Head and neck cancer cachexia

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A MULTIDIMENSIONAL APPROACH

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DISSERTATION

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TABLE OF CONTENTS

CHAPTER 1
GENERAL INTRODUCTION

The head and neck region is involved in the most valued activities of a human life; e.g. communicating, eating, drinking, showing emotions, intimacy, listening, talking, singing, and smelling. Any irregularities in this region can greatly affect our appearance, the way we talk and our interactions with other people. Head and neck cancer is a relatively rare but no less serious disease, which affects a patient's life beyond these valued activities.

In 2020, over 900.000 head and neck cancer cases were registered globally, from which over 3000 cases were reported in the Netherlands. [1][2] The majority of the malignant tumors are squamous cell carcinoma's, covering over 90% of all tumors of the head and neck. The incidence of head and neck cancer increases with age, and the prevalence is three to four times higher in men compared to women. [3]

Tumor locations include the oral cavity, oropharynx, hypopharynx, larynx and less frequently nasopharynx, paranasal sinuses, and salivary glands. (Figure 1).

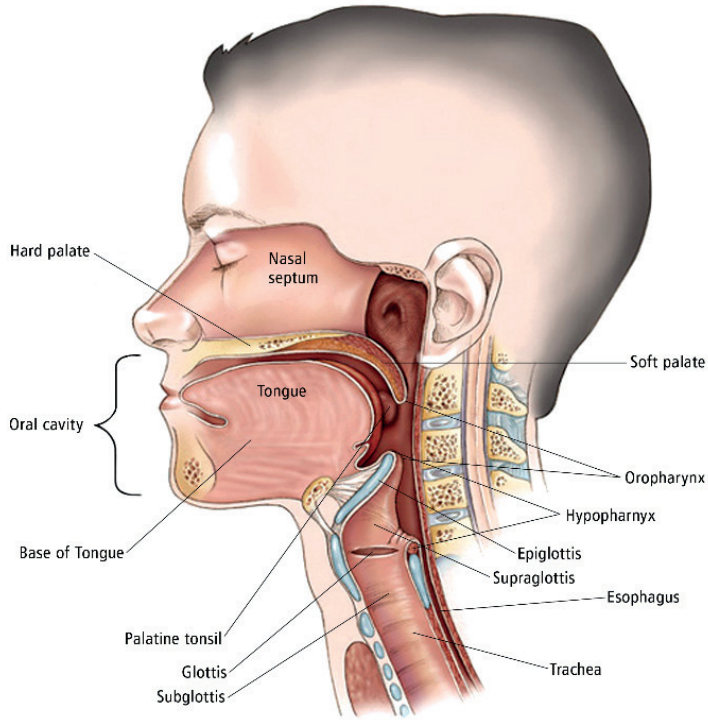

Figure 1 – Anatomy of the head and neck [85]

Excessive tobacco smoking and alcohol use are risk factors for the development of head and neck cancer. [4-6] Tobacco and alcohol-related tumors often occur in men aged over 60 with a vulnerable socioeconomic status. [7, 8] Another risk factor for the development of head and neck cancer is a sexually transmitted infection with human papilloma virus (HPV). [9, 10] HPV typically causes tumors originating from the tonsils or tongue base, referred to as subsites of the oropharynx. Where a small decrease in tobacco and alcohol-related tumors has been observed, the incidence of HPV-related oropharyngeal tumors has risen over the past decades. Between 1990 and 2020, the number of oropharyngeal carcinomas in the Netherlands increased from slightly over 250 to nearly 700 cases. [1] This has been attributed to an increase of HPV-related tumors.

Patients with HPV-related oropharyngeal carcinomas are often aged below 60, have a higher socioeconomic status, and have a better prognosis. [8] The second viral infection that may cause malignant tumors in the head and neck region is the infection with the Epstein Barr Virus (EBV). EBV-related tumors are typically located in the nasopharynx and have a higher incidence in non-western countries. [11]

Molecular features of head and neck squamous cell carcinoma subtypes

HPV-related tumors

HPV infects the host cell and uses its replication machinery causing viral gene amplification in the host's genome. High-risk HPV type 16 and 18 may cause cancerous growth through their expression of E6 and E7 oncogenes. E6 increases the turnover of p53, while E7 proteins bind to the tumor suppressor gene retinoplastoma (pRb), leading to uncontrolled cellular proliferation. [12] HPV-related tumors often express wild-type p53, have an upregulation of p16 and a downregulation of pRb.

HPV-negative tumors

HPV-negative tumors, primarily caused by excessive alcohol and tobacco abuse, contain a higher mutational load compared to HPV-related tumors and are considered more complex. In HPV-negative tumors, p53 mutations are typical and highly frequent (over 80%), accompanied by a decrease in p16 and an increase in pRb. [13, 14] Patients with p53 mutant tumors showed worse survival outcomes and therapy resistance compared to wild-type p53. [14]

HPV-related tumors in patients with a history of alcohol and tobacco abuse present the most complex pathogenesis. Moreover, the favorable biologic characteristics of an HPV-related tumor may be affected by tobacco exposure, as the risk of death in patients having a HPV-related tumor significantly increased with each additional pack-year of tobacco smoking. [15]

Malignant head and neck tumors can continue to grow by evading immunosurveillance. This evasion occurs through loss or downregulation of human leucocyte antigens (HLA) expression, impaired recognition of cancer cells by T-cells and activation of mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3) and Wnt/β-catenin signaling pathways. [12] The lack of tumor-infiltrating lymphocytes (CD3+ and CD8+ T-cells) in the tumor microenvironment is associated with worse overall survival. [16]

Tumor staging

Malignant tumors of the head and neck are staged according to the tumor-nodes-metastasis (TNM) classification. In 2017, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) published their 8th edition. [17-19] This classification system describing the size of the original tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastasis (M) is used to predict outcome. Due to the inadequacy of TNM-7 for HPV-related oropharyngeal tumors, the TNM-7 has been updated to TNM-8 and put into practice in 2018. [17, 18] A separate grading system has been made to stage HPV-related oropharyngeal tumors, with these tumors now being graded lower than in the TNM-7 as HPV-related tumors have a better prognosis compared to HPV-negative tumors. [20]

Diagnostic trajectory

The early symptoms of head and neck cancer include, amongst others, ulcers of the oral mucosa, a sore throat, hoarseness, swallowing problems, neck lumps, or a congested nose. The majority of these symptoms are not immediately linked to head and neck cancer by both patients and general practitioner. This may lead to a diagnostic delay, causing most patients to present with advanced tumor stages. [21]

In the Netherlands, eight head and neck cancer centers offer an outpatient clinic with a rapid diagnostic trajectory. [22] Within a few days, patients undergo

several diagnostic procedures, followed by an interdisciplinary meeting in which the otorhinolaryngologists, oral and maxillofacial surgeons, radiation oncologists, radiologists, pathologists, oncology nurses, and medical oncologists discuss the optimal treatment strategies for every individual. The diagnostics include imaging of the tumor, regional, and distant metastasis using ultrasound, computed tomography (CT) with or without positron emission tomography (PET), and magnetic resonance imaging (MRI) according to tumor site-specific protocols of the Dutch clinical practice guidelines for head-and-neck cancer. [23] A panendoscopy under local or general anesthesia is performed to determine the operability of the tumor (in case of an indication for upfront surgery or salvage surgery) and to obtain biopsies for histopathology.

This rapid diagnostic trajectory is developed to reduce the period of uncertainty for the patient and to limit the time frame in which the tumor can continue to grow due to delayed initiation of treatment. At the same time, this trajectory is also experienced as overwhelming and intense by patients almost like being on a roller coaster. Patients have a high level of psychological distress and are usually swept off their feet during the period of diagnosis. [24]

Chemoradiotherapy or bioradiotherapy of head and neck cancer

Small, localized tumors can be treated with monomodality treatment including several surgical procedures or radiotherapy. In case of locally advanced head and neck squamous cell carcinoma (LAHNSCC) (stage III-IV), a multimodal approach, including upfront radiotherapy and concurrent systemic therapy is recommended in an attempt to achieve curation in selected patients. [25]

In case of an indication for upfront concurrent chemoradiotherapy, cisplatin-based chemotherapy is regarded as standard of care for patients aged below 70 years, based on studies dating from before 2009. [26] In patients above the age of 70, no added value was found for concurrent systemic therapy to radiotherapy. Cisplatin is administered in three-weekly doses of 100 mg/m^2 (day 1, 22, and 43) or in one-weekly doses of 40 mg/m^2, during a six to seven-week period of radiotherapy. The minimal cumulative cisplatin dose for optimal efficacy is 200mg/m^2. [27] In case of contra-indications for cisplatin administration (e.g., cardiovascular or renal disease, neuropathy or hearing impairment), systemic therapy consists of carboplatin weekly

(various dosing strategies) [28, 29] or cetuximab 250mg/m^2 weekly, preceded by a loading dose of 400mg/m^2 one week before start of radiotherapy (bioradiotherapy). [30] Recent studies have showed that cetuximab is inferior to cisplatin in case of a curative chemoradiotherapy regimen for HPV-related tumors. [31] Therefore, in patients with HPV-related tumors and contra-indications for cisplatin, carboplatin is currently considered the best alternative, based on previous studies demonstrating the additional value of concurrent carboplatin with radiotherapy. [29] In the adjuvant setting, there is only evidence for platinum-based chemoradiotherapy in case of extranodal extension or irradical (R1) resection margins. [32]

Radiotherapy is applied using intensity-modulated radiotherapy (IMRT) or proton therapy. For primary upfront platinum-based chemoradiotherapy, radiotherapy is applied five times per week for seven weeks, in 35 fractions of 2 Gy daily to a total dose of 70 Gy. Patients on cetuximab are scheduled for 30 fractions of 2.3 Gy daily to a total dose of 69 Gy or accelerated fractionated radiotherapy twice daily in the final week of IMRT with a total dose of 68 Gy in 34 fractions. Patients undergoing adjuvant chemoradiotherapy receive a total dose of 66 Gy in 33 fractions concurrent with cisplatin or carboplatin.

Chemoradiotherapy and bioradiotherapy may induce severe toxicity affecting among others, the patient's oral intake. Frequent side effects include mucositis, dry mouth (xerostomia), dysphagia, oral pain, nausea, and vomiting. Despite the current use of analgesics and the medicinal management of nausea and vomiting, it remains challenging for patients to maintain sufficient oral nutritional intake during therapy. [33] Maintenance and/or optimization of nutritional status is important, because malnutrition may lead to muscle wasting, complications of wound healing, and suboptimal immune responses. [34] Early anticipation of the need for tube feeding through insertion of a prophylactic gastrostomy could prevent further decline in weight and physical condition. Prophylactic gastrostomy insertion used to be part of standard care in head and neck cancer patients undergoing chemoradiotherapy but has been updated in the recommendation list of the national clinical practice guidelines for head and neck cancer. [23] Data showed that approximately one-third of the prophylactically inserted tubes remained unused, [35, 36] and several studies suggested potential long-term swallowing dysfunction due to the "use it or lose it" principle, although current literature remained controversial about the latter. [37, 38] As a result, prophylactic gastrostomy insertion is recommended upon indication only. [23] However,

selection criteria have not yet been specified and therefore it remains difficult to predict which patients will become tube feeding dependent.

Treatment of recurrent or metastatic head and neck cancer

A small portion of patients with recurrent or metastatic head and neck cancer can be treated with curative intent. Unfortunately, the majority of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) has a poor prognosis and these patients are facing palliative treatment. In 2011, the United States Food and Drug Administration (FDA) approved cetuximab in combination with 5-fluorouracil (5-FU) and cisplatin or carboplatin for the treatment of patients with recurrent or metastatic HNSCC. [39] The treatment with platinum-5FU-cetuximab, also known as the EXTREME regimen, leads to a median overall survival ranging between 10 and 14 months. [39] More recently, a promising new treatment option has made its entrance: immune checkpoint inhibitors (ICI). Two ICI's, nivolumab and pembrolizumab, are currently approved by the FDA and European Medicines Agency (EMA) for recurrent or metastatic HNSCC. [40-42]

Nivolumab and pembrolizumab bind to the programmed death-1-receptor (PD1-receptor), preventing the interaction between the PD1-receptor and the ligands PD-L1 and PD-L2. These ligands can be expressed in tumors or other cells in the microenvironment of the tumor. Binding of PD-L1 and PD-L2 to PD-1 inhibits T-cell proliferation and the secretion of cytokines. Blocking the PD1-receptor by nivolumab and pembrolizumab allows for T-cell response and activation, including anti-tumor response.

PD-L1 expression in the tumor microenvironment has therefore become a predictive marker for treatment response. PD-L1 expression is calculated through the combined positive score (CPS): the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Based on the Keynote-048 study, [40] pembrolizumab is now registered as first line monotherapy in patients with recurrent and/or metastatic HNSCC, in case of PD-L1 CPS $\geq$ 20 and in combination with platinum and 5-FU for PD-L1 CPS 1-20. For patients without PD-L1 expression, chemotherapy in combination with cetuximab remains standard of care. Nivolumab is available as treatment for patients with platinum resistant HNSCC, defined as tumor progression during or within six months after finalizing a cisplatin-containing chemotherapy schedule.

Nevertheless, despite the introduction of the predictive biomarker PD-L1 CPS, the response rates for ICI are relatively low in recurrent and/or metastatic HNSCC. [43] Few patients reach complete remission of disease and may continue this treatment for years, while others do not respond to ICI at all. Despite PD-L1 CPS, it remains challenging to predict which patients will benefit from ICI treatment. Therefore, additional biomarkers and more in-depth patient and tumor characterization are needed for adequate patient selection and to ultimately improve treatment outcome.

When HNSCC's become resistant to ICI treatment, further treatment options are limited. Clinical trials using novel immune modulators (e.g., monalizumab, NCT04590963) are currently ongoing. Additionally, next generation sequencing (NGS) analysis of tumor tissue allows the identification of druggable targets and the inclusion into clinical trials (e.g., Drug rediscovery protocol (DRUP) study, NCT02925234) with targeted therapies. [44]

Cancer Cachexia

A malignant tumor in the head and neck region can be very mutilating and may lead to various functional impairments. In addition, paraneoplastic phenomena, such as cancer cachexia, may also have detrimental effects on clinical outcome and health-related quality of life. In many cancer types, cancer cachexia has been associated with a higher risk of treatment complications and worse overall survival. [45-47] The prevalence of cancer-associated cachexia differs per tumor type. [48] In head and neck cancer, the prevalence of cachexia is high and on average 55%, depending on tumor stage and location.

Key features of cancer cachexia include involuntary loss of body weight, skeletal muscle wasting, functional impairment, reduced oral food intake and systemic inflammation. The definition and classification of cancer cachexia was established in an international consensus statement. [46] A patient is considered cachectic when he/she experiences more than 5% loss of body weight or has a body mass index (BMI) below 20 kg/m^2 and more than 2% weight loss, or sarcopenia and ongoing weight loss of more than 2%. [46] Sarcopenia, literally translated as "flesh" (sarx) "poverty" (penia), is the condition of muscle mass loss, and was first described in the process of aging only (primary sarcopenia). Muscle mass loss in cancer and other chronic diseases is referred to as secondary sarcopenia.

Evaluation of muscle mass and muscle strength

The identification of the different tissue compartments contributing to weight loss can lead to further understanding of the pathophysiology of cancer cachexia. Body weight can be easily assessed using a weighing scale but assessment of body composition requires additional measurement tools. Whole-body MRI allows precise evaluation of regional muscle, whole-body muscle, and adipose tissue, but is expensive and time-consuming. CT and dual energy X-ray absorptiometry (DEXA) are more accessible tools for body composition measurement in scientific research and clinical practice. [49] Tissue delineation on a cross sectional slide in the axial plane of CT-scans is frequently used and validated for the level of the third lumbar vertebrae (L3). [50] However, L3 is only visible on abdominal CT-scans, which are not part of standard diagnostics for head and neck cancer. Swartz et al. showed a good correlation between skeletal muscle mass at the level of the third cervical vertebra (C3) and L3. [51] However, reliable measurements of skeletal muscle mass at C3 are challenging as tumors might extend into the surrounding prevertebral tissue, and treatment (surgery or (chemo)radiotherapy) may alter the anatomical structures. Additionally, evaluation of visceral adipose tissue cannot be performed at this level and external validation of the described C3 method yielded negative results. [52, 53] As a result, there is a demand for body composition measurements that are either applicable to already available imaging in the context of diagnostics, or that are easy to implement in daily clinical practice. Next to clinical CT-scan-based measurements of body composition, it would be of interest to evaluate the added value of bioelectrical impedance analysis (BIA) to measure the fat and fat-free mass as this is a relatively cheap and easy measurement technique with low burden for the patient. By placing skin electrodes on the hand and foot, BIA measures the resistance that the body offers to an alternating current at 50 kHz. The fat-free mass is subsequently calculated using a formula, in which next to resistance, weight, gender, and age are included. [54]

According to the new consensus on sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP), the diagnosis of sarcopenia is confirmed when low skeletal muscle mass is combined with low skeletal muscle performance. [55] Thus, information on both aspects (muscle mass and function) are required to diagnose sarcopenia in the clinic.

Biodex is an advanced dynamometer that can accurately test strength and endurance of arm and leg muscles. [56] Nevertheless, it is a fixed device of

considerable size and relatively expensive. Therefore, more manageable methods of measuring skeletal muscle strength in clinical practice would be convenient, such as handgrip strength (HGS) using a handheld dynamometer and the short physical performance battery (SPPB) to evaluate lower extremity function. [57] HGS has shown prognostic value in several cancer populations and the SPPB has proven its value in the elderly population. [58-61] The prognostic and predictive value of HGS and SPPB in head and neck cancer patients is underexplored.

Pathophysiology of cancer cachexia

Due to its multifactorial cause, cancer cachexia is a complex wasting syndrome. Both clinical and fundamental research are needed to unravel its pathophysiology. The key mechanisms include an imbalance between energy intake and energy expenditure, an imbalance between protein synthesis and protein breakdown, impaired skeletal muscle regeneration, and potentially also an altered cellular energy metabolism. [46, 48, 62] Next to direct effects of increased systemic inflammation on muscle tissue, there is emerging evidence pointing towards a role for the central nervous system affecting dietary intake regulation. [63]

Cancer-related changes in energy and protein metabolism are merely attributed to the effect of tumor-secreted or tumor-induced factors including pro-inflammatory cytokines (i.e., IL-1α, IL-1β, IL-6, interferon γ, and tumor necrosis factor (TNF)) and catabolic factors (i.e. Activins, myostatin, and tumor growth factor β (TGFβ)).

A key player in the process of inflammation is nuclear factor kappa B (NF-κB), which regulates the innate immune cells and T-cells and may be seen as a mediator of inflammatory cytokines. [64] Well studied pro-inflammatory factors produced by the tumor, tumor microenvironment and cells of the immune system include several interleukins (i.e., IL-1 and IL-6) and other cytokines such as TNF and IFNγ. [65] These mediators directly affect skeletal muscle cells through activation of the ubiquitin-proteasome pathway and autophagy systems, leading to selective destruction of myofibrillar proteins. These proteins play an important role in the development of sarcomeres and the provision of contractile function of the skeletal muscles. Consequently, disruption of these systems may lead to muscle atrophy and decreased muscle function. [66]

Furthermore, pro-inflammatory cytokines (i.e., IL-6 and TNF-α) have a marked effect on the lipid metabolism through the induction of lipolysis and glucose homeostasis.

[67] Lipolysis may fuel tumor growth and alterations in lipid-metabolic pathways have been associated with disease progression and metastasis in other cancers. [68] The mechanisms through which cytokines affect adipose tissue and vice versa are currently underexplored.

Besides cancer-induced skeletal muscle wasting, treatment, especially chemotherapy is known to affect the host metabolism and skeletal muscle maintenance. [69-71] A prospective exploratory study in HNSCC patients undergoing chemoradiotherapy showed a significant increase of systemic IL-1β, IL-6, and IL-10 (anti-inflammatory) at 7 weeks after treatment initiation as compared to baseline. Higher cytokine levels were associated with recurrent disease. [72] Cisplatin, the first chemotherapy of choice in LAHNSCC, has been shown to induce muscle wasting through increased oxidative stress, mitochondrial damage, and protein degradation (through an altered ubiquitin proteasome system and disturbed autophagy). [73] However, weight loss does not occur in every single patient treated with chemoradiotherapy. [74] Possibly, the host metabolism reacts or interacts differently with cisplatin metabolites, leading to divergent individual inflammatory and catabolic responses. The direct effects of cisplatin on muscle cells in the presence of cancer patient-specific circulating factors have never been evaluated.

Identification of circulating factors contributing to muscle wasting could eventually lead to the development of prognostic biomarkers and further optimization of patient-tailored treatment. Additionally, elucidating the underlying mechanisms of (chemotherapy-induced) muscle wasting could identify potential therapeutic targets for cancer cachexia.

