an HPV positive tumor. Also, SWAL-QOL scores were higher in the HPV negative group at both *t*1 and *t*2. The prevalence of trismus was comparable between in het HPV negative and positive group at t1 and at *t*2 HPV negative patients had less often trismus compared to HPV positive patients. Patients with an HPV negative tumor had slightly worse speech and voice outcomes, especially at *t*1. After adjusting for T and N classification, treatment and pretreatment modified diet, none of the differences were statistically significant, except at *t*2, patients with an HPV positive tumor had a smaller mouth opening.

Figure 5. Percentage of patients with a modified diet (FOIS < 7) (a), trismus (b) or speech problems (vowel space area < 80%) (c) at t0, t1 and t2 stratified by HPV status.



Appendix 9. Baseline characteristics stratified by HPV status. P values shown for Mann-Whitney U testa, linear-by-linear approximation of the Pearson's Chi-square testb or Fisher's exact Testc.

		HPV - *n* = 33	HPV + *n* = 70	*P* value
Gender	*Male*	20 (61)	50 (71)	.366[c]
	Female	13 (39)	20 (29)	
Age at baseline Median (range)		62 (44-75)	62 (39-79)	.511[a]
ACE-27	*0*	14 (42)	38 (54)	.151[b]
	1	13 (39)	24 (34)	
	2	3 (9)	7 (10)	
	3	3 (9)	1 (1)	
BMI Median (range)		24 (17-33)	26 (17-44)	**.001[a]**
SMM Median (range)		41 (27-54)	45 (22-64)	**.031[a]**
Sarcopenia	*No*	14 (42)	43 (61)	.090[c]
	Yes	19 (58)	27 (39)	

■ **Appendix 9.** (Continued).

		HPV - *n* = 33	HPV + *n* = 70	*P* value
Oropharyngeal tumor site	*Base of tongue*	10 (30)	24 (34)	.198[b]
	Tonsil	15 (46)	40 (57)	
	Other	8 (24)	6 (9)	
T classification	*T1*	1 (3)	26 (37)	<.001[b]
	T2	7 (21)	21 (30)	
	T3	15 (46)	11 (16)	
	T4	10 (30)	12 (17)	
N classification	*N0*	6 (18)	5 (7)	.026[b]
	N1	9 (27)	13 (19)	
	N2	18 (55)	49 (70)	
	N3	0 (0)	3 (4)	
AJCC stage	*III*	10 (30)	15 (21)	.336[c]
	IV	23 (70)	55 (79)	
Treatment modality	*RT*	6 (18)	32 (46)	.005[b]
	RT unfit for chemo	1 (3)	1 (1)	
	CRT (cetuximab)	18 (55)	30 (43)	
	CRT (cisplatin)	8 (24)	7 (10)	
Modified diet at *t*0 (FOIS < 7)	*No*	20 (61)	64 (91)	.001[c]
	Yes	13 (39)	6 (9)	
Trismus at *t*0	*No*	28 (90)	66 (97)	.175[c]
	Yes	3 (10)	2 (3)	
	Unknown	2	2	

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: BMI = body mass index, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 10. Functional outcomes at t1 and t2 stratified by HPV status. P values shown for multivariable regression adjusted for T and N classification, treatment and modified diet at t0.

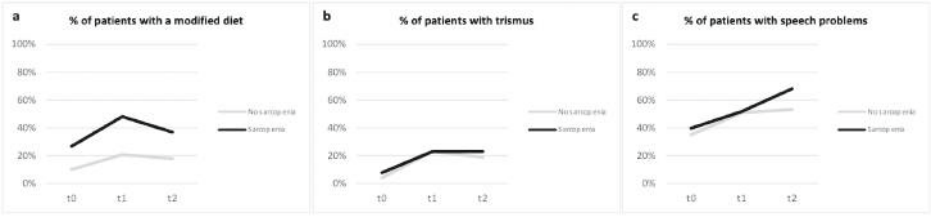
		*t*1			*t*2		
		HPV - n = 31	**HPV + n = 64**	**Adjusted *p* value**	**HPV - n = 18**	**HPV + n = 51**	**Adjusted *p* value**
Swallowing outcomes							
Modified diet (FOIS < 7)	*No*	19 (61)	43 (68)	.206	13 (72)	39 (77)	.460
	Yes	12 (39)	20 (32)		5 (28)	12 (24)	
	Unknown	0	1		0	0	
SWAL-QOL total score (0–100) Median (range)		21 (0-77)	8 (0-52)	.492	14 (0-32)	5 (0-43)	.652
SWAL-QOL ≥ 14	*No*	9 (38)	26 (65)	.868	8 (62)	29 (76)	.292
	Yes	15 (63)	14 (35)		5 (39)	9 (24)	
	Unknown	7	24		5	13	
Trismus outcomes							
Mouth opening in mm Median (range)		42 (18-54)	45 (16-63)	.627	45 (27-53)	43 (10-64)	**.046**
Trismus	*No*	23 (77)	43 (78)	.611	15 (88)	38 (76)	.086
	Yes	7 (23)	12 (22)		2 (12)	12 (24)	
	Unknown	1	9		1	1	
Perceived trismus	*No*	25 (86)	40 (80)	.074	15 (94)	39 (87)	.996
	Yes	4 (14)	10 (20)		1 (6)	6 (13)	
	Unknown	2	14		2	6	
Speech and voice outcomes							
Vowel Space Area (%) Median (range)		77 (58-100)	82 (49-107)	.913	77 (51-102)	76 (53-112)	.528
Vowel Space Area < 80%	*No*	13 (48)	43 (78)	.645	7 (44)	16 (41)	.463
	Yes	14 (52)	12 (22)		9 (56)	23 (59)	
	Unknown	4	9		2	12	
SHI total score (0–120) Median (range)		4 (0-61)	3 (0-52)	.896	1 (0-10)	0 (0-40)	.151
SHI ≥ 6	*No*	12 (60)	25 (69)	.995	11 (85)	24 (92)	.325
	Yes	8 (40)	11 (31)		2 (15)	2 (8)	
	Unknown	11	28		5	25	

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, t1 = six months after treatment, t2 = twelve months after treatment.

SARCOPENIA

Appendix 11 shows the baseline characteristics stratified by pretreatment sarcopenia. Patients with pretreatment sarcopenia were more often female, had a lower BMI, higher T-classifications, higher disease stages, more often an HPV negative tumor, and more often had a modified diet at baseline compared to patients without pretreatment sarcopenia. All outcomes stratified by pretreatment sarcopenia are presented in figure 6 and appendix 12. As presented in figure 6a, pretreatment sarcopenia was associated with more modified diet at all timepoints. Also, at *t*0 and *t*1, SWAL-QOL scores were higher in patients with sarcopenia, indicating more swallowing related problems. At *t*2, SWAL-QOL scores were comparable. Trismus outcomes were comparable between patients with and without sarcopenia at t0, t1 and t2. Prevalence of objective speech problems (vowel space area below 80%) was comparable at t0 and t1, but higher in patients with sarcopenia at t2. Patient reported speech problems, however, were more prevalent in patients with sarcopenia. After adjusting for AJCC stage and pretreatment modified diet, only modified diet and the total SWAL-QOL score at *t*1 were significantly higher in patients with pretreatment sarcopenia.

Figure 6. Percentage of patients with a modified diet (FOIS < 7) (a), trismus (b) or speech problems (vowel space area < 80%) (c) at t0, t1 and t2 stratified by pretreatment sarcopenia.



Appendix 11. Baseline characteristics stratified by pretreatment sarcopenia. *P* values shown for Mann-Whitney U test[a], linear-by-linear approximation of the Pearson's Chi-square test[b] or Fisher's exact Test[c].

		No sarcopenia N = 59	Sarcopenia N = 49	*P* value
Gender	*Male*	57 (97)	16 (33)	**< .001[c]**
	Female	2 (3)	33 (67)	
Age at baseline Median (range)		61 (39-81)	63 (47-79)	.095[a]
ACE-27	*0*	29 (49)	24 (49)	1.000[b]
	1	21 (36)	16 (33)	
	2	6 (10)	8 (16)	
	3	3 (5)	1 (2)	
BMI Median (range)		26 (18-44)	23 (17-35)	**< .001[a]**
Oropharyngeal tumor site	*Base of tongue*	22 (37)	13 (27)	.112[b]
	Tonsil	31 (53)	26 (53)	

Appendix 11. Baseline characteristics stratified by pretreatment sarcopenia. *P* values shown for Mann-Whitney U test[a], linear-by-linear approximation of the Pearson's Chi-square test[b] or Fisher's exact Test[c].

		No sarcopenia N = 59	Sarcopenia N = 49	*P* value
	Other	6 (10)	10 (20)	
T classification	*T1*	19 (32)	8 (16)	**.031[b]**
	T2	16 (27)	14 (29)	
	T3	16 (27)	13 (27)	
	T4	8 (14)	14 (29)	
N classification	*N0*	8 (14)	4 (8)	.287[b]
	N1	15 (25)	9 (18)	
	N2	34 (58)	35 (71)	
	N3	2 (3)	1 (20	
AJCC stage	*III*	20 (34)	8 (16)	**.048[c]**
	IV	39 (66)	41 (84)	
HPV	*Negative*	14 (25)	19 (41)	.090[c]
	Positive	43 (75)	27 (59)	
	Unknown	2	3	
Treatment modality	*RT*	27 (46)	12 (24)	.090[b]
	RT unfit for chemo	0 (0)	3 (6)	
	CRT (cetuximab)	9 (15)	8 (16)	
	CRT (cisplatin)	23 (39)	26 (53)	
Modified diet at *t*0 (FOIS < 7)	*No*	53 (90)	36 (74)	**.041[c]**
	Yes	6 (10)	13 (27)	
Trismus at *t*0	*No*	54 (96)	44 (92)	.411[c]
	Yes	2 (4)	4 (8)	
	Unknown	3	1	

NB: Not all percentages sum up exactly to 100% due to rounding. Abbreviations: BMI = body mass index, CRT = chemoradiotherapy (cisplatin or cetuximab based), HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = skeletal muscle mass below 43.2 cm^2/m^2.

Appendix 12. Functional outcomes at t1 and t2 stratified by pretreatment sarcopenia. P values shown for multivariable regression adjusted for AJCC stage and modified diet at t0.

		*t*1			*t*2		
		No sarcopenia n = 53	**Sarcopenia n = 46**	**Adjusted *p* value**	**No sarcopenia n = 44**	**Sarcopenia n = 27**	**Adjusted *p* value**
Swallowing outcomes							
Modified diet (FOIS < 7)	*No*	41 (79)	24 (52)	**.013**	36 (82)	17 (63)	.088
	Yes	11 (21)	22 (48)		8 (18)	10 (37)	
	Unknown	1	0		0	0	
SWAL-QOL total score (0–100) Median (range)		10 (0-41)	22 (0-77)	**.031**	9 (0-32)	8 (0-43)	.133
SWAL-QOL ≥ 14	*No*	23 (64)	12 (39)	.135	26 (70)	12 (75)	.783
	Yes	13 (36)	19 (61)		11 (30)	4 (25)	
	Unknown	17	15		7	11	
Trismus outcomes							
Mouth opening in mm Median (range)		45 (27-63)	44 (16-58)	.528	45 (27-64)	43 (10-52)	.143
Trismus	*No*	37 (77)	31 (78)	.662	35 (81)	20 (77)	.831
	Yes	11 (23)	9 (23)		8 (19)	6 (23)	
	Unknown	5	6		1	1	
Perceived trismus	*No*	37 (82)	30 (81)	.958	35 (90)	21 (88)	.892
	Yes	8 (18)	7 (19)		4 (10)	3 (13)	
	Unknown	8	9		5	3	
Speech and voice outcomes							
Vowel Space Area (%) Median (range)		80 (56-107)	79 (49-100)	.760	79 (51-112)	73 (53-102)	.731
Vowel Space Area < 80%	*No*	21 (49)	16 (49)	.085	18 (47)	6 (32)	.431
	Yes	22 (51)	17 (52)		20 (53)	13 (68)	
	Unknown	10	13		6	8	
SHI total score (0–120) Median (range)		0 (0-36)	3 (0-61)	.115	0 (0-23)	1 (0-40)	.210
SHI ≥ 6	*No*	24 (73)	15 (58)	.266	25 (89)	11 (85)	.563
	Yes	9 (27)	11 (42)		3 (11)	2 (15)	
	Unknown	20	20		16	14	

NB: Not all percentages sum up exactly to 100% due to rounding.Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, sarcopenia = skeletal muscle mass below 43.2 cm^2/m^2, t1 = six months after treatment, t2 = twelve months after treatment.

DISCUSSION

The objective of this study was to assess objective and subjective swallowing function, mouth opening and speech over a one-year period in a large cohort after RT (+) for advanced stage OPC treatment in conjunction with a dedicated preventive rehabilitation program, also focusing on the role of HPV status and pretreatment sarcopenia. These results are relevant for the optimization of current rehabilitation protocols. Patients were treated with IMRT with or without systemic therapy and a concurrent preventive rehabilitation program. Data collection was part of a systematic, intensive routine monitoring program at our institute. The study showed that the normalcy of oral intake and SWAL-QOL scores first deteriorated up to six months, and subsequently improved up until twelve months after treatment, but did not return to baseline levels. Rate of feeding tube dependency in this cohort was low, with none of the patients being feeding tube dependent at one year after treatment. Also, very few patients experienced pneumonia during the one-year follow-up. Trismus and speech problems showed the same trend as swallowing function, with increased prevalence of problems at six-month follow-up, and lower – but still above baseline – prevalence rates at one-year post-treatment. Patients treated with cisplatin-based RT+, HPV negative tumors, and patients with pretreatment sarcopenia were more likely to have functional limitations. Patients treated with RT+ had worse swallowing, trismus and speech and voice outcomes, compared to those treated with RT alone.

Most of the above summarized outcomes were in line with expectations and are comparable to those of other studies concluding that a substantial proportion of the patients have functional impairment after treatment. Although it is hard to compare the present results to other studies given the heterogeneity of cohorts and outcome measures currently used, some comparisons can be made. Starmer et al. evaluated 71 patients with OPC treated with IMRT with or without systemic therapy and preventive swallowing rehabilitation around 5 months post-treatment.[9] Probably because 92% of the patients received RT+, prevalence of a modified diet according to FOIS scores was higher in that study (86% compared to 34% in our study). Hunter et al. evaluated the two-year period after RT+ without preventive swallowing rehabilitation for stage III-IV OPC in 72 patients.[10] At six and twelve months after treatment respectively, 6% and 2% had grade 2 dysphagia (modified diet) and 6% and 1% had grade 3 dysphagia (feeding tube dependence) according to the Common Toxicity Criteria Adverse Effects (CTCAE) scale. The significantly lower percentage of patients with a modified diet in that study may, in part, be because another outcome measure was used (CTCAE scale versus FOIS). Congruent with our finding, other studies also found that functional limitations worsened the first months after therapy and improved through twelve months after treatment with minimal improvement in the year thereafter.[10,38]

Only few studies have investigated trismus within the first year after radiation-based treatment and a preventive rehabilitation protocol for advanced stage OPC. Kraaijenga et al. found that 9 of 24 patients (27%) after RT+ for OPC had trismus at a median follow-up of 13 weeks.[15] In our

study this concerned 23% at six-month follow-up and 20% at twelve-month follow-up. Incidence rates of trismus in other studies including all head and neck cancer localizations treated with surgery and/or radiation vary, but oropharyngeal localization of the tumor consistently seems a risk factor.[11–16,39] This is probably because treatment of the oropharynx causes fibrosis in the mastication musculature.[15] This hypothesis is also supported by our results showing that patients with tumor localizations within the oropharynx other than base of tongue have trismus more often.

Apparently, despite trismus preventing measures in our preventive rehabilitation program, trismus is still a prevalent problem in this cohort. Therefore, extra measures could be taken to prevent and treat trismus, for example, by selecting high risk patients for more intensive guidance, and emphasizing the need for trismus prevention stronger, prior to treatment. The consistent use of mouth opening exercises (e.g., with tongueblades or TheraBite®) in this patient group might have been advantageous.[40] The lack of reimbursement for TheraBite® in the Netherlands, preventing regular use of this medical device in our patient population, is noteworthy in this respect.

With respect to speech and voice outcomes, according to our results, observer-rated intelligibility was deteriorated at six-month follow-up and stayed stable up until twelve-month follow-up. Subjective speech outcomes, however, deteriorated up until six months and returned to baseline levels at twelve-month follow-up. This is most likely because patients get used to the altered speech. Vainshtein et al. found the same trend in patient-reported voice quality, which decreased maximally at one month after treatment and recovered to baseline after twelve to eighteen months.[41]In an earlier study from our institute, Jacobi et al. found comparable results. They reported that computer analyzed articulation and sound quality was impaired in head and neck cancer patients after RT+, especially with oral and oropharyngeal cancer sites.[42]

Our results suggest that patients treated with concomitant systemic therapy have more functional limitations than patients treated with RT alone. This might be due to the toxicity of systemic therapy, but might also be because of the higher tumor stages, and therefore also larger radiotherapy fields. Only 17 (16%) of the 108 included patients were treated with cetuximab based RT+ and therefore there is a high risk of atypical sampling and conclusions on functional outcomes relative to RT only or cisplatin-based RT+ based on these analyses should be made with caution. A recently published randomized study concluded that the degree of toxicities, including dysphagia, between cisplatin and cetuximab in HPV positive OPC was comparable.[5]

In our cohort, although HPV status was not associated with trismus and speech outcomes, patients with HPV positive tumors had less objective and subjective functional impairment. However, patients with HPV positive tumors also had more favorable baseline characteristics, including higher pretreatment SMI (as also reported by Chargi et al.[43]), lower T classification, were more often treated with RT only and less often had a modified diet before treatment.

When adjusting for baseline characteristics in multivariable analyses, HPV status was not significantly associated with functional limitations, except for a smaller mouth opening at one-year post-treatment. Although no definite conclusions can be drawn, it seems that HPV status itself does not influence post-treatment functional limitations.

Results in literature have contrasting results regarding the association of HPV status with functional limitations after RT (+). Vangelov et al. evaluated 100 patients with OPC treated with RT (+), and found that after adjusting for baseline characteristics (i.e., smoking, nodal stage, IMRT, and oropharyngeal RT dose), patients with an HPV positive tumor more often had tube feeding and weight loss, compared to patients with an HPV negative tumor.[44] Again, adjusted for baseline characteristics (i.e., age, gender, stage, treatment modality, RT dose, neck node irradiation, and pretreatment weight loss), Vatca et al., on the other hand, evaluated 72 OPC patients treated with RT+ and found that patients with an HPV positive tumor had more mucositis and weight loss during treatment.[45] Sharma et al. evaluated 228 OPC patients and found that quality of life in HPV positive patients was lower shortly after treatment but became comparable by one year after treatment, also adjusted for baseline differences[46], which is similar to our findings.

A low skeletal muscle mass, or sarcopenia, before treatment, was associated with an impaired diet before and after treatment. This is in line with results of a previous study performed at our institute which demonstrated that sarcopenia is a strong determinant for feeding tube use after RT+ for head and neck cancer.[20] Skeletal muscle loss is thought to be related to swallowing muscle loss, causing swallowing difficulties which might result in a modified diet or eventually tube dependency. Moreover, swallowing problems itself may result in skeletal muscle loss due to insufficient nutritional intake. Therefore, these results support the hypothesis that sarcopenia might be a relevant target to optimize patients' condition before as well as after treatment to improve functional status. Apparently, our current preventive rehabilitation protocol does not target muscle mass sufficiently and/or not sufficiently long enough to close the gap between sarcopenic and non-sarcopenic patients with regard to swallowing impairment. In view of the association between pretreatment sarcopenia and functional outcomes, integrating SMI determination before treatment is warranted.

LIMITATIONS

A limitation of this study is the suboptimal accrual during the first years of the data collection. These analyses were performed on data collected as part of standard care. Collecting data in this way usually introduced a risk for suboptimal inclusion especially during startup. Although at first inclusion rates were low, they improved over time with current inclusion rates between 79-85%, making it likely that this cohort is representative for the entire cohort. In addition, because baseline characteristics between included patients and not included patients were similar, no selection bias due to (non-)inclusion seems present.

CONCLUSION

Objective and patient-perceived swallowing, mouth opening, and speech function of patients treated with IMRT with or without systemic therapy combined with a preventive rehabilitation program for OPC deteriorate up until six months and improve until twelve months after treatment, but do not return to baseline levels. Patients treated with cisplatin-based CRT, HPV negative tumors and patients with pretreatment sarcopenia were more likely to have functional limitations. HPV negative status itself is not likely to be a cause of functional limitations, but the associated unfavorable patient and tumor characteristics are. Pretreatment sarcopenia might be a relevant target for prehabilitation strategies. Although for most patients in this cohort organ preserving treatment resulted in function preservation, there is a proportion of patients with functional problems, suggesting room for improvement of the current rehabilitation program.

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PART IV

Sarcopenia in elderly head and neck cancer patients

CHAPTER 18

Sarcopenia is a prognostic factor for overall survival in elderly patients with head and neck cancer

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ABSTRACT

Background

Sarcopenia is known as a geriatric syndrome associated with increased disability and decreased survival in elderly patients. In oncological patients, pretreatment low skeletal muscle mass (SMM), sometimes referred to as sarcopenia, is an emerging negative prognostic factor. Commonly, only SMM is assessed in cancer patients. Sarcopenia is defined as the combination of low SMM and low muscle function (MF). We investigated the relation between SMM, MF, sarcopenia (SMM and MF combined) and overall survival (OS) in a group of elderly patients with head and neck squamous cell carcinoma (HNSCC).

Material and methods

A retrospective study in elderly HNSCC patients treated between 2015 and 2018 was performed. The prognostic value of SMM and MF alone, and sarcopenia was investigated.

Results

Eighty-five patients were included of whom 48.2% had sarcopenia. The median OS was significantly worse for patients treated with curative intent with sarcopenia (12.07 months; IQR 3.64-21.82) compared to patients without sarcopenia (13.60 months; IQR 5.98-27.00) (HR 2.80; 95% CI 1.14-6.88; p=0.03). SMM and MF alone were not significant predictors of OS.

Conclusion

Sarcopenia is associated with impaired OS in elderly HNSCC patients. Sarcopenia, defined as the combination of low SMM and low MF, appears to be a better predictor of OS than low SMM or low MF separately.