Reduced oral food intake

In head and neck cancer, a reduced oral food intake occupies a large share in the process of weight loss. Both anorexia and functional challenges in eating impede the patients' oral intake. Anorexia may result from loss of appetite due to changes in smell (dysosmia or hyposmia) and taste (dysgeusia or hypogeusia), or because of the effects of pro-inflammatory cytokines on the central nervous system. [75] Cytokines may affect the hypothalamic axis, leading to disturbances in food intake mediators and sickness behavior. [75, 76] As a result, patients with systemic inflammation may experience a decreased appetite and limited oral intake.

In cancer patients undergoing chemotherapy, taste alterations are reported in approximately 20 to 70%. [77] In head and neck cancer, radiotherapy of the oral cavity and the taste buds may additionally worsen taste perception. Taste could be affected because of taste bud destruction, (C)RT-related xerostomia, and (C)RT-induced neuropathy of the facial nerve (cranial nerve VII) and the glossopharyngeal nerve (cranial nerve IX). A recent meta-analysis on taste dysfunction following radiotherapy of the head and neck reported acute taste dysfunction in approximately 96% of the patients. [78]

Oral intake of head and neck cancer patients is also threatened by the presence of oropharyngeal dysphagia (OD). Patients with hypopharyngeal and oropharyngeal tumors are most prone to develop OD due to the primary tumor site comprising crucial swallowing structures. [79] Additionally, early and late side effects of anti-cancer treatment such as mucositis, xerostomia, and fibrosis as a result of (chemo) radiotherapy may contribute to impaired swallowing function. [26, 80] Furthermore, anti-cancer treatment may affect the sensory-motor innervation and the anatomy of the swallowing apparatus, contributing to aspiration. [81]

The swallowing apparatus is a delicate organ composed of the multiple cranial nerves and muscles in the oral cavity, larynx, and pharynx. Except for the esophagus, the upper digestive tract is fully constructed of striated or skeletal muscle tissue. Therefore, it would be a logical hypothesis that the metabolic and inflammatory processes in cancer cachexia may also affect the muscles of the swallowing apparatus, creating a vicious circle. This aspect of cancer cachexia requires further investigation.

Evaluation of swallowing function

OD is a prevalent symptom in head and neck cancer patients that requires early detection, continuous monitoring during and after oncological therapy, and interdisciplinary treatment (i.e., nutritional intervention, speech and language therapy, dental restorations). [82, 83]

The Association of Community Cancer Centers published a guideline for the development of care pathways to standardize and optimally integrate multidisciplinary care for head and neck cancer. [84] In this document, baseline videofluoroscopic swallowing study (VFSS) or fiberoptic endoscopic evaluation of swallowing (FEES) is recommended in patients undergoing concurrent

chemoradiotherapy. A VFSS is a dynamic radiological imaging technique. The patient's upper aerodigestive tract is visualized using X-ray, while he or she processes barium-modified foods and liquids. This method provides direct visualization of bolus flow and structural movement during the oral preparatory, oral, pharyngeal, and upper esophageal stages of swallowing. [83] FEES allows the anatomical assessment of the pharynx and larynx and the evaluation of the pharyngeal phase of swallowing using transnasal flexible endoscopy. It provides an excellent visualization of the upper aerodigestive tract after surgery and/or (C)RT. FEES and VFSS are both well-established instruments for swallowing assessment each with different advantages and disadvantages providing complementary information. [83]

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CHAPTER 2
AIMS AND OUTLINE OF THIS THESIS

In case of an indication for upfront concurrent chemoradiotherapy, cisplatin-based chemotherapy is regarded as standard of care for patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) aged below 70 years. When salvage surgery is not an option after chemoradiotherapy (CRT), there is no alternative but palliative treatment. Therefore, it is of utmost importance to elucidate factors affecting the course of treatment and treatment outcome, so treatment can be tumor and patient tailored. Cancer cachexia has a large share in the prognosis of head and neck cancer. The overall aim of this thesis is to assess how weight loss and changes in body composition influence treatment outcome in head and neck cancer patients both in the curative and palliative setting, and to evaluate determinants of involuntary weight loss. (Figure 2)

The first section of this thesis sheds light on the multidimensional profiling of patients, using different methods of body composition evaluation in different settings (chapter 3-5). The second section includes studies on factors influencing oral intake and optimization of nutritional management (chapter 6-9).

In **chapter 3** we investigate the body composition of head and neck cancer patients starting CRT or bioradiotherapy (BRT), using bioelectrical impedance analysis (BIA). We evaluate the prognostic and predictive value of a low fat-free mass index on treatment outcome, including dose limiting toxicity, hospital admissions, and overall survival. In a subset of patients, we also explore body composition changes during treatment. This provides insight in the composition of weight loss and the effect of nutritional interventions with tube feeding hereon.

To gain insight in the potential underlying mechanisms of involuntary weight loss during treatment, a comparison of body compositional changes is made between LAHNSCC and non-small cell lung carcinoma (NSCLC) patients in **chapter 4**. NSCLC and LAHNSCC patients share similar risk factors such as smoking and receive comparable treatment regimen, but the clinical differences including tumor size, location, and challenges in oral intake may provide additional insights in understanding the pathophysiology of weight loss.

While previous chapters describe patterns of weight loss in head and neck cancer patients undergoing curative treatment, **chapter 5** focusses on the predictive and prognostic value of weight loss during palliative immune checkpoint inhibitor (ICI) treatment. The mechanisms of action of chemotherapy and immunotherapy cannot be compared to each other, and may also affect body composition in a

different way. In this retrospective multicenter study, body composition is assessed at baseline and at first tumor evaluation through tissue delineation on the third lumbar level on computed tomography (CT) scans of patients treated with ICI monotherapy.

In the rapid diagnostic trajectory phase prior to radiotherapy, an important role is reserved for the dentist. Teeth and other dental remnants considered as potential foci of infection are extracted to prevent osteoradionecrosis of the mandible and maxilla, a rare but highly feared toxicity of radiotherapy. Tooth extractions may influence the patient's ability to masticate and swallow, subsequently leading to a decreased oral intake and weight loss. Therefore, in **chapter 6** we evaluate the effect of incomplete dentition and tooth extractions on weight loss during CRT or BRT and the need for tube feeding during CRT/BRT in a subset of patients with oropharyngeal carcinoma.

In **chapter 7** we investigate the relationship between cancer cachexia and patient-reported oropharyngeal dysphagia (OD) plus videofluoroscopic signs of dysphagia in head and neck cancer patients prior to CRT/BRT.

As described earlier, side effects of CRT/BRT may lead to tube feeding dependency in a subset of patients. Ideally, patients at risk of prolonged tube feeding are identified prior to treatment, so they can be provided with a gastrostomy before the onset of side effects potentially complicating insertion, (e.g. mucositis (painful insertion) and neutropenia (infection risk)), and prevent further weight loss due to a delay in tube feeding initiation. In **chapter 8 and 9** we develop and externally validate a prediction model to identify patients who would benefit from such a prophylactic gastrostomy insertion.

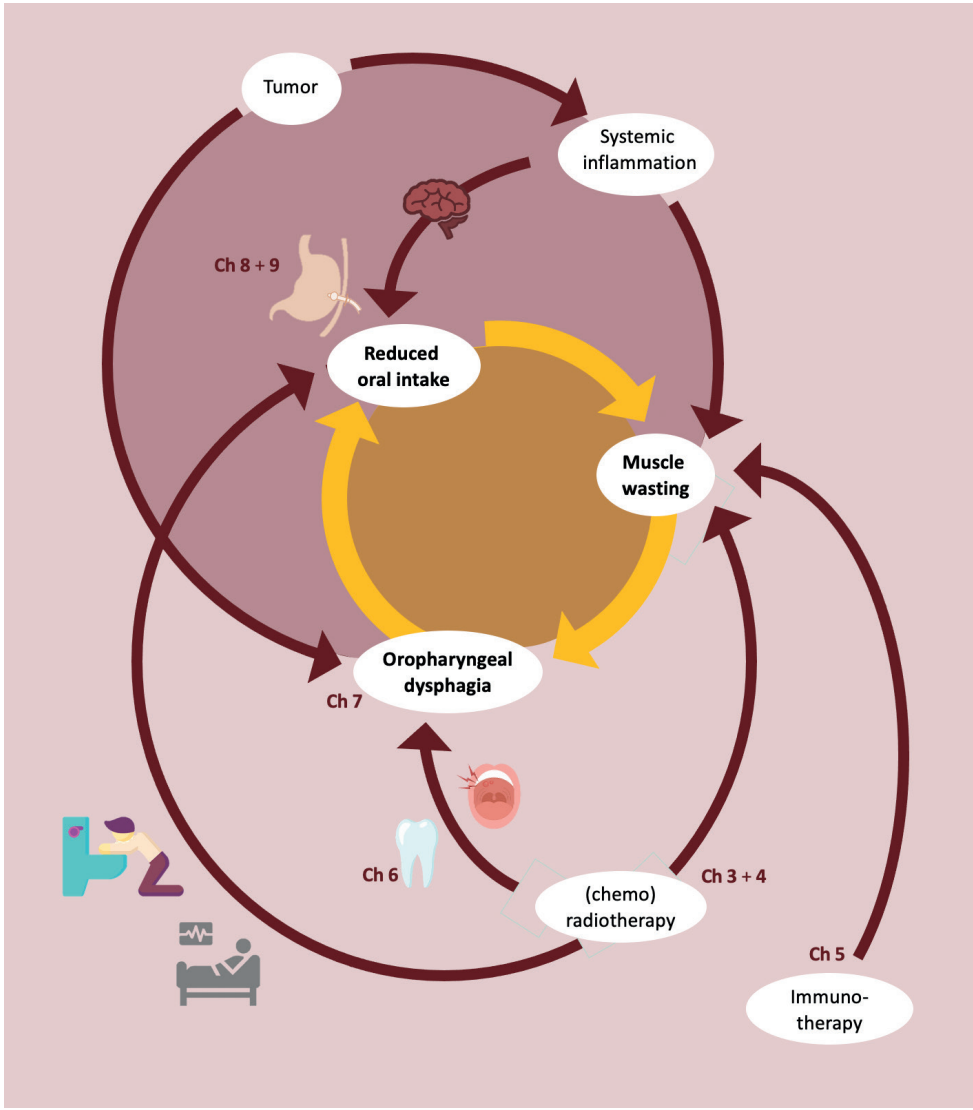

Figure 2 – Outline of thesis

MULTIDIMENSIONAL PROFILING OF HEAD AND NECK CANCER PATIENTS

CHAPTER 3

DISEASE INDUCED AND TREATMENT INDUCED ALTERATIONS IN BODY COMPOSITION IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: Chemo- or bioradiotherapy (CRT/BRT) of locally advanced head and neck squamous cell carcinoma (LAHNSCC) comes with high toxicity rates, often leading to temporary tube feeding (TF) dependency. Cachexia is a common problem in LAHNSCC. Yet, changes in body composition and muscle weakness during CRT/BRT are underexplored. Strong evidence on the effect of TF on body composition during treatment is lacking.

The aim of this cohort study was to assess (1) the relationship of fat-free mass index (FFMI) and handgrip strength (HGS) with CRT/BRT toxicity and outcome, (2) body composition in patients treated with CRT (cisplatin) versus BRT (cetuximab), and (3) the effect of the current TF regime on body composition and muscle strength.

Methods: LAHNSCC patients treated with CRT/BRT between January 2013-December 2016 were included (n = 137). Baseline measurements of body composition (bioelectrical impedance analysis) and HGS were performed. Toxicity grades (CTCAE) were scored. In a subset of 69 patients, weight loss, body composition, and HGS were additionally assessed during and after CRT/BRT. TF was initiated according to the Dutch guidelines for malnutrition.

Results: In this cohort (68% male, mean age 59±8 years), the incidence of baseline muscle wasting, defined as FFMI<P_{10}, was 29%. Muscle wasting was present in 23/100 (23%) CRT patients and 17/37 (46%) BRT patients (p=0.009). Muscle-wasted patients required more unplanned hospitalizations during CRT (p=0.035). In the CRT subset, dose limiting toxicity was significantly higher in wasted versus non-wasted patients (57% vs. 25%, p=0.004). Median follow-up was 32 months. Multivariate Cox regression analysis identified muscle wasting as independent unfavorable prognostic factor for overall survival (HR 2.1 [95% CI 1.1-4.1], p=0.022) and cisplatin as favorable prognostic factor (HR 0.3 [95% CI 0.2-0.6], p=0.001).

Weight and HGS significantly decreased during CRT/BRT; -3.7 ± 3.5 kg (p<0.001) and -3.1 ± 6.0 kg (p<0.001) respectively. Sixty-four percent of the patients required TF 21 days (range 0-59) after CRT/BRT initiation. Total weight loss during CRT/BRT was significantly (p=0.007) higher in the total oral diet group (5.5 ± 3.7 kg) compared to the TF group (3.0 ± 3.2 kg). Loss of FFM and HGS was similar in both groups.

Conclusions: In LAHNSCC patients undergoing CRT/BRT, FFMI<P_{10} is an unfavorable prognostic factor for OS, treatment toxicity, and -tolerance. Patients experience significant weight and FFM loss during treatment. Current TF regime attenuates weight loss but does not overcome loss of muscle mass and function during therapy. Future interventions should consider nutritional intake and additional strategies specifically targeting metabolism, loss of muscle mass, and function.

INTRODUCTION

Patients suffering from advanced cancer often develop cachexia, a multifactorial syndrome with unintended loss of skeletal muscle mass, caused by a variable combination of reduced food intake and changes in metabolic processes. [1] In head and neck squamous cell carcinoma (HNSCC) patients, the prevalence of cachexia is 3-52% at diagnosis, depending on tumor location and stage. [2, 3] Resection of tumors in the head and neck region can be truly mutilating, preventing sufficient oral intake, which can lead to increased weight loss. Preparatory procedures for radiotherapy (RT), such as tooth extractions, [4] also contribute to a more difficult oral intake. During post-operative chemoradiotherapy (CRT) or primary CRT or bioradiotherapy (BRT) of locally advanced HNSCC (LAHNSCC), weight loss, in terms of reduction in fat mass (FM), fat-free mass (FFM) or a combination of both, is induced even further due to therapy-related toxicity, also interfering with oral intake[5] (mucositis, taste loss, oropharyngeal dysphagia (OD)) or putative catabolic effects on skeletal muscle mass. [6-8]

Low skeletal muscle mass in HNSCC patients is associated with increased (chemo) radiotherapy induced toxicity (e.g. mucositis, radiation dermatitis, neutropenia, nephrotoxicity); this leads to treatment interruptions causing decreased treatment efficacy and cure rates. [3, 9] Furthermore, skeletal muscle mass loss during the course of RT has been associated with higher mortality rates. [10]

Therefore, assessment of body composition prior to and during treatment is of interest in LAHNSCC patients undergoing surgery and/or CRT/BRT to individually tailor interventions that optimize weight in general and muscle mass in particular. A body mass index (BMI) measurement alone cannot reveal a low muscle mass. Ideally, a rapid screening method for muscle mass such as bioelectrical impedance instead of more advanced imaging methods would be suitable for this purpose. Nowadays standard nutritional intervention includes the administration of tube feeding (TF), to stabilize weight loss when oral intake is impaired throughout the total course of LAHNSCC therapy. [11] It is expected that TF partially limits loss in fat mass. However, optimizing and maintaining muscle mass might require additional anabolic and/or anti-catabolic ingredients and/or interventions besides TF.

Yet, strong evidence of the effect of TF on the exact course and composition of weight loss during therapy is lacking, limiting insight on recovery or cachexia prevention. Previous work has focused on long-term weight loss (minimum 2-3 months after

CRT/BRT completion). [12] Short-term changes in body composition, as well as differences in weight-and muscle loss between patients receiving cetuximab versus cisplatin as radiosensitizer during RT have not yet been sufficiently studied.

The aim of this cohort study was to assess (1) the relationship of fat-free mass index (FFMI) and handgrip strength (HGS) with CRT/BRT toxicity and outcome, (2) changes in body composition in patients treated with chemoradiotherapy (cisplatin) versus bioradiotherapy (cetuximab), and (3) the effect of the current TF regime on body composition and muscle strength.

PATIENTS AND METHODS

Study design and population

Patients with LAHNSCC, who were treated with CRT or BRT (as postoperative or primary radiation treatment) in the Maastricht University Medical Center (MUMC+) and Maastro Clinic between January 2013 and December 2016, were included in this study. Patients were prospectively followed as part of a larger prospective non-interventional registration study for head and neck cancer patients treated with RT, CRT or BRT, which was approved by the Institutional Review Board of Maastro Clinic (ClinicalTrials.gov Identifier: NCT01985984). Additional data was extracted from the medical patient files, which was approved by the medical ethics committee of the MUMC+ according to the non-WMO obligatory Medical Research Involving Human Subjects Act. [13] All patients received primary chemo- or bioradiotherapy (cisplatin or cetuximab respectively) or adjuvant postoperative chemoradiotherapy (cisplatin) therapy with curative intent. Exclusion criteria were: palliative treatment, esophageal tumors, histology other than squamous cell carcinoma, no administration of systemic therapy, and age below 18 years.

Oncological treatment

Cisplatin was administered intravenously on days 1, 22, and 43, in doses of 100 mg/m^2. [14, 15] Cetuximab was indicated in patients not fit for cisplatin; for example in case of prior cerebrovascular accidents, myocardial infarction, intermittent claudication, neuropathy, renal function loss or pre-existent severe hearing loss. A loading dose of 400 mg/m^2 was administered intravenously one week before RT initiation, followed by 250 mg/m^2 weekly during RT. [16]

For patients receiving definitive RT with concurrent cisplatin, intensity-modulated radiotherapy (IMRT) was applied five times per week for seven weeks, in 35 daily fractions of 2 Gy to a total dose of 70 Gy in 47 days. Patients receiving cetuximab as part of definitive bioradiotherapy received accelerated fractionated RT with twice-daily fractions in the final week of RT to a total of 68 Gy in 34 fractions in 38 days. For patients undergoing adjuvant postoperative chemoradiotherapy a total of 66 Gy in 35 fractions over 45 days was administered concurrently with cisplatin.

Nutritional treatment

TF was started when patients met the criteria described in the Dutch guidelines for malnutrition. [17] All patients were screened and counselled on a weekly basis by a dietician for nutritional status and requirements for their support plan. In brief, patients who reached 75-100% of their nutritional requirements received protein and energy enriched/fortified main meals and between meal snacks and if required oral nutritional supplements (ONS). The support plans were monitored and adjusted if required. Patients with intake between 50% and 75% of the calculated nutritional requirements were initially advised to use ONS or TF in addition to daily oral intake. When intake was less than 50% of the calculated nutritional need, full TF was indicated, supplemented with any possible safe oral intake. Patients were stimulated to practice swallowing in order to maintain oropharyngeal function. [18] TF was administered through a nasogastric tube (NGT) or gastrostomy, the latter either as a percutaneous endoscopic gastrostomy (PEG) or a percutaneous radiological gastrostomy (PRG).

Measurements

Weight was measured weekly before and during treatment at the standard visits to the dietician, medical oncologist and radiation oncologist. Height was measured only once at baseline. Body composition was determined by bioelectrical impedance analysis (BIA) using an Omron device, model BF306 (OMRON Healthcare Group, Hoofddorp, The Netherlands). A Jamar hydraulic hand dynamometer was used to measure grip strength (JA Preston Corporation, Jackson, MI, USA). The highest value of three measurements on both hands was noted. HGS values of the dominant hand were then binary divided in normal and low grip strength with a cut-off value based on the tenth percentile reference values described by Spruit et al. [19] Pre-RT weight loss was patient-reported by asking whether and how much weight was unintentionally lost during the previous months. As pretreatment weight loss was only patients-reported,

it was decided to define muscle wasting based on a FFMI <17 kg/m^2 (for men) or <15 kg/m^2 (for women), based on reference values of the tenth percentile in Caucasians. [20]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, New York, USA). Descriptive statistics were reported in frequency distributions and absolute numbers by using independent samples T-test and Chi-square test. Paired samples T-test was used for determination of mass loss. Kaplan Meier was performed with Log Rank (Mantel-Cox). Univariate Cox regression was performed and subsequently, multivariate Cox regression was carried out by means of backward Log Rank to plot overall survival (OS). Significance was assumed in case of $p<0.05$. In multivariate Cox regression, probability for stepwise removal was set at 0.10.

RESULTS

Disease induced muscle wasting

Between 2013 and 2016, 192 patients with LAHNSCC were treated with CRT/BRT. In 137 cases, body composition measurements (BIA) at baseline (pre-RT) were collected and this cohort represents the population of the current analysis. In 69 of these patients, additional measurements were collected in week 3 to 4 of treatment and 1 to 2 weeks after CRT/BRT completion.

At start of CRT/BRT, 40 out of 137 patients (29%) met the criteria for muscle wasting based on a FFMI<P_{10}. [21] These patients were also characterized by a lower World Health Organization (WHO) performance status (PS), lower HGS, and a higher incidence of OD ≥ grade 2 according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) (Table 1). Muscle wasting was not prevalent in patients receiving adjuvant CRT as compared to patients receiving primary CRT/BRT (19% versus 32% respectively, $p=0.138$). When evaluating the cisplatin subgroup only, the incidence of muscle wasting did not significantly differ between patients starting primary and postoperative CRT (26% versus 15% respectively, $p=0.283$). The presence of OD was significantly higher in patients with oropharyngeal or oral cavity tumors compared to other tumor sites (36% versus 16% respectively, $p=0.012$) and was significantly higher in patients who underwent surgery and postoperative CRT compared to primary CRT/BRT (41% versus 23% respectively, $p=0.047$). T-stage did not significantly differ between patients with and without OD, nor between the wasted and non-wasted patients.

In patients receiving cetuximab, a significantly larger proportion of patients had a FFMI<P_{10} compared to patients receiving cisplatin (46% versus 23%, *p*=0.009), but this was not reflected in significant differences in BMI (24.9 ± 4.4 kg/m^2 versus 24.5 ± 5.9 kg/m^2, *p*=0.629). Cetuximab patients more often showed CTCAE OD ≥ grade 2 at start of CRT/BRT and had significantly higher levels of tobacco and alcohol use (Table A1). No significant difference was found in WHO PS between cisplatin receivers and cetuximab receivers (*p*=0.119).

Table 1 Baseline characteristics – Normal FFMI versus FFMI below the tenth percentile (P_{10}) (n=137).

Variables	**Normal FFMI** *n=97* (71%)	**FFMI<P_{10}** *n=40* (29%)	***p*-value**
Patient characteristics			
Age (years)	59.2 ± 7.3	59.6 ± 8.2	0.769♦
Sex			
Male	71 (73%)	22 (55%)	**0.038**Δ
Female	26 (27%)	18 (45%)	
BMI (kg/m^2)	27.0 ± 3.9	19.6 ± 2.0	**<0.001**♦
Mean pretreatment weight loss (%)	2.6 ± 4.3	3.8 ± 5.1	0.158♦
CTCAE OD ≥ grade 2 at start RT			
Yes	18 (19%)	19 (48%)	**0.001**Δ
No	79 (81%)	21 (52%)	
Tobacco use			
Yes	87 (90%)	38 (95%)	0.318Δ
No	10 (10%)	2 (5%)	
Alcohol consumption of at least 1 per day			
Yes	55 (57%)	26 (65%)	0.369Δ
No	42 (43%)	14 (35%)	
WHO performance status			
0	19 (20%)	1 (3%)	**0.034**Δ
1	75 (77%)	37 (93%)	
2	3 (3%)	2 (5%)	
Handgrip strength (kg)			
Male	47 ± 11	38 ± 8	**<0.001**♦
Female	29 ± 5	24 ± 5	**0.043**♦
Tumor characteristics			
Primary tumor site			
Nasopharynx	5 (5%)	2 (5%)	0.854Δ
Oropharynx	39 (41%)	14 (30%)	
Hypopharynx	12 (13%)	7 (19%)	
Oral cavity	17 (16%)	5 (14%)	
Larynx	20 (21%)	11 (30%)	
Unknown primary	2 (2%)	1 (3%)	
Other	2 (2%)	0 (0%)	

Variables	**Normal FFMI** *n=97* (71%)	**FFMI<P_{10}** *n=40* (29%)	***p*-value**
T classification			
Tx	3 (3%)	1 (3%)	0.356$^{\Delta}$
T0	5 (5%)	0 (0%)	
T1	13 (14%)	2 (5%)	
T2	19 (20%)	7 (16%)	
T3	23 (24%)	14 (35%)	
T4	34 (34%)	16 (41%)	
N classification			
N0	15 (15%)	11 (30%)	0.152$^{\Delta}$
N1	14 (14%)	2 (5%)	
N2	66 (69%)	25 (60%)	
N3	2 (2%)	2 (5%)	
Tumor stage			
Stage II-III	17 (17%)	7 (19%)	0.997$^{\Delta}$
Stage IV	80 (83%)	32 (81%)	
p16			
p16+ oropharynx	24 (25%)	3 (8%)	**0.024**$^{\Delta}$
Other	73 (75%)	36[a] (92%)	
Treatment characteristics			
CRT timing			
Primary	71 (75%)	34 (86 %)	0.138$^{\Delta}$
Adjuvant	26 (25%)	6 (14%)	
Systemic therapy			
Cisplatin	77 (80%)	23 (57%)	**0.009**$^{\Delta}$
Cetuximab	20 (20%)	17 (43%)	
Radiotherapy on neck			
Unilateral	7 (7%)	1 (3%)	0.451$^{\Delta}$
Bilateral	89 (92%)	39 (97%)	
No neck RT	1 (1%)	0 (0%)	
Tube feeding administration			
Yes	60 (62%)	28 (70%)	0.366$^{\Delta}$
No	37 (38%)	12 (30%)	
Type of feeding tube			
No feeding tube	26 (27%)	6 (15%)	0.247$^{\Delta}$
NGT only	7 (7%)	1 (3%)	
PEG	8[b] (8%)	3 (8%)	
PRG	56[c] (58%)	30[d] (75%)	

BMI, body mass index; CRT, chemoradiotherapy; NGT, nasogastric tube; OD, oropharyngeal dysphagia (Common Terminology Criteria for Adverse Events grade 2 OD or higher); PEG, percutaneous endoscopic gastrostomy; PRG, percutaneous radiologic gastrostomy; RT, radiotherapy; Tumor, nodes, and metastasis (TNM) classification 7th edition. [78] WHO, world health organization;

[a] one missing. [b] one patient did not use feeding tube, [c] ten patients did not use feeding tube, [d] six patients did not use feeding tube. ♦independent samples T test, $^{\Delta}$Chi squared. Due to rounding off, percentages may not add up to exactly 100. Bold values denote statistical significance at the p<0.050 level.

Treatment induced changes in body composition

Information on body composition and grip strength throughout the course of CRT/BRT was available in 69 patients. Baseline characteristics in this subset were comparable to the total cohort of 137 patients shown in Table 1.

The incidence of muscle wasting at baseline in the subgroup of 69 patients was 20/69 (29%), comparable to the incidence rate of the total group. The incidence of muscle wasting increased to 25/69 (36%) at the end of CRT/BRT. Seven patients with a normal FFMI (14%) reached FFMI<P_{10} during or at the end of CRT/BRT (four received TF*)* and two muscle wasted patients (10%) had a normal FFMI after CRT/BRT completion. Both of them used additional TF.

The mean weight loss over the course of CRT/BRT was 3.7 ± 3.5 kg (p<0.001) in which FFM covered 1.8 ± 3.7 kg and FM 1.9 ± 3.1 kg. In addition, HGS significantly decreased during treatment by 3.1 ± 6.0 kg (p<0.001). Dividing the population in a TF (n=48) and total oral diet (TOD) (n=21) group, the total weight loss throughout CRT/BRT was significantly higher in the TOD group when compared to the TF group: 5.5 ± 3.7 kg and 3.0 ± 3.2 kg respectively (p=0.007). FM and FFM decreased significantly in both subgroups. In addition, HGS decreased by 3.1 ± 5.4 kg (p<0.001) in the TF subgroup and by 3.0 ± 7.2 kg (p=0.067) in the TOD subgroup. Specification of weight loss and HGS is shown in Table A2.

TF was initiated at a median of 21 days (range 0-59) after the first RT fraction. Despite this nutritional support, patients receiving TF continued to lose weight (1.7 ± 2.8 kg, p<0.001) in both FM (0.8 ± 3.5 kg, p=0.112) and FFM (0.9 ± 3.2 kg, p=0.054) and lost handgrip strength significantly during the course of treatment (3.1 ± 5.4 kg, p<0.001). Full details of mass and function loss are available in the appendix. When investigating cisplatin and cetuximab receivers separately, the mean weight loss throughout the course of CRT/BRT (from RT start up to two weeks after CRT/BRT completion) was 4.1 ± 3.7 kg (p<0.001) and 2.7 ± 3.0 kg (p<0.002) respectively. The in-between group difference was not statistically significant (p=0.184).

When comparing changes in body composition between patients with a prophylactically inserted feeding tube (n=41, inserted before start of first RT or within seven days after RT initiation) to patients with reactively inserted feeding tubes (n=7), no statistically significant differences could be shown. However, total weight loss throughout the course of therapy tends to be higher in the subgroup with

reactively inserted gastrostomies when compared to prophylactic gastrostomies: 4.8 ± 2.6 kg versus 2.7 ± 3.3 kg respectively (p=0.118).

Muscle wasting and side effects of CRT/BRT

Eighteen out of 40 muscle-wasted patients (45%) at start of treatment did not complete CRT/BRT as planned, due to scheme changes such as treatment interruptions, dose reductions, postponement or adjustment of RT or chemotherapy administration. These treatment changes were significantly (p=0.019) more frequent than in the non-wasted patients (25%).

Hematologic toxicity, ototoxicity, and renal failure were only determined in the population who received cisplatin as radiosensitizer, since cetuximab is not myelosuppressive and less nephrotoxic and neurotoxic than cisplatin. [22] Overall dose-limiting toxicity (including neutropenia, renal failure, ototoxicity, etc.) was significantly higher in muscle-wasted (57%) compared to non-wasted (25%) patients (p=0.004). (Specification in appendix Table A3)

Mean cumulative doses of administrated cisplatin significantly differed between the muscle-wasted and non-wasted population, namely 230 mg/m^2 versus 268 mg/m^2 respectively (p=0.011). However, only three patients received less than 200 mg/m^2, considering the effective cumulative dose (two non-wasted and one wasted). [23]

Furthermore, from the 137 patients, 53 were additionally admitted to the hospital for reasons other than the planned admissions during CRT/BRT. Patients receiving cisplatin required significantly more additional hospital admissions compared to patients receiving cetuximab, 48% versus 14% respectively (p<0.001).

The incidence of unplanned hospitalizations tends to be higher in non-wasted patients who received cisplatin; 40 out of 70 (52%) non-wasted and eight out of 23 (35%) wasted patients had unplanned admissions (p=0.148). The mean additional days of hospital admissions for any reason in the total cohort of non-wasted and wasted patients were 4.3 ± 6.8 and 2.3 ± 6.3 respectively (p=0.112). Indications for hospitalization varied and included renal failure, dehydration, fever, obstipation, gastrostomy complications, nausea, and electrolyte imbalances. Reasons for hospitalization did not significantly differ between baseline muscle-wasted and non-wasted patients.

Tube feeding

Eighty-eight out of 137 (64%) patients got TF during the course of CRT/BRT or within 30 days after the final fraction of RT. Sixty-nine out of 100 (69%) cisplatin receivers became (temporarily) TF-dependent and nineteen out of 37 (51%) of the cetuximab receivers required TF (p=0.056). At six months after CRT/BRT completion, fifteen out of 85 TF-users (18%) were still TF-dependent (one loss to follow up, one not reported, one deceased). From these fifteen subjects, four had postoperative CRT, seven had muscle wasting at start of CRT/BRT, and nine had CTCAE OD ≥ grade 2 at start of CRT/BRT.

Muscle wasting as a predictor of overall survival

Using univariate Cox regression analysis a negative prognostic value for OS was found for patients with baseline FFMI<P_{10}, for patients with baseline BMI <21 kg/m^2, for patients with CTCAE OD ≥ grade 2, and for patients receiving cetuximab as radiosensitizer versus cisplatin. However, p16+ oropharyngeal tumors showed a positive prognostic value for OS. Multivariate Cox regression analysis showed an independent prognostic value for the variable FFMI<P_{10} and for type of systemic agent (Table 2).

Figure 1 shows the Cox regression survival plot of different body composition profiles. Patients with a low BMI and normal FFMI showed the best OS and patients with a low BMI and FFMI<P_{10} showed the worst OS.

At the time of censoring, 41 out of 137 patients (30%) were deceased. The median follow up was 32 months (range 3 - 62). OS for all patients was 75.9% at 2 years and 63.0% at 5 years. The 2-year and 5-year OS rate specified for muscle-wasted patients was 57.3% and 35.7% respectively. In non-wasted patients this OS rate was significantly higher, namely 83.5% and 74.5% at 2 years and 5 years respectively (Kaplan Meier, Log Rank (Mantel-Cox) significance p<0.001, Figure A1.

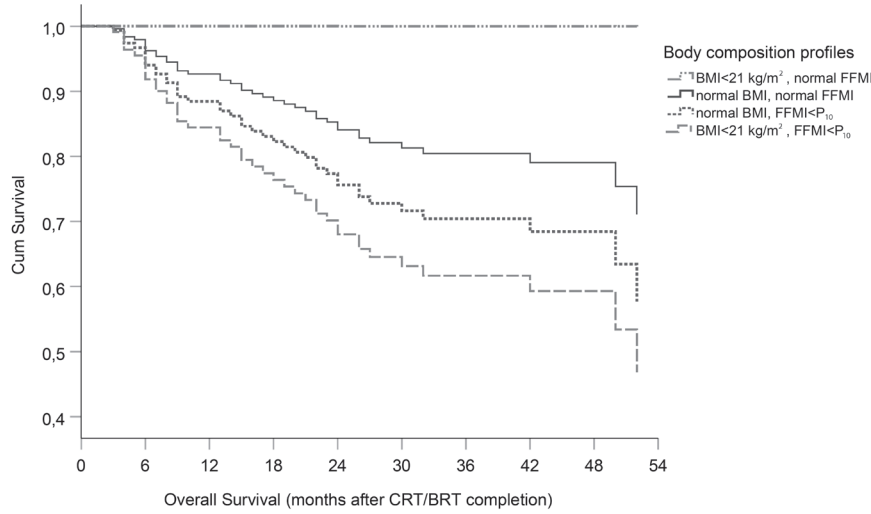
In the 21 deceased muscle-wasted patients, twelve had a LAHNSCC-related death, five a non-LAHNSCC-related death, and in two patients the cause of death was unknown. In the non-wasted group, nineteen patients died of disease progression and in one case, the cause of death was unknown.

Table 2 – Univariate and multivariate Cox regression analysis of prognostic factors for overall survival in 137 LAHNSCC patients.

Variable	Univariate analysis			Multivariate analysis*		
	HR	**CI 95%**	***p*-value**	**HR**	**CI 95%**	***p*-value**
Gender Male vs. female	0.941	0.487 - 1.818	0.858			
Age ≥60 vs. <60	0.706	0.381 - 1.306	0.267	0.543	0.285 - 1.035	0.064
WHO PS 1-2 vs. 0	3.941	0.950 - 16.359	0.059			
Baseline BMI <21 kg/m^2 vs. higher	2.363	1.269 - 4.401	**0.007**			
Baseline FFMI <P_{10} vs. normal	2.907	1.574 - 5.368	**0.001**	2.090	1.083 - 4.035	**0.028**
Baseline OD CTCAE ≥ 2 vs. <2	3.177	1.717 - 5.880	**<0.001**	1.876	0.951 - 3.701	0.069
Tumor stage ≥ stage IV vs. <stage IV	1.614	0.633 - 4.116	0.316			
p16+ oropharynx p16+ oropharynx vs. others	0.308	0.095 - 0.998	**<0.050**			
Type of systemic agent Cetuximab vs. cisplatin	3.608	1.942 - 6.706	**<0.001**	3.322	1.682 - 6.560	**0.001**

*BMI, body mass index; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events v4.0; FFMI, fat-free mass index; HR, hazard ratio; OD, oropharyngeal dysphagia; WHO PS, World Health Organization performance status; *Backward LR analysis. Bold values denote statistical significance at the p<0.050 level.*

Figure 1 – Multivariate Cox regression analyses



Patients at risk										
Normal BMI, Normal FFMI	94	89	84	80	72	53	38	26	15	10
BMI<21kg/m^2 FFMI<P_{10}	31	27	25	23	17	14	13	7	3	2
Normal BMI, FFMI<P_{10}	9	9	8	6	5	5	5	4	2	1
BMI<21kg/m^2 Normal FFMI	3	3	3	3	3	3	3	3	1	1

Multivariate Cox regression analyses for different body composition profiles, in which the following factors were taken into account: Age <60 (p=0.078), CTCAE grade 2 OD at start of CRT (p=0.065), systemic therapy (cisplatin, cetuximab) (p=0.001). FFMI< P_{10}, fat-free mass index below tenth percentile; BMI, body mass index below 21 kg/m^2 [79]

DISCUSSION

Due to high rates of mucositis and OD limiting oral diet intake, weight loss during CRT/BRT in LAHNSCC patients seems almost inevitable despite current measures according to the Dutch guidelines for malnutrition. Furthermore, many patients already have a poor nutritional status at start of treatment. Tumor-induced OD and pre-RT interventions such as tooth-extractions and surgery may cause impaired oral intake in patients starting CRT/BRT.

In this Dutch patient cohort, a FFMI< P_{10} was found in 29% (n=40/137) of the patients at start of CRT, which is slightly higher than reported in present literature. [24, 25] Kwon et al. reported a much lower pretreatment incidence of cachexia in Korean

patients, namely 6.1% (n=22/361). [26] These differences can probably partially be explained by the different diagnostic criteria that were used for muscle wasting and cachexia. [27] In the present study, pre-diagnostic patient self-report weight loss was considered insufficiently reliable to identify cachexia. Nevertheless, a cut-off point of FFMI<P_{10} was considered appropriate to identify muscle wasting, as is recommended in the international guidelines. [20, 21, 28] Especially in head and neck cancer, pretreatment muscle wasting is considered a multifactorial syndrome. Both tumor- and patient characteristics may influence patient's oral intake and metabolism, leading to weight loss and muscle wasting.

One of the important factors influencing oral intake in LAHNSCC patients is the presence of OD. This is indeed reflected in the present and other study populations where cachectic patients have been shown to have OD significantly more often at diagnosis. [29] OD increases the risk of malnutrition due to restrictive dietary adaptations made by the patient. [30, 31] It has been suggested that OD is mainly caused by tumor invasion. However, T-stage did not significantly differ between patients with and without OD. Nevertheless, primary tumor site was indeed significantly related to the presence of OD. The frequency of OD was significantly higher in patients with oropharyngeal or oral cavity tumors compared to other tumor sites (p=0.012). In the head and neck cancer population OD is usually caused by tumor-and treatment related anatomical and neurophysiological changes in the swallowing-related structures (e.g. larynx, tongue, pharynx) such as xerostomia, pharyngeal muscular fibrosis, decreased laryngeal sensation (radio- and chemotherapy-induced neuropathy), loss of laryngeal closure coordination and trismus. [32-34]

Since cachexia is a muscle-wasting syndrome, it would be likely that this muscle wasting also occurs in the swallowing muscles, thereby contributing to the development of OD. However, evidence supporting this theory is scarce. [35]

Another patient characteristic that significantly differed between wasted and non-wasted subjects was gender. Despite different cut off points for male and female patients, a significantly higher proportion of muscle wasting was found in the female subjects. The present literature does not provide an explanation for this difference. [9, 10, 36, 37] In the present cohort, a significant difference in the distribution of p16+ oropharyngeal tumors was observed between muscle-wasted and non-wasted patients. In the p16+ oropharyngeal tumor group, lower numbers

of wasted patients were seen at start of CRT/BRT. A plausible explanation might be that p16+ tumors are usually characterized by an advanced nodal stage and an early primary tumor stage. [38, 39] A smaller primary tumor may cause less oral intake-related problems when compared to an advanced tumor stage. In addition, patients with p16+ tumors are generally non-smokers and non-drinkers and presumably have a healthier lifestyle and less comorbidity compared to p16– patients. [40]

The present study also showed that pretreatment muscle wasting is an independent prognostic factor for OS in LAHNSCC patients. Kaplan Meier and Cox regression analysis showed a significantly worse OS in patients with pretreatment muscle wasting, which is consistent with previous studies. [25, 26, 41-45]

This study is the first to evaluate the effect of different body 'wasting' profiles in LAHNSCC on OS and the risk of misleading information when relying only on BMI. Although the sample size of the subgroups is small, Figure 1 suggests that a low BMI does not necessarily mean that patients are malnourished, nor if they are at risk for malnutrition-related therapeutic consequences. The low-BMI and normal FFMI subgroup (i.e. the lean 'athletic' phenotype) even had the best OS outcome. More convincingly, there is a distinct difference in outcome between the two groups with normal BMI but FFMI<P_{10} versus normal FFMI. These results highlight the importance of assessing body composition in the diagnostic trajectory and that even a simple tool such as BIA may provide clinically meaningful information.

Muscle wasting did influence the course of treatment as a higher level of treatment toxicity was found in the muscle-wasted group compared to the non-wasted group. Muscle-wasted patients receiving cisplatin had more often neutropenia and renal failure interfering with HNSCC treatment. Higher numbers of early cessation of CRT in this group also reflects this. These higher frequencies of dose-limiting toxicities are in line with previous results for LAHNSCC, [9, 44, 46] and other cancer types. [47-49] This finding demands for early identification of muscle wasting to allow personalized measures in order to obviate potential side effects of HNSCC treatment.