INTRODUCTION

Research into the field of body composition and specifically low skeletal muscle mass (SMM), sometimes also referred to as sarcopenia, has increasingly gained interest over the last decade in the field of oncology. In geriatrics, sarcopenia is known as an age-related syndrome with a multifactorial etiology, characterized by generalized loss of SMM and loss of muscle strength.[1]

Risk factors for the presence of sarcopenia are malnutrition, immobilization and illness. Sarcopenia is a risk factor for various adverse outcomes including physical disability, decreased quality of life, and ultimately death.[1] In human aging, muscle wasting is an imminent process. It is estimated that the prevalence of sarcopenia in the general population is 5-13% for people aged 60-70 years, and up to 50% for those aged 80 years or above.[2] Independent of age, sarcopenia is impaired in various diseases due to inflammation, malnutrition and immobilization. Cachexia is a complex metabolic syndrome in which inflammation is the key feature and weight loss (≥ 5% of body weight during the past 12 months) is the key diagnostic criterium. Cachexia can be an underlying condition in patients with sarcopenia.[3]

The majority of research within the oncological community has defined sarcopenia as radiologically assessed low SMM and/or low skeletal muscle quality. Previous research in elderly people showed that the correlation between SMM and muscle strength is moderate to weak and the relationship between muscle strength and SMM is not linear.[4,5] For this reason, the European working group on sarcopenia in older people (EWGSOP) recommended diagnosing sarcopenia based on the presence of both low SMM and low muscle function (MF; strength or performance).[1]

Within the field of oncology, radiologically assessed low SMM appears to be a negative predictive and prognostic factor for various outcomes including disease progression and survival in a variety of cancer types.[6] For example, radiologically assessed low SMM is associated with chemotherapy dose-limiting toxicity in patients with head and neck cancer[7], breast cancer[8] and renal cell carcinoma[9] ; increased incidence of postoperative complications in patients with head and neck cancer[10,11], esophageal squamous cell carcinoma[12] and colorectal cancer[13]; and decreased survival in patients with head and neck cancer[11,14], colorectal cancer[15] and pancreatic adenocarcinoma[16].

In the majority of studies on the effect of sarcopenia on survival of cancer patients, and in all studies regarding head and neck cancer patients, only radiologically assessed low SMM was used to define sarcopenia. There are very few studies available in cancer patients that assess the prognostic value of sarcopenia as defined by the combination of low SMM and low MF. One study performed with gastric cancer patients who underwent gastrectomy showed that patients with sarcopenia, as defined by the combination of low SMM and low MF, showed a significantly higher complication rate compared to patients without sarcopenia[17]. In head and neck cancer, no studies are available on the relationship between sarcopenia, as defined

by the combination of low SMM and low MF, and adverse outcomes. The aim of this study is to explore the relationship between sarcopenia and overall survival in elderly patients with head and neck cancer.

MATERIALS AND METHODS

PATIENTS AND STUDY DESIGN

This study was designed as a single-center retrospective study. We reviewed elderly patients (≥70-year-old) with pathologically proven head and neck squamous cell carcinoma (HNSCC) who had a geriatric assessment during their diagnostic workup between April 2015 and February 2018. In our center elderly HNSCC patients are offered geriatric assessment, but patients may refuse. Histologic tumor types other than squamous cell carcinoma were excluded. The design of this retrospective study was approved by the Medical Ethical Research Committee of our center (approval ID 17-365/C). Factors with known or suspected relation with HNSCC treatment outcomes and with sarcopenia were collected: age, sex, body mass index (BMI), weight loss in the past six months, risk of malnutrition assessed with the malnutrition universal screening tool (MUST), smoking status, alcohol use, comorbidity expressed as a Charlson Comorbidity Index (CCI) score, tumor type (primary, second primary or recurrence), tumor site, human papillomavirus (HPV) status (for oropharyngeal cancer), tumor-node-metastasis (TNM) stage, hematological and biochemical markers at diagnosis, including hemoglobin (Hb), leukocytes, C-reactive protein (CRP), creatinine and albumin, and treatment intention.

DEFINITION OF SARCOPENIA

Sarcopenia was defined as the combination of low SMM and low MF, as determined by muscle strength or physical performance measurements.[1]

SKELETAL MUSCLE MASS

Skeletal muscle mass was measured as muscle cross-sectional muscle area (SMA) on pre-treatment 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.[18] For MRI, muscle area was manually segmented, and fatty tissue was manually excluded.

Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (Tomovision, Canada). Cross-sectional muscle area at the level of C3 was converted to CSMA at the level of L3 using a previously published formula.[19] The lumbar skeletal muscle index (SMI) was calculated by correcting SMM at the level of L3 for height. Patients had a low SMI if this value was ≤43.2cm^2/m^2; this cutoff value was established in a separate cohort of head and neck cancer patients.[7]

MUSCLE STRENGTH

Isometric handgrip strength (HGS) is strongly related with overall muscle strength [20]. Handgrip strength was measured using a Jamar Hydraulic Handheld Dynamometer according to the recommendations of the American society of hand therapist's (ASHT) and expressed in kilograms (kg). Patients were asked to squeeze maximally with each hand. The average score of the left and right hand was used for analysis. Patients had low HGS if the HGS was below 30kg (men) or below 20kg (women) [1].

MUSCLE PERFORMANCE

The four-meter gait speed is a reflection of individual's lower limb muscle function. It is a widely accepted way to assess muscle performance.[20] Gait speed was measured as the average speed during a four-meter walking test. The time measured to complete a four-meter walk was measured. Patients had low muscle performance if the four-meter gait speed was below 0.8m/s.[1]

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. Likelihood ratio (LR) Chi-square statistics were used for analyzing associations of the percentages of each categorical variable with the presence or absence of sarcopenia. Independent sample t-tests were used for comparing the means of the hematological and biochemical markers with the presence or absence of sarcopenia. Pearson's correlation was used to assess the correlation between SMM, MF parameters, age and BMI. Only patients with curative treatment intent were selected for overall survival analysis. Survival was visualized using Kaplan Meier survival curves and number at risk tables. We defined overall survival as the time elapsed between the date of histologic diagnosis and death or date of last follow-up, whichever occurred first. We calculated the 3-year overall survival rate for patients with sarcopenia and without sarcopenia, Wilcoxon test was used for analyzing the statistical significance of the difference in 3-year overall survival rate. A cox proportional hazard regression model was used for univariate and multivariate analysis of survival. 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 described in Table 1. A total of 85 patients were included with a mean age of 81.5 years (SD 6.5). The majority of patients were female (55.3%) with a mean BMI of 26.9 kg/m^2 (SD 4.8). Most patients were former smokers (54.1%) with mean pack years of 21-40 years. Most patients had multiple comorbidities, as represented by a high Charlson Comorbidity Index score (CCI). Most patients underwent treatment with curative intent (83.5%). The median follow-up time was 11.14 months (IQR 3.64-21.83 months); 33 patients (38.8%) died during the study period.

Table 1. Patient characteristics

Characteristics	Frequencies n, (%) or Mean (SD)
Gender	
Female	47 (55.3)
Male	38 (44.7)
Age (years) (mean, SD)	81.5 (6.5)
BMI (kg/m^2) (mean, SD)	26.9 (4.8)
Smoking status	
Never	30 (35.3)
Former	46 (54.1)
Current	9 (10.6)
Pack-years	
1-20	8 (9.4)
21-40	10 (11.8)
41-60	4 (4.7)
≥61	7 (8.2)
Alcohol use	
Never	28 (32.9)
Former	8 (9.4)
Current	49 (57.6)
Alcohol intake (units/day)	
<2	37 (43.5)
2-4	12 (14.1)
≥5	-
Charlson comorbidity index	
Mild (0-3)	4 (4.7)
Moderate (4-5)	10 (11.8)
Severe (≥6)	71 (83.5)
Weight loss in the past six months	
None	56 (65.9)
<10%	23 (27.1)
≥ 10%	6 (7.1)

Table 1. (Continued)

Characteristics	Frequencies n, (%) or Mean (SD)
MUST-score	
<2	66 (77.6)
≥2	19 (22.4)
TNM-stage	
I	11 (12.9)
II	19 (22.4)
III	16 (18.8)
IV	39 (45.9)
Tumor type	
Primary	65 (76.5)
Second primary	6 (7.1)
Recurrent	14 (16.5)
Tumor site	
Oral cavity	52 (61.2)
Nasopharynx	2 (2.4)
*Oropharynx**	5 (5.9)
Hypopharynx	3 (3.5)
Larynx	8 (9.4)
Skin	12 (14.1)
Salivary glands	1 (1.2)
Paranasal sinuses	2 (2.4)
Treatment intention	
Curative	71 (83.5)
Palliative	14 (16.5)

Legend: *. Four patients had HPV-negative oropharyngeal cancer; one patient had missing data on HPV-status.

Of the 85 included patients; 69 patients (81.2%) had low SMI, 50 patients (58.8%) had low HGS, and 58 patients (68.2%) had low gait speed. Forty-one patients (48.2%) were classified as sarcopenic; of these patients 31 patients (75.6%) had low SMI in combination with low HGS and low gait speed, 6 patients (14.6%) had low SMI in combination with low gait speed and normal HGS, and 4 patients (9.8%) had low SMI in combination with low HGS and normal gait speed.

Table 2 and table 3 show the general characteristics and the hematological and biochemical markers of the included patients according to the presence or absence of sarcopenia. Patients with sarcopenia were most likely to smoke (77.8% versus 22.2%; LR 8.37, p=0.02), to have lower mean hemoglobin levels at diagnosis (8.09 mmol/L (SD 1.06) versus 8.67 mmol/L (SD 1.12); p=0.03) and to die (63.6% versus 36.4%; LR 5.17, p<0.01).

Table 2. General characteristics of the study patients by the presence of sarcopenia.

	Sarcopenia N (%)		**Without sarcopenia N (%)**		*Likelihood Ratio p-value (LR)*	
Age (years)					8.82	0.08
70-75	7	43.8	9	56.3		
76-80	8	32	17	68		
81-85	12	48	13	52		
86-90	5	62.5	3	37.5		
>90	9	81.8	2	18.2		
BMI (kg/m²)					7.70	0.07
≤18.5	3	100	-	-		
18.5-25	17	56.7	13	43.3		
25-30	14	46.7	16	53.5		
≥30	7	31.8	15	68.2		
MUST-score					0.19	0.80
<2	31	47.0	35	53.0		
≥2	10	52.6	9	47.4		
Smoker					8.37	**0.02***
No	18	60	12	40		
Yes	7	77.8	2	22.2		
Former	16	34.8	30	65.3		
Pack-years					2.26	0.55
1-20	5	62.5	3	37.5		
21-40	3	30	7	70		
41-60	2	50	2	50		
≥61	4	57.1	3	42.9		
Alcohol use					4.57	0.23
No						
Former	17	60.7	11	39.3		
Current	4	50	4	50		
≤ 2 units/day	17	45.9	20	54.1		
≥ 2 units/day	3	25	9	75		
CCI					4.00	0.07
≤6	11	34.3	21	65.6		
>6	30	56.6	23	43.4		
TNM-stage					0.94	0.84
I	5	45.4	6	54.5		
II	8	42.1	11	57.9		
III	7	43.8	9	56.3		
IV	21	53.8	18	46.2		
Treatment intention					1.74	0.25
Curative	32	45.1	39	54.9		
Palliative	9	64.3	5	35.7		
Radiotherapy					0.45	0.87
No	24	49	25	51		
Yes, primary	8	42.1	11	57.9		
Yes, adjuvant	9	52.9	8	47.1		

Table 2. (Continued)

	Sarcopenia N (%)		Without sarcopenia N (%)		*Likelihood Ratio p-value (LR)*	
Surgery					0.47	0.62
No	12	54.5	10	45.5		
Yes	29	46	34	54		
Synchronous tumor					1.82	0.36
No	40	50	40	50		
Yes	1	20	4	80		
Metachronous tumor					0.95	0.62
No	40	49.4	41	50.6		
Yes	1	25	3	75		
Recurrence					0.20	0.65
No	35	47.3	39	52.7		
Yes	6	54.5	5	45.5		
Dead					5.17	**0.03***
No	20	38.5	32	61.5		
Yes	21	63.6	12	36.4		
SMI					24.54	**<0.01****
Low	41		28	40.6		
High	-	59.4	16	100		
HGS					24.57	**<0.01****
Low	35	70	15	30		
High	6	17.1	29	82.9		
Gait speed					19.14	**<0.01****
Low	37	63.8	21	36.2		
High	4	14.8	23	85.2		

Legend: **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed)

Table 3. Hematological and biochemical markers of the study patients by the presence or absence of sarcopenia.

	Sarcopenia (mean, SD)	Without Sarcopenia (mean, SD)	Mean difference *(SD)*	95% CI	*p-value*
Hb (mmol/L)	8.09 (1.06)	8.67 (1.12)	-0.58 (0.26)	-1.10- -0.05	**0.03***
CRP (mg/L)	9.93 (15.10)	8.12 (11.86)	1.81(3.38)	-4.93-8.56	0.59
Leukocytes (x10^9/L)	10.78 (8.24)	8.15 (2.45)	2.63(1.44)	-0.25-5.51	0.07
Albumin (g/L)	39.56 (2.28)	40.98 (2.53)	-1.42 (1.14)	-3.83-0.99	0.23
Creatinine (mmol/L)	87.55 (30.95)	95.38 (51.06)	-7.84 (10.43)	-28.65 -12.98	0.46

Legend: *. Correlation is significant at the 0.05 level (2-tailed)

CORRELATION ANALYSIS

Results from the correlation analyses are shown in Table 4. Significant low to moderately strong correlation coefficients is seen for SMI and BMI (r=0.49), SMI and age (r=-0.37), HGS and age (r=-0.46), gait speed and age (r=0.28) and for gait speed and HGS (r=-0.39).

Table 4. Pearson correlation analysis for variables associated with sarcopenia.

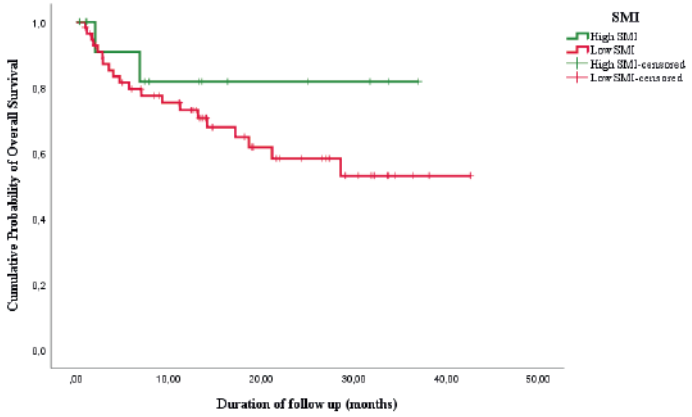
Measures	SMI	HGS	Gait speed	Age	BMI
SMI	-	0.16	-0.15	**-0.37****	**0.49****
HGS	0.16	-	-**0.39****	**-0.46****	-0.04
Gait speed	-0.15	**-0.39****	-	**0.28***	0.05
Age	**-0.37****	**-0.46****	**0.28***	-	-0.02
BMI	**0.49****	-0.04	0.05	-0.02	-

Legend: **. Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)

SURVIVAL ANALYSIS

Results from the Kaplan Meier survival analysis are shown in Figures 1-4. As seen in Figures 1-3, the median overall survival appears to be shorter for patients treated with curative intent with high SMI compared with patients with low SMI (10.58 versus 13.34 months; log rank test p=0.29), but this difference was not statistically significant. The differences in OS between patients with low HGS compared with patients with high HGS (13.31 versus 13.17 months; log rank test p=0.25) and for patients with low gait speed compared with patients with high gait speed (11.94 versus 16.36 months; log rank test p=0.16) were not significant either. The median overall survival was significantly shorter for patients treated with curative intent with sarcopenia compared to patients without sarcopenia (12.07 versus 13.60 months; log rank test p=0.02), as is illustrated in Figure 4. The overall 3-year survival rate was significantly shorter for patients treated with curative intent with sarcopenia compared to patients without sarcopenia (39% versus 75%; Wilcoxon Statistic 4.48, p=0.03). Results from the univariate and multivariate cox regression analysis for overall survival are shown in Table 5. Sarcopenia (HR 2.80; 95% CI 1.14-6.88; p=0.03) and TNM-stage IV (HR 15.64; 95% CI 1.99-122.88; p=0.01) were significant prognostic factors for overall survival in univariate cox regression analysis. In multivariate cox regression analysis, model 1 shows that sarcopenia (HR 2.66; 95% CI1.07-6.58; p=0.04) remained a significant prognostic factor for overall survival independent of age, Hb level, BMI, MUST-score and comorbidity. However, sarcopenia did not remain a significant prognostic factor when TNM-stage was included (model 2). TNM-stage IV was a significant prognostic factor for overall survival in multivariate cox regression analysis (HR 15.64; 95% CI 1.99-122.88; p=0.01). A subgroup analyses according to TNM-stage was performed, of which the results are shown in Table 6. Sarcopenia was a statistically significant prognostic factor for overall survival in patients with TNM-stage I-III (HR 9.19; 95% CI 1.07-78.74; p=0.04). However, sarcopenia was not a statistically significant prognostic factor for overall survival in patients with TNM-stage IV (HR 0.90; 95% 0.32-2.55; p=0.85).

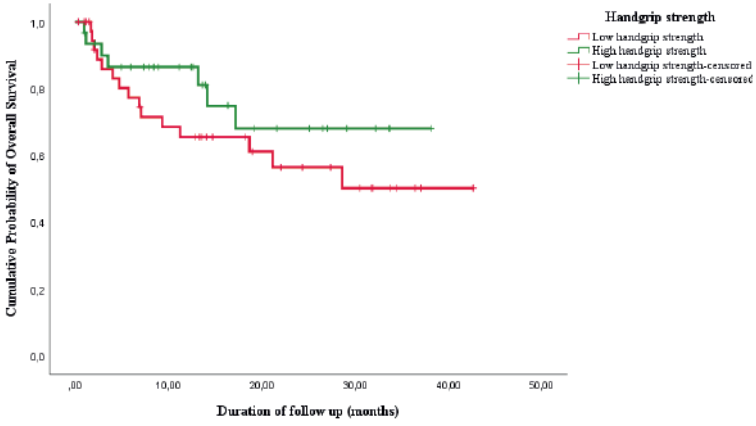
Figure 1. Kaplan-Meier overall survival curves and number at risk table for patients with low SMI and high SMI showed no statistically significant difference (Log rank Chi-Square 1.14; p=0.29)



Skeletal muscle index (SMI) and overall survival (OS)

	T= 0	T=12	T=24	T=36
Low SMI	57	33	15	3
High SMI	14	7	4	1

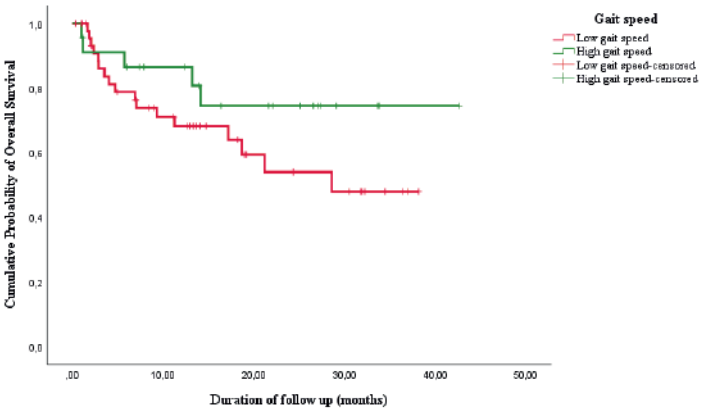
Figure 2. Kaplan-Meier overall survival curves and number at risk table for patients with low HGS and high HGS showed no statistically significant difference (Log rank Chi-Square 1.35; p=0.25)



Handgrip strength (HGS) and overall survival (OS)

	T= 0	*T=12*	*T=24*	*T=36*
Low HGS	*40*	*22*	*11*	*3*
High HGS	*31*	*18*	*8*	*1*

Figure 3. Kaplan-Meier overall survival curves and number at risk table for patients with low gait speed and high gait speed showed no statistically significant difference (Log rank Chi-Square 1.95; p=0.16)

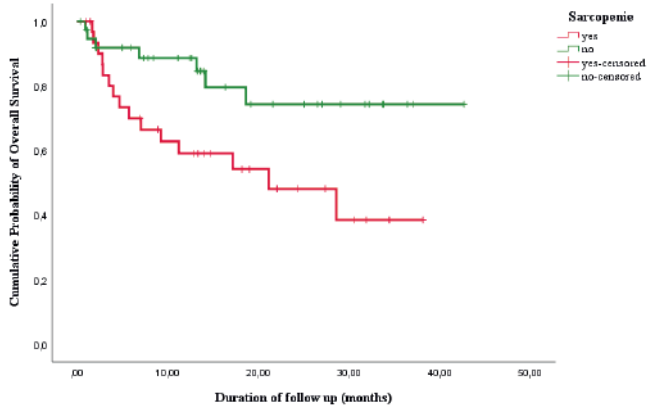


Gait speed (GS) and overall survival (OS)

	T= 0	*T=12*	*T=24*	*T=36*
Low gait speed	*48*	*24*	*10*	*3*
High gait speed	*23*	*16*	*9*	*1*

Figure 4. Kaplan-Meier overall survival curves and number at risk table for patients with and without sarcopenia showed statistically significant difference (Log rank Chi-Square 5.50; p=0.02)

Sarcopenia and overall survival (OS)



	T= 0	*T=12*	*T=24*	*T=36*
Sarcopenia	*32*	*16*	*7*	*1*
Without Sarcopenia	*39*	*24*	*12*	*3*

Table 5. Univariate and multivariate analysis of the hazard ratios for sarcopenia, age, Hb level, BMI, MUST-score, CCI and TNM-stage as independent prognostic factors for overall survival.