Unlike the side effects in the muscle-wasted patient group, the need for additional hospital admissions tends to be higher in the non-wasted group of cisplatin receivers. However, this remarkable finding was not statistically significant and there is no clear explanation for this observation. Cisplatin is known for its high toxicity rates, especially nephrotoxicity requiring intravenous fluid administration

to resolve, [22] and this probably explains the difference in hospitalizations between cetuximab and cisplatin receivers. Besides muscle wasting, systemic therapy showed to be an independent predictor of OS too, in favor of cisplatin. Table A1 on baseline characteristics shows a higher rate of FFMI<P_{10} in the cetuximab subgroup, suggesting a higher prevalence of comorbidity contraindicating cisplatin administration. Strikingly, this subgroup consisted mainly of patients with a normal BMI. In the Cox regression, patients receiving cetuximab showed significant worse OS rates compared to the cisplatin group.

Patients eligible for cisplatin appear to have better survival rates than patients requiring cetuximab due to contraindications for CRT. [50-53] In patients with comorbidity and muscle wasting, one can doubt the beneficial effect of bioradiotherapy relative to the high treatment burden. Based on the current results, conclusions cannot be drawn on whether or not muscle-wasted patients with comorbidity can be treated with curative intent, but it does raise questions regarding current treatment protocols. Future studies should determine if the benefit of concurrent systemic therapy outweighs the increased toxicity in muscle-wasted patients.

Despite the convincing impact of muscle wasting on OS, the current Dutch malnutrition guideline lacks standardized diagnostic and treatment strategies to tackle muscle wasting. Currently clinicians try to influence overall weight loss by counseling and enriching the normal diet according to the Dutch guidelines, and in case of poor nutritional intake by administrating TF. This study shows that this strategy does not completely overcome the problem. The mean weight loss during the weeks of CRT was 3.7 ± 3.5 kg, of which FFM loss covered 47%. These findings differ slightly from two previous publications [54, 55] in which weight loss during CRT, measured through Dual Energy X-ray Absorptiometry (DEXA), was around 10 kg, of which 66-71% was Lean Body Mass (LBM) loss. However, the majority of the population in these studies were overweight or obese at the start of CRT, which has been shown to be linked to higher levels of weight loss during oncological treatment. [56] The current results are however comparable to Atasoy et al. [57] Despite TF administration, weight loss was still substantial and reached a mean of 3.0 ± 3.2 kg after CRT completion. However, this was significantly lower (p<0.001) than the weight loss in the TOD group (5.5 ± 3.7 kg). Remarkably, the TOD group did not significantly lose weight during the first half of therapy, but increasingly lost weight during the second half. A logical idea following these results would be to start TF prophylactically in the

future. However, this strategy has been investigated by among others Brown et al. [58] and did not show any beneficial effects on weight loss and health-related quality of life. [59] In spite of that, Brown showed that early tube feeding can improve patient adherence to clinically indicated tube feeding during treatment. [60] Therefore, it would be a logical thought that prophylactic tube insertion might lead to better patient adherence than in those receiving a feeding tube on demand (reactively). Our study was not designed to evaluate potential differences in prophylactic and reactive feeding tube insertion, but a trend could be objectified towards less weight loss in the prophylactic tube receivers when compared to the reactive group. Based on our study, we cannot comment on whether this difference in weight loss is due to a later TF initiation because of a wait-and-see attitude of the treating physician, due to a poorer patient compliance or a combination of both.

On the other hand, the use of prophylactic feeding tubes has been argued because of potential harm to the long term swallowing function. Shune et al. [61] hypothesized the 'use it or lose it' principle: when the gastrostomy tube is used, oral intake is often reduced to a minimum causing sensorimotor deprivation of the upper aerodigestive tract and pharyngeal constrictor muscle fibroses. This leads to deconditioning of the swallowing mechanism. However, the present literature is ambiguous on the relationship between prophylactic TF and long-term OD. [18, 62-66] Therefore, supplemental TF to maximize the chance to reach the nutritional target remains to be a regime that deserves validation.

Despite starting TF in the present population, patients still lost weight especially in the form of FFM and TF did not prevent loss of function (HGS) either. This underlines the idea that muscle wasting in LAHNSCC is not a nutritional problem on its own, but that it is accompanied by cancer and therapy related metabolic and inflammatory processes that are involved in muscle wasting, energy metabolism and weight loss too. Consequently, it cannot be ruled out that the nutritional needs in these patients are higher than what is currently recommended and applied. Jager-Wittenaar et al. [67] reported that patients with head and neck cancer undergoing treatment with an intake of >35 kcal/kg/d and >1.5 g protein/kg/d lost significantly less body weight and lean mass than those patients consuming <35 kcal/kg/d and <1.5 g protein/kg/d. Furthermore, anabolic and anti-catabolic strategies like exercise and specific nutrients (e.g. Ω3 fatty acids) or drugs are not applied in current practice.

The decrease in FFM was endorsed by a parallel significant decrease in HGS. This is in line with the study by Arribas et al. [68], but in contrast with Cosway et al. [69]

who did not find a decreased HGS between start of therapy and three months post-treatment. However, in the latter study only weight loss was reported without any information on body composition.

Atasoy et al. [57] did not find changes in LBM and body fat mass during CRT and Isenring et al. [70] found a trend towards increased FFM in the nutritional intervention group compared to usual care. Differences in nutritional intervention strategies might explain this dissimilarity.

In order to improve the decision and timing of TF administration and feeding tube insertion, the development of a decision model and subsequent nomogram on prophylactic gastrostomy insertion is in progress.

In the present population, the amount of weight loss throughout the course of CRT/BRT was not significantly related to a worse OS. Strikingly, literature provides divergent results as two studies [71, 72] found that patients with increased weight loss showed better OS outcomes when compared to patients who gained weight during treatment, referring to the obesity paradox. Contrary to these findings, Ghadjar et al. reported a decreased OS in those who lost weight during CRT. [41] Unfortunately, these study populations are quite heterogeneous, complicating definite analysis and the identification of prognostic subgroups. Additionally, the relatively small study populations might also have influenced the reliability of the results.

The current study has some limitations. The analysis revealed several statistically significant results; however, the sample size was probably too small to allow detailed group stratification to detect all relevant relations. Nevertheless, the population of included patients was a realistic representation of patients receiving CRT/BRT for LAHNSCC, which gives insight in the overall severity of muscle wasting, body composition, and OS in this group. Furthermore, measurements on HGS and BIA were collected prospectively according to the standardized protocol. However, information on TF was collected retrospectively and therefore the results of this study might be prone to (selection) bias. Specification of TF and actual amount administered could not be traced. Another limitation is the minimal dietary information on the normal diet, the dietary enrichment and ONS in the TOD group. No exact records were kept of these specific items. Comorbidities were not reported so the impact of this confounder on group differences between CRT and BRT receivers could not be confirmed, nor ruled out.

Whole-body magnetic resonance imaging (MRI) and Computed tomography (CT) are considered the gold standards in measuring body composition. [73] Since whole-body CT-scans are not part of standard practice, these whole-body CT-scans were not available in the present cohort for body composition evaluation. Determining fat mass and muscle mass on slices of CT-scans, a derivative of whole-body CT [74] was not preferred, since it could not provide information on the different body composition profiles. BIA measurement, a convenient and non-invasive technique, [75, 76] in combination with BMI enables researchers to verify these profiles and was therefore considered appropriate in this research.

CONCLUSION

Muscle wasting is common in LAHNSCC as nearly 30% of the present population undergoing CRT/BRT had muscle wasting at start of CRT/BRT. Additionally, FFMI<P_{10} is an unfavorable prognostic factor for OS, treatment toxicity and tolerance. Patients experience significant weight and FFM loss during treatment. The current TF regime attenuates weight loss, but does not overcome loss of muscle mass and function during therapy. Future interventions should consider proactive monitoring of risk factors for muscle wasting, nutritional support tailored to reach the energy and protein requirements of the patients, as well as specific anabolic and anti-catabolic nutrients, together with additional strategies targeting metabolism, loss of muscle mass, and function.

Further work will focus on the potential contributing factors, both intake dependent and metabolic drivers of muscle wasting, to allow for early identification of (pre) cachexia and personalized treatment strategies.

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APPENDIX

Figure A1 – Kaplan Meier Survival Plot – Muscle-wasted patients at start of CRT/BRT versus non-wasted patients. n=137, Log Rank (Mantel-Cox) significance *p*<0.001

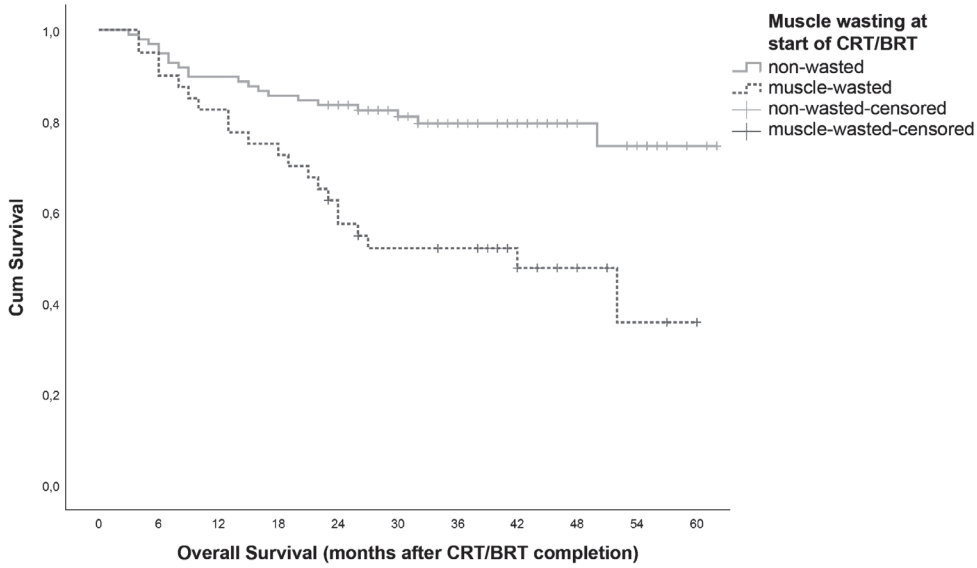

Table A1 – Baseline characteristics – cisplatin versus cetuximab (n=137).

Variables	**Cisplatin** *n*=100 (73%)	**Cetuximab** *n*=37 (27%)	***p*-value**
Patient characteristics			
Age (years)	58.3±7.9	62.0±5.9	**0.010**♦
Sex			
Male	73 (73)	20 (55)	**0.035**Δ
Female	27 (27)	17 (45)	
BMI (kg/m^2)	24.9 ± 4.4	24.5 ± 5.9	0.629♦
Mean pre diagnostic weight loss (%)	2.4 ± 3.6	4.3 ± 6.3	**0.027**♦
FFMI			
Normal FFMI	77 (77)	20 (54)	**0.009**Δ
FFMI < P_{10}	23 (23)	17 (46)	
Patient reported OD at start RT			
Yes	20 (20)	17 (46)	**0.002**Δ
No	80 (80)	20 (54)	
Tobacco use			
Yes	88 (88)	37 (100)	**0.027**Δ
No	12 (12)	0 (0)	
Alcohol consumption of at least 1 per day			
Yes	54 (54)	27 (73)	**0.045**Δ
No	46 (46)	10 (27)	

Variables	**Cisplatin** *n*=100 (73%)	**Cetuximab** *n*=37 (27%)	***p*-value**
WHO performance status			
0	17 (17)	3 (8)	0.119[△]
1	81 (81)	31 (84)	
2	2 (2)	3 (8)	
Handgrip strength (kg)			
Male	46 ± 11	41 ± 11	0.122[♦]
Female	29 ± 8	23 ± 5	**0.010**[♦]
Tumor characteristics			
Primary tumor site			
Nasopharynx	7 (7)	0 (0)	0.361[△]
Oropharynx	37 (37)	16 (43)	
Hypopharynx	14 (14)	5 (14)	
Oral cavity	19 (19)	3 (8)	
Larynx	20 (20)	11 (30)	
Unknown primary	2 (2)	1 (3)	
Other	1 (1)	1 (3)	
T classification			
Tx	3 (3)	1 (3)	0.480[△]
T0	5 (5)	0 (0)	
T1	12 (12)	3 (8)	
T2	21 (21)	5 (14)	
T3	24 (24)	13 (35)	
T4	35 (35)	15 (41)	
N classification			
N0	18 (18)	8 (22)	0.259[△]
N1	15 (15)	1 (3)	
N2	64 (64)	27 (73)	
N3	3 (3)	1 (3)	
Tumor stage			
Stage II-III	20 (20)	4 (19)	0.209[△]
Stage IV	80 (80)	33 (81)	
p16			
p16+ oropharynx	22 (22)	5 (14)	0.257[△]
Others	77[a] (78)	32 (86)	
Treatment characteristics			
CRT timing			
Primary	74 (74)	31 (84)	0.229[△]
Adjuvant	26 (26)	6 (16)	
Radiotherapy on neck			
Unilateral	7 (7)	1 (3)	0.168[△]
Bilateral	93 (93)	35 (95)	
No neck RT	0 (0)	1 (3)	
Tube feeding administration			
Yes	69 (69)	19 (51)	0.056[△]
No	31 (31)	18 (49)	

BMI, body mass index; CRT, chemoradiotherapy; OD, oropharyngeal dysphagia (Common Terminology Criteria for Adverse Events grade 2 OD or higher); RT, radiotherapy; Tumor, nodes, and metastasis (TNM) classification 7th edition, [78] WHO, world health organization. [a]one missing. [♦]independent samples T test, [△]Chi squared. Bold values denote statistical significance at the p<0.050 level.

Table A2 – Mean loss of masses and function during CRT, tube feeding versus total oral diet.

	Tube feeding (n=48)		**Total oral diet** (n=21)		**Between groups**	
	Loss in kg	***p*-value**◊	**Loss in kg**	***p*-value**◊	**Mean difference**	***p*-value**♦
Mass loss week 1 – 4 of CRT in kg						
W	1.3 ± 2.6	**0.002**	1.4 ± 3.3	0.062	0.2 ± 0.7	0.828
FM	0.9 ± 3.1	**0.044**	0.3 ± 2.1	0.457	-0.6 ± 0.7	0.438
FFM	0.3 ± 3.2	0.474	1.1 ± 3.0	0.112	0.7 ± 0.8	0.376
Mass loss week 4 – end of CRT in kg						
W	1.7 ± 2.8	**<0.001**	4.0 ± 3.3	**<0.001**	2.3 ± 0.8	**0.004**
FM	0.8 ± 3.5	0.112	2.1 ± 3.3	**0.008**	1.3 ± 0.9	0.151
FFM	0.9 ± 3.2	0.054	1.9 ± 4.4	0.064	1.0 ± 0.9	0.298
Mass loss from start to end of CRT in kg						
W	3.0 ± 3.2	**<0.001**	5.5 ± 3.7	**<0.001**	2.5 ± 0.9	**0.007**
FM	1.7 ± 2.7	**<0.001**	2.5 ± 3.9	**0.008**	0.7 ± 0.8	0.373
FFM	1.2 ± 3.3	**0.012**	3.0 ± 4.3	**0.005**	1.7 ± 1.0	0.075
Loss of handgrip strength in kg						
start - week 4	1.7 ± 4.5	**0.013**	1.8 ± 5.1	0.132	0.1 ± 1.2	0.948
week 4 - end	1.5 ± 5.2	0.057	1.3 ± 5.4	0.291	-0.2 ± 1.4	0.901
start - end	3.1 ± 5.4	**<0.001**	3.0 ± 7.2	0.067	-0.0 ± 1.6	0.981

◊*Paired samples T-test.* ♦*Independent Samples T Test. Add-up values from rows can slightly differ due to rounding off to one decimal. FFM, fat-free mass loss; FM, fat mass loss; W, total weight loss. Bold values denote statistical significance at the p<0.050 level.*

Table A3 – Dose-limiting toxicity in cisplatin subgroup specified – muscle wasted versus non-wasted.

Variables	**Normal FFMI** *n*= 77 (77%)	**FFMI < P_{10}** *n*= 23 (23%)	***p*-value**
Neutropenia	10/77 (13%)	1/23 (4%)	0.245
Renal failure	4/77 (5%)	5/23 (22%)	**0.015**
Ototoxicity	6/77 (8%)	6/23 (26%)	**0.018**
Packed cells transfusion for anemia	16/77 (21%)	8/23 (35%)	0.168

FFMI, fat-free mass index. Bold values denote statistical significance at the p<0.050 level.

CHAPTER 4

EARLY LOSS OF FAT MASS DURING CHEMORADIOTHERAPY PREDICTS OVERALL SURVIVAL IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE LUNG, BUT NOT IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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ABSTRACT

Background: Cancer cachexia is highly prevalent in advanced non-small cell lung cancer (NSCLC) and locally advanced head and neck squamous cell carcinoma (LAHNSCC), and compromises treatment tolerance and overall survival (OS). NSCLC and LAHNSCC patients share similar risk factors, and receive comparable anti-cancer treatment regimens.

The aim of this study was to determine the predictive value of body composition assessed by bioelectrical impedance analysis (BIA) and handgrip strength (HGS) (baseline and early changes during therapy) on OS in NSCLC and LAHNSCC patients treated with platinum-based chemoradiotherapy (CRT) or cetuximab-based bioradiotherapy (BRT). To elucidate potential underlying determinants of early changes in body composition and HGS, specific (fat and fat-free) mass loss patterns of squamous NSCLC (sNSCLC) were compared to human papilloma virus negative (HPV-) LAHNSCC patients treated with CRT.

Methods: Between 2013 and 2016, BIA and HGS were performed at baseline and after three weeks of CRT/BRT in LAHNSCC and NSCLC patients treated with curative intent.

Results: Two hundred thirty-three patients were included for baseline measurements. Fat-free mass index (FFMI) and HGS<10th percentile of reference values at baseline were both prognostic for poor OS in NSCLC and LAHNSCC (HR 1.64 [95%CI 1.13-2.39], p=0.01 and HR 2.30 [95%CI 1.33-3.97], p=0.003 respectively), independent of Charlson Comorbidity Index, cancer site, and gross tumor volume. Early fat mass (FM) loss during CRT was predictive for poor OS in sNSCLC (n=64) (HR 3.80 [95%CI 1.79-8.06] p<0.001) but not in HPV- LAHNSCC (n=61). In patients with significant weight loss (>2%) in the first three weeks of CRT (sNSCLC n=24, HPV- LAHNSCC n=23), the FM change was -1.4 ± 14.5% and -8.7 ± 9.0% in sNSCLC and HPV- LAHNSCC patients respectively (p<0.05). Fat fee mass change was -5.6 ± 6.3% and -4.0 ± 4.3% for sNSCLC and HPV- LAHNSCC respectively (p=0.31).

Conclusion: FFMI and HGS<10th percentile at baseline are independent prognostic factors for poor OS in NSCLC and LAHNSCC patients treated with CRT/BRT. The specific composition of mass loss during first three weeks of CRT significantly differs between sNSCLC and HPV- LAHNSCC patients. Early FM loss was prognostic in sNSCLC only.

INTRODUCTION

In clinical practice, patients with head and neck squamous cell carcinoma (HNSCC) and non-small cell lung cancer (NSCLC) share comparable disease and patient characteristics. For example, smoking is a risk factor for developing both cancer types and histopathologically, in case of squamous cell carcinoma (SCC), one cannot easily distinguish HNSCC from NSCLC. [1, 2] Furthermore, the prevalence of comorbidity such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease is high in both HNSCC and NSCLC. [3-6] Before the introduction of immunotherapy, standard treatment of locally advanced NSCLC (stage III) included platinum-based chemoradiotherapy (CRT) with disappointing 3 and 5-year overall survival (OS) rates of 43% and 30%. [7] However, addition of treatment with durvalumab after concurrent CRT has improved OS to a 3-year OS rate of 57%. [8] CRT regimens are also being used in patients with locally advanced HNSCC (LAHNSCC, stage III-IV), and their 5-year OS rates of 34-49% are slightly higher. [9, 10] To improve success rates of CRT, it is highly desirable that patients' physical condition and body composition is optimal upon start and maintained during treatment, so patients are more likely to complete the planned treatment trajectory without interruptions of chemotherapy and/or radiation dose reduction due to grade 3-4 toxicity. [11-15]

The efficacy of treatment is not only dependent on tumor aspects, but research in many cancer populations has shown that individual patient characteristics including body weight and body composition play an important role. Cancer cachexia, a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, [16] is known for being a negative prognostic factor in a wide range of cancer patients, including locally advanced NSCLC and LAHNSCC. [17] A significant adverse effect of early weight loss during CRT on OS was observed in stage III NSCLC patients, independent of the onset of therapy induced esophagitis. [18-21] In LAHNSCC, significant weight loss was also observed in the first three weeks of CRT, which is before onset of the expected therapy induced oral and pharyngeal mucositis. [22, 23] In addition to body weight, data on body composition and the presence of sarcopenia/cancer cachexia, could provide information on the expected prognosis of the patient and may therefore support the multidisciplinary team in clinical decision-making. However, loss of skeletal muscle mass on CT scan has shown to be of negative prognostic value in both NSCLC as head and neck cancer. [24-26] Furthermore, this technique is expensive and time consuming and

therefore not routinely feasible in daily clinical practice Bioelectrical impedance analysis (BIA) combined with handgrip strength (HGS) measurements can easily be implemented in daily clinical care and in a community setting to assess fat mass (FM), fat-free mass (FFM), and muscle strength, during treatment. [27] Studies have shown that loss of FM and FFM during therapy measured by BIA were correlated to loss of health-related quality of life. [28, 29] However, the effect of specific (fat or fat-free) body mass loss during the first three weeks of treatment on OS, measured by BIA and HGS, has not been investigated for locally advanced NSCLC and LAHNSCC. The aim of this study was to assess the relationship between FM, FFM, and HGS at baseline and changes hereof during first three weeks of treatment on the one hand versus OS on the other hand in advanced cancer patients treated with concurrent CRT or cetuximab-based bioradiotherapy (BRT) with curative intent. In order to clarify potential underlying determinants of changes in body composition and HGS, we also compared specific (fat and fat-free) mass loss patterns of NSCLC to LAHNSCC patients. Because differences in histology (squamous versus non-squamous), tumorgenesis (human papilloma virus positive (HPV+) versus HPV negative (HPV-)), and treatment (cetuximab vs platinum based) may influence metabolism and therapy response, [30-33] this analysis is performed in a more homogeneous subgroup of squamous NSCLC (sNSCLC) and HPV- LAHNSCC patients treated with platinum-based CRT. We hypothesize that a low fat-free mass index (FFMI), as a proxy for total body muscle mass, before start of treatment is a negative predictor for OS in both locally advanced NSCLC and LAHNSCC. We expect total weight loss and in particular FM loss to be higher in LAHNSCC due to an additional impaired oral intake in a subset of these patients, depending on tumor site, the presence of oropharyngeal dysphagia, prior head and neck surgery, and dental extraction prior to receiving high dose radiotherapy. [34, 35] Presuming comparable treatment induced systemic catabolic activity in LAHNSCC and NSCLC patients, we expect no differences between the groups in FFM changes during the first three weeks of CRT.

MATERIALS AND METHODS

Study design and population

Patients were followed as part of a larger prospective cohort study conducted at MAASTRO Clinic, Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands (ClinicalTrials.gov Identifier: NCT01985984, LAHNSCC population

only). The Institutional Review Board of MAASTRO Clinic approved the study. Patients with stage III NSCLC were referred from four different hospitals in the Netherlands to MAASTRO Clinic for radiotherapy as part of a concurrent platinum-based CRT protocol with curative intent between January 2013 and June 2015. Patients with LAHNSCC undergoing primary or adjuvant concurrent CRT/BRT with curative intent in MAASTRO Clinic and MUMC+ between 2013 and 2016 were included. All patients with body weight assessment, BIA measurements, and HGS measurements at baseline and during week three of treatment were included in the study. Patients presenting concurrent malignancies beside the locally advanced NSCLC or LAHNSCC were excluded.

First, the effect of baseline characteristics on OS (part I) was evaluated in NSCLC and LAHNSCC patients undergoing radiotherapy and any concurrent systemic therapy.

In order to elucidate possible underlying mechanisms contributing to weight loss in the first three weeks of therapy in both patient groups (part II), exclusion of potential confounders was considered essential. Only patients with SCC were included in the second part of this study. LAHNSCC patients receiving cetuximab as radiosensitizer, and tumors that were positive for p16 (p16+), a surrogate marker for HPV, were excluded. In this cohort, the p16 status was available for all oropharyngeal tumors, but subsequent HPV RT-PCR analysis was not performed in all cases. For the convenience of the reader, p16+ tumors are referred to as HPV+ in this manuscript.

Oncological treatment

For NSCLC, the concurrent systemic therapy consisted of three cycles of cisplatin (100 mg/m^2 q3w) or carboplatin (AUC5 on day 1) in combination with etoposide (100 mg/m2 day 1-3) administered every three weeks. Radiotherapy was applied in 30-33 daily fractions of 2 Gy up to a total dose of 60-66 Gy. [36, 37]

In LAHNSCC patients, concurrent cisplatin was administered intravenously on days 1, 22, and 43, in doses of 100 mg/m^2 in case of primary and adjuvant treatment. [15, 38] Adjuvant CRT was given in case of extra nodal extension in neck dissections and/or irradical tumor resection margins. In case of contra-indications for cisplatin, and only in a primary treatment setting, cetuximab was administered weekly in doses of 250 mg/m^2, preceded by a loading dose of 400 mg/m^2, one week before

radiotherapy initiation in a primary treatment setting only. [14] Radiotherapy was applied in 33-35 fractions up to a total dose of 66-70 Gy.

Measurements

Body composition was assessed using single-frequency (50 kHz) BIA (Omron Healthcare Group, Hoofddorp, The Netherlands). FFMI was calculated by dividing FFM in kg by height in meters squared. Low FFM was defined as a FFMI below the 10th percentile (FFMI<P_{10}), corrected for age and gender according to Schutz et al. [39]

HGS was measured with a Jamar hydraulic hand dynamometer (JA Preston Corporation, Jackson, MI, USA). The measurements were repeated three times for the left and right hand and the highest value for both sides was registered. Follow up HGS was chosen based on the side with the highest value at baseline. Low HGS was defined as HGS below the 10th percentile (HGS<P_{10}) of the UK Biobank reference values, taking gender, age and height into account. [40]

Weight, BIA and handgrip strength measurements were performed in the outpatient clinic within office hours and prior to chemotherapy infusion to minimalize the influence of chemotherapy and fluid.

World Health Organization Performance Status (WHO PS) was assessed by the radiation oncologist at the initial visit. The Charlson Comorbidity Index (CCI) [41] was determined by review of individual medical records. The current malignant disease was not taken into account when rating “solid tumor” in the CCI. The cut-off for high CCI was set at ≥4.

Weight loss, FM loss, and FFM loss were turned into binary variables, where losses were compared to stable or increased mass. The cut-off for significant weight loss was set on -2% based on recent guidelines. [42] To minimize potential effects of measurement errors, the cut-off values for the specific mass losses (FM and FFM) were set at 1% mass loss.

Gross tumor volume (GTV) was retrieved from records of radiation dosimetry data and divided in GTV of primary tumor (GTV_p), GTV of involved lymph nodes (GTV_n), and the total GTV of primary tumor and lymph nodes combined (GTV_{total}). For LAHNSCC patients, all GTV data were retrieved from patients that underwent

primary CRT/BRT. In patients undergoing postoperative CRT, GTV's were only registered in case of tumor residue or regrowth in the period between surgery and start of radiotherapy.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, New York, USA). Descriptive statistics were reported in frequency distributions and absolute numbers by using independent samples t-test and χ^2 test. Paired samples t-test was used to evaluate mass loss.

Survival analysis was performed through Kaplan Meier (Logrank Mantel–Cox test) and Cox regression. All variables were screened for their effect on OS through univariable Cox regression. Factors with $p<0.30$ were selected as potentially relevant predictor variables and were entered in a multivariable Cox regression model. Stepwise backward elimination was carried out to omit all variables without an effect on OS from the model using a *p*-value for selection of 0.10.

RESULTS

Patients and baseline characteristics

Between January 2013 and July 2015, 172 patients with pathologically proven stage III NSCLC were referred to MAASTRO Clinic for concurrent CRT. In 124 patients, HGS and BIA measurements were performed at baseline and during treatment (part I). Sixty-four of the 124 NSCLC patients had histologically proven SCC and were included in part II of the study. Hundred-ninety-two LAHNSCC patients were treated with primary or adjuvant CRT/BRT between 2013 and 2016. Baseline and follow-up measurements in week three of CRT were available in 109 patients (part I), of which 61 were HPV- tumors receiving cisplatin as radiosensitizer (part II). Table 1 summarizes the baseline patient characteristics.

Table 1 – Baseline characteristics (n=233).

Variables		
Gender	Male	159
	Female	74
Age	Mean ± SD, years	62 ± 9
Smoking status	Active/former	214
	Never	14
	Unknown	5
Cancer site	Lung	124
	Head and neck	109
Histology	Squamous	173
	Non-squamous	60
GTV_p	Total (Mean ± SD, cm^3)	52.1 ± 88.4
	Squamous NSCLC	86.2 ± 131.9
	Non-squamous NSCLC	69.4 ± 86.5
	Primary LAHNSCC	29.3 ± 35.5
	Post-op LAHNSCC*	4.6 ± 4.4
GTV_n	Total (Mean ± SD, cm^3)	19.0 ± 26.5
	Squamous NSCLC	24.9 ± 30.6
	Non-squamous NSCLC	23.4 ± 23.3
	Primary LAHNSCC	16.5 ± 27.0
	Post-op LAHNSCC*	8.9 ± 14.8
GTV_{total}	Total (Mean ± SD, cm^3)	71.3 ± 91.8
	Squamous NSCLC	111.0 ± 132.9
	Non-squamous NSCLC	93.4 ± 84.6
	Primary LAHNSCC	45.8 ± 41.7
	Post-op LAHNSCC*	13.5 ± 14.1
Mean heart dose (NSCLC only)	Total (Mean ± SD, Gy)	9.0 ± 8.0
	Squamous NSCLC	9.1 ± 8.5
	Non-squamous NSCLC	8.9 ± 7.4
Systemic therapy	Platinum + etoposide (NSCLC)	124
	Platinum (LAHNSCC)	84
	Cetuximab (LAHNSCC)	29
BMI (kg/m^2)	Total	24.4 ± 4.2
	Male	24.8 ± 4.1
	Female	23.5 ± 4.4
FMI (kg/m2)	Total	6.8 ± 2.8
	Male	6.4 ± 2.6
	Female	7.7 ± 3.2
FFMI (kg/m^2)	Total	17.6 ± 2.5
	Male	18.4 ± 2.2
	Female	15.8 ± 1.9
FFMI	$<P_{10}$	71
	P_{10} or higher	162
HGS	$<P_{10}$	20
	P_{10} or higher	213
WHO PS	0 - 1	218
	2	15
History of COPD	Yes	165
	No	66
	Unknown	2

Variables		
CCI	0-3	175
	4 or higher	58
Disease stage	IIIA	52
NSCLC only	IIIB	53
	IIIC	19
Disease stage	II	3
LAHNSCC only	III	19
	IV	88
Dysphagia	CTCAE ≥ 2	30
LAHNSCC only	CTCAE < 2	79
p16 status	Positive oropharynx tumor	23
LAHNSCC only	Others	86
Adjuvant or primary	Primary	23
LAHNSCC only	Adjuvant	86

*Disease stage is based on TNM 7 classification. [55] Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FMI, fat mass index; FFMI, fat-free mass index; P_{10}, tenth percentile according to reference values Spruit [40] and Schutz [39]; GTV_p, gross tumor volume of primary tumor; GTV_n, gross tumor volume of lymph nodes involved, GTV_{total} combined GTV of both primary tumor and lymph nodes, HGS, handgrip strength; WHO PS, world health organization performance status. p16 is a surrogate marker for Human Papillomavirus infection, Mean values are presented with ± SD. *Only from five patients with tumor residual or regrowth after surgery.*

Part I - Prognostic value of baseline characteristics for overall survival

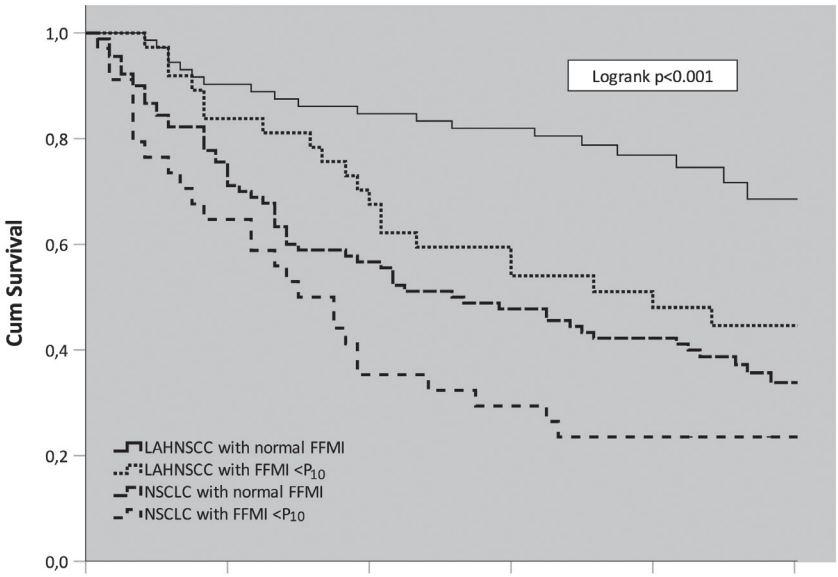
A Cox regression analysis was performed in the total cancer population (n=233) to determine any confounding factors for OS within the baseline characteristics (Table 2). Using univariable analysis for the total population, the following variables yielded a *p*-value <0.30 and were considered potentially relevant prognostic factors suitable for multivariate analysis: age, WHO PS, CCI, cancer site (NSCLC vs. LAHNSCC), history of COPD, FFMI<P_{10}, HGS<P_{10}, and GTV. Using multivariable Cox regression analysis, only CCI ≥ 4, cancer site being NSCLC, FFMI<P_{10}, HGS<P_{10}, and GTV_{total} remained statistically significant and were considered independent prognostic factors for OS. Kaplan Meier survival curve plotted in Figure 1 shows significant differences in OS for four different categories: LAHNSCC patients with normal FFMI, LAHNSCC patients with FFMI<P_{10}, NSCLC patients with normal FFMI, and NSCLC patients with FFMI<P_{10} (Logrank Mantel Cox p<0.001). Two and five year OS rate for LAHNSCC patients with normal FFMI was 85% and 69% respectively, compared to 68% and 45% for LAHNSCC patients with FFMI<P_{10}. For NSCLC patients, two and five year OS rate was 57% and 34% respectively for those with normal FFMI, compared to 35% and 24% for NSCLC patients with FFMI<P_{10}.

Table 2 – Cox regression analysis of baseline characteristics on OS (n=233).

	Univariate analysis				Multivariate analysis			
		CI 95%				CI 95%		
Covariate	**HR**	**Lower**	**Upper**	***p*-value**	**HR**	**Lower**	**Upper**	***p*-value**
Male gender	1.10	0.75	1.62	0.62				
Age	1.03	1.01	1.06	**0.004**				
WHO PS (≥ 2)	2.49	1.37	4.53	**0.003**	1.78	0.94	3.38	**0.08**
CCI ≥ 4	1.89	1.30	2.76	**0.001**	1.52	1.02	2.27	**0.04**
Active/past smoker	1.13	0.60	2.12	0.70				
Cancer site (NSCLC)	2.51	1.72	3.67	**<0.001**	2.12	1.40	3.22	**<0.001**
History of COPD*	1.35	0.93	1.97	0.12				
FFMI ≤ P10	1.61	1.12	2.31	**0.01**	1.64	1.13	2.39	**0.01**
FMI ≤ P10	1.06	0.63	1.79	0.83				
HGS < p10	2.51	1.48	4.26	**0.001**	2.30	1.33	3.97	**0.003**
GTV_p	1.003	1.001	1.004	**0.001**				
GTV_n	1.009	1.004	1.014	**0.001**				
GTV_{total}	1.003	1.002	1.005	**<0.001**	1.002	1.000	1.004	**0.02**

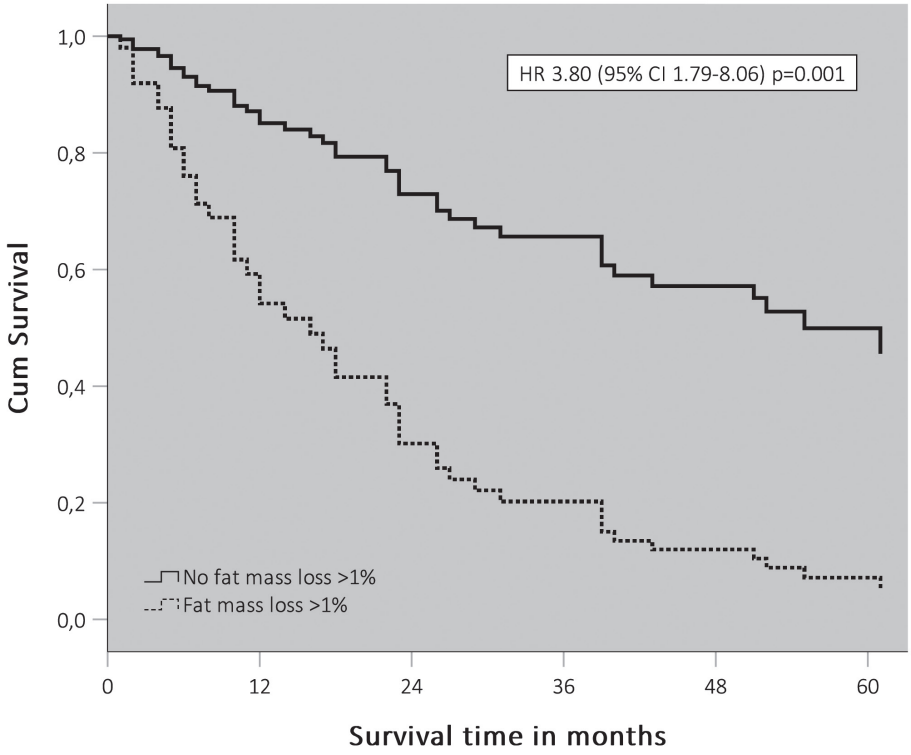
*Disease stage is based on TNM 7 classification. [55] *two missing. Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FFMI, fat-free mass index; FMI, fat mass index; GTV_n, gross tumor volume of lymph nodes involved; GTV_p, gross tumor volume of primary tumor; GTV_{total} combined GTV of both primary tumor and lymph nodes; HGS, handgrip strength; P_{10}, tenth percentile according to reference values Spruit [40] and Schutz [39]; WHO PS, world health organization performance status.*

Figure 1 - Kaplan Meier survival plot of baseline FFMI< P_{10} per cancer site



No. at risk						
LAHNSCC with normal FFMI	72	65	61	59	34	12
LAHNSCC with FFMI <P_{10}	37	31	25	20	15	6
NSCLC with normal FFMI	90	67	51	43	38	14
NSCLC with FFMI <P_{10}	34	22	12	10	8	6

Figure 2 - Cox regression survival plot of early fat mass loss in squamous NSCLC



Part II - Fat mass, fat-free mass and handgrip strength changes

As stated in the method section, a sub analysis was performed to rule out potential confounders affecting weight loss. Supplemental Table A1 provides an overview of baseline characteristics of the 64 sNSCLC and 61 HPV- LAHNSCC patients. No statistically significant group differences were observed for the variables gender, smoking status, BMI, FMI, FFMI, HGS, WHO PS, and history of COPD. Mean GTV's were significantly higher in sNSCLC patients and a CCI ≥ 4 was more prevalent in sNSCLC patients compared to HPV- LAHNSCC patients, which might be explained by an additional significantly younger age of the latter group.

To evaluate the effect of early mass loss (FM or FFM) on OS, Cox regression analysis was performed for the sNSCLC (n=64) and HPV- LAHNSCC (n=61) subgroup separately. Multivariable Cox regression analysis in the sNSCLC population showed

the independent prognostic value of age (HR 1.08 [95%CI 1.03-1.14] *p*=0.001), WHO PS ≥ 2 (HR 2.59 [95%CI 1.05-6.36] *p*=0.04), FM loss >1% in first three weeks of therapy (HR 3.80 [95%CI 1.79-8.06] *p*=0.001), and GTV_n (HR 1.016 [95%CI 1.006-1.026] *p*=0.002). A trend of worse OS could be observed in case of FFM loss >1% (HR 1.85 [95%CI 0.90-3.82] *p*=0.09) (Table 3a and figure 2). In HPV- LAHNSCC patients treated with CRT, multivariable analysis displayed no independent prognostic factors (Table 3b).

Tabel 3a – Cox regression analysis of early mass loss in sNSCLC (n=64).