Variable	Overall survival								
	Univariate analysis			Multivariate analysis (*)					
				Model 1			Model 2		
	HR	95% CI	P-value	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Sarcopenia	2.80	1.14-6.88	**0.03***	2.66	1.07-6.58	**0.04***	1.36	0.48-3.83	0.56
Age (years)	1.03	0.95-1.11	0.48	1.02	0.94-1.11	0.59	1.05	0.97-1.13	0.26
Hb (mmol/L)	0.82	0.58-1.16	0.26	0.90	0.61-1.32	0.58			
BMI (kg/m²)									
<18.5	-			-			-		
18.5-25	Ref.	-	-	Ref.	-	-	Ref.	-	-
25-30	0.54	0.21-1.38	0.20	0.54	0.21-1.39	0.20	0.50	0.19-1.31	0.16
≥30	0.34	0.10-1.20	0.10	0.45	0.12-1.64	0.23	0.70	0.18-2.72	0.61
MUST-score									
<2	Ref.			Ref.					
≥2	1.75	0.68-4.53	0.25	1.36	0.47-3.95	0.57			
CCI									
<6	Ref.			Ref.			Ref.		
≥6	1.22	0.52-2.86	0.65	0.92	0.35-2.40	0.86	1.47	0.58-3.74	0.42
TNM-stage									
I	Ref.						Ref.		
II	0.96	0.06-15.40	0.98				0.96	0.06-15.40	0.98
III	5.24	0.57-48.46	0.14				5.24	0.57-48.46	0.14
IV	15.64	1.99-122.88	**0.01***	-	-	-	15.64	1.99-122.88	**0.01***

Legend: *. Correlation is significant at the 0.05 level (2-tailed) (*) Model 1 includes the variables; sarcopenia, age, hb value, BMI, MUST-score and CCI. Model 2 includes the variables; sarcopenia, age, BMI, CCI and TNM-stage.

Table 6. Subgroup analyses according to TNM-stage and sarcopenia showed sarcopenia as a statistically significant prognostic factor for overall survival in all patients with curative treatment intention (HR 2.80; 95% CI 1.14-6.88; p=0.03) and in all patients with TNM-stage I-III (HR 9.19; 95% CI 1.07-78.74; p=0.04)

Subgroup	***Overall survival***			
	Sarcopenia			
	Frequency	***HR***	***95% CI***	***P-value***
TNM-stage I-III	32	9.19	1.07-78.74	**0.04***
TNM-stage IV	39	0.90	0.32-2.55	0.85
Curative treatment intention	71	2.80	1.14-6.88	**0.03***

*. Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

Sarcopenia is a common and highly prevalent clinical problem in the elderly patient. Literature showed that sarcopenia is associated with several negative outcomes, however literature mainly focuses on radiologically assessed low SMM rather than the combination of SMM and MF.[6,7,16,8–15] In addition, no studies report on the impact of sarcopenia on survival in the elderly head and neck cancer patient. Identification of the impact of low SMM and low MF on prognosis in the elderly head and neck cancer patient will stimulate the development of novel interventions to gain SMM and MF which may improve the prognosis of these patients. Regardless of the success of an intervention, information on prognosis can be used for patient counseling and treatment decision making.

In this study, we included 85 patients of whom 41 patients (48.2%) were classified as sarcopenic. This number is in accordance with recent medical literature which estimated the prevalence of sarcopenia in elderly patients diagnosed with different types of cancer between 14%-78.7%.[21] The prevalence estimates of sarcopenia in the elderly non-cancer patients are lower, ranging between 5-50%. Sarcopenia is prevailing in elderly cancer patients because of the frequent weight loss caused by low food intake, increased catabolic pathways, increased inflammation, increased lipolysis and increased proteolysis associated with both old age and malignancy.[21]

This study shows that SMM, muscle strength and physical functioning separately had no significant prognostic value for overall survival. A combination of muscle mass and muscle strength or muscle performance did show a significant prognostic value for overall survival in elderly patients with head and neck cancer. This is in accordance with previous studies in other tumor types, which have demonstrated that not only SMM but also MF is related with several health outcomes[21–23]. Previous studies in patients with esophageal cancer did not show a significant prognostic value of sarcopenia on overall survival, however sarcopenia was defined as low

radiologically assessed SMM only rather than a combination of low SMM and low MF.[24–27] Our study highlights the importance of defining sarcopenia as a combination of SMM and MF.

In multivariate analysis including the covariates age, Hb level, MUST-score, BMI and comorbidity; sarcopenia remained a statistically significant prognostic factor for overall survival. When including TNM-stage in the multivariate analysis, sarcopenia did not remain a statistically significant prognostic factor for overall survival. Subgroup analyses according to TNM-stage and, treatment intention shows that sarcopenia is a statistically significant prognostic factor for overall survival in patients with TNM-stage I-III and in all patients with curative treatment intention. In patients with TNM-stage IV, sarcopenia is not a statistically significant prognostic factor for overall survival. In this study, 39 patients (45.9%) had an TNM-stage IV, it is possible that sarcopenia did not remain a significant prognostic factor in model 2 of the multivariate analysis because of the high number of patients with TNM-stage IV. This finding is in accordance with a previous study performed in patients with gastric cancer which showed that sarcopenia is a significant prognostic factor for overall survival in patients with TNM-stage II-III.[28] It is also in accordance with a recent systematic review, which showed that sarcopenia is a significant prognostic factor for overall survival in different types of cancers independent of TNM-stage.[29]

The existing literature on sarcopenia in patients with head and neck cancer is scarce and focuses mainly on low SMM in patients who receive (chemo)radiotherapy[7] or patients who undergo a total laryngectomy[10,11] To our knowledge, our study is the first to investigate the impact of sarcopenia, defined as a combination of SMM and MF, in elderly (≥ 70-year-old) head and neck cancer patients.

This study has some limitations. It was designed as a retrospective single-center study, which increases the risk for systemic errors. It had limited number of included patients which may have led to type II errors. Only patients with available data on SMM and MF were included in the study. As it is more likely that MF parameters were examined for frail patients than for fit patients, this may have resulted in a biased study population in which it is probably more difficult to show the prognostic value of sarcopenia. Therefore, sarcopenia as combination of SMM and MF should be further evaluated as a prognostic factor for overall survival in elderly patients with head and neck cancer.

Concerning the imaging techniques used to assess SMM, we decided to include both CT scans and MRI scans of the head and neck area to assess SMM, in order to maximize the number of patients that could be included. Whenever available, we used CT imaging instead of MRI because most research on SMM in cancer patients is performed using CT imaging. However, the CT measurement method for SMM was formulated on MRI-based research.[30–32] Theoretically there is no difference in SMM between CT imaging and MRI, as both methods are very accurate for SMM assessment. Therefore, we believe it is acceptable to use MRI for SMM measurement when CT imaging is not available. Research should be conducted to investigate this further.

In retrospective studies, data on MF will probably rarely be available, whereas CT or MRI is often routinely performed in head and neck cancer patients. We propose to conduct further prospective studies for the measurement of both MF and SMM and to perform routine handgrip strength measurements in every newly diagnosed head and neck cancer patient.

In conclusion, sarcopenia is present in half of the elderly HNSCC patients. Skeletal muscle mass index and muscle function, as determined by muscle strength or physical performance measurements, were not prognostic separately in elderly HNSCC patients, but the combination of both was prognostic for overall survival. Therefore, it may be preferable to define sarcopenia as the combination of low skeletal muscle mass and low muscle function and not by radiologically assessed skeletal muscle mass alone.

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CHAPTER 19

Sarcopenia measured with handgrip strength and skeletal muscle mass to assess frailty in older patients with head and neck cancer

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ABSTRACT

Background

Patients with head and neck cancer (HNC) have a risk of sarcopenia which is associated with adverse health outcomes. Frailty is also associated with adverse outcomes and is diagnosed by a comprehensive geriatric assessment (CGA). Because a CGA is time-consuming and not all patients benefit from it, frailty screening questionnaires are used to select patients for CGA. Sarcopenia measurement may be a biomarker for frailty. Our objective was to examine the association between sarcopenia and a frailty screening questionnaire.

Materials and methods

In this single-center retrospective study, 150 patients (≥ 60-years old) with HNC were reviewed. Sarcopenia was defined as the combination of reduced handgrip strength and loss of skeletal muscle mass, calculated as skeletal muscle index (SMI), according to the EWGSOP-criteria. Frailty screening was performed using the Geriatrics 8 (G8) questionnaire.

Results

In total, 150 patients were included, 101 men and 49 women. Frail patients were more likely to be sarcopenic at diagnosis. G8 frailty score showed a significant though weak correlation with SMI. Univariate regression analysis with frailty as a dependent variable distinguished comorbidity score, handgrip strength, SMI, and sarcopenia as significant. These variables were subjected to a multivariate analysis in which comorbidity score and SMI remained significant.

Conclusion

There is an association between sarcopenia and the G8 frailty screening questionnaire. Therefore, sarcopenia measurement could be interchangeable with the G8 frailty screening questionnaire. Further research should compare the gold standard for frailty, i.e., CGA, with sarcopenia.

INTRODUCTION

Worldwide the annual incidence of head and neck cancer (HNC) accounts for more than 650,000 cases and 330,000 deaths.[1] Compared to patients with other malignancies, patients with HNC have a higher risk of severe malnutrition, mostly due to swallowing problems.[2] This could lead to sarcopenia. Sarcopenia is defined as a generalized and progressive loss of muscle function and skeletal muscle mass.[3] Previous studies showed that sarcopenia based on loss of skeletal muscle mass is present in 35.5–54.5% of patients with HNC and is related to adverse health outcomes.[4,5] For example, low skeletal muscle mass is associated with chemotherapy dose-limiting toxicity[6], increased incidence of postoperative complications, and decreased survival in patients with HNC[7,8]. Patients with sarcopenia thus represent an important group that should be identified as they are at risk for complications of treatment and poor survival.

Frailty is also associated with poor outcomes and higher risks of treatment complications.[9] Frailty is often mentioned as an age-related syndrome of physiological decline and vulnerability, leading to an increased risk of adverse health outcomes.[10] A comprehensive geriatric assessment (CGA) that evaluates physical, psychological, functional, and social capabilities, and limitations of geriatric patients is the gold standard assessment for diagnosing frailty. In geriatric oncology, a CGA is used to detect disabilities, and comorbid conditions that potentially contribute to an older adult patient's vulnerabilities, which could predispose them to poor outcomes and treatment complications.[11]

However, such assessments are time-consuming, leading many cancer specialists to seek a shorter screening tool that can separate fit older adults with cancer, who can receive standard cancer treatment, from vulnerable patients, who should subsequently receive a full assessment to guide tailoring of their treatment regimens.[12] One such tool is the Geriatrics 8 (G8) screening tool, which was developed specifically for older adults with cancer. Another potential predictor of toxicity and poor outcomes is sarcopenia.[13] Zwart et al. found that sarcopenia as measured by skeletal muscle mass on screening CTs was a potential biomarker for frailty in patients with HNC. In their study low skeletal muscle mass, was independently associated with frailty screening based on the G8 questionnaire.[14]

However, Williams et al. were unable to find an association between sarcopenia, based on skeletal muscle mass, and frailty diagnosed with the Carolina Frailty Index in older adult patients with cancer.[15] Dunne et al., in their investigation of 100 older adults with cancer found no significant association between skeletal muscle mass, as measured at the level of the third lumbar vertebral body, and any components of the CGA.[16] Zwart et al.[11] and Dunne et al.[17] conducted only skeletal muscle mass measurements on CT of the third cervical or lumbar vertebrae to determine sarcopenia.

According to the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia is a combination of muscle function and skeletal muscle mass.[13]

The association between sarcopenia and frailty could possibly be improved when a combination of skeletal muscle mass and muscle function, examined with handgrip strength, is used to assess sarcopenia.[13] The aim of this study was to examine the association between sarcopenia, defined as reduced handgrip strength and loss of skeletal muscle mass, and frailty screening, as assessed by the G8 questionnaire in older adults with HNC.

MATERIALS 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 (Version 2008) and its later amendments or comparable ethical standards. All data were handled according to general data protection regulation (GDPR).

PATIENTS AND STUDY DESIGN

In this single-center retrospective study, older adult patients' (≥ 60-years old) with pathologically proven HNC diagnosed between September 2018 and January 2020 records were reviewed. In our clinic, these patients routinely undergo handgrip strength measurement and fill out the G8 questionnaire on their first outpatient clinic visit. Patients were included if they had a geriatric assessment screening (G8), handgrip strength measurement, and had recent (< four weeks) pre-treatment imaging scans (CT or MRI) of the head and neck. This resulted in an initial inclusion of 180 patients. Patients were excluded due to insufficient quality of diagnostic imaging (incomplete imaging at the time of diagnoses (fifteen), presence of artifacts (twelve), no reliable differentiation between muscle and surrounding tissue (three) which impaired measurements of skeletal muscle mass. This resulted in the final inclusion of 150 patients. Relevant demographic and clinical variables were collected from patients' medical records: age, sex, body mass index (BMI), weight loss in the past six months, smoking status, alcohol use, comorbidity as evaluated by the Adult Comorbidity Evaluation-27 index (ACE-27), tumor localization, tumor type (primary, second primary or recurrence), histology, the TNM stage according to the 8th edition of the UICC tumor classification of malignant tumors and imaging technique (CT or MRI) were scored.

DEFINITION OF SARCOPENIA

As recommended by the EWGSOP we used the combination of low muscle function, as determined by handgrip strength measurements, and low muscle quantity, as determined by skeletal muscle mass, for the diagnosis of sarcopenia.[13]

MUSCLE FUNCTION

Overall muscle function is strongly related to handgrip strength.[18] Handgrip strength was measured using a Jamar hydraulic handheld dynamometer according to the recommendations of the American society of hand therapists (ASHT) and expressed in kilograms (kg). Patients were asked to squeeze maximally with each hand. The average score of the left and right hands was used for analysis. Patients had low handgrip strength if the handgrip strength was below twenty-seven kg (men) or below sixteen kg (women).[13]

SKELETAL MUSCLE MASS

Skeletal muscle mass was measured in all patients at the level of the third cervical vertebrae (C3) as cross-sectional muscle area (CSMA) on CT or MRI imaging before initiating treatment. The axial slice of the imaging which showed both transverse processes and the entire vertebral arc was selected for the segmentation of muscle tissue (Figure 1). 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.[19] For MRI, muscle area was manually segmented, and fatty tissue was manually excluded. Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (version 5.0, Tomovision, Canada). The first author (CM) performed skeletal muscle mass measurements in all 150 patients.

The cross-sectional muscle area at the level of C3 was converted to CSMA at the level of L3 using a formula published by Swartz et al.[20] The lumbar skeletal muscle index (SMI) was calculated by correcting skeletal muscle mass at the level of L3 for squared height. Patients had a low SMI if this value was ≤43.2 cm^2/m^2; this cut-off value was established in a separate cohort of patients with HNC.[14]

Figure 1. Example of segmentation of skeletal muscle tissue at the level of the third cervical vertebra (C3)

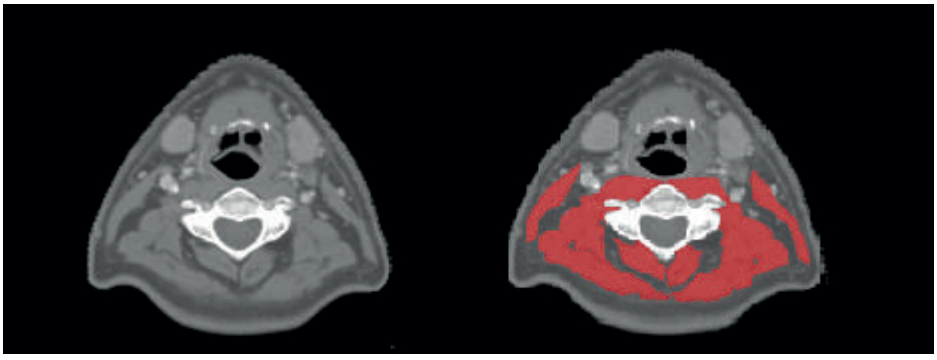


Figure shows two identical axial computed tomography (CT) slides at the level of C3; left shows the muscle tissue unsegmented, right shows both sternocleidomastoid and paravertebral muscles segmented in red.

FRAILTY

For frailty screening, we used the G8 frailty questionnaire. This frailty screening tool consists of eight items which cover multiple geriatric domains, including nutritional status, physical capacity, mood, and polypharmacy. The G8 is specifically designed for older adult patients with cancer. Scores range from zero to seventeen, with scores ≤ fourteen representing potential frailty.[21]

STATISTICAL ANALYSIS

Data analyses were performed using IBM SPSS statistics 25. Bassline clinical characteristics were collected, and continuous data are represented as mean ± standard deviation (SD). Categorical data are represented as a number and percentage of total. The skeletal muscle mass was presented dichotomously as low SMI and normal SMI based on previously published specific cut-offs for SMI. Muscle function was presented dichotomously as low muscle function and normal muscle function based on previously published gender-specific cut-offs for handgrip strength. Sarcopenia was presented dichotomously as sarcopenic (if patients had a low muscle function and low SMI) and non- sarcopenic (all other patients).Frailty was presented dichotomously as frail and non-frail based on previously published cut-offs for the G8 frailty screening questionnaire.

Correlation between SMI, handgrip strength and the G8 frailty score were analyzed with bivariate Pearson's r-correlation coefficients. Independent sample t-tests or Chi-square statistics were used for analyzing differences between the frequencies of each categorical variable with the presence or absence of frailty and presence or absence of sarcopenia.

Univariate logistic regression analyses were performed, with frailty or sarcopenia as dependent variables and the baseline variables as independent variables. Variables were selected based on clinical relevance. Variables that were statistically significant ($p< 0.05$) in the univariate regression were included in the multivariate logistic regression with odds ratios (ORs) and 95% CIs provided.

RESULTS

PATIENT CHARACTERISTICS

In total 150 patients with HNC diagnosed between September 2018 and January 2020 were included. Patient characteristics are presented in Table 1. The majority of the patients (67%) were male. Stage IV was the most common stage (43%). Of the included patients, 60 patients (40%) were screened as frail according to the G8 questionnaire. The majority of the patients (61%) had low SMI at diagnosis. Low handgrip strength at diagnosis was seen in a minority of the included patients (22%). Of the included patients, 21 patients (14%) were sarcopenic, as defined by low handgrip strength and low SMI. The mean time between G8 questionnaire and handgrip strength measurement (first consultation) and the CT/MRI scan was 1.8 weeks.

Table 1. Characteristics of HNC patients with and without frailty [1]

	Total N=150		**Frail N=60**		**Non-Frail N=90**		χ^2	***p-value***
Age (years) (M, SD)	70.3	7.26	71.5	8.7	69.5	6.0	NA	0.14
Sex (n, %)								
Male	101	67	36	60	65	72	2.45	0.1
Female	49	33	24	40	25	28		
Weight loss 6 months prior to diagnosis (n, %)								
Non	117	78	40	66	77	86	13.23	**0.001***
<10%	26	17	13	22	13	14		
≥ 10%	7	5	7	12	0	0		
BMI (kg/m²) (n, %)								
<20	53	35	26	43	27	30	21.03	**0.000***
20-24.9	9	6	9	15	0	0		
25-29.9	64	43	20	33	44	49		
≥ 30	24	16	5	9	19	21		
Smoker (n, %)								
No	26	17	10	17	16	18	1.67	0.434
Former	73	49	26	43	47	52		
Current	51	34	24	40	27	30		
Alcohol use (n, %)								
No	29	18	11	18	18	20	0.27	0.88
Yes	101	62	40	67	61	68		
Former	20	12	9	15	11	12		
ACE-27 score (n, %)								
Non	49	33	12	20	37	41	11.93	**0.008***
Mild	54	36	21	35	33	37		
Moderate	29	19	15	25	14	15		
Severe	18	12	12	20	6	7		
Localization (n, %)								
Oral cavity	32	21	13	22	19	21	5.40	0.71
Nasal cavity	6	4	3	5	3	3		
Nasopharynx	6	4	2	3	4	5		
Oropharynx	37	25	19	31	18	20		
Hypopharynx	11	7	5	8	6	7		
Larynx	29	19	10	17	19	21		
Salivary glands	17	11	5	9	12	13		
Skin	2	1	0	0	2	2		

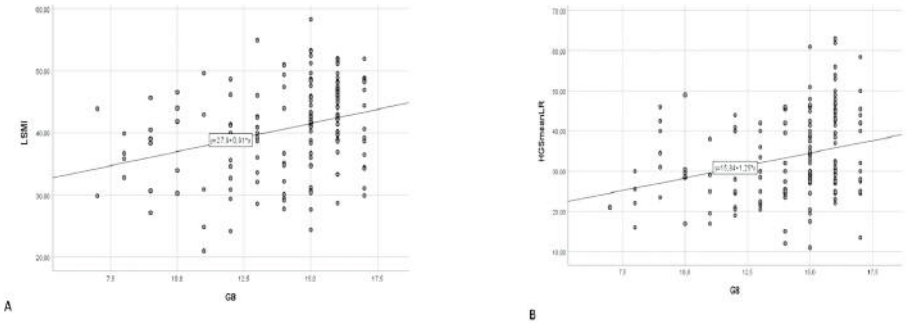
Table 1. (Continued)

	Total N=150		**Frail N=60**		**Non-Frail N=90**		χ^2	***p-value***
Age (years) (M, SD)	70.3	7.26	71.5	8.7	69.5	6.0	NA	0.14
Unknown primary	10	7	3	5	7	8		
Type of tumor (n, %)								
Primary	143	95	59	98	84	93	2.12	0.35
Recurrent	1	1	0	0	1	1		
Second primary	6	4	1	2	5	6		
Histology (n, %)								
Squamous	119	79	50	82	69	77	1.34	0.51
Adenocarcinoma	18	12	5	9	13	14		
Other	13	9	5	9	8	9		
TNM Stage (n, %)								
I	23	15	8	13	15	17	8.01	**0.046****
II	30	20	6	10	24	27		
III	33	22	14	23	19	21		
IV	64	43	32	54	32	35		
Type of imaging (n, %)								
CT	92	61	39	65	53	59	0.57	0.45
MRI	58	39	21	35	37	41		
Low muscle function (n, %)								
No	117	78	43	72	74	82	2.34	0.13
Yes	33	22	17	28	16	18		
Low SMI (n, %)								
No	58	39	14	23	44	49	9.91	**0.002***
Yes	92	61	46	77	46	51		
Sarcopenia (n, %)								
No	129	86	47	78	82	91	4.88	**0.027****
Yes	21	14	13	22	8	9		

Correlation analysis of sarcopenia and frailty score

SMI showed a significant though weak correlation with the G8 frailty score (r=0.252, p<0.01). handgrip strength showed a significant but weak correlation with the G8 frailty score (r=0.284, p<0.01). A stronger and significant correlation was identified between SMI and the handgrip strength (r=0.512, p<0.01). Scatterplots, with SMI, hand grip strength, and the G8 frailty score are presented in Figure 2.