	Univariate analysis				Multivariate analysis			
		CI 95%				CI 95%		
Covariate	**HR**	**Lower**	**Upper**	***p*-value**	**HR**	**Lower**	**Upper**	***p*-value**
Male gender	0.99	0.47	2.05	0.97				
Age	1.06	1.01	1.11	**0.01**	1.08	1.03	1.14	**0.001**
WHO PS (≥ 2)	3.03	1.33	6.88	**0.008**	2.59	1.05	6.36	**0.04**
CCI ≥ 4	1.35	0.74	2.48	0.33				
Active/past smoker	1.25	0.37	4.18	0.72				
History of COPD	1.25	0.68	2.30	0.47				
Disease stage								
IIIA	1.34	0.67	2.66	0.53				
IIIB	1.53	0.70	3.34	0.41				
IIIC				0.29				
FFM loss >1%	1.73	0.94	3.15	**0.08**	1.85	0.90	3.82	0.09
FM loss >1%	2.23	1.23	4.06	**0.008**	3.80	1.79	8.06	**0.001**
HGS loss >1%	0.87	0.48	1.57	0.64				
GTV^p	1.001	0.998	1.004	0.46				
GTV^n	1.008	1.001	1.016	**0.03**	1.016	1.006	1.026	**0.002**
GTV^{total}	1.002	0.999	1.004	0.18				
Mean heart dose	1.029	0.995	1.066	0.10				

*Disease stage is based on TNM 7 classification; Underlined values indicate p-*value *below 0.30. Bold values indicate statistical significance at the p-*value *of 0.050. Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease. FFM, fat-free mass, FM, fat mass,* GTV_n*, gross tumor volume of lymph nodes involved,* GTV_p*, gross tumor volume of primary tumor;* GTV_{total} *combined GTV of both primary tumor and lymph nodes; HGS, handgrip strength; WHO PS, world health organization performance status.*

The proportion of patients experiencing significant weight loss (>2%) during first three weeks of therapy did not significantly differ between sNSCLC and HPV- LAHNSCC, 24/64 versus 23/61 respectively (*p*=0.98). In these weight losing patients, proportional weight loss did not significantly differ between sNSCLC and LAHNSCC, -4.8 ± 2.6% (mean ± SD) and -5.2 ± 2.1% respectively, *p*=0.62. However,

when distinguishing the composition of body mass loss, a significant difference was observed: FM change was -1.4 ± 14.5% and -8.7 ± 9.0% in sNSCLC and HPV- LAHNSCC patients respectively (p<0.05). FFM change was -5.6 ± 6.3 and -4.0 ± 4.3% for sNSCLC and HPV- LAHNSCC respectively (p=0.31). Specification of the composition of body mass loss for the total 125 patients is provided in the supplemental Table A2.

Table 3b – Cox regression analysis of early mass loss in HPV- LAHNSCC receiving platinum based systemic therapy (n=61).

	Univariate analysis				**Multivariate analysis**			
		CI 95%				**CI 95%**		
Covariate	**HR**	**Lower**	**Upper**	***p*-value**	**HR**	**Lower**	**Upper**	***p*-value**
Male gender	2.93	0.87	9.45	0.08	2.93	0.87	9.45	0.08
Age	0.98	0.93	1.02	0.34				
WHO PS (≥ 2)	1.53	0.21	11.5	0.68				
CCI ≥ 4	1.34	0.18	10.0	0.77				
Active/past smoker	0.48	0.14	1.62	0.24				
History of COPD	1.09	0.42	2.78	0.86				
Disease stage								
II	0.39	0.04	3.50	0.80				
III	0.57	0.08	4.34	0.40				
IVa	0.37	0.02	5.97	0.59				
IVb				0.48				
Dysphagia CTCAE ≥ 2	0.87	0.32	2.35	0.78				
Adjuvant	0.99	0.40	2.4	0.98				
FFM loss >1%	1.03	0.45	2.39	0.94				
FM loss >1%	1.63	0.60	4.41	0.34				
HGS loss >1%	1.25	0.51	3.06	0.63				
GTV_p	1.004	0.996	1.012	0.33				
GTV_n	1.005	0.980	1.031	0.68				
GTV_{total}	1.004	0.996	1.012	0.28				

*Disease stage is based on TNM 7 classification; Underlined values indicate p-value below 0.30. Bold values indicate statistical significance at the p-*value *of 0.050. Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease. FFM, fat-free mass, FM, fat mass, GTV_n, gross tumor volume of lymph nodes involved, GTV_p, gross tumor volume of primary tumor; GTV_{total} combined GTV of both primary tumor and lymph nodes; HGS, handgrip strength; WHO PS, world health organization performance status.*

DISCUSSION

This study was conducted to elucidate the effect of body composition and HGS before start of treatment and early changes of FM, FFM, and HGS during CRT on OS in patients diagnosed with NSCLC or LAHNSCC.

HGS and FFMI $<P_{10}$ at baseline as a surrogate marker for muscle wasting were both negative prognostic factors for OS, independent of cancer site (NSCLC or LAHNSCC) and GTV. This is in full accordance with the current literature on muscle wasting in cancer patients. [43-45] While the effect of muscle wasting on OS is not new, our results emphasize that simple measurements such as BIA and HGS can detect muscle wasting in NSCLC and LAHNSCC patients in an early phase of treatment.

Previously, our group revealed the prognostic significance of early weight loss in NSCLC patients. [20] In the current study, we confirmed this finding and unraveled the components of this early weight loss and the effect on OS. Strikingly, in multivariable Cox regression analysis, FM loss remained a significant prognostic factor for OS in sNSCLC, but not in HPV- LAHNSCC patients.

The analysis of specific mass loss patterns was carried out presuming comparable patient characteristics between both cancer populations, by leaving out adenocarcinoma, HPV+ LAHNSCC, and cetuximab as systemic therapy (part II). However, our analysis revealed a higher CCI in sNSCLC, as a result of an additional higher mean age of this group, which is a parameter in the CCI calculation. Also, GTV was higher in NSCLC compared to LAHNSCC. Yet, despite these differences, body composition parameters were similar for both groups, which allowed further comparison.

While we hypothesized to find a higher weight loss in LAHNSCC due to tumor location related factors impairing oral intake, our results show otherwise. The percentage of early weight loss (first three weeks of CRT) was comparable between NSCLC and LAHNSCC patients, and the proportion of patients that experienced significant weight loss (>2%) was similar between both cancer sites. Nevertheless, evaluating the composition of weight loss, in particular FM and FFM loss, our data revealed different patterns for both sub groups. CRT receiving HPV- LAHNSCC patients with significant weight loss seemed to lose FM in particular, which was significantly higher than in sNSCLC patients. sNSCLC patients with significant weight loss (>2%) seem to lose predominantly FFM. Both sNSCLC and HPV-

LAHNSCC patients experiencing significant weight loss showed a decrease in FFM, with a trend towards higher FFM loss in sNSCLC patients.

We believe potential explanations for the differences in body composition changes and the prognostic value of early weight loss are multifactorial, including patient characteristics, tumor metabolism and load, and treatment related factors.

The higher CCI and the higher prevalence of COPD in sNSCLC patients suggest an additional burden on systemic inflammation, which is known to contribute to muscle wasting. [46] However, one would also expect baseline group differences in body composition, which were not observed. Additionally, there could be an underestimation of the COPD prevalence in LAHNSCC patients, as these patients are not routinely tested for COPD. Furthermore, when evaluating the subgroup of HPV-LAHNSCC patients receiving cisplatin as radiosensitizer (part II), the CCI may be lower than in sNSCLC due to the strictly applied selection criteria for receiving platinum-based CRT in LAHNSCC: In case of significant (cardiac, pulmonary, and renal) comorbidity, platinum based treatment is withheld in LAHNSCC and cetuximab is used as radiosensitizer. The latter was excluded in the subanalysis of part II. Therefore, organ dysfunction related to comorbidities is probably barely present in the HPV-LAHNSCC treated with cisplatinum-based CRT subgroup, in contrast to the sNSCLC patients, where carboplatin is offered in case of contraindications for cisplatin. [47]

Tumor characteristics such as location, size, and tumor metabolism differ between the sNSCLC and HPV- LAHNSCC group. The higher amount of FM loss in LAHNSCC might be due to oral intake-related factors (tumor location, prior head and neck surgery, odynophagia, or dysphagia) rather than high catabolic activity causing muscle wasting, which was more pronounced in NSCLC. Early dietary consultation in LAHNSCC has a positive effect on weight maintenance. [48] Conceivably, administration of oral nutritional supplements or tube feeding in LAHNSCC may have blurred the effects of weight loss on OS. Unfortunately, reliable information on the exact nutritional support given could not be retrieved from the medical records. Interventions to improve or maintain body weight and muscle mass in particular are under investigation, but have not resulted in standardized supportive treatment protocols yet. The current study results support the need for further research into interventions for these patient groups.

Yet, a key point in cancer cachexia is that it cannot be fully reversed by nutritional support, and systemic inflammation plays an important role in both muscle

and FM loss. [49] Both tumor and host tissue can produce cytokines leading to inflammation. It has been reported that systemic inflammation is correlated with tumor volume [50] and previous studies have shown the prognostic value of GTV. [51] Our results show the prognostic value of GTV independent of baseline FFMI<P_{10}, suggesting higher systemic inflammation in more voluminous tumors. [50]

It is likely that also oncological treatment related factors play a role in the prognostic value of early mass loss in NSCLC but not in LAHNSCC. While concurrent systemic therapy for LAHNSCC consists of cisplatin only, platinum derivatives combined with etoposide are used for NSCLC. Platinum-based regimens are known to induce the release of pro-cachectic cytokines and myostatin, activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which is associated with muscle wasting. [52] Etoposide has also shown to induce muscle wasting. [53] The combination of both drugs might accelerate muscle wasting in NSCLC. Also, GTV was higher in NSCLC versus LAHSNCC, meaning that more cells will experience DNA-damage during radiation, which can result in a higher pro-inflammatory environment. [54]

We are aware that our research has limitations. Generally accepted cut off points for FM and FFM loss have not been defined in the literature. For exploratory purposes, we chose an arbitrary cut-off on an empirical basis. Additionally, standardized information on oral intake and the use of nutritional supplements or tube feeding was lacking. Evaluating FM through BIA does not provide information on the type of fat being lost, e.g. visceral adipose tissue or subcutaneous adipose tissue. Furthermore, BIA does not allow for separate analysis of changes in skeletal muscle index only, but FFMI reflects skeletal muscle mass. The last limitation we would like to address is our study did not include progression free or disease free survival analyses. However, CCI was added in our OS analyses to adjust for the effects of comorbidities on OS.

In conclusion, our study showed that low (<P_{10}) HGS and FFMI at baseline are independent prognostic factors for poor OS in NSCLC and LAHNSCC patients treated with CRT/BRT with curative intent. Despite comparable patient characteristics, treatment, and histological tumor characteristics, the specific composition of mass loss during the first three weeks of CRT significantly differs between sNSCLC and HPV- LAHNSCC patients and early loss of FM was prognostic in sNSCLC only. Further research is needed to unravel the pathophysiology of early weight loss during oncological treatment in order to develop patient-tailored intervention studies.

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APPENDIX

Table A1 – Baseline characteristics squamous NSCLC and HPV- LAHNSCC treated with platinum-based systemic therapy.

Variables		**LAHNSCC** n=61 (%)	**NSCLC** n=64 (%)	***p*-value**
Gender	Male	43 (70)	50 (78)	0.33
	Female	18 (30)	14 (22)	
Mean age	Mean ± SD, years	58 ± 8	67 ± 8	**<0.001**
Smoking status	Never	5 (8)	1 (2)	0.11
	Active/former	56 (92)	61 (95)*	
BMI (kg/m^2)	Total	23.9 ± 4.0	24.6 ± 4.0	0.33
	Male	23.9 ± 3.8	24.6 ± 4.0	0.44
	Female	23.8 ± 4.5	24.7 ± 4.1	0.58
FMI (kg/m2)	Total	6.3 ± 2.6	6.8 ± 2.8	0.29
	Male	5.7 ± 2.1	6.3 ± 2.6	0.17
	Female	7.8 ± 3.1	8.4 ± 3.0	0.55
FFMI (kg/m^2)	Total	17.6 ± 2.5	17.8 ± 2.0	0.65
	Male	18.3 ± 2.4	18.2 ± 1.9	0.94
	Female	16.0 ± 2.2	16.2 ± 1.6	0.78
FFMI	<P_{10}	22 (36)	19 (30)	0.57
	P_{10} or higher	39 (64)	45 (70)	
HGS	<P_{10}	3 (5)	8 (13)	0.21
	P_{10} or higher	58 (95)	56 (87)	
WHO PS	0 - 1	59 (97)	57 (89)	0.16
	2	2 (3)	7 (11)	
History of COPD	Yes	16 (26)	24 (38)	0.16
	No	45 (74)	39 (62)**	
CCI	0-3	59 (97)	40 (63)	**<0.001**
	4 or higher	2 (3)	24 (37)	
Disease stage	IIIA	-	25 (39)	-
	IIIB	-	26 (41)	
	IIIC	-	13 (20)	
Disease stage	II	2 (3)	-	-
	III	14 (23)	-	
	IVa	42 (69)	-	
	IVb	3 (5)		
GTV_p	Mean ± SD, cm^3	31.9 ± 41.4	86.2 ± 131.9	**0.01**
GTV_n	Mean ± SD, cm^3	11.4 ± 18.7	24.9 ± 30.6	**0.01**
GTV_{total}	Mean ± SD, cm^3	43.3 ± 42.2	111.0 ± 132.9	**0.002**
Mean heart dose	Mean ± SD, Gy	-	9.1 ± 5.7	-
Dysphagia	CTCAE ≥ 2	15 (25)	-	-
	CTCAE <2	46 (74)	-	
Adjuvant or primary	Primary	42 (69)	-	-
	Adjuvant	19 (31)	-	

*Percentages do not always add up to 100% due to rounding off to whole numbers. Continuous numbers are presented with ± SD. Bold values indicate statistical significance at the p-value of 0.050. *two missing, **one missing. Disease stage is based on TNM 7 classification. BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary*

disease; FMI, fat mass index; FFMI, fat-free mass index; GTV_p, gross tumor volume of primary tumor; GTV_n, gross tumor volume of lymph nodes involved, GTV_{total} combined GTV of both primary tumor and lymph nodes; HGS, handgrip strength; P_{10}, tenth percentile according to reference values Spruit and Schutz; WHO PS, world health organization performance status; For LAHNSCC, GTV is only displayed for the 42 patients treated with primary CRT.

Table A2 – Percentage changes in weight, fat mass, fat-free mass and handgrip strength in squamous NSCLC and HPV- LAHNSCC, treated with platinum-based systemic therapy.

Variables	**Total population** (n=125)	***p*-value**	**LAHNSCC** (n=61)	***p*-value**	**NSCLC** (n=64)	***p*-value**	***p*-value between LAHNSCC and NSCLC**
Weight	-1.3 ± 3.9	**<0.001**	-1.6 ± 3.3	**<0.001**	-1.0 ± 4.4	0.08	0.38
FM	-0.9 ± 20.5	0.62	-3.2 ± 24.7	0.32	1.2 ± 15.4	0.53	0.23
FFM	-0.9 ± 7.1	0.15	-0.8 ± 7.1	0.36	-1.0 ± 7.1	0.26	0.90
HGS	-4.5 ± 14.3	**0.001**	-6.2 ± 11.2	**<0.001**	-2.9 ± 16.6	0.17	0.19

Mean values are presented with ± SD. Bold values indicate statistical significance at the p-value of 0.050. Abbreviations: FFM, fat-free mass; FM, fat mass; HGS, handgrip strength.

CHAPTER 5

THE PREDICTIVE AND PROGNOSTIC VALUE OF WEIGHT LOSS AND BODY COMPOSITION PRIOR TO AND DURING TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH RECURRENT OR METASTATIC HEAD AND NECK CANCER

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ABSTRACT

Purpose: Response rates of immune checkpoint inhibitor (ICI) therapy for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) are relatively low. This study evaluates the predictive and prognostic value of weight loss and changes in body composition prior to and during ICI therapy for R/M HNSCC.

Methods: This retrospective multicenter cohort study included ninety-eight patients. Patient, tumor, and treatment characteristics were retrieved from health records, including neutrophil and platelet-lymphocyte-ratio (NLR and PLR). PD-L1 expression was additionally determined on residual material. Cachexia was defined according to Fearon et al. (2011). Skeletal muscle (SM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were evaluated on baseline and follow-up computed tomography scans at the third lumbar vertebrae level. Univariable and multivariable regression analyses were performed for six months progression free survival (PFS6m) and overall survival (OS).

Results: Thirty-four patients (35%) experienced significant early weight loss (>2%) during the first six weeks of therapy. This subgroup presented a significantly higher NLR and PLR at baseline. NLR and PLR were inversely correlated with SM and VAT index. Independent predictors of PFS6m were lower world health organization performance status (WHO PS) (HR 0.16 [0.04-0.54] p=0.003), higher baseline SAT index (HR 1.05 [1.02-1.08] p= 0.003), and weight loss <2% (HR 0.85 [0.74-0.98] p=0.03). WHO PS and baseline cachexia in combination with >2% early weight loss were independent predictors of OS (HR 2.09 [1.11-3.92] p=0.02, HR 2.18 [1.13-4.21] p=0.02).

Conclusion: The combination of cachexia at baseline and weight loss during ICI therapy is associated with worse OS in R/M HNSCC patients, independent of PD-L1 expression.

INTRODUCTION

Immune checkpoint inhibitors (ICI) have become of undeniable value in anti-tumor treatment, providing successful outcomes in a selection of patients. While ICI therapy is standard of care for first-line therapy of melanoma and non-small cell lung carcinoma (NSCLC), ICI therapy for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is still relatively new. Three pivotal phase III trials concerning programmed death ligand 1 (PD-L1) targeted immunotherapy in R/M HNSCC have been published. [1-3] An increase in median overall survival (OS) in comparison to standard chemotherapy was found with a durable response. The phase III trial CheckMate 141 trial resulted in the approval of nivolumab in the second-line cisplatin refractory R/M HNSCC setting. [3] Furthermore, the phase III KEYNOTE 040 trial showed similar results with pembrolizumab. [1] Lastly, the phase III KEYNOTE 048 trial demonstrated the efficacy of pembrolizumab as first-line treatment for a subgroup of R/M HNSCC patients. [2] Indeed, unfortunately, only 13-23% of patients ultimately benefitted from anti-PD-1 therapy in these studies, emphasizing the need for better predictive biomarkers to improve patient selection prior to ICI therapy. Patients with tumor cells or tumor infiltrating T-cells expressing PD-L1 seem to benefit more from ICI therapy, but PD-L1 negative tumors are not necessarily ICI-resistant. [1-3] The combined positive score (CPS, total number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100) now serves as a predictive marker of ICI response. [2] Besides PD-L1 expression, the number of tumor infiltrating lymphocytes, tumor microenvironment, and tumor mutational burden are being investigated as potential predictive biomarkers. [4, 5] With PD-L1 CPS as the only predictive biomarker in a standard practice, it remains challenging to identify those patients with low chances of response to avoid unnecessary toxicity and costs without treatment benefit.

Cancer cachexia, a multifactorial syndrome characterized by involuntary weight loss consisting of skeletal muscle and fat mass loss, is a common metabolic problem in HNSCC patients due to the disease itself, to the location of the tumor interfering with adequate caloric intake, and to previous oncological therapy. Cachexia is often accompanied by systemic inflammation, causing a catabolic state that imbalances energy reserves and leads to muscle protein turnover. In turn, this may cause weight loss and muscle mass loss. [6] This syndrome is associated with higher treatment toxicity and shorter survival. [7] Whereas the prognostic value of low muscle mass and weight loss during (chemo)radiotherapy in HNSCC has been well established, [8-

10] the effects of weight loss and changes in body composition before and during ICI therapy are still underexplored. Studies in lung cancer have presented early weight loss during ICI therapy in terms of visceral and subcutaneous adipose tissue (VAT and SAT) loss and low SM mass at start of the ICI therapy as predictors for OS. [11, 12] A recent study of Arribas et al. has determined the prognostic importance of skeletal muscle mass index (SMI) at baseline in a population of HNSCC patients receiving ICI therapy with or without concurrent chemotherapy. [13] However, weight loss and changes in body composition prior to and during ICI monotherapy were not studied and adipose tissue compartments were not evaluated separately. Therefore, the aim of this study is to evaluate the predictive and prognostic value of weight loss and changes in body composition prior to and during ICI therapy, considering additional patient, disease, and immune system characteristics. In this context, the effects of weight loss and changes in body composition on six-month progression free survival (PFS6m), OS, and autoimmune toxicity in R/M HNSCC were explored.

METHODS

Study design and patient selection

A retrospective study design was completed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. [14] This study was approved by the Medical Ethics Committee of Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands (METC 2019-1403) and University Hospitals Leuven (UZL), Leuven, Belgium (S65364). The study sample was derived from a population with R/M HNSCC who presented for PD-1 or PD-L1 inhibitor monotherapy at the department of General Medical Oncology of UZL/ Leuven Cancer Institute and the Comprehensive Cancer Center of MUMC+ between January 1st 2014 and March 17th 2020. Patients were excluded in case they received concomitant chemotherapy or other immune modulators (e.g., cytotoxic T-lymfocyte associated protein 4 (CTLA-4) inhibitors), had a second primary malignancy, had no baseline and/or first follow-up computed tomography (CT) scan at the level of the third lumbar vertebrae (L3), or if baseline weight measurement was lacking.