Figure 2. Scatterplots for skeletal muscle index, handgrip strength and frailty scores. The figure illustrates the correlation of skeletal muscle index (SMI) and G8 frailty scores (A); handgrip strength (HSG) and frailty scores (B).



As seen in Table 1 , statistically significant differences were seen between patients with and without frailty in the presence of sarcopenia, low SMI, amount of comorbidity as evaluated by the ACE-27 score, and TNM stage. Frail patients were more likely to be sarcopenic (combination of low handgrip strength and low SMI) at diagnosis (22% versus 9%, p<0.05), to have low SMI at diagnosis (77 % versus 51%; p<0.01), to have a severe comorbidity defined by the ACE-27 score (20 % versus 7%; p<0.01), and to have a stage IV disease (54 % versus 35%; p<0.05).

Statistically significant differences were found between patients with and without sarcopenia for frailty measured by the G8, age at diagnosis, and comorbidity scores as evaluated by the ACE-27 score (Table 2). Sarcopenic patients were more likely being frail (22% versus 9%, p<0.05), to be older of age at diagnosis (mean 77 years versus 69 years; p<0.01), and to have a mild ACE-27 score (57 % versus 32%; p<0.01).

Table 2. Characteristics of HNC patients with and without sarcopenia[2]

	Total N=150		**Sarcopenic N=21**		**Non Sarcopenic N=129**		χ^2	***p-value***
Age (years) (M, SD)	70.3	7.26	77	8.6(SD)	69	6.4(SD)	NA	**0.000***
Sex (n, %)								
Male	101	67	12	57	89	69	1.15	0.28
Female	49	33	9	43	40	31		
Weight loss 6 months prior to diagnosis(n, %)								
Non	117	78	16	76	101	78	1.38	0.50
<10%	26	17	3	14	23	18		
≥ 10%	7	5	2	10	5	4		
BMI (kg/m²) (n, %)								
<20	53	35	10	48	43	33	4.58	0.21

Table 2. (Continued)

	Total N=150		**Sarcopenic N=21**		**Non Sarcopenic N=129**		χ^2	***p-value***
20-24.9	9	6	0	0	9	7		
25-29.9	64	43	10	48	54	42		
≥ 30	24	16	1	4	23	18		
Smoker (n, %)								
No	26	17	4	19	22	17	0.05	0.98
Former	73	49	7	33	44	34		
Current	51	34	10	48	63	49		
Alcohol use (n, %)								
No	29	18	4	19	25	19	0.71	0.70
Yes	101	62	13	62	88	68		
Former	20	12	4	19	16	13		
ACE-27 score (n, %)								
Non	49	33	0	0	49	38	12.2	**0.007***
Mild	54	36	12	57	42	32		
Moderate	29	19	6	29	23	18		
Severe	18	12	3	14	15	12		
Localization (n, %)								
Oral cavity	32	21	5	24	27	21	4.72	0.79
Nasal cavity	6	4	0	0	6	5		
Nasopharynx	6	4	0	0	6	5		
Oropharynx	37	25	4	19	33	25		
Hypopharynx	11	7	1	5	10	8		
Larynx	29	19	5	24	24	19		
Salivary glands	17	11	4	19	13	10		
Skin	2	1	0	0	2	1		
unknown primary	10	7	2	9	8	6		
Type of tumor (n, %)								
Primary	143	95	21	100	122	94	1.20	0.55
Recurrent	1	1	0	0	1	1		
Second primary	6	4	0	0	6	5		
Histology (n, %)								
Squamous	119	79	17	81	102	80	0.15	0.93
Adenocarcinoma	18	12	2	9	16	12		
Other	13	9	2	10	11	8		
TNM Stage (n, %)								

Table 2. (Continued)

	Total N=150		Sarcopenic N=21		Non Sarcopenic N=129		χ^2	*p-value*
I	23	15	6	29	17	13	4.23	0.24
II	30	20	2	9	28	22		
III	33	22	4	19	29	22		
IV	64	43	9	43	55	43		
Type of imaging (n, %)								
CT	92	61	12	57	80	62	0.18	0.67
MRI	58	39	9	43	42	38		
Low muscle function (n, %)								
No	117	78	0	0	117	91	86.58	**0.000***
Yes	33	22	21	100	12	9		
Low SMI (n, %)								
No	58	39	0	0	58	45	15.39	**0.000***
Yes	92	61	21	100	71	55		
G8 Frailty questionnaire (n, %)								
Not frail > 14	129	86	47	78	82	91	4.88	**0.027****
Frail ≤ 14	21	14	13	22	8	9		

UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION

Univariate and multivariate logistic regression analysis with frailty or sarcopenia as the dependent variable was performed. Table 3 shows the univariate regression analysis with frailty as the dependent variable which distinguished ACE-27 score (OR 6.17, 95% CI 1.90-20.00, P =0.002), handgrip strength (OR 0.94, 95% CI 0.90–0.97, P < 0.000), SMI (OR 0.92, 95% CI 0.87–0.96, P < 0.000), and sarcopenia (OR 2.84, 95% CI 1.10-7.34, P =0.032) as significant variables for predicting frailty. These significant variables were subjected to two different multivariate analyses. The first with sarcopenia and the second with hand grip strength and SMI because of assumed multicollinearity. In the first multivariate analysis only ACE-27 score (OR 5.47, 95% CI 1.67-17.98, P =0.005) remained significant. In the second ACE-27 score (OR 8.08, 95% CI 2.21-29.60, P =0.003) and SMI (OR 0.92, 95% CI 0.86-0.98, P=0.006) remained significant.

Table 4 shows the univariate regression analysis with sarcopenia as dependent variables distinguished age (OR 3.68, 95% CI 1.27-10.64, P = 0.016) and G8 (OR 2.84, 95% CI 1.10-7.34, P = 0.032) as significant variables associated with sarcopenia. These significant variables were subjected to a multivariate analysis in which age (OR 3.65, 95% CI 1.25-10.71, P = 0.018) and G8 (OR 2.81, 95% CI 1.06-7.43, P = 0.037) remained significant.

Table 3. Univariate and multivariate logistic regression analysis for analyzing variables associated with frailty in patients with HNC[3]

Frailty	Univariate analysis			Multivariate analysis					
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)									
<70	Ref.								
≥ 70	1.20	0.62-2.29	0.59						
Gender									
Male	Ref.								
Female	1.73	0.87-3.46	0.12						
ACE-27 score									
Non	Ref.			Ref.			Ref.		
Mild	1.96	0.84-4.59	0.12	1.62	0.67-3.94	0.29	1.90	0.75-4.81	0.17
Moderate	3.30	1.24-8.78	**0.02****	2.80	1.03-7.63	**0.04****	3.59	1.21-10.60	**0.002***
Severe	6.17	1.90-20.00	**0.002***	5.47	1.67-18.0	**0.01***	8.08	2.21-29.60	**0.003***
TNM Stage									
I	Ref.								
II	0.47	0.14-1.62	0.23						
III	1.38	0.46-4.16	0.57						
IV	1.88	0.70-5.04	0.21						
Handgrip strength	0.94	0.90-0.97	**0.000***				0.97	0.93-1.02	0.21
SMI	0.92	0.87-0.96	**0.000***				0.92	0.86-0.98	**0.01***
Sarcopenia									
No	Ref.			Ref.					
Yes	2.84	1.10-7.34	**0.03****	2.29	0.83-6.28	0.11			

Table 4. Univariate and multivariate logistic regression analysis for analyzing variables associated with sarcopenia in patients with HNC[4]

Sarcopenia	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)						
<70	Ref.			Ref.		
≥ 70	3.68	1.27-10.64	**0.02****	3.65	1.25-10.71	**0.02****
Gender						
Male	Ref.					
Female	0.59	0.23-1.54	0.29			
Weight loss 6 months prior to diagnosis						
Non	Ref.					

Table 4. (Continued)

Sarcopenia	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
<10%	0.82	0.22-3.06	0.77			
≥ 10%	2.52	0.45-14.13	0.29			
BMI (kg/m²)	0.97	0.86-1.08	0.56			
TNM Stage						
I	Ref.					
II	0.20	0.04-1.12	0.07			
III	0.39	0.10-1.58	0.19			
IV	0.46	0.14-1.49	0.20			
G8 Frailty						
No	Ref.			Ref.		
Yes	2.84	1.10-7.34	**0.03****	2.81	1.06-7.43	**0.04****

DISCUSSION

This retrospective study, conducted in 150 patients with HNC, showed that there is an association between sarcopenia and frailty as assessed by the G8. There is also a significant but weak correlation between sarcopenia and frailty, based on the G8 frailty screening instrument. To our knowledge, this study is the first that used the novel definition of the EWGSOP for sarcopenia, defined as skeletal muscle mass and muscle function, and its correlation with frailty screening questionnaires in patients with HNC. Zwart et al. found also a low but significant correlation between skeletal muscle mass, defined as SMI, and frailty ($r = 0.38$, $P < 0.001$).[11] In contrast to our study, they defined sarcopenia based on only SMI. We included muscle function as well. In our study, skeletal muscle mass, defined as SMI, was more significantly associated with G8 frailty screening compared to sarcopenia, defined as the combination of skeletal muscle mass and muscle function. Based on both studies, skeletal muscle mass may be interchangeable with the G8 frailty screening questionnaire. However, G8 is a more global assessment and sarcopenia looks at a very specific geriatric syndrome. Moreover, at this moment G8 is easier to collect from patients than manually analyzing a CT scan using specific software.

Since a comprehensive geriatric assessment takes about 60-90 minutes, and more importantly, not all patients will necessarily benefit from a CGA, a short prognostic tool that can separate fit older patients, who can receive standard cancer treatment, from vulnerable patients, who may benefit from a CGA and need tailoring of their treatment regimens would be of use. G8 is a fast-screening tool of only eight simple questions and has a high sensitivity for diagnosing frailty, but a poor specificity and negative predictive value.[10] Fast assessment of skeletal muscle mass on CT needs specific software and takes about 5-10 minutes, limit-

ing incorporating skeletal muscle mass into clinical practice in real-time. It is expected that automated methods, e.g., automated computed tomography segmentation, will accelerate body composition research and, eventually, facilitate the integration of body composition measures into clinical care.[22]

The interest in the role of sarcopenia in oncology has been increasing over the past decade. Several articles exhibit the negative impact of sarcopenia on adverse health outcomes.[23] Frailty is also related to adverse health outcomes[9]. Sarcopenia and frailty are linked to each other, even though the treatments and suggested underlying concepts differ. Treatment of sarcopenia is focused on combining exercise and adequate protein intake to increasing muscle mass and strength, while frailty is focused on a broader set of physical and non-physical domains.[24]

Thereby several definitions of frailty are in use, depending on how frailty is measured.[25] The majority of frailty tools have been based upon one of two concepts of frailty: physical phenotype (Fried) or the multiple deficit model (Rockwood).[26,27] Additionally, several definitions of sarcopenia are used i.e., the EWGSOP- or IWGS-criteria.[28] But more recent proposals for the definition of sarcopenia include muscle function in addition to muscle mass.[13,29] Studies using a physical definition of frailty tend to show more similarities with sarcopenia.[1230] So, both the concepts of frailty and sarcopenia are evolving, and there is still no full consensus on which to use in clinical practice. It is also important that frailty screening tools should be used to determine which patients should benefit from a CGA; not to diagnose frailty. The CGA is the current gold standard test for defining frailty. The G8 frailty screening questionnaire has insufficient discriminative power[10], and it is not yet known if assessment of skeletal muscle mass is suitable for screening of patients who need to undergo a CGA[10]. This needs to be investigated by comparing skeletal muscle mass with the CGA. Research in muscle density is another interesting field, as recently, muscle density on CT imaging was reported to be more associated with frailty than muscle mass.[31]

As mentioned before, previous studies indicate that sarcopenia, based on loss of skeletal muscle mass, occurs in 35.5–54.5% of the patients with HNC.[32,33] In our cohort, sarcopenia was based on a combination of handgrip strength and at CT/MRI measured skeletal muscle mass. Using those two factors the prevalence of sarcopenia in our cohort was only 14 %, likely due to the small prevalence of low handgrip strength. Reiss et al reported on the consequences of applying the new EWGSOP2 guideline instead of the former EWGSOP1 guideline for sarcopenia diagnosis in older adults and expressed their concerns regarding missing sarcopenic patients due to the novel EWGSOP definition in which lower cut-off values for handgrip strength measurements are used.[34]

Our study has limitations. The use of two different imaging techniques may raise concerns. Either CT or MRI imaging were used for the assessment of skeletal muscle mass, to maximize the number of patients that could be included. But recent research shows that these two different imaging modalities show significant correlation in quantifying skeletal muscle mass

when measured by CSA at the level of C3.[35] Other limitations of our study are its retrospective and small nature.

Our study also has important strengths. First, the study was performed in a large group of 150 patients. Second, because G8 and handgrip strength are routinely obtained at our institution, a consecutive series of patients were available for analysis. Third, the main observer (CM) was not aware of the diagnoses of frailty or sarcopenia in the patients. Fourth, a short period between the first consultation with G8 questionnaire and handgrip strength measurement and quantification of skeletal muscle mass was found (1.8 weeks). Fifth, all the segmentation of muscle tissue was manually performed by the first author. Because an excellent inter-observer agreement for skeletal muscle mass measurement at the level of C3 was demonstrated, these SMI measurement findings can be used globally to select patients for potential suitable therapy.[36]

In conclusion, in this study there was s an association between sarcopenia and frailty assessed by the G8. Therefore, assessment of skeletal muscle mass may be used as an alternative screening tool for the G8 questionnaire for frailty screening, i.e., selection of patients who need a full CGA. Further research should ideally retest our findings in a larger, prospective cohort study and test for associations between sarcopenia and a full CGA.

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CHAPTER 20

Low skeletal muscle mass predicts frailty in elderly head and neck cancer patients

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Submitted ■

ABSTRACT

Background

Treatment of head and neck cancer (HNC) carries a high risk of adverse outcomes in patients, especially in frail elderly. Therefore, it is important to identify patients in which treatment benefits outweighs the risk of any adverse outcome. Although the comprehensive geriatric assessment (CGA) identifies frailty, it is a time-consuming tool. Instead, measurement of skeletal muscle mass and strength (sarcopenia) may be a promising and time-efficient biomarker for frailty. The aim of this study was to examine the association between sarcopenia and frailty assessment tools such as the CGA, Fried criteria and the Groningen Frailty Indicator (GFI).

Material and methods

A retrospective study was performed in elderly patients (≥70-years) with HNC. Sarcopenia was defined as the combination of reduced handgrip strength (HGS) and low skeletal muscle mass (SMM), according to the EWGSOP-criteria. SMM was measured on routinely available diagnostic imaging and corrected height: skeletal muscle index (SMI). A CGA was performed by a geriatrician. Frailty screening was performed using the GFI and the Fried criteria.

Results

In total, 73 patients were included of which 33 were men (45.2%) and 40 women (54.8%). Frail patients diagnosed by CGA were more likely to have low SMI, sarcopenia, more comorbidities and were at high risk for malnutrition (all $p<0.05$). In multivariate regression analysis, the only significant predictor for frailty diagnosed by CGA was SMI (OR 0.9, $p<0.01$) independent of comorbidity and muscle strength.

Conclusion

Low SMI and sarcopenia is associated with frailty in elderly HNC patients. Low SMI predicts frailty and is a promising time-efficient and routinely available tool for clinical practice.

INTRODUCTION

Head and neck cancer (HNC) is among the most frequent malignant tumors in the world with an annual incidence of more than 650,000 cases and 330,000 deaths.[1] Of these patients, more than 60% have an age at diagnosis of 60 years or more.[2] With the global aging of the worldwide population, it is to be expected that the incidence of HNCs will increase. Besides advanced age, the significant amount of pre-existent comorbidities in HNCs patients are additional negative prognostic factors that reduce overall survival.[3]

Treatment of HNCs is often complex and requires, based on tumor-specific and patient-specific characteristics, surgery with or without adjuvant (chemo)radiotherapy or radiotherapy with or without chemotherapy with salvage surgery in reserve for residual or recurrent loco regional disease.[4] These treatments are effective, but have significant risk of toxicities, complications, and even mortality.[5] Treatment could also decrease quality of life, for instance speech problems, fatigue or trouble with social eating caused by dry mouth, and swallowing problems.[6,7]

Due to the growing incidence of both HNCs worldwide and the global aging of the population it is of great importance to identify key predictive and prognostic factors for treatment outcomes in older patients with HNC. This knowledge can be useful for clinicians and patients in (shared) decision making weighing suitability of treatment, prognosis, and expected quality of life. Although this knowledge is also important in younger HNC patients, it is even more warranted in older HNC patients due to their vulnerability, decreased physical and mental compensation mechanisms compared to younger patients. This vulnerability is also being referred to as frailty.

A comprehensive geriatric assessment (CGA) is the most appropriate way to detect frailty.[8] A CGA is a multidisciplinary, multidimensional, and systematic assessment, and consists of validated scales to identify impairments in the four geriatric domains: somatic, functional, nutritional, and psychosocial[9]. Frailty is associated with poor treatment outcomes and health-related quality of life.[7] Because performing CGA is time consuming and not all patients will benefit from a CGA, screening methods have been developed to identify those at risk for adverse health outcomes and who may benefit from a CGA. However, the available frailty screening methods may have insufficient discriminative power to select patients for further assessment.[10]

Sarcopenia also frequently observed in older patients is suggested as a more reliable, inexpensive and easy alternative for frailty screening questionnaires in HNC patients[11]. However, there is much discussion on different definitions of frailty and sarcopenia.[12] By the European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia is described as a generalized and progressive loss of muscle function (MF) and skeletal muscle mass (SMM), caused by adverse muscle changes that accrue across a lifetime.[13] Sarcopenia itself is also related with

adverse health outcome, such as chemotherapy dose-limiting toxicity[14], increased incidence of postoperative complications, and decreased survival.[15,16]

The relation between low skeletal muscle mass, measured using CT of the head and neck, and frailty screening methods was recently reported by Zwart et al[11]. However, the direct relation of sarcopenia end CGA, as gold standard for frailty, has yet to be determined. Therefore, the aim of this study was to examine the association between sarcopenia, defined as the combination of low muscle strength and low muscle mass, and frailty, diagnosed by CGA. Our secondary aim was to examine the association between sarcopenia and the frailty Fried criteria and the Groningen Frailty Indicator (GFI) frailty screening test.

MATERIALS 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 (Version 2008) and its later amendments or comparable ethical standards. All data were handled according to general data protection regulation (GDPR).

PATIENTS AND STUDY DESIGN

This study was designed as a single-center retrospective study. Older patients (≥70-years old) with pathologically proven head and neck squamous cell carcinoma (HNSCC) treated between April 2015 and February 2018 with routinely performed CGA, Fried Frailty criteria, GFI screening questionnaire, and pre-treatment CT or MRI during their diagnostic workup between April 2015 and February 2018. Histologic tumor types other than squamous cell carcinoma were excluded. Relevant demographic and clinical variables were collected from patient's medical record: age at diagnosis, sex, body mass index (BMI), percentage of weight loss in 6 months prior to diagnosis, smoking status, alcohol use, nutritional status at diagnosis as evaluated by the Malnutrition Universal Screening Tool (MUST), comorbidities as evaluated by the Charlson comorbidity index (CCI), localization of the tumor, tumor type (primary, second primary or recurrence), and the TNM stage according the 8th edition of the UICC tumor classification of malignant tumors.

SARCOPENIA

Definition of sarcopenia

Sarcopenia was defined as the combination of low MF, as determined by muscle strength, and low muscle quantity, as determined by SMM, according to the recommendation by the EWGSOP and further explained below.[13]

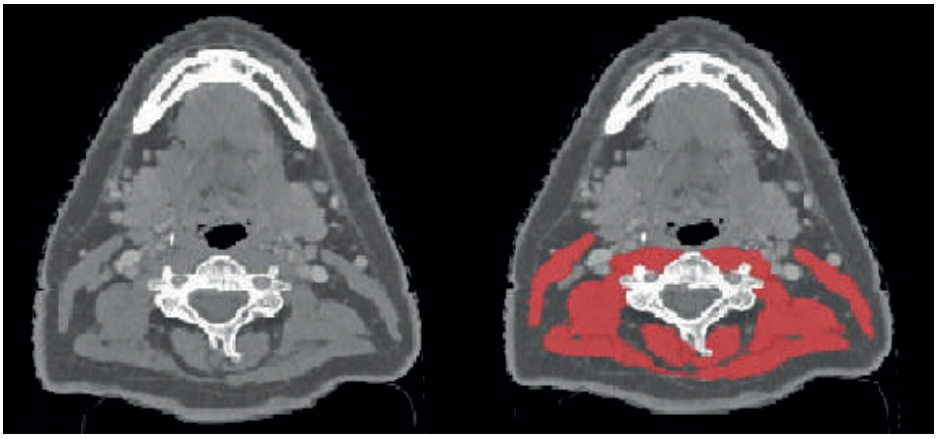
Muscle function: muscle strength

Overall muscle strength is strongly related with isometric handgrip strength (HGS).[17] HGS was measured using a Jamar hydraulic handheld dynamometer according to the recommendations of the American society of hand therapist's (ASHT) and expressed in kilograms (kg). Patients were asked to squeeze maximally with each hand. The average score of the left and right hands was used for analysis. Patients had low HGS if the mean HGS was below 27kg (men) or below 16kg (women).[13]

Skeletal muscle mass

SMM was measured as cross-sectional muscle area (CSMA) 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 the segmentation of muscle tissue. For CT imaging, muscle area was defined as the pixel area between the radio density range of −29 and +150 Hounsfield units (HU), which is specific for muscle tissue.[18] For MRI, muscle area was manually segmented, and fatty tissue was manually excluded (Figure 1).

Figure 1. Example of segmentation of skeletal muscle tissue at the level of the third cervical vertebra (C3)



Two identical axial contrast enhanced computed tomography (CT) slides at the level of C3; left shows the muscle tissue unsegmented, right shows both sternocleidomastoid and paravertebral muscles segmented in red.

Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (version 5.0, Tomovision, Canada) by a single researcher (C.M.) who was blinded for outcome regarding frailty and sarcopenia. Cross-sectional muscle area at the level of C3 was converted to CSMA at the level of L3 using a previously published formula.[19] The lumbar skeletal muscle index (SMI) was calculated by correcting SMM at the level of L3 for height. Patients had a low SMI if this value was ≤43.2 cm^2/m^2; this cut-off value was established in a separate cohort of patients with head-and-neck cancer.[14]

COMPREHENSIVE GERIATRIC ASSESSMENT (CGA)

The CGA conducted in this study consists of four domains; the somatic, psychological, functional and social domains and was performed by a geriatrician. Specific, validated tools per geriatric domain were used. For the somatic domain the Charlson Comorbidity Index (CCI)[20], the Malnutrition Universal Screening Tool (MUST)[21], and polypharmacy are used. The psychological domain was examined by the Mini Mental State Examination (MMSE)[22] for cognitive function and Geriatric Depression Scale (GDS)[23] for depression. For the functional domain, activities of daily living (ADL) was examined with The Katz Activities of Daily Living (*KATZ-6)*[24] and KATZ-9 was used for scoring Instrumental ADL[25]. Social status was determent on questions about current living situation, social activities, presence of informal care system/social support. Each instrument was defined as abnormal according to validated cutoff scores. The cutoff scores are listed in table 1. Overall, a patient was considered frail if the CGA had an abnormal outcome on at least two of the instruments used.

Table 1. Overview of the selected screening instruments for CGA

Geriatric domain		Measure	Score range or (cut-off)
Somatic	*Comorbidity*	*CCI*	0 - 31
	Nutrition	*MUST*	0 - 3 (≥ 2)
	Medication	-	Ordinal (> 4)
Psychological	*Cognition*	*MMSE*	0 - 30 (≤ 24)
	Depression	*GDS-2 or*	0 - 2 (≥ 1)
		GDS 15	0 - 15 (≥ 6)
Functional	*Function*	*ADL KATZ*	0 - 6, (≥ 1)
		IADL KATZ	0 - 9, (≥ 1)
Social		*Living situation, social activities and informal care system*	0 - 3 (≥ 2)

ADL= Activities of Daily Living, IADL= Instrumental Activities of Daily Living, MMSE= Mini-Mental State Exam, GDS= Geriatric Depression Scale, MUST= Malnutrition Universal Screening Tool, CCI= Charlson comorbidity index.

FRIED FRAILTY CRITERIA

The Fried Frailty criteria is an operational definition of physical frailty based on the presence of three or more of the following five criteria: unintentional weight loss, exhaustion, low physical activity level, slow gait speed, and low handgrip strength.[26] In older patients with cancer the sensitivity and specificity of the Fried frailty criteria for predicting frailty, based on CGA, are amongst 25% to 37% and 86% to 96%, respectively.[10] The Fried frailty criteria are known to be a useful in predicting complications, length of hospital stay and other adverse health outcome in patients with HNC.[27]

GRONINGEN FRAILTY INDICATOR

GFI is a 15-item frailty screening tool to evaluate frailty status in geriatrics through loss of function and resources in physical, social, and psychological domains. Patients were categorized as non-frail (GFI < 4) and frail (GFI ≥ 4).[28] In older patients with cancer the sensitivity and specificity of the GFI for predicting frailty, based on CGA, are amongst 39% to 62% and 69% to 87%, respectively.[10] The GFI is also useful in predicting postoperative complications, however this questionnaire is not special designed for oncological patients.[27]

STATISTICAL ANALYSIS

Data analyses were performed using IBM SPSS statistics 25. Firstly, the patient cohort was described regarding the baseline. Continuous data are represented as mean ± standard deviation (SD). Categorical data are represented as a number and percentage of total.

MF was presented dichotomously as low MF and normal MF based on previously published gender specific cut-offs for HGS. The SMM, was presented dichotomously as low SMI and normal SMI based on previously published specific cut-offs for SMI. Sarcopenia was presented dichotomously as sarcopenic (only if patients had a low HGS and low SMI) and non-sarcopenic (all other patients).

Frailty was presented dichotomously as frail and non-frail based on abovementioned and previously published cut-offs for frailty based on the CGA, Fried criteria or GFI. Independent sample t-tests or Chi-square statistics were used for analyzing differences between the frequencies of each categorical variable with the presence or absence of sarcopenia and presence or absence of frailty.

Univariate logistic regression analyses were performed, with sarcopenia or frailty as dependent variable and the baseline variables as independent variables. Variables were selected based on clinical relevance by exploring literature. Variables that were statistically significant ($\alpha < 0.05$) in the univariate regression were included in the multivariate logistic regression. In this way, odds ratios (ORs) and 95% CIs were provided.

RESULTS

In total, 73 patients were included. The mean age was 81.73 (6.24 SD). The majority of the patients was female (55%). The mean BMI was 26.80 (5.70 SD) and most of the patients did not report loss of weight 6 months prior to diagnosis (63%). The majority of the patients used alcohol (56%) and were former smokers (55%). Most patients had a high CCI comorbidity score of >6 (63%). According to the TNM-classification most patients had stage IV disease (44%). Of the included 73 patients, 33 (45%) patients had low muscle strength, 58 (79%) had low SMI. A total of 24 (33%) patients were defined as sarcopenic. Based on the CGA 39 (54%) patients were defined as frail. Based on the frailty Fried criteria 21 (29%) patients were defined as frail,

as the GFI defined 38 (52%) patients frail. An overview of the characteristics of patients are listed in table 2.

Table 2.1. Characteristics of patients with and without sarcopenia

	Total		**Sarcopenic**		**Non sarcopenic**		χ^2	***p-value***
	N=73		N=24		N=49			
Age (years) (M, SD)	81.73	6.24(SD)	83.7	5.73(SD)	80.24	6.21(SD)	NA	**0.03**
Gender (n, %)								
Male	33	45	10	42	23	47	0.18	0.67
Female	40	55	14	58	26	53		
Weight loss 6 months prior to diagnosis (n, %)								
Non	46	63	15	63	31	63	0.39	0.82
<10%	20	27	6	25	14	29		
≥ 10%	7	10	3	13	4	8		
BMI (kg/m²)	26.80	5.70(SD)	25.12	4.99(SD)	27.92	4.49(SD)	NA	**0.02**
Smoker (n, %)								
No	25	34	11	46	14	29	2.60	0.27
Former	40	55	10	42	30	61		
Current	8	11	3	13	5	10		
MUST score (n, %)								
0	53	72	18	75	35	71	0.53	0.77
1	1	2	0	0	1	2		
2	19	26	6	25	13	27		
Alcohol use (n, %)								
No	25	34	9	38	16	33	1.34	0.72
Yes	41	56	14	58	27	55		
Former	7	10	1	4	6	12		
Charlson comorbidity index (n, %)								
Low ≤ 6	27	37	6	25	21	43	2.20	0.14
High > 6	46	63	18	75	28	57		
Localization (n, %)								
Oral cavity	46	63	14	58	32	65	12.28	0.58
Nasopharynx	2	3	1	4	1	2		
Oropharynx	2	3	0	0	2	4		
Hypopharynx	3	4	1	4	2	4		
Larynx	7	10	2	8	5	10		
Salivary glands	3	4	2	8	1	2		
Skin	8	11	3	13	5	10		

Table 2.1. (Continued)

	Total		**Sarcopenic**		**Non sarcopenic**		χ^2	***p-value***
	N=73		N=24		N=49			
Age (years) (M, SD)	81.73	6.24(SD)	83.7	5.73(SD)	80.24	6.21(SD)	NA	**0.03**
Paranasal sinuses	2	2	1	4	2	4		
Type of tumor (n, %)								
Primary	56	77	17	71	39	80	1.02	0.60
Recurrent	11	15	4	17	7	14		
Second primary	6	8	3	13	3	6		
TNM Stage (n, %)								
I	8	11	5	21	3	6	3.71	0.30
II	19	26	5	21	14	29		
III	14	19	4	17	10	20		
IV	32	44	10	42	22	45		
Low Muscle strength (n, %)								
No	40	55	0	0	40	82	43.34	**0.000**
Yes	33	45	24	100	9	18		
Low SMI (n, %)								
No	15	21	0	0	15	31	9.26	**0.002**
Yes	58	79	24	100	34	69		
Frailty Fried criteria (n, %)								
No	52	71	10	42	42	86	15.25	**0.000**
Yes	21	29	14	58	7	14		
Frailty GFI (n, %)								
No	35	50	9	38	26	53	1.56	0.21
Yes	38	52	15	63	23	47		
Frailty CGA (n, %)								
No	34	46	7	29	27	55	4.36	**0.04**
Yes	39	54	17	71	22	45		

BMI= Body Mass Index. MUST= Malnutrition Universal Screening Tool. SMI= Skeletal Muscle Index. GFI= Groningen Frailty Indicator. CGA= Comprehensive Geriatric Assessment.

CORRELATIONS

Table 2.1 shows statistically significant differences in CGA, Fried criteria, age at diagnosis, and BMI between patients with and without sarcopenia. Patients with sarcopenia were more likely to be frail according to the CGA (71% versus 45%; $p<0.05$) and the Fried criteria (58% versus 14%; $p<0.00$), to be older of age (mean 83.7 years versus 80.24 years; $p<0.05$), and to have a lower BMI at diagnosis (25.12 versus 27.92, $p<0.05$). Table 2.2 shows statistically significant differences in sarcopenia, age at diagnosis, sex, low SMI, Fried criteria, and GFI between

patients with and without frailty, diagnosed with CGA. Frail patients were more likely to be sarcopenic (44% versus 21%, p<0.05), to be older of age (mean 83.5 years versus 79.0 years; p<0.05), to be female (69% versus 38%, p<0.05), to have a low SMI at diagnosis (90% versus 68%, p<0.05), to be frail according to the Fried criteria (49% versus 6%; p<0.00), and the GFI (77% versus 24%; p<0.00).

Table 2.2. Characteristics of patients with and without frailty based on the CGA

	Total		**Frail**		**Non frail**		χ^2	***p-value***
	N=73		N=39		N=34			
Age (years) (M, SD)	81.73	6.24(SD)	83.49	6.47(SD)	78.96	5.03(SD)	NA	**0.002**
Sex (n, %)								
Male	33	45	12	31	21	62	7.05	**0.01**
Female	40	55	27	69	13	38		
Weight loss 6 months prior to diagnosis (n, %)								
Non	46	63	22	56	24	71	1.84	0.40
< 10%	20	27	12	31	8	24		
≥ 10%	7	10	5	13	2	6		
BMI (kg/m²)	26.80	5.70(SD)	26.98	5.66(SD)	27.02	3.69(SD)	NA	0.97
Smoker (n, %)								
No	25	34	15	38	10	29	3.07	0.22
Former	40	55	18	46	22	65		
Current	8	11	6	15	2	6		
MUST score (n, %)								
0	53	72	24	62	29	85	7.531	0.02
1	1	2	0	0	1	3		
2	19	26	15	38	4	12		
Alcohol use (n, %)								
No	25	34	15	38	10	29	1.50	0.68
Yes	41	56	21	54	20	59		
Former	7	10	3	8	4	12		
Charlson comorbidity index (n, %)								
Low ≤6	27	37	10	26	17	50	4.62	0.03
High >6	46	63	29	74	17	50		
Localization (n, %)								
Oral cavity	46	63	27	69	19	56	17.39	0.24
Nasopharynx	2	3	1	3	1	3		
Oropharynx	2	3	1	3	1	3		
Hypopharynx	3	4	0	0	3	9		

Table 2.2. (Continued)

	Total		**Frail**		**Non frail**		χ^2	***p-value***
	N=73		N=39		N=34			
Age (years) (M, SD)	81.73	6.24(SD)	83.49	6.47(SD)	78.96	5.03(SD)	NA	**0.002**
Larynx	7	10	2	5	5	15		
Salivary glands	3	4	2	5	1	3		
Skin	8	11	5	13	3	9		
Paranasal sinuses	2	2	1	3	1	3		
Type of tumor (n, %)								
Primary	56	77	28	72	28	82	5.78	0.06
Recurrent	11	15	5	13	6	18		
Second primary	6	8	6	15	0	0		
TNM Stage (n, %)								
I	8	11	5	13	3	9	1.05	0.79
II	19	26	11	28	8	24		
III	14	19	6	15	8	24		
IV	32	44	17	44	15	44		
Low Muscle strength (n, %)								
No	40	55	20	51	20	59	0.42	0.52
Yes	33	45	19	49	14	41		
Low SMI (n, %)								
No	15	21	4	10	11	32	5.43	**0.02**
Yes	58	79	35	90	23	68		
Frailty Fried criteria (n, %)								
No	52	71	20	51	32	94	16.27	**0.000**
Yes	21	29	19	49	2	6		
Frailty GFI (n, %)								
No	35	50	9	23	26	76	20.75	**0.000**
Yes	38	52	30	77	8	24		
Sarcopenia (n, %)								
No	49	67	22	56	27	79	4.36	**0.04**
Yes	24	33	17	44	7	21		

BMI= Body Mass Index. MUST= Malnutrition Universal Screening Tool. SMI= Skeletal Muscle Index. GFI= Groningen Frailty Indicator. CGA= Comprehensive Geriatric Assessment

UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION

Table 3.1 shows the univariate and multivariate logistic regression analysis with sarcopenia as the dependent variable. The univariate regression analysis with sarcopenia as dependent variables distinguished age at diagnosis (OR 3.39, 95% CI 1.51-9.99, P=0.027), BMI (OR 0.87,

95% CI 0,78-0,98, P=0.024), frailty according CGA (OR 2.98, 95% CI 1.05-8.47, P=0.040), and frailty according Fried criteria (OR 1.92 95% CI 1.28-2.87, P=0.002) as significant variables for predicting sarcopenia. These significant variables were subjected to two different multivariate analyses. The first with frailty CGA and the second with frailty Fried criteria because of assumed multicollinearity. In the first multivariate analysis only BMI (OR 0.87, 95% CI 0.77-0.98, P=0.022) remained significant. In the second age at diagnosis (OR 3.59, 95% CI 1.02-12.58, P=0.046), frailty Fried criteria (OR 1.89, 95% CI 1.22-2.93, P=0.004), and BMI (OR 0.87, 95% CI 0.76-0.99, P=0.033) remained significant.

Table 3.1. Univariate and multivariate logistic regression analysis for analyzing variables associated with sarcopenia in HNC patients

Sarcopenia	**Univariate analysis**			**Multivariate analysis**					
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age (years)									
≤80	Ref.			Ref.			Ref.		
>80	3.39	1.51-9.99	0.027**	3.196	1.0-10.3	0.05	3.6	1.0-12.6	**0.05****
Gender									
Male	Ref.								
Female	1.24	0.46-3.32	0.671						
Weight loss 6 months prior to diagnosis									
Non	Ref.								
<10%	0.89	0.3-2.8	0.83						
≥ 10%	1.55	0.3-7.8	0.60						
BMI (kg/m²)	0.87	0.8-1.0	**0.02****	0.87	0.8-1.0	**0.02****	0.9	0.8-1.0	**0.03****
Charlson comorbidity index	1.30	1.0-1.7	0.06						
TNM Stage									
I	Ref.								
II	0.21	0.0-1.2	0.09						
III	0.24	0.0-1.5	0.13						
IV	0.27	0.1-1.4	0.12						
Frailty Fried criteria	1.92	1.3-2.9	**0.002***				1.9	1.2-2.9	**0.004***
Frailty GFI									
No	Ref.								
Yes	1.88	0.7-5.1	0.21						
Frailty CGA									
No	Ref.			Ref.					
Yes	2.98	1.1-8.5	**0.04****	2.54	0.8-7.8	0.1			

The first with multivariate analysis is conducted with Frailty CGA and the second with Frailty Fried criteria because of assumed multicollinearity. BMI= Body Mass Index. GFI= Groningen Frailty Indicator. CGA= Comprehensive Geriatric Assessment. *. Correlation is significant at the 0.01 level (2-tailed)**. Correlation is significant at the 0.05 level (2-tailed)

Table 3.2 shows the univariate and multivariate logistic regression analysis with frailty, based on CGA, as the dependent variable. The univariate regression analysis with frailty as dependent variables distinguished CCI (OR 1.35 95% CI 1,03-1,76, P=0.029), HSG (OR 0.92, 95% CI 0,87-0,97, P=0.006), SMI (OR 0.89, 95% CI 0,83-0,96, P=0.002), and sarcopenia (OR 2.98, 95% CI 1.05-8.47, P=0.040) as significant variables for predicting frailty. These significant variables were subjected to a multivariate analysis. The first with sarcopenia and the second with HSG and SMI because of assumed multicollinearity. In the second only SMI (OR 0.89, 95% CI 0.82-0.96, P=0.003) remained significant.

Table 3.2. Univariate and multivariate logistic regression analysis for analyzing variables associated with frailty based on CGA in HNC patients

Frailty	**Univariate analysis**			**Multivariate analysis**					
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age (years)									
≤ 80	Ref.								
> 80	2.53	1.0 - 6.6	0.06						
Charlson comorbidity index	1.35	1.0 - 1.8	**0.03****	1.3	1.0 - 1.7	0.06	1.33	1.0 - 1.8	0.06
TNM Stage									
I	Ref.								
II	0.83	0.2 - 4.5	0.82						
III	0.45	0.1 - 2.7	0.38						
IV	0.68	0.1 - 3.3	0.63						
HSG	0.92	0.9 - 1.0	**0.01***				0.94	0.8 - 1.0	0.06
SMI	0.89	0.8 - 1.0	**0.002***				0.89	0.8 - 1.0	**0.003***
Sarcopenia									
No	Ref.								
Yes	2.98	1.1 - 8.5	**0.04****	2.5	0.9 - 7.3	0.1			

The first with multivariate analysis is conducted with Frailty CGA and the second with Frailty Fried criteria because of assumed multicollinearity. BMI= Body Mass Index. GFI= Groningen Frailty Indicator. CGA= Comprehensive Geriatric Assessment. *. Correlation is significant at the 0.01 level (2-tailed)**. Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

In this study the association between sarcopenia and frailty in 73 participants was retrospectively examined. Sarcopenia is associated with frailty defined with the CGA and Fried criteria, but not with the GFI frailty screening. Furthermore, the Fried criteria and BMI are significant predictors for sarcopenia. Frailty based on the CGA shows associations with the SMI and sarcopenia. Moreover, SMI shows to be a reliable predictor for frailty based on CGA.

To our knowledge, this is the first study that examined the association between sarcopenia, as defined by low MF and low SMI, and frailty, as determined by CGA, in HNC patients.

With the aging of the global population the incidence of frail and sarcopenic patients with HNC will increase. Understandings of the underlying interrelationship of sarcopenia and frailty are of great importance as they are both associated with adverse health outcome.[7,29] Frailty and sarcopenia are important concepts in preventing physical dependence, as geriatrics are shifting towards identification of early stage of disability. Definitions of both sarcopenia and frailty are still developing, and both concepts clearly overlap in their physical aspects.[12,30] Frailty is a pre-disability syndrome where an older person can be identified as being at risk when exposed to stressors associated with high risk for disability or needing to be hospitalized[31]. Two major frailty definitions exist. The physical phenotype of frailty (Fried) [26] and the multiple deficit model (Rockwood).[32] An CGA is the most appropriate way to detect frailty. Frailty is predisposed by advancing age in combination with physiological deterioration, especially a loss of muscle mass. So, sarcopenia is a major driver of frailty, because of decline of MF with low SMM. This increases the risk of falls, which can lead to loss of independence and disability. And low SMM increases the risk of comorbidity's like diabetes mellitus and cardiovascular diseases by changing the body fat composition.[31]

Studies using "physical" frailty as definition in examining the interrelationship with sarcopenia are suggested to have more overlap.[30] In this study sarcopenic patient were more likely to be frail, according to the Fried criteria. Moreover, the Fried criteria were an independent predictor for sarcopenia. GFI was not associated with sarcopenia. Presumably because GFI uses also social, and psychological domains rather than only physically items like the Fried criteria. This confirms that "physical" frailty, like the Fried criteria, are more associated with sarcopenia than definitions based upon the multiple deficit model (Rockwood).

A previous retrospective study found a significant association between sarcopenia and frailty based on the G8 questionnaire (OR 0.76, 95% CI 0.6-0.89, $P < 0.001$).[11] In that study sarcopenia was based only on low SMI, so according to the EWGSOP-criteria insufficient as sarcopenia which include muscle function as well. Also, frailty screening was based on different screening questionnaires, i.e., G8, Timed Up and Go test, and Malnutrition Universal Screening Tool. In our study SMI, but not the combination of low MF and low SMI (defined as sarcopenia by the EWGSOP), was independently associated with frailty based on CGA (OR 0.89, 95% CI 0.82-0.96, $P=0.003$). The suggestion that SMI could possibly be able to predict frailty, in particularly the physical part of frailty, in patients with HNC and is easier to use and implement then a CGA or questionnaires to diagnose frailty is in accordance with the study of Zwart et al, although in our study SMI was directly associated with CGA instead of the G8 frailty screening questionnaire.[11]

Our study has some limitations. It was designed as a retrospective single-center study, with a limited number of included patients. Only patients with the available data on MF and SMI were included in the study. As it is more likely that MF parameters were examined for frail patients

than for fit patients, this may have resulted in selection bias. Also, both CT and MRI imaging are used to for the assessment of SMI, to maximize the number of patients that could be included. This could raise concerns but these two different imaging modalities show significant correlation in quantifying SMI when measured by CSA at the level of C3.[33] A strength of our study is that all of the muscle tissue was manually performed by a single researcher who was blinded for outcome regarding frailty and sarcopenia. Because an excellent inter-observer agreement for SMI measurement at the level of C3 was demonstrated, these SMI measurements findings can be used globally to select patients fort suitable therapy.[34]

In conclusion there is an association between sarcopenia and frailty defined by CGA. Low muscle mass, based on SMI, may be able to predict some CGA domain outcomes in older patients with HNC and is easier to use and implement then a CGA. These findings should ideally be validated in a larger, prospective cohort study.

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CHAPTER 21

Summary and general discussion with future perspectives

SUMMARIZING DISCUSSION

This thesis presents research that focuses on diagnostic measurements of skeletal muscle mass and to evaluate the predictive and prognostic value of low skeletal muscle mass in patients with head and neck cancer. Besides radiologically assessed skeletal muscle mass at diagnosis, the impact of muscle function, especially in the elderly head and neck cancer patients, is investigated. The results of this thesis lead to improved pre-treatment risk-stratification, development of personalized treatment protocols, improved prediction of prognosis and last but not least improved shared decision-making.