Clinical characteristics including patient, tumor, (previous) oncological treatment characteristics, and the amount of previous palliative systemic treatment lines were retrospectively extracted from the electronic health records. At baseline the World Health Organization performance status (WHO PS) [15] was determined for every patient by the oncologist. The individual Charlson comorbidity index (CCI)

[16] was calculated based on the medical history in the electronic health records. The CCI was then dichotomized based on the median. Autoimmune toxicity was evaluated by the oncologist throughout the treatment trajectory using Common Terminology Criteria for Adverse Events (CTCAE). [17] This variable was dichotomized into CTCAE grade 2 or higher versus CTCAE grade 0 or 1. Based on results from Weber et al., [18] the cut-off for the evaluation period of autoimmune toxicity was set at six months after ICI initiation.

Long-term responders were defined as patients receiving ICI therapy for at least six months, in other words, patients who had a progression free survival of more than six months (PFS6m) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines. [19] The six month cut-off was chosen based on a recent meta-analysis, reporting that six month durable response is prognostic of twelve month OS in ICI studies. [20] OS was evaluated from the first day of ICI administration to the date of death or the date of last follow-up.

Body composition

Abdominal CT scans performed at baseline and at first evaluation as per internal protocol were collected from the database of the radiology department at UZL and MUMC+, and subsequently pseudonymized. Baseline scans were not older than 30 days at start of ICI therapy. The most cranial CT slice on level L3 clearly displaying both vertebral transverse processes was selected for delineation using sliceOmatic software v5.0 (TomoVision, Montreal, Quebec, Canada). An experienced researcher (over 750 measured CT scans) delineated the areas of interest on the scans and performed the body composition measurements. The observer was blinded to the moment of CT assessment (baseline versus follow-up) and to the identity and medical history of the patients. Cross sectional areas (CSA) of SM, VAT, and SAT were measured using pre-established thresholds of Hounsfield units (SM −29 to 150, VAT −150 to −50, and SAT −190 to −30). SMI, VAT index (VATI), and SAT index (SATI) were calculated using the CSA of SM, VAT, and SAT each divided by square of the height (m^2).

Low SMI was defined using the cut-off values for SMI described in 2013 by Martin et al. [21] Cachexia was defined as weight loss >5% during the past six months or body mass index (BMI) <20 and weight loss >2% or low SMI and weight loss >2%. [7] Weight loss during the first six weeks of ICI therapy was considered clinically significant in case of 2% or more loss based on the consensus definition of cachexia and the American Society of Clinical Oncology (ASCO) guideline. [7, 22]

Inflammatory parameters

Systemic inflammation was evaluated using the inflammatory indices neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR). [23] They were defined as the absolute neutrophil count divided by the absolute lymphocyte count and absolute platelet count divided by the absolute lymphocyte count respectively, obtained from complete blood count at baseline.

Immunohistochemistry

Representative tumor sections were immunohistochemically stained for PD-L1 expression using the standardized 22C3 pharmDx assay on the Dako Link 48 platform (Dako, Carpinteria, California, USA). This assay has been used as standard in the KEYNOTE-048. [2]

Pathological assessment of PD-L1 staining

Stained slides were assessed by a dedicated head and neck pathologist, certified for PD-L1 testing, and an experienced head and neck researcher. Any discrepancies were resolved through a consensus discussion. Specimens were scored using CPS. This score was defined as the number of positive tumor cells, lymphocytes and macrophages, divided by the total number of viable tumor cells multiplied by 100. Clinically relevant cut-offs of ≥1 and ≥20 for CPS were used. Slides that contained less than 100 viable tumor cells were excluded.

Statistical analysis

Normally distributed variables were reported as means (± standard deviation (SD)). Non-normally distributed variables were reported as medians (interquartile range (IQR)). Differences between groups were analyzed using independent samples T-test and the Mann-Whitney U test respectively. Categorical variables were analyzed with the Pearson's Chi^2 test and Fisher's Exact test where appropriate. Correlations were evaluated using Pearson correlation coefficient. The distributions of OS were estimated by the Kaplan-Meier method and compared by means of the log-rank test. Cox-proportional hazard models were used to estimate the hazard ratio (HR) and calculate the corresponding 95% confidence intervals (CI's) for OS. Univariable and multivariable binary logistic regression analysis was performed for long-term response and autoimmune toxicity. Potential predictive and prognostic

variables were selected for multivariable analysis using forward stepping analysis with *p* for entry ≤0.10 and *p* to remove upon entry >0.05. Significance was set at the value $p<0.05$. Changes in CSA of SM, VAT, and SAT were corrected for days between the baseline and follow-up CT scan in the regression analyses.

All statistical analyses were performed using SPSS (IBM version 25 for Windows, Armonk, New York, USA). For the Fisher's Exact test with more than 2 by 2 items, the online calculator http://vassarstats.net/fisher2x4.html was used.

RESULTS

Out of the 177 patients treated with ICI, 98 patients met the inclusion criteria for this study. Information on weight change during the six months prior to ICI initiation was available for 87 patients. NLR and PLR could be retrieved for 93 patients. PD-L1 CPS could be determined in 79 patients.

Baseline characteristics of the study population

Baseline characteristics are displayed in Table 1. The population was predominantly male (85%) with a mean age of 63 years and the majority suffered from distant metastatic disease (67%). Forty patients (41%) received ICI therapy as first line palliative treatment. The majority of the patients was treated with nivolumab (61%).

More than half of the population (53%) had low SMI at start of ICI therapy and 39 out of 87 patients with available data on pre-treatment weight loss were classified as cachectic.

Early changes in weight and body composition

During the first six weeks of ICI therapy, 34 patients (35%) experienced significant weight loss, defined as more than 2% total body weight loss. When compared to patients with stable or increasing weight during ICI therapy, this subgroup presented a significantly higher NLR and PLR at baseline. Additionally, patients with significant weight loss during the first six weeks of ICI therapy had a lower BMI at baseline (20.9 ± 3.6 versus 22.9 ± 4.5 kg/m^2), which was also reflected in significantly lower SMI and VATI.

To visualize what happened to the specific tissues over time in patients with significant weight loss compared to those with stable or increased weight, the

number of days between baseline and follow-up CT scans were plotted against the percentage change of SM, VAT, and SAT (Figure 1). Patients with early weight loss during six weeks of ICI therapy predominantly experienced VAT (1B) and SAT (1C) loss, while loss of SM mass was not distinct (1A).

Systemic inflammation

Neutrophil-lymphocyte-ratio

Baseline NLR was not correlated with baseline BMI (r=-0.20, *p*=0.06), but did show a significantly negative correlation with the SMI and VATI (r=-0.22, *p*=0.03 and r=-0.27, *p*=0.009 respectively). No significant correlation was found between NLR and the SATI (r=-0.17, *p*=0.12).

Platelet-lymphocyte-ratio

Baseline PLR showed a significant correlation with the baseline BMI (r=-0.30, *p*=0.003), reflected in correlations with the SMI (r=-0.25, *p*=0.02) and VATI (r=-0.37, *p*<0.001) but again not significantly correlated with the SATI (r=-0.20, *p*=0.06).

Table 1 – Baseline characteristics. Patients with at least 2% weight loss during the first six weeks of ICI therapy versus patients with stable or increased weight.

Variable	**Total n=98**	**Stable or increased weight during six weeks ICI** n=64	**At least 2% weight loss 2% during six weeks ICI** n=34	***p*-value**
Patient characteristics				
Female Male	15 (15) 83 (85)	7 (11) 57 (89)	8 (24) 26 (77)	0.10[c]
Age (mean ± SD)	63.2 ± 8.0	63.6 ± 7.9	62.5 ± 8.5	0.52[a]
WHO PS 0 WHO PS 1 WHO PS 2	32 (33) 61 (62) 5 (5)	25 (39) 37 (58) 2 (3)	7 (21) 24 (71) 2 (9)	0.14[d]
CCI below 7 CCI 7 or higher	35 (36) 63 (64)	20 (31) 44 (69)	15 (44) 19 (56)	0.21[c]
Never smoked Current smoker Former smoker Missing	6 (6) 43 (44) 48 (49) 1	5 (8) 26 (41) 32 (51) 1	1 (3) 17 (50) 16 (47) 0	0.50[c]
No alcohol use Current alcohol user Former alcohol user Missing	4 (5) 50 (64) 24 (31) 20	1 (2) 35 (71) 13 (27) 15	3 (10) 15 (52) 11 (38) 5	0.09[d]

Variable	Total n=98	Stable or increased weight during six weeks ICI n=64	At least 2% weight loss 2% during six weeks ICI n=34	*p*-value
Disease characteristics				
Oropharynx	37 (38)	21 (33)	16 (47)	0.48[c]
Hypopharynx	14 (14)	12 (19)	2 (6)	
Oral cavity	23 (23)	15 (23)	8 (24)	
Larynx	12 (12)	9 (14)	3 (9)	
Unknown primary	7 (7)	4 (6)	3 (9)	
Other	5 (5)	3 (5)	2 (6)	
Distant metastatic disease	66 (67)	47 (73)	19 (56)	0.08[c]
Locoregional recurrent disease	32 (33)	17 (27)	15 (44)	
p16+ and/or HPV+ oropharynx	15 (16)	11 (18)	4 (13)	0.47[c]
Other	77 (84)	49 (82)	28 (88)	
Missing	*6*	*4*	*2*	
PD-L1 expression				
Low (CPS < 1)	22 (28)	16 (31)	6 (21)	0.64[c]
Intermediate (CPS 1-19)	36 (46)	22 (43)	14 (50)	
High (CPS ≥ 20)	21 (27)	13 (26)	8 (29)	
Missing	*19*	*13*	*6*	
Treatment characteristics				
PD-1 inhibitor	80 (82)	55 (86)	25 (74)	0.13[c]
PD-L1 inhibitor	18 (18)	9 (14)	9 (27)	
First line palliative systemic therapy	40 (41)	28 (44)	12 (35)	0.42[c]
Second line or higher	58 (59)	36 (56)	22 (65)	
Previous tumor surgery	43 (44)	26 (41)	17 (50)	0.37[c]
No previous tumor surgery	55 (56)	38 (59)	17 (50)	
Previous (chemo)radiation	82 (84)	51 (80)	31 (91)	0.17[d]
No previous (chemo)radiation	16 (16)	13 (20)	3 (9)	
Previous EXTREME regimen	47 (48)	29 (45)	18 (53)	0.47[c]
No previous EXTREME regimen	51 (52)	35 (55)	16 (47)	
Platinum refractory	54 (55)	33 (52)	21 (62)	0.33[c]
Non platinum refractory	44 (45)	31 (48)	13 (38)	
Anti-tumor therapy in six months prior to ICI	60 (61)	37 (58)	23 (68)	0.34[c]
No anti-tumor therapy in six months prior to ICI	38 (39)	27 (42)	11 (32)	
Weight and body composition				
Weight loss in six months prior to ICI (%) (median (IQR))	-1.9 (13.2)	-1.9 (12.9)	-3.3 (16.3)	0.63[b]
n	87	57	30	
BMI (mean ± SD)	22.2 ± 4.3	22.9 ± 4.5	20.9 ± 3.6	**0.03**[a]
SMI total (median (IQR))	44.7 (9.6)	45.1 (9.9)	42.2 (10.0)	**0.03**[b]
VATI total (median (IQR))	23.2 (30.6)	25.4 (40.9)	18.8 (23.2)	**0.02**[b]
SATI total (median (IQR))	31.4 (33.1)	35.2 (30.4)	24.6 (36.2)	0.13[b]
Low SMI	52 (53)	32 (50)	20 (59)	0.41[c]
Normal SMI	46 (47)	32 (50)	14 (41)	
Cachexia	39 (45)	24 (42)	15 (50)	0.48[c]
No cachexia	48 (55)	33 (58)	15 (50)	

Variable	Total n=98	Stable or increased weight during six weeks ICI n=64	At least 2% weight loss 2% during six weeks ICI n=34	*p*-value
Laboratory findings				
NLR (median (IQR)) n	4.3 (3.5) 93	3.7 (2.8) 60	5.4 (4.5) 33	**0.008**[b]
PLR (median (IQR)) n	241.9 (189.8) 93	217.2 (185.0) 60	302.7 (167.3) 33	**0.01**[b]
Albumin (mean ± SD) n	39.9 ± 4.3 94	40.1 ± 4.4 61	39.5 ± 4.3 33	0.56[b]

BMI, body mass index; CCI, Charlson Comorbidity Index; CPS, combined positivity score; EXTREME regimen including platinum-based chemotherapy, 5-fluorouracil and cetuximab [46] NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; WHO PS, world health organization performance status. All variables are considered at baseline (start ICI) unless reported otherwise. Percentages do not always add up to 100% due to rounding off. Bold values denote statistical significance at the p<0.05 level. [a]Independent samples T test, [b]Mann-Whitney U Test, [c]Pearson Chi-Square, [d]Fisher's Exact Test.

Long-term responders

Thirty-three patients (34%) continued treatment for six months or longer and were considered as long-term responders in the current study.

Using univariable analysis the following variables showed potential prognostic value ($p \leq 0.10$) for long-term response: lower WHO PS, metastatic disease, PD-L1 CPS ≥1, higher SMI, higher VATI, higher SATI, and absence of significant weight loss during the first six weeks of treatment (Table 2).

The WHO PS, SATI, and weight loss during the first six weeks of ICI therapy remained significant predictors for long-term response in multivariable analysis.

Figure 1 – Changes in body compartments over time

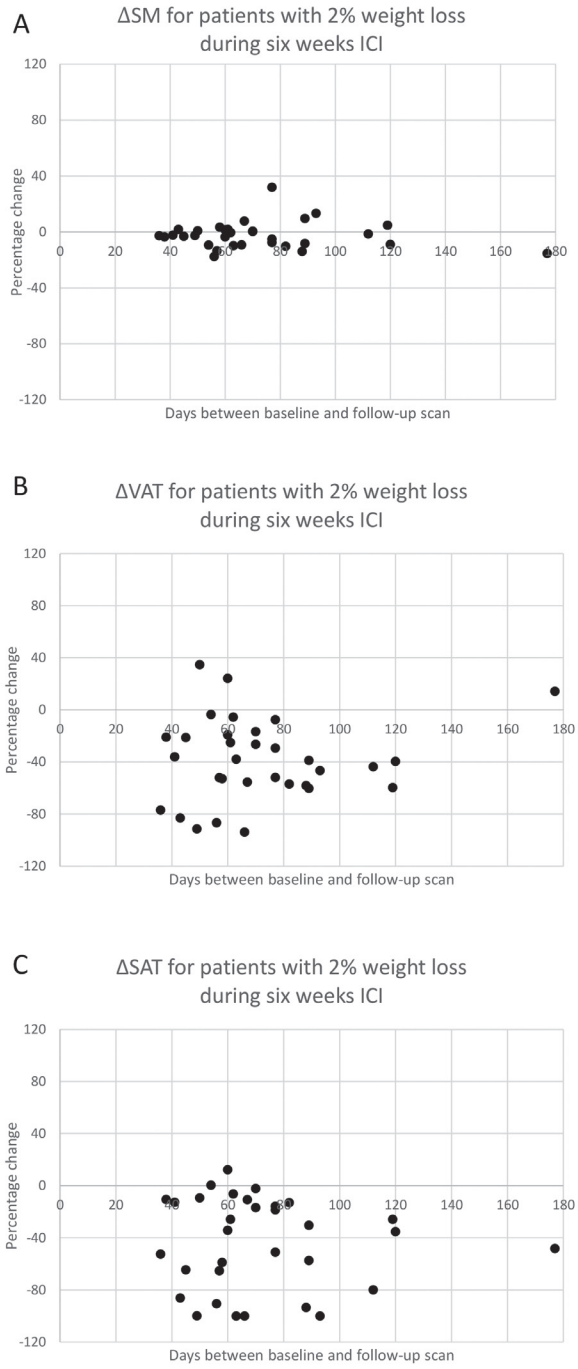


Table 2 – Logistic regression analysis for long-term response defined as more than 6 months progression free survival and ICI therapy continuation.

Covariate	n	Univariable analysis 95% CI				Multivariable analysis 95% CI			
		HR	Lower	Upper	p-value	HR	Lower	Upper	p-value
Gender (male)	98	1.48	0.43	5.05	0.53				
Age	98	0.99	0.94	1.04	0.68				
WHO PS 1 or 2 compared to WHO PS 0	98	0.23	0.09	0.57	**0.001**	0.16	0.04	0.54	**0.003**
CCI 7 or higher compared to CCI <7	98	1.78	0.71	4.43	0.22				
Distant metastatic disease versus recurrent only	98	2.32	0.88	6.14	0.09				
p16+/HPV+ oropharyngeal tumors	92	1.47	0.47	4.60	0.51				
PD-L1 expression									
Low (CPS <1)	22				0.10				
Intermediate (CPS 1-19)	36	4.52	1.13	18.09	**0.03**				
High (CPS ≥ 20)	21	3.17	0.69	14.46	0.14				
Second line or higher palliative systemic therapy	98	0.75	0.32	1.75	0.51				
Platinum refractory	98	0.94	0.42	2.24	0.94				
Weight loss in six months prior to ICI (%, continuous)	87	0.98	0.96	1.01	0.29				
Cachexia and weight loss >2% during six weeks ICI (ref)	15				0.14				
Cachexia and stable weight during six weeks ICI	24	10.00	1.13	88.91	**0.04**				
No cachexia and weight loss >2% during six weeks ICI	15	5.09	0.50	52.29	0.17				
No cachexia and stable weight during six weeks ICI	33	10.32	1.21	87.94	**0.03**				
Catabolic category versus others	87	0.11	0.01	0.90	**0.04**				
BMI	98	1.19	1.06	1.34	**0.003**				
SMI	98	1.07	1.01	1.13	**0.02**				
VAT index	98	1.02	1.002	1.04	**0.03**				
SAT index	94	1.03	1.01	1.05	**0.002**	1.05	1.02	1.08	**0.003**
Low SMI	98	0.76	0.33	1.76	0.52				
Cachexia	87	0.66	0.26	1.63	0.36				
Weight loss during first six weeks of ICI (%, continuous)	98	0.89	0.80	0.99	**0.03**	0.85	0.74	0.98	**0.03**
NLR	93	0.94	0.80	1.10	0.41				
PLR	93	1.00	1.00	1.00	0.92				
Albumin	94	1.11	0.99	1.24	0.07				

BMI, body mass index; catabolic category is defined as the group of patients with cachexia at baseline and further weight loss >2% during six weeks immune checkpoint inhibitors; CCI, Charlson Comorbidity Index; ICI, immune checkpoint inhibitors; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; VAT, visceral adipose tissue; WHO PS, world health organization performance status. All variables are considered at baseline (start ICI) unless reported otherwise. Bold values denote statistical significance at the p<0.05 level.

Overall survival

At the time of censoring, 69 out of 98 patients (70.4%) had deceased. The median follow-up was 9 months (range 1-64). At six months, OS rate was 72.2% and at one year 36.7%.

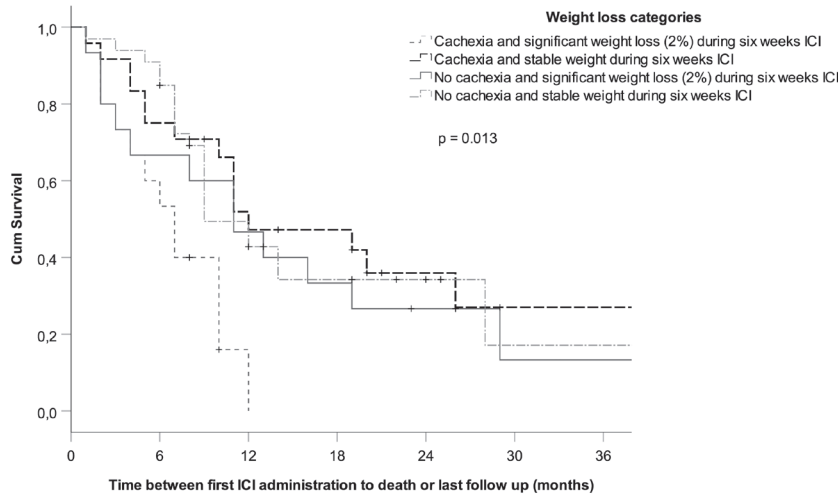
Using univariable Cox regression analysis, the following variables showed a potential predictive value ($p \leq 0.10$) for OS: WHO PS, metastatic disease, PD-L1 CPS ≥1, second line palliative systemic treatment or higher, weight loss during the six months prior to ICI initiation, weight loss categories, catabolic category (explanation below), VATI, and weight loss during the first six weeks of ICI therapy.

As weight loss during the six months prior to ICI initiation and during the first six weeks of ICI therapy were potential predictors for OS, four categories were created to further elucidate the underlying relationships. The cachexia progression categories are as follows: (1) Cachexia at baseline and weight loss >2% during six weeks of ICI therapy, n=15, (2) Cachexia at baseline and stable weight during six weeks of ICI therapy, n=24, (3) No cachexia and weight loss >2% during six weeks of ICI therapy, n=15, and (4) No cachexia and stable weight during six weeks of ICI therapy, n=33. The first category was then defined as the catabolic category including patients with progressive weight loss prior and during ICI therapy. The Kaplan Meier curve for these cachexia progression categories is shown in Figure 2.