Research on skeletal muscle mass as a biomarker is increasing the last decade due to improved diagnostics in clinical practice. Measurement of lean body mass, of which skeletal muscle mass is the largest contributor, is in clinical practice mostly performed with the use of dual x-ray absorptiometry (DEXA) and bioelectrical impedance (BIA). These diagnostic tools are however confounded by alterations in hydration, edema and food intake. Therefore, its use in assessing body composition of patients with cancer is not favored. Research on body composition, specifically skeletal muscle mass, is mostly performed on computed tomography (CT) imaging because of relatively ease, fast and accurate segmentation of muscle by use of the muscle-specific radiodensity range of -29 till +150 Hounsfield units (HU). An advantage of using skeletal muscle mass as a biomarker in clinical practice is that it can be evaluated by the use of already available CT imaging that are routinely obtained for head and neck cancer diagnosis and treatment evaluation.

Skeletal muscle mass is determined by segmenting the area of skeletal muscles visible on one specific two-dimensional axial slice.[1] The most used landmark on CT for muscle segmentation is at the level of the third lumbar vertebrae (L3) visible on abdominal CT imaging, in which the area of the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques and rectus abdominis muscles is segmented. Previous studies showed that there is a linear relationship between a person's height and the skeletal muscle area at the level of L3, therefore the obtained skeletal muscle area is adjusted for height, to calculate the lumbar skeletal muscle mass index (SMI in cm^2/m^2).[2,3] The SMI provides an estimation of total skeletal muscle mass in proportion to stature. The first described study that performed skeletal muscle mass segmentation on CT to evaluate the relationship between body composition and adverse outcomes in patients with cancer is performed in 2008 by Prado et al.[2]

In head and neck cancer, abdominal CT imaging is only performed in patients with locally advanced cancer for staging purposes. Therefore, a previous study by Swartz et al. developed a measurement method of skeletal muscle mass at the level of the third cervical vertebrae (C3) which is visible on head and neck CT imaging.[4] **Part I** of this thesis presents the studies performed to further evaluate the skeletal muscle mass measurement at this level (C3) in head and neck cancer patients. In **Chapter** 2, a validation study is performed for skeletal muscle mass measurements at the level of C3 and L3 in order to validate the results found in

the study by Swartz et al. The results of this study show a good correlation (r=0.75, p<0.01) between segmented cross-sectional skeletal muscle area at the level of C3 and L3. When using the multivariable prediction formula proposed by Swartz et al. to calculate the skeletal muscle area at the level of L3 using skeletal muscle area at C3, gender, age and weight, the correlation between skeletal muscle area at C3 and L3 improved (r = 0.82, p<0.01). There was some difference in the identification of patients with low skeletal muscle mass based on the calculated lumbar skeletal muscle index and the actual lumbar skeletal muscle index (Cohen's κ: 0.57; 95% CI 0.45-0.69), although the sensitivity of identifying patients with low skeletal muscle mass using the estimated lumbar skeletal muscle index was high (84.4%). This study shows that a measurement of skeletal muscle mass at the level of C3 provides an easy and robust alternative for estimation of the skeletal muscle mass of a patient. **Chapter 3** presents an association study for skeletal muscle mass measurements at the level of C3 on CT and magnetic resonance imaging (MRI). MRI does not allow for radiodensity-based segmentation of muscle tissue and is therefore subject to observer interpretation (i.e., the total muscle surface). A large proportion of head and neck cancer patients undergo diagnostic MRI instead of CT imaging in the diagnostic process. Therefore, patients' skeletal muscle mass was segmented on both CT and MRI and the association between these measurements was analyzed. An excellent intraclass coefficient was found (0.97; 95% CI 0.94-0.98, p<0.01). The mean difference of skeletal muscle area measurements between CT and MRI was less than $1cm^2$. Occasionally, skeletal mass measurement at the level of C3 may be impaired by extension of primary tumor, lymph nodes or previous treatment. Therefore, **Chapter 4** presents a correlation study to investigate whether skeletal muscle mass measurements of a single muscle, the masseter muscle, correlates with measurements of skeletal muscle mass on a single slice at the level of C3 and L3. The masseter muscle was chosen because it is consistently present on routine head and neck imaging, is rarely impacted by disease or treatment and is quick and easy to characterize. Several masseter muscle parameters (muscle mass volume, muscle mass area, muscle thickness) were significantly correlated with skeletal muscle area at the level of C3 and L3. However, these correlations varied from moderately to strong, with the strongest correlation found between skeletal muscle area at C3 and masseter mass volume (r=0.67). Skeletal muscle area of the masseter muscle had only moderate correlation with skeletal muscle area at the level of L3 (r=0.47) and C3 (r=0.57). The prognostic impact of low skeletal muscle mass, obtained by measurement of the masseter muscle index, for survival was additionally investigated and this showed that low masseter muscle index was a significant prognostic for decreased survival (HR 3.0, p<0.05). In patients without cross-sectional imaging at level L3 or C3 or with impaired C3 measurements, masseter muscle parameters could serve as an alternative for skeletal muscle mass assessed by skeletal muscle area measurements at these vertebral levels. Because of the lack of reference values of skeletal muscle mass in the general population and the heterogeneity in cut-off values for low skeletal muscle mass in literature, **Chapter 5** presents a study performed in a large cohort of head and neck cancer patients (n=1415) to develop cut-off values for low skeletal muscle mass measured at the level of C3. Because of the significant correlation between skeletal muscle mass index with gender (r^2=0.4, p<0.01) and body-mass index (BMI) (r^2=0.4, p<0.01), gender and BMI-specific

cut-off values were calculated. For male patients with a BMI <25 kg/m^2, a CSMI ≤6.8 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤8.5cm^2/m^2 was defined for low skeletal muscle mass. For female patients with a BMI <25 kg/m^2, a CSMI ≤5.3 cm^2/m^2 was defined and with a BMI ≥25kg/m^2 a CSMI ≤6.4 cm^2/m^2 was defined for low skeletal muscle mass. This study is the first to provide standardized cut-off values for low skeletal muscle mass at the level of C3 in patients with head and neck cancer. This information may aid in the uniformity of low skeletal muscle mass definition in research.

Part II of this thesis presents the predictive and prognostic impact of skeletal muscle mass in surgically treated head and neck cancer patients. **Chapter 6** presents the predictive value of low skeletal muscle mass in 78 oral cavity cancer patients who underwent mandibular reconstruction with a free fibula flap in University Medical Center Utrecht, the Netherlands. Low SMM was significantly associated with an increased risk for flap-related complications (HR 4.3, p<0.05) and for severe surgical complications (Clavien-Dindo grade III-IV) (HR 4.0, p<0.05). Low skeletal muscle mass was also prognostic for decreased overall survival (OS) (HR 2.4, p<0.05). Although several previous studies investigated the predictive value of several patient-related and surgery-related factors for surgical complications in patients who underwent microvascular free flap reconstruction, this was the first study to examine the predictive and prognostic value of low skeletal muscle mass in these patients. **Chapter 7** presents a cohort study performed in a larger cohort of patients undergoing microvascular free flap head and neck reconstruction. This large cohort study was performed at the department of Oral and Maxillofacial surgery in collaboration with dr. Parmar at the Queen Elizabeth hospital in Birmingham, United Kingdom. In total, 616 patients were included. Besides skeletal muscle mass, the predictive and prognostic role of systemic inflammation was evaluated in these patients. Elevated neutrophil-to-lymphocyte ratio (NLR) was used as a marker for systemic inflammation. Non-flap and flap-related complications occurred in 39.3% and 12.3% of patients, respectively. Flap-failure rate was 4.7%. For oncological cases, elevated NLR showed to be a significant predictor for surgical complications in all types of flap-surgery (OR 1.5, p<0.05), low SMM in radial forearm flap surgery (OR 2.1, p<0.05) and elevated NLR combined with low SMM in fibula flap surgery (OR 5.2, p<0.05). Patients with solely elevated NLR were at significant risk for flap-related complications (OR 3.0), severe complications (Clavien-Dindo grade >IIIa) (OR 2.2, p<0.05) and when combined with low SMM for increased length of hospital stays (LOS) (+3.9 days, p<0.05). In early-stage HN squamous cell carcinoma (HNSCC), low SMM (HR 2.3, p<0.05) and combined elevated NLR with low SMM (HR 2.3, p<0.05) were prognostics for OS. Skeletal muscle mass and NLR are routinely available biomarkers, and this study provides evidence that these biomarkers may aid the clinician in the identification of patients at risk of a poor outcome. **Chapter 8** presents another study in 224 surgically treated patients with oral cavity cancer to investigate the predictive impact of low skeletal muscle mass on perioperative complications. Low skeletal muscle mass was a significant predictor for the presence of perioperative complications (HR 1.5, p<0.01) and the number of perioperative complications (HR 1.5, p<0.01). Besides skeletal muscle mass, arterial calcification is also assessed on routine diagnostic CT imaging and could be used as an additional image-based biomarker. Therefore,

in **Chapter 9**, a study is presented which investigated the predictive impact of arterial calcification and low skeletal muscle mass for the occurrence of pharyngocutaneous fistula formation in 224 patients undergoing laryngectomy. Arterial calcifications were a common finding in patients undergoing laryngectomy, with only 1.3% percent of patients having no arterial calcification present and 7.1% of patients having at most mild arterial calcifications present. Arterial calcifications at several locations, most notably of the descending aorta and the origo of the brachiocephalic arteries, were significantly associated with pharyngocutaneous fistula formation. A higher total arterial calcification score was also significantly associated with pharyngocutaneous fistula formation. Moderate to severe arterial calcification at the location of the descending aorta was more often present in patients with low skeletal muscle mass as compared to patients without low skeletal muscle mass ($p<0.01$). At the other locations, no significant difference was observed. In multivariable logistic regression analysis, both the total arterial calcification score (OR 1.05, $p<0.05$) and low skeletal muscle mass (OR 1.86, $p<0.05$) were independently associated with the formation of pharyngocutaneous fistula.

Besides surgery, head and neck cancer patients, especially those with locally advanced cancer, are treated with (chemo- or bio)radiotherapy. Therefore, **Part III** of this thesis presents the predictive and prognostic impact of low skeletal muscle mass in head and neck cancer patients treated with (chemo- or bio)radiotherapy. **Chapter 10** presents a study in 343 patients with locally advanced head and neck squamous cell carcinoma (HNSCC) who were treated with cisplatin-based chemoradiotherapy. The predictive value of low skeletal muscle mass for cisplatin dose-limiting toxicity was investigated. Dose-limiting toxicity was defined as any toxicity resulting in a cisplatin dose-reduction of ≥ 50%, a treatment delay of ≥4 days or a termination of treatment after the first or second cycle of cisplatin. Majority of these patients had low skeletal muscle mass before treatment (58%). Also, a large percentage of patients (44.9%) experienced dose-limiting toxicities. Low skeletal muscle mass was predictive factor for cisplatin-dose limiting toxicity (HR 1.8, $p<0.05$). **Chapter 11** presents a study in 156 locally advanced HNSCC patients who were treated with cisplatin-based chemoradiotherapy in the Antoni van Leeuwenhoek hospital, Amsterdam. In this cohort, the predictive impact of low skeletal muscle mass on cisplatin-dose limiting toxicity was also investigated. Similar percentage of patients (54.9%) were diagnosed with low skeletal muscle mass. For this cohort, cisplatin dose-limiting toxicity was defined as any toxicity resulting in receiving a cumulative cisplatin dose below 200mg/m^2, the prescribed cumulative cisplatin dose in cisplatin-based chemoradiotherapy is 300mg/m^2. Compared to the previous study in chapter 10, a smaller percentage of patients (24.2% versus 44.9%) experienced cisplatin dose-limiting toxicity. Nevertheless, low skeletal muscle mass was a significant predictor (HR 4.0, $p<0.05$) for cisplatin-dose limiting toxicity. Not all patients with locally advanced head and neck cancer are physically fit to undergo cisplatin-based chemoradiotherapy, mainly due to comorbidities such as vascular diseases and kidney diseases. **Chapter 12** presents a study in 91 cisplatin-unfit patients who received cetuximab-based bioradiotherapy to evaluate the predictive impact for dose-limiting toxicities in this group of HNSCC patients. A higher percentage of patients with low skeletal muscle mass (74.7%) was found in this study compared to the cisplatin-fit

patients described in chapter 10 and 11 (58% and 54.9%, respectively). Although previous studies showed a predictive impact of low skeletal muscle mass for cisplatin dose-limiting toxicity, no predictive impact of low skeletal muscle mass for cetuximab dose-limiting toxicity (OR 0.83, p=0.74) could be found. To evaluate the findings in Chapter 10-12, a systematic review and meta-analysis was performed on the predictive impact of low skeletal muscle for anti-cancer drug toxicity in all types of cancer (head and neck cancer and non-head and neck cancer), this study is presented in **Chapter 13**. In total, 31 studies were included in the systematic review, sample size ranged from 21 to 414 patients and the occurrence of low skeletal muscle mass ranged from 12.2% to 89.0%. Most research on low skeletal muscle mass and anti-cancer drug toxicity was performed in esophageal, renal, colorectal, breast and head and neck cancer. Patients with low skeletal muscle mass had a higher risk of severe toxicity (OR 4.08, $p < 0.001$) and dose-limiting toxicity (OR 2.24, $p < 0.001$) compared to patients without low skeletal muscle mass. This shows that the predictive value of low skeletal muscle mass for anti-cancer drug toxicity can be observed across cancer types. The mechanisms as to why low skeletal muscle mass is associated with the occurrence of cisplatin dose-limiting toxicity in head and neck cancer patients undergoing chemoradiotherapy is unknown. A hypothesis for this phenomenon is that the pharmacokinetics of cisplatin is altered with respect to the distributional volume in patients with a low skeletal muscle mass and normal to high adipose tissue mass. Cisplatin is a hydrophilic chemotherapeutical agent, and mainly distributes into the fat-free body mass, of which skeletal muscle mass is the largest component.[5–7] Cisplatin is dosed using the body surface area of a patient, and does not take into account individual body composition.[8,9] It was therefore hypothesized that patients with low skeletal muscle mass and normal or high adipose tissue mass may actually receive a relatively high dose of cisplatin. Data on the relationship between body composition and pharmacokinetic characteristics of cisplatin was not yet available. Therefore, **Chapter 14** presents the prospective observational PLATISMA study performed in 45 patients with locally advanced head and neck cancer in which patients skeletal muscle mass was measured before treatment and blood cisplatin levels were measured during the first cycle of treatment. A pharmacokinetic analysis was performed to assess the relationship between cisplatin pharmacokinetics and skeletal muscle mass. As hypothesized, a significant relationship between cisplatin pharmacokinetics and skeletal muscle mass was found. However, this relationship was also seen between cisplatin pharmacokinetics and body weight. Further studies are needed to evaluate whether cisplatin dosing based on skeletal muscle mass is superior to dosing based on body surface area with regards to the occurrence of toxicities and overall and disease-free survival. Besides the role of skeletal muscle mass in cisplatin toxicity, cisplatin itself is thought to cause muscle wasting. Therefore, **Chapter 15** presents a study performed in 235 patients with locally advanced head and neck cancer undergoing cisplatin-based chemoradiotherapy to investigate the patterns, predictors and prognostic value of skeletal muscle mass loss after treatment. Skeletal muscle mass was measured on pre-chemoradiotherapy and post-chemoradiotherapy imaging, the skeletal muscle area was significantly lower than before treatment (31.62cm^2 versus 33.34 cm^2, $p<0.01$). Majority of patients (54.9%) experienced moderate loss of skeletal muscle mass, 38.7% had stable skeletal muscle mass, 13% had a moderate gain of skeletal

muscle mass, 0.4% had a large gain of skeletal muscle mass and only 0.4% had a large loss of SMM. Significant predictive factors for loss of skeletal muscle mass after treatment were being overweight or obese (HR 1.75, p<0.05 and HR 1.80, p<0.05, respectively) and a tumor site in the oropharynx (HR 1.85, p< 0.05). Patients with a ECOG performance status of 1 (HR 0.62, p<0.05), who were treated in a postoperative setting (HR 0.55, p<0.02) and who were able to receive an absolute cumulative dose of cisplatin ≥ 300mg (HR 0.57, p<0.05) were significantly less likely to experience loss of skeletal muscle mass after treatment. Low skeletal muscle mass at diagnosis or loss of skeletal muscle mass after treatment were not prognostic for OS nor DFS. As the incidence of oropharyngeal cancer is increasing due to the increase of sexually transmitted infections with the human papillomavirus, we also investigated the role of skeletal muscle mass in patients with oropharyngeal cancer**. Chapter 16** presents a study in 216 patients with oropharyngeal squamous cell carcinoma and investigated the prognostic impact of low skeletal muscle mass. A large percentage of low skeletal muscle mass (64.8%) was found in these patients. The prognostic impact of sarcopenic obesity was evaluated, which is the combination of low skeletal muscle mass and obesity. Six percent of patients were identified with sarcopenic obesity. Sarcopenic obesity was associated with a decreased OS (HR 4.42, p<0.05) and disease-free survival (DFS) (HR 3.90, p<0.05), independent from other well-known strong prognostic factors such as an HPV-positive tumor. **Chapter 17** presents a prospective observational study in 108 patients with locally advanced oropharyngeal carcinoma in which, among other things, the impact of low skeletal muscle mass on functional outcomes during the first year after radiation-based treatment. Swallowing, mouth opening, and speech function were collected before treatment and at six-and twelve-month follow-up as part of ongoing prospective assessments by speech language pathologists. Objective and patient-perceived function deteriorated until six months and improved until twelve months after treatment. However, functional outcomes did not return to baseline levels, of the included patients 25%, 20% and 58% had objective dysphagia, trismus and speech problems, respectively. Of the included patients, 45% had low skeletal muscle mass at diagnosis. At six months, patients with low skeletal muscle mass had significantly higher modified diets and higher total swallow quality of life (SWAL-QOL) scores, indicating more swallowing related problems, compared to patients without low skeletal muscle mass.

Besides low skeletal muscle mass seen in patients with cancer, also referred to as secondary sarcopenia, muscle mass declines gradually with increasing age. Low skeletal muscle mass in older people caused by the ageing process, is also referred to as primary sarcopenia. Due to the ageing population, clinicians are treating more elderly patients with cancer. The elderly population with head and neck cancer will grow gradually during the upcoming years. Therefore, **Part IV** of this thesis, presents the studies performed to investigate the impact of low skeletal muscle mass in elderly head and neck cancer patients. **Chapter 18** presents a study performed in 85 elderly HNSCC patients (≥70 years). Previous research in elderly people showed that the correlation between skeletal muscle mass and muscle strength is moderate to weak and the relationship between muscle strength and muscle mass to be non-linear.[10,11] Therefore, the European working group on sarcopenia in older people (EWGSOP) recommended diagnosing

sarcopenia in older patients based on the presence of bot low muscle mass and low muscle function (strength or performance).[12] This study investigated the prognostic impact of low skeletal muscle mass, low muscle function and the prognostic impact of both low skeletal muscle mass and muscle function for survival. Of the 85 patients, 48.2% had both low muscle mass and muscle function. Solely, low skeletal muscle mass or low muscle function were not prognostic for overall survival. However, patients with both low skeletal muscle mass and low muscle function (sarcopenia definition by EWGSOP) had a significantly decreased overall survival compared to patients without sarcopenia (12.07 months versus 13.60 months, HR 2.80, $p<0.05$). The 3-years overall survival was significantly shorter for elderly with sarcopenia compared to elderly patients without sarcopenia (39% versus 75%, $p<0.05$). **Chapter 19** presents a study performed in 150 elderly head and neck cancer patients (≥60 years). Elderly patients are both at risk for having sarcopenia as well as frailty. Both are associated with adverse outcomes. As previously mentioned, sarcopenia in elderly is measured by both skeletal muscle mass and muscle function (strength or function). Frailty is screened with use of the G8 frailty questionnaire and diagnosed by a time-consuming comprehensive geriatric assessment (CGA).[13] This study was performed to investigate whether sarcopenia may be a marker for frailty. Frail patients were significantly more likely to be sarcopenic ($\chi^2 = 4.88$, $p<0.05$). Multivariate regression analysis showed that significant predictors were comorbidity score (OR 5.5, $p<0.01$) and skeletal muscle mass index (OR 0.9, $p<0.01$) for frailty and age (OR 3.7, $p<0.05$) and G8 frailty score (OR 3.7, $p<0.05$) for sarcopenia. Therefore, assessment of skeletal muscle mass may be used as an alternative screening tool for the G8 questionnaire for frailty screening, i.e., selection of patients who need a time-consuming CGA. **Chapter 20** presents a study performed in 73 elderly head and neck cancer patients (≥70-years) to investigate the association between sarcopenia (low muscle mass and muscle function) and a comprehensive geriatric assessment (CGA). Frail patients diagnosed by CGA were more likely to have a low SMI and to be sarcopenic at diagnosis. Multivariate regression analysis with frailty diagnosed by CGA as dependent variable distinguished skeletal muscle mass index as a significant predictor of frailty (OR 0.89, $p<0.05$). Low muscle mass, based on SMI, may be able to predict some CGA domain outcomes in older patients with head and neck cancer and is easier to use then a CGA. These findings should ideally be validated in a larger, prospective cohort study.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis provided key knowledge of the predictive and prognostic impact of low skeletal muscle mass, also referred to as sarcopenia, in head and neck cancer patients. The promising next steps are to develop and implement (automated) time-efficient sarcopenia measurement tools for clinical practice and to investigate whether improving muscle mass also improves treatment outcomes and prognosis in patients with head and neck cancer. During the past decade several therapeutic interventions to prevent and treat skeletal muscle mass loss are described in literature. These therapeutic interventions include physical exercise, nutritional support and pharmacological interventions. Due to the various factors contributing to low skeletal muscle mass such as malnutrition and reduced physical exercise, optimal pre-habilitation of patients with low SMM requires a multimodal approach and contributions from members of a multidisciplinary team (e.g., physiotherapist, dietician).

PHYSICAL EXERCISE

For surgically treated patients, focus on enhancing physical fitness before surgery to enable the patient to withstand the stress of surgery has gained increased attention, this is also called pre-habilitation. The effectiveness of rehabilitation programs has already been demonstrated in a variety of medical fields including abdominal[14], lung[15] and pancreatic cancer[16] surgery.

Minnella et al. performed a randomized-controlled trial in patients with esophageal cancer, 26 patients received pre-habilitation consisting of pre-operative exercise and nutrition optimization, and 25 control patients received usual care.[17] The primary outcome was a change in functional capacity, measured with an absolute change in 6-minute walk distance. Postoperative data from 4 to 8 weeks after surgery were also compared. They found that pre-habilitation significantly improved functional capacity before and after surgery. Faithfull et al. performed a systematic review of studies investigating the effect of pre-habilitation in patients with cancer and found a significant improvement in postoperative mobilization and self-reported physical function in patients who received pre-habilitation.[18] To date, only few small exercise studies were performed in patients with head and neck cancer. Steegmann et al. recently performed a randomized clinical trial in 69 patients undergoing surgical treatment of head and neck cancer.[19] They found that patients in the intervention group (personalized pre-treatment exercise plan) showed significantly less postoperative morbidity and had a significantly shorter hospital stay. In addition, Capozzi et al. have also shown that pre-treatment exercise is safe and feasible in patients with head and neck cancer and can help negate cachexia and improve common cancer adverse effect such as cancer-related fatigue and reduced physical function.[20]

Although these small studies show a positive effect of pre-habilitation for treatment outcomes in surgically treated head and neck cancer patients, there is still no consensus whether pre-habilitation contributes to reduction in postoperative complications, faster recovery and improvement in quality of life and on integrating pre-habilitation in clinical practice. Samuel et al. performed a randomized controlled trial in 148 patients with head and neck cancer undergoing chemoradiotherapy to evaluate the effectiveness of exercise on functional ca-

pacity.[21] They found that a significant improvement in the functional capacity, quality of life and prevention of worsening of fatigue in the exercise group.

Multimodal and multidisciplinary pre-habilitation with engagement of patients and health care teams may lead to more effective and sustainable clinical practice. However, the challenge in head and neck cancer is that there is often just a 4-week window of opportunity to undergo this pre-habilitation because treatment must begin within 4-6 weeks after diagnosis or in the adjuvant setting after surgery. Although it is not known if pre-habilitation in head and neck cancer patients is feasible in this short window of opportunity, it has already been shown that this time frame is sufficient in patients with colorectal cancer.[22] In addition, Bhatia et al. conducted an randomized controlled trial in lung cancer patients in which they have also shown that pre-habilitation in a short time frame (median 25 days) was effective and safe.[23] Pre-operative high-intensity interval training (HIT) significantly increased cardio-respiratory fitness and walk capacity compared to patients who received usual care. The adherence to HIT in the pre-habilitation group was high 87% (SD 18%).

Recently, Boright et al. proposed a protocol for physical therapist-administered head and neck cancer pre-habilitation program and also did a feasibility study for three patients.[24] The authors conclude that their developed pre-habilitation protocol consisting of a home exercise program (strength, endurance and range of motion) and nutritional support is feasible in patients with head and neck cancer. Due to the short window of opportunity to train muscle mass in head and neck cancer, it is proposed that HIT is the preferred form of exercise training in pre-habilitation. Although there is no universal definition, HIT generally refers to repeated sessions of relatively short intermittent exercise. Exercise in HIT is performed at a high intensity close to VO_2max during few seconds with previous warming up period, peak-exercise of minutes and followed up by a cooling down, this is repeated 4-6 times per training session. Dunham et al. performed a randomized controlled trial in which they showed that HIT offers a time-efficient alternative to endurance training in aerobic capacity and performance.[25] Considering the similar beneficial effects of HIT than endurance training in a shorter period of time, this physical exercise training system seems to the best option in a pre-habilitation program in order to not delay the surgery. The work rate in the HIT training needs however to be adjusted by the physiotherapist on each patient and session to target near VO_2max without being too intensive for the patient's physical capacity.

NUTRITIONAL SUPPORT

A mandatory prerequisite in preventing muscle loss and stimulating muscle mass growth is an adequate intake of nutrients. Patients with head and neck cancer are prone for malnutrition due to tumor site and treatment-related side effects such as xerostomia, nausea, mucositis and fibrosis. It has already been shown that weight loss and systemic inflammation leads to hypermetabolism in which the resting energy expenditure is increased.[26,27] This high resting energy expenditure leads to a loss of skeletal muscle mass.[27] The higher catabolic and inflammatory state in patients with cancer leads to further deterioration of skeletal muscle mass

status by mechanisms including proteolysis and lipolysis.[28] The current strategies in clinical practice to combat metabolic disorders in head and neck cancer patients generally focus on weight maintenance whereby patients are encouraged to eat as many calories as possible and when they experience swallowing problems calories are supplemented either by oral or parenteral nutrition. However, due to the various mechanisms that cause malnutrition and the accompanying loss of skeletal muscle mass in patients with head and neck cancer, reversing malnutrition is not simple done by stimulating caloric intake. Because of heterogeneity of body composition types in head and neck cancer, nutritional support must be personalized to the individual needs. This personalized approach can be supported by measurement of patients' resting energy expenditure by a caloric meter, this provides information about the amount of calories a patient need. Besides caloric supplementation, protein supplementation should play a major role in reversing malnutrition in head and neck cancer. Increasing evidence suggests that protein intake should consist of a daily intake of 1.5-2/kg/day in order to increase muscle protein synthesis and reduce proteolysis.[29] Nutritional supplements are also under investigation for the treatment of low skeletal muscle mass. For surgically treated head and neck cancer patients, supplementation with eicosapentaenoic acid (EPA), which is analpha-3-omega fatty acid found in fish oil, showed short-term benefit in combatting loss of muscle mass, however long-term follow-up is needed.[30]

PHARMACOLOGICAL INTERVENTION

Drugs that target overactivation of catabolic processes, cell injury and inflammation are promising in the field of combatting muscle mass loss. Drugs that exhibit these characteristics are selective androgen receptor modulators, anti-inflammatory drugs such as anti-cytokine agents or ghreline analogues.[31,32] Ghrelin is hormone secreted by the stomach that stimulates appetite and muscle anabolism.[33] Anamoreline, a ghrelin analogue, has been investigated in a randomized controlled trial in >450 cachectic patients with advanced lung cancer.[32] Patients who received anamoreline for 12 weeks showed a significant increase in muscle mass and patients that had increased muscle mass also showed a significantly increased overall survival from 9 to 13 months. Because of the role of inflammation in muscle wasting, anti-inflammatory drugs may be promising in counteracting muscle loss. Randomized controlled trials investigating the role of anti-inflammatory drugs such as tocilizumab (anti-Il-6-receptor antibody), infliximab (anti-tumor necrosis factor (TNF)-alpha agent) and canakinumab (anti-IL-1 antibody) in the prevention of skeletal muscle mass loss in head and neck cancer patients are needed. Previous studies in patients with rheumatoid arthritis showed that treatment with tocilizumab lead to gain in skeletal muscle mass.[34] This anabolic effect of tocilizumab has also been in shown in a patient with lung cancer.[35]

ADDITIONAL REMARK: THE ROLE OF ARTIFICIAL INTELLIGENCE

In order to facilitate implementation of skeletal muscle mass as a biomarker in clinical practice, it is of outmost importance to improve speed efficiency in measurements. Speed efficiency in image analysis can be performed by use of artificial intelligence (AI) such as deep learning and machine learning. Research on the role of AI in body composition measurements is increasing.

Cespedes Feliciano et al. recently published a promising study in which skeletal muscle mass and adipose tissue was automatically segmented in patients with non-metastatic colorectal (n=3102) and breast cancer (n=2888) at the level of L3 using automated software.[36] They also performed manual skeletal muscle mass and adipose-tissue segmentations. There was strong agreement between manual and automatic segmentations overall and within subgroups of age, sex, body mass index, and cancer stage: average Jaccard scores and intra-class correlation coefficients exceeded 90% for all tissues. However, the authors describe that automated segmentation performance was lowest for the <2% of patients who were underweight or had anatomic abnormalities. Head and neck cancer patients are more likely to have low body weight at diagnosis than patients with colorectal cancer or breast cancer, therefore further studies investigating the implication of automatic segmentation of body composition in head and neck cancer patients are warranted. Another study performed by Edwards et al. used deep learning, fully convolutional neural network for the segmentation of abdominal muscle on CT and showed a mean Dice similarity coefficient of 0.92, a mean precision of 0.93, and a mean recall of 0.91 in an independent test set.[37] Another study performed by Blanc-Durand et al. in 189 patients with lung cancer showed that deep-learning was able to distinguish subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and muscular body mass (MBM) with mean Dice similarity coefficients in the validation set were 0.95, 0.93, and 0.91 for SAT, VAT, and MBM, respectively.[38] The by deep-learning obtained BSA-normalized VAT/SAT ratio was shown to be an independent predictor for survival in lung cancer patients. Currently, no AI studies for body composition are performed in head and neck cancer patients.

CONCLUSION

In conclusion, in head and neck cancer patients, low skeletal muscle mass is a prevalent problem which occurs in approximately 55% of patients. Skeletal muscle mass can be easily assessed on a single slice at the level of C3 (or L3) on routinely performed CT or MRI scans which are performed for head and neck cancer diagnosis and treatment evaluation. Skeletal muscle mass is a promising as imaging biomarker which predicts negative treatment outcomes in various treatment strategies applied in head and neck cancer management. Besides negative treatment outcomes, low skeletal muscle mass has also shown to be prognostic for decreased survival.

We hypothesize that multimodal pre-habilitation will improve skeletal muscle mass status of the patient before treatment which will lead to an enhanced recovery trajectory with reduced operative complications and postoperative adverse effects in surgically treated patients and to reduced treatment-related toxicities in patients treated with (chemo- or bio) radiotherapy. We also hypothesize that multimodal pre-habilitation leads to a reduced duration of hospital stay, reduced health care costs and improved quality of life. In addition, pre-habilitation is an opportunity to foster patient empowerment which increases patient's autonomy and self-management. This may facilitate an improved quality of life before treatment and may positively affect long-term health. Therefore, the aims of a future randomized controlled trial should be to compare the effect of a multimodal pre-habilitation program including exercise, nutritional

support and psychological support with usual care on treatment outcomes and prognosis for patients with head and neck cancer, particularly those with low skeletal muscle mass.

Further research is needed to validate these hypotheses. This thesis provides information that can contribute to the development of these studies.

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CHAPTER 22

Nederlandse samenvatting

About the author

Dankwoord

NEDERLANDSE SAMENVATTING

Dit proefschrift beschrijft onderzoek naar de veelbelovende patiënt-specifieke biomarker voor behandeluitkomsten en prognose in de hoofd-halsoncologie: skeletspiermassa. Het onderzoek in dit proefschrift richt zich op de diagnostiek van skeletspiermassa en de predictieve en prognostische waarde van lage skeletspiermassa bij patiënten met hoofd-halskanker. Door de vergrijzing zal de incidentie van ouderen met hoofd-halskanker toenemen, daarom is er in dit proefschrift ook aandacht voor de rol van spiermassa en spierfunctie bij oudere patiënten met hoofd-halskanker. De resultaten van dit proefschrift dragen bij aan een verbeterde risicostratificatie vóór behandeling, de ontwikkeling van gepersonaliseerde behandelprotocollen, een betere voorspelling van de prognose en een verbetering van de gedeelde besluitvorming met de patiënt.

Onderzoek naar de rol van skeletspiermassa als biomarker is de afgelopen decennium sterk toegenomen, mede door de verbeterde diagnostische middelen in de klinische praktijk. Meting van de vetvrije massa, waarvan de skeletspiermassa de grootste bijdrage levert, wordt in de klinische praktijk reeds verricht met behulp van een 'Dual Energy X-ray absorptiometry' (DEXA) scan en de 'bio-elektrische impedantieanalyse' (BIA). Een nadeel van deze diagnostische hulpmiddelen is echter het feit dat de betrouwbaarheid afneemt bij afwijkende hydratatie-status bijvoorbeeld bij oedeem. Het gebruik van DEXA en BIA voor het beoordelen van lichaamssamenstelling van patiënten met kanker heeft daarom niet de voorkeur. Onderzoek naar lichaamssamenstelling, met name skeletspiermassa, wordt voornamelijk uitgevoerd middels computertomografie (CT) beeldvorming vanwege de relatief gemakkelijke, snelle en nauwkeurige segmentatie van spier door het instellen van 'Hounsfield unit' (HU)-grenswaarden van -29 tot +150HU. Skeletspiermassa kan in de klinische praktijk gemakkelijk als biomarker worden geëvalueerd door het gebruik van reeds beschikbare scans die routinematig worden verkregen voor de diagnose van hoofd-halskanker en de evaluatie van de behandeling.

Een veelgebruikte methode om de spiermassa te meten bij oncologische patiënten is middels segmentatie van de oppervlakte van de spieren zichtbaar op één specifieke twee-dimensionale axiale slide.[1] Deze 'single-slide' wordt ook wel het referentiepunt genoemd. De meest gebruikte referentiepunt op CT voor spiersegmentatie is ter hoogte van de derde lendenwervel (L3), deze is zichtbaar op een CT-scan van het abdomen. Ter hoogte van L3 worden de psoas, erector spinae, quadratus lumborum, transversus abdominis, externe en interne obliques en rectus abdominis-spieren gesegmenteerd. Eerdere studies toonden al aan dat er een lineair verband bestaat tussen de lengte van een persoon en de skeletspiermassa oppervlakte op het niveau van L3, daarom wordt de verkregen skeletspiermassa oppervlakte aangepast voor lengte om de lumbale skeletspiermassa-index (SMI in cm^2/m^2) te berekenen.[2,3] De SMI geeft een schatting van de totale skeletspiermassa in verhouding tot de lengte. In 2008 is door Prado et al. voor het eerst een onderzoek beschreven waarin segmentatie van skeletspiermassa op CT uitgevoerd werd om de relatie tussen lichaamssamenstelling en ongunstige uitkomsten te evalueren bij oncologische patiënten.[2]

Binnen hoofd-halsoncologie wordt CT-beeldvorming van het abdomen alleen uitgevoerd voor stadiëringsdoeleinden bij patiënten met een lokaal gevorderde tumor. Hierdoor is een CT-scan van het abdomen niet routinematig beschikbaar voor alle hoofd-halskanker patiënten. Daarom hebben Swartz et al. een meetmethode ontwikkeld om middels een CT-scan van het hoofd-halsgebied de skeletspiermassa ter hoogte van L3 te bepalen, hiervoor is de derde halswervel (C3) als referentiepunt gekozen.[4] **Deel I** van dit proefschrift presenteert de uitgevoerde onderzoeken om de meting van de skeletspiermassa op C3 verder te evalueren bij patiënten met hoofd-halskanker. In **Hoofdstuk 2** wordt een validatiestudie uitgevoerd voor de meetmethode van Swartz et al. De resultaten van deze studie laten een goede correlatie zien ($r = 0,75$, $p < 0,01$) tussen de gesegmenteerde skeletspiermassa oppervlakte op het niveau van C3 en L3. Bij gebruik van de multivariabele predictie formule opgesteld door Swartz et al. om de skeletspieroppervlakte op het niveau van L3 te berekenen met behulp van de skeletspieroppervlakte op C3 en de variabelen geslacht, leeftijd en gewicht, verbeterde de correlatie tussen de skeletspiermassa oppervlakte op C3 en L3 ($r = 0,82$, $p < 0,01$). Er was echter enig verschil in de identificatie van patiënten met een lage skeletspiermassa op basis van de berekende lumbale SMI middels de multivariabele predictie formule en de werkelijke lumbale SMI (Cohen's κ: 0,57; 95% BI 0,45-0,69). De sensitiviteit van het identificeren van patiënten met lage skeletspiermassa met behulp van deze berekende lumbale SMI bleek desondanks hoog (84,4%). Deze studie laat zien dat een meting van skeletspiermassa op het niveau van C3 een eenvoudig en robuust alternatief biedt voor het schatten van de skeletspiermassa van een patiënt. **Hoofdstuk 3** presenteert een associatiestudie voor metingen van skeletspiermassa op het niveau van C3 op een CT-scan en op een 'magnetic resonance imaging' (MRI) scan. Zoals eerder beschreven kan voor de precieze segmentatie van skeletspiermassa oppervlakte op een CT-scan gebruik worden gemaakt van de HU grenswaarden van spiermassa. Gezien dit niet mogelijk is op een MRI-scan is segmentatie van spiermassa oppervlakte op een MRI-scan onderhevig aan de interpretatie van de beoordelaar. Een groot deel van de hoofd-halskanker-patiënten ondergaat in het diagnostische proces een diagnostische MRI-scan in plaats van een CT-scan. In deze associatiestudie werd de skeletspiermassa van patiënten gesegmenteerd op zowel CT als MRI op het niveau van C3 en werd het verband tussen deze metingen geanalyseerd. Er werd hierbij een uitstekende intraclasscoëfficiënt gevonden (0,97; 95% BI 0,94-0,98, $p < 0,01$). Het gemiddelde verschil in metingen van het skeletspiergebied tussen CT en MRI was minder dan $1cm^2$. Deze resultaten laten zien dat naast routinematig verkregen CT-scans ook MRI-scans kunnen worden gebruikt voor het bepalen van de skeletspiermassa van de patiënt. Af en toe kan de meting van de skeletspiermassa oppervlakte op het niveau van C3 worden verstoord door uitbreiding van de primaire tumor, lymfeklieren metastases en/of eerdere behandeling. Daarom beschrijft **Hoofdstuk 4** een correlatie studie die gedaan is om te onderzoeken of metingen van skeletspiermassa van een enkele spier, de musculus masseter, correleren met metingen van skeletspiermassa op een 'single-slide' op het niveau van C3 en L3. De musculus masseter werd gekozen omdat deze consequent aanwezig is bij routinematige beeldvorming van het hoofd-halsgebied, zelden wordt beïnvloed door ziekte of behandeling en snel en gemakkelijk te karakteriseren is.

Verschillende parameters van de musculus masseter (skeletspiermassa-volume, skeletspiermassa-oppervlak, skeletspiermassa-dikte) waren significant gecorreleerd met skeletspiermassa oppervlakte op het niveau van C3 en L3. Deze correlaties varieerden echter van matig tot sterk, waarbij de sterkste correlatie werd gevonden tussen de skeletspiermassa oppervlakte op C3 en de skeletspiermassa-volume van de musculus masseter (r = 0,67). Skeletspiermassa oppervlakte van de musculus masseter had slechts een matige correlatie met skeletspiermassa oppervlakte op het niveau van L3 (r = 0,47) en C3 (r = 0,57). De prognostische impact van lage skeletspiermassa, verkregen door meting van de musculus masseter SMI, op overleving werd aanvullend onderzocht en dit toonde aan dat een lage skeletspiermassa van de musculus masseter een significante prognostische biomarker was voor verminderde overleving (HR 3,0, p <0.05). Bij patiënten zonder kwalitatief goede beeldvorming op het niveau van L3 of C3, zouden musculus masseter parameters kunnen dienen als een alternatief voor de beoordeling van skeletspiermassa. Vanwege het ontbreken van referentiewaarden van skeletspiermassa in de algemene bevolking en de heterogeniteit in afkapwaarden voor lage skeletspiermassa in de literatuur is in **Hoofdstuk 5** een onderzoek gepresenteerd dat is uitgevoerd in een groot cohort van hoofd-halskankerpatiënten (n=1415) om afkapwaarden te ontwikkelen voor lage skeletspiermassa gemeten op het niveau van C3. Vanwege de significante correlatie tussen SMI en geslacht (r^2= 0,4, p <0,01) en SMI en body-mass index (BMI) (r^2= 0,4, p <0,01), werden geslacht- en BMI-specifieke afkapwaarden berekend. Voor mannelijke patiënten met een BMI <25 kg/m^2 werd een SMI ≤6,8 cm^2/m^2 gedefinieerd en met een BMI ≥25 kg/m^2 werd een SMI ≤8,5 cm^2/m^2 gedefinieerd voor een lage skeletspiermassa. Voor vrouwelijke patiënten met een BMI <25 kg/m^2 werd een CSMI ≤5,3 cm^2/m^2 gedefinieerd en met een BMI ≥25 kg/m^2 werd een SMI ≤6,4 cm^2/m^2 gedefinieerd voor een lage skeletspiermassa. Deze studie levert voor het eerst gestandaardiseerde afkapwaarden op voor lage skeletspiermassa op het niveau van C3 bij patiënten met hoofd-halskanker. Deze informatie kan helpen bij de uniformiteit van de definitie van lage skeletspiermassa.

Deel II van dit proefschrift presenteert de predictieve en prognostische impact van skeletspiermassa bij patiënten met chirurgische behandelde hoofd-halskanker. In **Hoofdstuk 6** wordt een onderzoek gepresenteerd naar de predictieve waarde van een lage skeletspiermassa op chirurgische complicaties bij patiënten met mondholtekanker (n=78) die een tumorresectie en aanvullende mandibulaire reconstructie ondergingen middels een vrij-gevasculariseerd fibula transplantaat in het Universitair Medisch Centrum Utrecht. Lage skeletspiermassa was significant geassocieerd met een verhoogd risico op transplantaat-gerelateerde complicaties (HR 4,3, p <0,05) en op ernstige chirurgische complicaties (Clavien-Dindo graad III-IV) (HR 4,0, p <0,05). Een lage skeletspiermassa was ook prognostisch voor een verminderde algehele overleving (HR 2,4, p <0,05). **Hoofdstuk 7** presenteert een onderzoek dat is uitgevoerd in een groter cohort van patiënten (n=616) die een reconstructie ondergingen in het hoofd-halsgebied middels een microvasculaire vrije lap transplantatie. Het onderzoek werd uitgevoerd in het buitenland op de afdeling orale en maxillofaciale chirurgie in samenwerking met Dr. S. Parmar van het Queen Elizabeth Hospital in Birmingham, Verenigd Koninkrijk.

Naast skeletspiermassa werd bij deze patiënten de predictieve en prognostische impact van systemische inflammatie onderzocht. Verhoogde neutrofiel-tot-lymfocytverhouding (NLR) werd gebruikt als een marker voor systemische inflammatie. Non-transplantaat- en transplantaat-gerelateerde complicaties kwamen voor bij respectievelijk 39,3% en 12,3% van de patiënten. Het percentage transplantaat falen was 4,7%. Voor oncologische patiënten waren significante voorspellers gevonden voor chirurgische complicaties een verhoogd NLR bij alle types van transplantaat reconstructies (OR 1,5, p <0,05), lage skeletspiermassa bij radialis onderarm transplantaat reconstructies (OR 2,1, p <0,05) en de combinatie van een verhoogd NLR en lage skeletspiermassa bij vrij-gevascularisseerd fibula transplantaat reconstructies (OR 5,2, p <0,05). Patiënten met uitsluitend een verhoogd NLR liepen een significant risico op voor transplantaat-gerelateerde complicaties (OR 3,0), ernstige chirurgische complicaties (Clavien-Dindo graad >IIIa) (OR 2,2, p <0.05) en in combinatie met een lage skeletspiermassa op langere ziekenhuisopname (+3,9 dagen, p <0,05). Bij patiënten met een stadium I-II hoofd-hals plaveiselcelcarcinoom waren lage skeletspiermassa (HR 2,3, p <0.05) en de combinatie van verhoogd NLR en lage skeletspiermassa (HR 2,3, p <0.05) prognostisch voor verminderde algehele overleving. Skeletspiermassa en NLR zijn routinematig beschikbare biomarkers en deze studie toont aan dat deze biomarkers de clinicus kunnen helpen bij het identificeren van patiënten met slechtere behandeluitkomsten en prognose.

Hoofdstuk 8 presenteert een onderzoek bij patiënten met chirurgisch behandelde mondholte plaveiselcelcarcinoom (n=224) om de predictieve impact van een lage skeletspiermassa op perioperatieve complicaties te onderzoeken. Een lage skeletspiermassa was een significante voorspeller voor de aanwezigheid van perioperatieve complicaties (HR 1,5, p <0,01) en het aantal perioperatieve complicaties (HR 1,5, p <0,01). Naast skeletspiermassa kan arteriële calcificatie ook beoordeeld worden op routinematige diagnostische CT-scans en deze zou kunnen worden gebruikt als een aanvullende op beeldvorming gebaseerde biomarker. **Hoofdstuk 9** presenteert daarom een onderzoek dat verricht is om de predictieve impact van arteriële calcificatie en lage skeletspiermassa voor het optreden van faryngocutane fistelvorming te onderzoeken bij 224 hoofd-halskanker patiënten die een laryngectomie ondergingen. Arteriële calcificaties waren veel voorkomend bij patiënten die een laryngectomie ondergingen, waarbij slechts 1,3% procent van de patiënten geen arteriële calcificatie had en 7,1% van de patiënten hoogstens milde arteriële calcificaties hadden. Arteriële calcificaties op verschillende locaties, met name van het dalende deel van de aorta en de origo van de brachiocefale arteriën, waren significant geassocieerd met faryngocutane fistelvorming. Een hogere totale arteriële calcificatiescore was ook significant geassocieerd met faryngocutane fistelvorming. Matige tot ernstige arteriële calcificatie ter plaatse van het dalende deel van de aorta kwam vaker voor bij patiënten met een lage skeletspiermassa dan bij patiënten zonder een lage skeletspiermassa (p <0,01). Op de andere locaties werd geen significant verschil waargenomen. In multivariabele logistische regressieanalyse waren zowel de totale arteriële calcificatiescore (OR 1,05, p <0,05) als een lage skeletspiermassa (OR 1,86, p <0,05) onafhankelijk geassocieerd met de vorming van faryngocutane fistels.

Naast operatieve behandeling worden hoofd-halskankerpatiënten, met name degenen met een lokaal gevorderde tumor, behandeld met (chemo- of bio) radiotherapie. Daarom presenteert Deel III van dit proefschrift de predictieve en prognostische impact van een lage skeletspiermassa bij hoofd-halskankerpatiënten die behandeld worden met (chemo- of bio) radiotherapie. **Hoofdstuk 10** presenteert een onderzoek bij 343 patiënten met lokaal gevorderd hoofd-hals plaveiselcelcarcinoom die werden behandeld met concurrente chemoradiotherapie met het middel cisplatinum. De predictieve waarde van een lage skeletspiermassa voor cisplatinum dosis-limiterende toxiciteit werd onderzocht. Dosis-limiterende toxiciteit werd gedefinieerd als elke toxiciteit die resulteerde in een cisplatinum dosisverlaging≥ 50%, een vertraging van de behandeling met ≥4 dagen of een stopzetting van de behandeling na de eerste of tweede cyclus van cisplatinum. De meerderheid van deze patiënten had vóór de behandeling een lage skeletspiermassa (58%), ook ondervond een groot percentage van de patiënten (44,9%) dosis-limiterende toxiciteit. Een lage skeletspiermassa was een predictieve factor voor cisplatinum dosis-limiterende toxiciteit (HR 1,8, p <0,05). **Hoofdstuk 11** presenteert een onderzoek bij 156 patiënten met lokaal gevorderd hoofd-hals plaveiselcelcarcinoom die werden behandeld met concurrent chemoradiotherapie met het middel cisplatinum in een ander centrum, namelijk het Antoni van Leeuwenhoek ziekenhuis te Amsterdam. In dit cohort werd ook de predictieve impact van een lage skeletspiermassa op de dosis-limiterende toxiciteit van cisplatinum onderzocht. Een vergelijkbaar percentage van de patiënten (54,9%) werd gediagnosticeerd met een lage skeletspiermassa. De voorgeschreven cumulatieve dosis cisplatinum bij chemoradiotherapie is 300 mg/m^2, voor dit cohort werd de dosis-limiterende toxiciteit van cisplatinum gedefinieerd als elke toxiciteit die resulteert in het ontvangen van een cumulatieve dosis cisplatinum van minder dan 200 mg/m^2. Op basis van deze definitie ervaarde 24,2% van de patiënten dosis-limiterende toxiciteit voor cisplatinum, dit percentage ligt lager dan het onderzoek gepresenteerd in Hoofdstuk 10, dit komt mede door een andere definitie van dosis-limiterende toxiciteit. Nochtans was ook in dit cohort een lage skeletspiermassa een significante voorspeller (HR 4,0, p <0,05) voor cisplatinum dosis-limiterende toxiciteit. Niet alle patiënten met een lokaal gevorderde tumor in het hoofd-halsgebied is fysiek in staat om concurrente cisplatinum-gebaseerde chemoradiotherapie te ondergaan, voornamelijk vanwege co-morbiditeit zoals vaatziekten en nieraandoeningen.

Hoofdstuk 12 presenteert daarom een studie bij 91 cisplatinum-ongeschikte patiënten die cetuximab-gebaseerde bioradiotherapie ondergingen om de predictieve impact van lage skeletspiermassa voor dosis-limiterende toxiciteit in deze groep patiënten met hoofd-hals plaveiselcelcarcinoom te evalueren. Een hoger percentage patiënten met een lage skeletspiermassa (74,7%) werd gevonden in deze studie vergeleken met de cisplatinum-fitte patiënten beschreven in Hoofdstuk 10 en 11 (respectievelijk 58% en 54,9%). Hoewel eerdere studies een predictieve impact van lage skeletspiermassa voor cisplatinum dosis-limiterende toxiciteit van cisplatinum toonden, kon geen predictieve impact van lage skeletspiermassa voor cetuximab dosis-limiterende toxiciteit (OR 0,83, p = 0,74) worden gevonden. Om de bevindingen in Hoofdstuk 10-12 te evalueren, werd een systematische review en meta-analyse uitgevoerd naar de predictieve impact van lage skeletspiermassa op de toxiciteit van oncolytica bij alle soorten

tumoren (hoofd-halskanker en niet-hoofd-halskanker), dit onderzoek wordt gepresenteerd in **Hoofdstuk 13**.

In totaal werden 31 studies geïncludeerd in de systematische review, de steekproefomvang varieerde van 21 tot 414 patiënten en de prevalentie van lage skeletspiermassa varieerde van 12,2% tot 89,0%. Het meeste onderzoek naar lage skeletspiermassa en toxiciteit van oncolytica bij kanker werd uitgevoerd bij slokdarmkanker, nierkanker, colorectale kanker, borstkanker en hoofd-halskanker. Patiënten met een lage skeletspiermassa hadden een hoger risico op ernstige toxiciteit (OR 4,08, p <0,001) en dosis-limiterende toxiciteit (OR 2,24, p <0,001) in vergelijking met patiënten zonder lage skeletspiermassa. Dit toont aan dat de predictieve waarde van een lage skeletspiermassa voor toxiciteit van oncolytica bij kanker kan worden waargenomen bij alle soorten kanker. Het mechanisme waarom een lage skeletspiermassa in verband wordt gebracht met het optreden van dosis-limiterende toxiciteit van cisplatinum bij patiënten met hoofd-halskanker die chemoradiotherapie ondergaan, is onbekend. Een hypothese voor dit fenomeen is dat de farmacokinetiek van cisplatinum verandert door het veranderde distributievolume bij patiënten met een lage skeletspiermassa en een normale tot hoge vetweefselmassa. Cisplatinum is een hydrofiel chemotherapeutisch middel en verdeeld zich in het lichaam met name over de vetvrije lichaamsmassa, waarvan de skeletspiermassa de grootste component is.[5–7] Cisplatinum wordt op dit moment gedoseerd op de lichaamsoppervlakte van een patiënt en houdt geen rekening met de individuele lichaamssamenstelling.[8,9] Hypothetisch gezien wordt daarom aangenomen dat patiënten met een lage skeletspiermassa en een normale of hoge vetweefselmassa in feite een relatief hoge dosis cisplatinum zouden kunnen krijgen als er gedoseerd wordt op lichaamsoppervlakte. Gegevens over de relatie tussen lichaamssamenstelling en farmacokinetische eigenschappen van cisplatinum waren tot dusver niet beschikbaar. Daarom is het onderzoek verricht dat in **Hoofdstuk 14** werd gepresenteerd. Het onderzoek betreft de prospectieve observationele PLATISMA-studie uitgevoerd bij 45 patiënten met lokaal gevorderd hoofd-halskanker, waarbij de skeletspiermassa van de patiënten werd gemeten voorafgaand aan de behandeling en de cisplatinum bloedspiegels werden gemeten tijdens de eerste behandelingscyclus. Een farmacokinetische analyse werd uitgevoerd om de relatie tussen de farmacokinetiek van cisplatinum en skeletspiermassa te beoordelen. Zoals werd verondersteld, werd een significante relatie gevonden tussen de farmacokinetiek van cisplatinum en skeletspiermassa. Er werd ook een relatie gezien tussen de farmacokinetiek van cisplatinum en lichaamsgewicht, het lichaamsgewicht wordt meegenomen in de berekening van de dosering op basis van lichaamsoppervlakte. Verdere studies zijn nodig om te beoordelen of de dosering van cisplatinum op basis van skeletspiermassa superieur is aan dosering op basis van lichaamsoppervlakte met betrekking tot het optreden van toxiciteit en algehele en ziektevrije overleving. Naast de rol van skeletspiermassa bij de toxiciteit van cisplatinum wordt aangenomen dat cisplatinum zelf ook spierverlies veroorzaakt.

Daarom presenteert **Hoofdstuk 15** een onderzoek uitgevoerd bij 235 patiënten met lokaal gevorderd hoofd-halskanker die cisplatinum-gebaseerde chemoradiotherapie ondergingen om de patronen, voorspellers en prognostische waarde van skeletspiermassa verlies na be-

handeling te onderzoeken. De skeletspiermassa werd gemeten op beeldvorming vóór en na chemoradiotherapie. Skeletspiermassa oppervlakte was significant lager dan voor de behandeling (31,62 cm^2 versus 33,34 cm^2, p <0,01). De meerderheid van de patiënten (54,9%) ervoer een matig verlies van skeletspiermassa, 38,7% had stabiele veranderingen in skeletspiermassa, 13% had een matige toename van skeletspiermassa, 0,4% had een grote toename van skeletspiermassa en slechts 0,4% had een groot verlies van skeletspiermassa. Significante voorspellende factoren voor verlies van skeletspiermassa na behandeling waren overgewicht of obesitas (respectievelijk HR 1,75, p <0,05 en HR 1,80, p <0,05) en een tumor in de orofarynx (HR 1,85, p <0,05). Patiënten met een ECOG-performance status van 1(symptomatisch, maar ambulant) (HR 0,62, p <0,05), die werden behandeld met chemoradiotherapie in een postoperatieve setting (HR 0,55, p <0,02) en die in staat waren om een absolute cumulatieve dosis van cisplatinum ≥ 300 mg (HR 0,57, p <0,05) te ontvangen, hadden significant minder kans op verlies van skeletspiermassa na behandeling. Lage skeletspiermassa bij diagnose of verlies van skeletspiermassa na behandeling waren niet prognostisch voor algehele of ziektevrije overleving. Aangezien de incidentie van orofaryngeale tumoren toeneemt als gevolg van de toename van besmettingen met het seksueel overdraagbare humaan papillomavirus, wordt in dit proefschrift ook onderzoek gepresenteerd naar de rol van skeletspiermassa bij patiënten met oropharynxcarcinoom. **Hoofdstuk 16** presenteert een onderzoek verricht bij 216 patiënten met orofaryngeaal plaveiselcelcarcinoom en onderzocht de prognostische impact van een lage skeletspiermassa. Bij deze patiënten werd een groot percentage lage skeletspiermassa (64,8%) gevonden. De prognostische impact van sarcopene obesitas werd geëvalueerd, de combinatie van een lage skeletspiermassa en obesitas. Zes procent van de patiënten werd geïdentificeerd met sarcopene obesitas. Sarcopene obesitas was geassocieerd met een verminderde algehele overleving (HR 4,42, p <0,05) en ziektevrije overleving (HR 3,90, p <0,05), onafhankelijk van andere bekende sterk prognostische factoren zoals een HPV-positieve tumor. **Hoofdstuk 17** presenteert een prospectieve observationele studie bij 108 patiënten met lokaal gevorderd oropharynxcarcinoom waarbij onder andere de impact van een lage skeletspiermassa op de functionele uitkomsten gedurende het eerste jaar na bestraling werd onderzocht. Slikfunctie, mondopening en spraakfunctie werden verzameld vóór behandeling en na zes en twaalf maanden follow-up. De objectieve en door de patiënt ervaren functie verslechterde tot zes maanden en verbeterde tot twaalf maanden na de behandeling. De functionele uitkomsten keerden echter niet terug naar de uitgangswaarden, van de geïncludeerde patiënten hadden respectievelijk 25%, 20% en 58% objectieve dysfagie, trismus en spraakproblemen. Van de geïncludeerde patiënten had 45% bij diagnose een lage skeletspiermassa. Na zes maanden hadden patiënten met een lage skeletspiermassa significant vaker een aangepast dieet en hogere scores op de totale slikkwaliteit (SWAL-QOL), wat duidt op meer slikproblemen, vergeleken met patiënten zonder een lage skeletspiermassa.

Naast een lage skeletspiermassa die wordt gezien bij patiënten met kanker, ook wel secundaire sarcopenie genoemd, neemt de spiermassa geleidelijk af naarmate de leeftijd toeneemt. Lage skeletspiermassa bij oudere mensen, veroorzaakt door het verouderingsproces, wordt ook wel primaire sarcopenie genoemd. Vanwege de vergrijzing behandelen clinici meer oudere

patiënten met kanker. De ouderenpopulatie met hoofd-halskanker zal de komende jaren geleidelijk aan groeien. Daarom werd in **Deel IV** van dit proefschrift onderzoeken gepresenteerd die werden uitgevoerd betreffende een lage skeletspiermassa bij oudere hoofd-halskankerpatiënten. **Hoofdstuk 18** presenteert een onderzoek dat is uitgevoerd bij 85 oudere patiënten (≥70 jaar) met hoofd-halsplaveiselcelcarcinoom. Eerder onderzoek bij ouderen toonde aan dat de correlatie tussen skeletspiermassa en spierkracht matig tot zwak is en de relatie tussen spierkracht en spiermassa niet-lineair is.[10,11] Daarom heeft de 'European working group on sarcopenia in older people' (EWGSOP) geadviseerd om sarcopenie bij oudere patiënten te diagnosticeren op basis van de aanwezigheid van een combinatie van lage spiermassa en lage spierfunctie (spierkracht of spierprestatie).[12] In dit onderzoek werd de prognostische impact onderzocht van lage skeletspiermassa, lage spierfunctie en sarcopenie gedefinieerd volgens de EWGSOP. Van de 85 geïncludeerde patiënten had 48,2% zowel een lage spiermassa als spierfunctie. Alleen een lage skeletspiermassa of een lage spierfunctie was niet prognostisch voor de algehele overleving. Patiënten met zowel een lage skeletspiermassa als een lage spierfunctie (definitie van sarcopenie door EWGSOP) hadden echter een significant verminderde algehele overleving vergeleken met patiënten zonder sarcopenie (12,07 maanden versus 13,60 maanden, HR 2,80, p <0,05). De 3-jaars overleving was significant korter voor ouderen met sarcopenie in vergelijking met oudere patiënten zonder sarcopenie (39% versus 75%, p <0,05). **Hoofdstuk 19** presenteert een onderzoek uitgevoerd bij 150 oudere patiënten met hoofd-halskanker (≥ 60 jaar). Oudere patiënten lopen zowel risico op sarcopenie als frailty (kwetsbaarheid). Beide houden verband met ongunstige resultaten. Zoals eerder vermeld, wordt sarcopenie bij ouderen gemeten door zowel skeletspiermassa als spierfunctie (spierkracht of spierprestatie). Frailty wordt gescreend met behulp van de G8-vragenlijst en gediagnosticeerd door een tijdrovende en uitgebreide geriatrische beoordeling; de 'comprehensive geriatric assessment' (CGA) genoemd.[13] In dit onderzoek is onderzocht of sarcopenie een biomarker is voor frailty. Patiënten met frailty in dit onderzoek hadden significant vaker sarcopenie (p <0,05). Multivariate regressieanalyse toonde aan dat comorbiditeit (OR 5,5, p <0,01) en SMI (OR 0,9, p <0,01) significant voorspellers waren voor frailty. Leeftijd (OR 3,7, p <0,05) en de G8 score (OR 3,7, p <0,05) waren significante voorspellers voor sarcopenie. De beoordeling van de skeletspiermassa kan derhalve worden gebruikt als een alternatief screeningsinstrument voor de G8-vragenlijst ter screening van frailty, d.w.z. in het selecteren van patiënten die een tijdrovende CGA daadwerkelijk nodig hebben. **Hoofdstuk 20** presenteert een studie uitgevoerd bij 73 oudere hoofd-halskankerpatiënten (≥70 jaar) om de associatie tussen sarcopenie (lage spiermassa en spierfunctie) en een uitgebreide geriatrische beoordeling (CGA) te onderzoeken. Patiënten met frailty gediagnosticeerd door de CGA hadden meer kans op een lage skeletspiermassa en hadden vaker sarcopenie bij de diagnose. Multivariate regressieanalyse met frailty gediagnosticeerd door CGA als afhankelijke variabele onderscheidde SMI als een significante voorspeller van frailty (OR 0,89, p <0,05). Skeletspiermassa kan relatief snel en gemakkelijk bepaald worden en kan daarmee mogelijk als alternatief dienen voor bepaalde CGA-domeinen in het diagnosticeren van frailty. Deze bevindingen zouden echter eerst moeten worden gevalideerd in een grotere, prospectieve cohortstudie.

CONCLUSIE

Concluderend, bij patiënten met hoofd-halskanker is een lage skeletspiermassa een prevalent probleem dat voorkomt bij ongeveer 55% van de patiënten. Skeletspiermassa kan eenvoudig worden gemeten op een 'single-slide' op het niveau van C3 (of L3) op CT- of MRI-scans die reeds routinematig worden uitgevoerd voor de diagnose van hoofd-halskanker en de evaluatie van de behandeling. Skeletspiermassa is een veelbelovende biomarker die negatieve behandeluitkomsten voorspelt in verschillende behandelingsstrategieën die worden toegepast bij de behandeling van hoofd-halskanker. Naast negatieve behandelingsresultaten is een lage skeletspiermassa ook prognostisch gebleken voor een verminderde overleving.

Op basis van de resultaten van dit proefschrift is te veronderstellen dat verbetering van de skeletspiermassa status middels multimodale prehabilitatie voorafgaand aan de behandeling zal leiden tot een verbeterd hersteltraject met verminderde operatieve complicaties bij operatief behandelde patiënten en tot verminderde dosis-limiterende toxiciteit bij patiënten behandeld met (chemo- of bio)radiotherapie. Multimodale prehabilitatie zal mogelijk ook leiden tot een kortere opnameduur, lagere kosten voor gezondheidszorg en een betere kwaliteit van leven. Bovendien is pre-habilitatie een kans om de empowerment van de patiënt te bevorderen, wat de autonomie en het zelfmanagement van de patiënt vergroot. Dit kan bijdragen aan een verbeterde kwaliteit van leven vóór de behandeling en kan een positieve invloed hebben op de gezondheid op lange termijn. In de toekomst dient een prospectief gerandomiseerde gecontroleerde studie uitgevoerd te worden om het effect van een multimodaal prehabilitatieprogramma bestaande uit lichaamsbeweging, voedingsondersteuning en psychologische ondersteuning te vergelijken met de gebruikelijke zorg op de behandelresultaten en prognose voor patiënten met hoofd-halskanker, in het bijzonder voor de patiënten met lage skeletspiermassa.

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ABOUT THE AUTHOR

Najiba Chargi was born on the 8th of July 1991 in Nijmegen, the Netherlands. After graduating from secondary school in 2009 (SSGN, Nijmegen), she started both Medical school (Radboud University, Nijmegen) and Pharmacy school (University of Utrecht, Utrecht). She graduated as a medical doctor in 2016 and as a pharmacist in 2019. After medical school, she started as a surgical resident not in training at the Maasziekenhuis Pantein, Boxmeer. She also worked as a resident not in training at the emergency department of this hospital. Besides her work as a resident not in training, she worked as a University teacher at the Health Academy of the Radboud University Medical Center in Nijmegen where she participated in the Dutch Clinical Skills Assessment (DCSA) for international medical graduates and in clinical skills teaching for medical students and physician assistants.

In July 2018, she started as a PhD-student at the Department of Head and Neck Surgical Oncology at the University Medical Center Utrecht under supervision of prof. dr. R. de Bree and dr. L.A. Devriese. She focused her research on the predictive and prognostic impact of low skeletal muscle mass on treatment outcomes in head and neck cancer patients. She supervised several students during their scientific internships and gave several presentations at national and international congresses. She went abroad for several months for a research fellowship to investigate the role of low skeletal muscle mass in patients undergoing reconstructive flap surgery under supervision of mr. S. Parmar at the Department of Oral and Maxillofacial Surgery of the Queen Elizabeth Hospital in Birmingham, the United Kingdom.

In June 2020, she started as an Oral and Maxillofacial resident not in training at the Radboud University Medical Center in Nijmegen and in September 2020 she started Dental school for medical doctors. Najiba will pursue her residency training for Oral and Maxillofacial Surgery at the Department of Oral and Maxillofacial Surgery at the Radboud University Medical Center in Nijmegen under supervision of prof. dr. S.J. Bergé and dr. M.E.L. Nienhuijs.

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