In multivariable forward stepwise Cox regression analysis including all the above-mentioned potential predictors, WHO PS and the catabolic category remained independent significant predictors for OS in the final model (Table 3). When additionally corrected for PD-L1 expression, only the catabolic category remained a significant predictor.

To assess which body compartment (SM, VAT, SAT) contributed most to the prognostic value of early weight loss, regression analysis was repeated for change in body composition corrected for days between the baseline and first follow-up CT scans. In univariable regression analysis, change in VAT was predictive for OS (HR 0.99 [95%CI 0.98-0.99], p=0.009), while SAT change and SM change were not significant (data not shown). VAT change did not remain an independent prognostic factor when entered in multivariable forward stepwise Cox regression including the previously mentioned potential predictors from Table 3.

Figure 2 – Kaplan Meier survival curve for different weight loss categories



Number of patients at risk by time							
Baseline cachexia and 2% early weight loss	15	8	0	0	0	0	0
Baseline cachexia and stable weight	24	18	10	9	4	2	2
No baseline cachexia and 2% early weight loss	15	10	7	5	3	1	1
No baseline cachexia and stable weight	33	27	11	8	5	1	1

Immunotherapy induced toxicity

Eighteen patients (18%) experienced autoimmune toxicity CTCAE grade 2 or higher within 6 months after ICI initiation. Autoimmune toxicity included dermatitis (n=6), thyroiditis (n=5), colitis or gastritis (n=3), arthritis (n=2), pneumonitis (n=1), and pericarditis (n=1). Univariable regression analysis to identify potential predictors of autoimmune toxicity revealed a significant predictive value for age with older patients experiencing less immune therapy-related adverse events (HR 0.92 [0.86-0.99] *p*=0.02).

Table 3 – Cox regression analysis for overall survival

Covariate	n	Univariable analysis				Multivariable analysis			
			95% CI				95%CI		
		HR	Lower	Upper	*p*-value	HR	Lower	Upper	*p*-value
Gender (male)	98	0.73	0.37	1.44	0.36				
Age	98	1.010	0.98	1.04	0.53				
WHO PS 1 or 2 compared to WHO PS 0	98	2.56	1.44	4.55	**0.001**	2.09	1.11	3.92	**0.022**
CCI 7 or higher compared to CCI <7	98	0.76	0.47	1.25	0.28				
Distant metastatic disease versus recurrent only	98	0.66	0.40	1.09	0.10				
p16+/HPV+ oropharyngeal tumors	92	1.08	0.55	2.12	0.82				
PD-L1 expression									
Low (CPS <1)	22	0.62	0.34	1.15	0.31				
Intermediate (CPS 1-19)	36	0.74	0.37	1.48	0.13				
High (CPS ≥ 20)	21				0.39				
Second line or higher palliative systemic therapy	98	1.57	0.94	2.60	0.08				
Platinum refractory	98	1.19	0.74	1.92	0.48				
Weight loss in six months prior to ICI (%, continuous)	87	1.02	1.00	1.04	0.06				
Cachexia and weight loss >2% during six weeks ICI (ref)					**0.02**				
Cachexia and stable weight during six weeks ICI		0.33	0.15	0.71	**0.005**				
No cachexia and weight loss >2% during six weeks ICI		0.44	0.19	1.00	**0.05**				
No cachexia and stable weight during six weeks ICI		0.38	0.19	0.77	**0.007**				
Catabolic category versus others	87	2.68	1.41	5.11	**0.003**	2.18	1.13	4.21	**0.02**
BMI	98	0.95	0.89	1.02	0.15				
SMI continuous	98	0.98	0.95	1.01	0.21				
VAT index	98	0.99	0.98	1.00	0.10				
SAT index	94	1.00	0.99	1.01	0.86				
Low SMI	98	1.23	0.76	1.97	0.40				
Cachexia	87	1.19	0.72	1.97	0.50				
Weight loss during first six weeks of ICI (%, continuous)	98	1.05	1.00	1.10	0.06				
NLR	93	1.04	0.96	1.13	0.38				
PLR	93	1.00	1.00	1.00	0.90				
Albumin	94	0.96	0.91	1.01	0.14				

BMI, body mass index; catabolic category is defined as the group of patients with cachexia at baseline and further weight loss >2% during six weeks immune checkpoint inhibitors; CCI, Charlson Comorbidity Index; ICI, immune checkpoint inhibitors; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SAT, subcutaneous adipose tissue. SMI, skeletal muscle index; VAT, visceral adipose tissue; WHO PS, world health organization performance status. All variables are considered at baseline (start ICI) unless reported otherwise. Bold values denote statistical significance at the p<0.05 level.

DISCUSSION

This study was conducted to evaluate the predictive and prognostic value of weight loss and changes in body composition prior to and during ICI therapy.

Prognostic and predictive value of weight loss and body composition

In the present population, 45% of the patients were cachectic prior to the start of ICI therapy. The prevalence of cachexia in R/M HNSCC patients specifically has not been described previously, but our results are comparable to NSCLC patients starting ICI therapy. [24] This relatively high prevalence of cachexia at baseline may be partially related to previous therapies with known catabolic effects, such as cisplatin-based chemotherapy. [25] However, in the current study population, no significant differences in pre-ICI weight loss were observed between patients who did or did not receive oncological treatment in the previous six months (including platinum refractory disease) (data not shown).

Thirty-five percent of the total population experienced significant weight loss (>2%) during the first six weeks of ICI therapy. Besides a lower WHO PS and higher baseline SATI, the absence of significant weight loss (>2%) during the first six weeks was predictive for treatment continuation of six months or longer (long-term responders). Conversely, we can conclude that patients experiencing >2% early weight loss during the first six weeks of ICI therapy are more likely to show disease progression within six months after ICI initiation.

Only few studies have reported on these early changes in body composition during ICI therapy, none in HNSCC patients. [12, 26] Crombé et al. performed a retrospective study in patients with metastatic solid tumors treated with ICI therapy. Their population mainly consisted of patients with NSCLC (55%) and no HNSCC patients were included. The authors reported that baseline body composition parameters measured on CT scans at the level of L3 did not affect the PFS, while decrease in the psoas muscle index and SATI during the first weeks of treatment were predictive for worse PFS. In addition, low fat mass after ICI initiation contributed to a higher risk of disease progression. OS analysis was not performed in this study. [26] Previous research in NSCLC patients treated with nivolumab has shown that weight loss, characterized by loss of VAT and SAT at week 6 of treatment, is a significant prognostic factor for poor OS in patients with stage IV NSCLC. [12]

One third of our study population (34%) was classified as long-term responder, defined as treatment continuation longer than six months. Reported PFS6m ranged from 19.7% in the Checkmate 141 study, [27] 25.6% in KEYNOTE-040, [1] and 25% in the KEYNOTE-048 (arm with pembrolizumab monotherapy). [2] This percentage might be higher in our study population as patients continued treatment not only based on radiographic evaluation but also based on observed clinical benefit at the treating oncologist discretion. Patients with stabilizing or ameliorating symptoms might have continued therapy despite CT graphic progression, mislabeling some with true progression as pseudo-progressive tumors. PD-L1 CPS ≥1 was no predictor of PFS6m after multivariate analysis in our population, maybe because the percentage of patients with intermediate and high CPS was different than in the KEYNOTE-048 trial (CPS 1-19 46% and CPS ≥20 27% in our population versus CPS 1-19 41% and CPS ≥20 44% in KEYNOTE-048). A secondary analysis of KEYNOTE-048 trial showed that treatment with pembrolizumab monotherapy compared to chemotherapy was associated with shorter PFS in patients with an intermediate CPS and a trend for better PFS in the CPS ≥20 subgroup. [28] As PFS seemed a challenging outcome measure due to the concept of pseudo-progression, [29] formal PFS analysis was not performed. Instead, OS was used as the primary outcome measure. [30]

When focusing on OS outcomes, our results showed that a higher WHO PS and the catabolic category (cachexia at baseline and weight loss >2% during six weeks ICI therapy) both independently heralded a decrease in OS. Remarkably, PD-L1 CPS was not a prognostic factor in this study population as opposed to previous data. [2, 31] In clinical practice, PD-L1 CPS is used as criteria for reimbursement and a predictive biomarker. [32, 33] Different from KEYNOTE-048, we included a heterogeneous population with recurrent and metastatic disease, including patients who already received multiple treatment lines. Despite the fact that PD-L1 did not yield significant prognostic value in our study, the catabolic category remained a significant prognostic factor, also when corrected for PD-L1 expression.

It should be noted that the weight loss prior to ICI therapy however did not continue during ICI in a subset of patients. This subgroup (cachexia at baseline and stable weight during six weeks of ICI therapy) presented better treatment outcomes compared to the catabolic category. Strikingly, baseline SMI was not associated with OS in the current study. This is in contrast with a recent publication by Arribas et al. [13] In a population of 61 HNSCC patients treated with ICI +/- other agents, including

chemotherapy, the authors concluded that a low SMI was associated with worse OS. However, information on weight loss prior to ICI initiation and on performance status, both being strong predictors in our study, was not provided in the study Arribas et al. [13] One could argue whether the weight loss prior to ICI initiation, as observed in our current data, could nullify the prognostic value of SMI at baseline, because the process of weight loss potentially provides more information on ongoing metabolic or catabolic activity than a potentially stable low muscle mass. The OS results of the present study are comparable to a Japanese retrospective analysis of 42 R/M HNSCC patients treated with nivolumab. [34] Ueki et al. reported an independent prognostic value of WHO PS as well and of the modified Glasgow prognostic score. Additionally, body weight loss >5% over the six months prior to ICI therapy showed a trend towards worse OS in univariable analysis. [34] The prognostic value of the modified Glasgow prognostic score emphasizes the role for systemic inflammation, since this score includes a combination of C-reactive protein and albumin levels. CRP was not retrieved in the present study, but NLR and PLR were used as inflammatory markers and showed an inverse correlation with body composition parameters. As our population had a higher percentage of patients with metastatic disease (67% compared to 52% in Ueki et al), and possibly a higher response rate as seen in the KEYNOTE 48 trial, this might explain the higher statistical significance in our data.

Predictive value of weight and body composition on the development of autoimmune toxicity

Age at start of treatment with immunotherapy was a predictive factor for the development of autoimmune toxicity during the first six months of ICI therapy in this population. In several studies, high BMI (≥30 kg/m^2) and pre-existing autoimmune disease were associated with an increased risk of immune-related adverse events in cancer patients treated with PD-(L)1 inhibitors. [35, 36] The association between BMI and autoimmune toxicity was not evident in our data, probably due to the small number of patients with BMI ≥30 kg/m^2 (n=3, data not shown).

Patient characterization

Patients who experienced weight loss during the first six weeks of ICI therapy, had a significantly lower BMI at baseline than those with stable or increasing weight. Hypothetically, these patients are in a wasting state that continues during ICI

therapy. The low BMI in the subgroup of weight losing patients was reflected in lower values of all three tissue compartments (SMI, VAT, SAT). This subgroup also exhibited a higher NLR and PLR at baseline, as a marker of inflammation.

So, a selection of patients with a low body mass at baseline continued to lose weight during therapy. This ongoing catabolic process failed to be reversed by immunotherapy and this subset of patients subsequently had survival disadvantage. Patients presenting with cachexia at baseline but stable weight during ICI therapy, indicating an arrest in catabolism, showed significantly better survival outcomes. Although baseline cachexia may not predict treatment outcome, the evolution of body weight appears a relevant parameter. When evaluating early tumor response, it may help to judge early whether a patient would have a reasonable chance to benefit from treatment or not. Additional research is needed to define if the catabolic subgroup can be identified at baseline by liquid or tumor-related (inflammatory) biomarkers.

Major contribution of adipose tissue

Overall, weight loss during ICI therapy remains of prognostic value, more than just baseline cachexia. This weight loss seems to consist of mainly fat mass loss, both VAT and SAT. Maintenance of SAT was found to be an important indicator of clinical outcomes in the current study cohort, which is consistent with the findings of Martini et al. [37] A study in 55 nivolumab-treated NSCLC patients showed that low subcutaneous fat mass was significantly associated with poor overall survival. [38] These results support the hypothesis that maintenance of fat tissue might play a bigger role in ICI therapy compared to chemotherapy.

Studies on body composition in cancer patients receiving chemotherapy mainly showed a reduction of muscle mass and function during treatment. The findings concern head and neck cancer, lung cancer as well as other cancer sites. [39-42] The catabolic effects of chemotherapy probably play a major role here. For example, cisplatin is known to activate nuclear factor kappa-B cells (NF-κB), a key player in inflammation and a trigger for muscle wasting. [25] In terms of immunotherapy, an interaction between ICI and adipose tissue is considered plausible. Adipose tissue is an important endocrine organ and regulates the immune system and the patient's metabolism through circulating adipokines as observed in obesity. [43] It is interesting to note that PD-L1 expression on adipocytes increases during

adipogenesis, [44] which suggests that a higher fat mass may promote tumor immune evasion, which can be reversed with ICI therapy by causing increased effector T-cell activity. Maintenance of adipose tissue may lead to a more robust host immune response to immunotherapy. [37]

Limitations

The results need to be considered in the light of a number of limitations. First, accurate body composition evaluation requires CT scans at the level of L3 and therefore patients without baseline and follow-up CT abdomen were excluded. This could have led to a higher percentage of patients with metastatic disease in the study sample, as these patients received extended CT scans instead of a CT scan of the head and neck region only. Patients with distant metastatic disease receiving ICI therapy had better response in the KEYNOTE-048 study compared to patients with locoregional recurrence only. [2, 45] Even so, 67% of our population had metastatic disease compared to 72% in KEYNOYE-048 and 47% in CHECKMATE-141. [1, 2, 27] Hence, despite our exclusion criteria, recurrent disease was adequately represented in this real life data set.

Because of the multi-center study setting, CT scan-protocols may have differed in slice thickness and dose between the two centers. Nevertheless, standardized reference points were used for L3 slide selection, and the structures were delineated by the same experienced researcher.

Furthermore, the TNM-classification changed from the seventh to the eighth edition during the study period. So, in our dataset both the seventh and eight editions have been used for staging. However, the definition of metastatic HNSCC did not change in the new edition and tumor stages at the initial diagnosis were not included in the present analysis.

Lastly, a trend was observed towards more patients with locoregional recurrent disease experiencing significant weight loss compared to patients with distant metastatic disease. In HNSCC, weight maintenance is particularly challenging due to tumor and previous treatment induced symptoms such as xerostomia, oropharyngeal dysphagia, or odynophagia. The contribution of these factors to weight loss could not be evaluated in this study sample. Retrospective analysis of nutritional interventions was considered unreliable and therefore not included in the analysis.

Clinical implications

Distinguishing between tumor response or progression is not always clear-cut based on radiological criteria alone, especially at the first evaluation during therapy. Recognizing clinical patterns regarding symptom control and changes in body composition could prove helpful in these circumstances. As such, tracking of weight changes and body composition may prove valuable in the early decision making regarding (dis)continuation of ICI therapy. A better understanding of the relationship between a patient's metabolic state and ICI response will help to select patients more accurately and improve the efficacy of ICI treatment in the R/M setting.

CONCLUSION

The combination of cachexia at baseline and ongoing weight loss during ICI therapy is associated with worse OS in R/M HNSCC patients, independent of PD-L1 expression, and is predominantly reflected in loss of fat mass. Reversal of weight loss during ICI therapy predicts significant better OS. The underlying mechanisms of continuous weight loss remain unclear and demand further research to define biomarkers, identifying the catabolic patient subgroup and additionally pave the way towards improving ICI efficacy.

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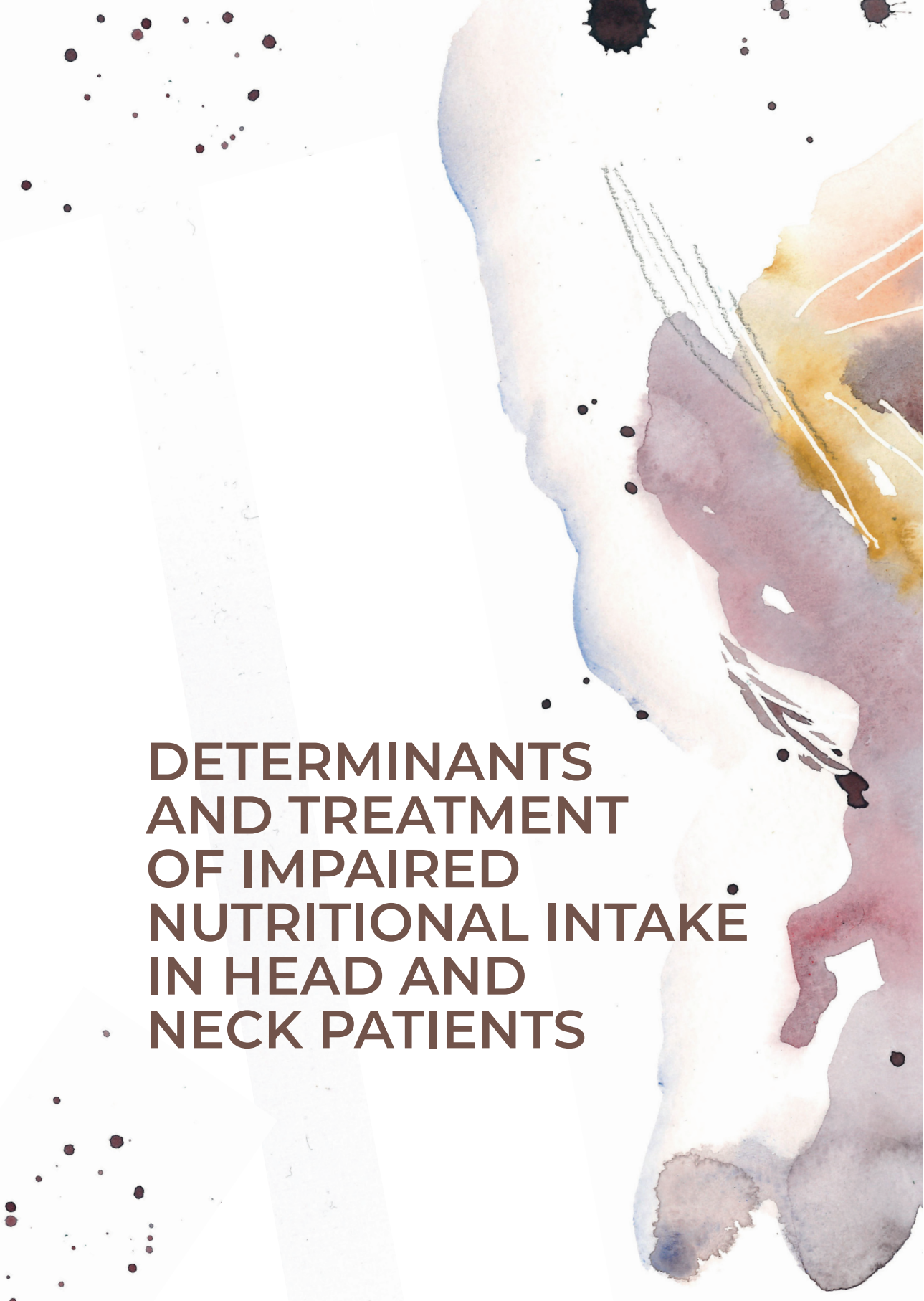

DETERMINANTS AND TREATMENT OF IMPAIRED NUTRITIONAL INTAKE IN HEAD AND NECK PATIENTS

CHAPTER 6

TOOTH EXTRACTIONS PRIOR TO CHEMORADIOTHERAPY OR BIORADIOTHERAPY ARE ASSOCIATED WITH WEIGHT LOSS DURING TREATMENT FOR LOCALLY ADVANCED OROPHARYNGEAL CANCER

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ABSTRACT

Purpose: Prior to radiotherapy combined with chemotherapy (CRT) or biotherapy (BRT) for oropharyngeal squamous cell carcinoma (OPSCC), teeth with poor prognosis that pose a risk for post-RT osteoradionecrosis (ORN) are removed. The effect of tooth loss on body weight loss and tube feeding (TF) dependency during CRT/BRT is unknown. This study aimed to evaluate the effect of incomplete dentition, tooth extractions prior to CRT/BRT, and the subsequent loss of functional units on: (1) weight loss during CRT/BRT and (2) the need for TF during CRT/BRT for OPSCC.

Methods: OPSCC patients treated with CRT/BRT between 2013 and 2016 were included in this retrospective cohort study. Dental status was determined during the dental assessment at first visit and after tooth extractions prior to the start of CRT/BRT. Weight loss during CRT/BRT was scored dichotomously, comparing weight loss >5% to stable or increased weight. Potential factors associated with weight loss were identified, including patient, tumor, and treatment characteristics.

Results: Seventy-seven OPSCC patients were included. Forty patients (52%) experienced weight loss >5% during CRT/BRT. Extractions were performed in 66% of the OPSCC patients. The mean number of extracted teeth was 4.1± 5.6 per patient. Tooth extractions prior to CRT/BRT were associated with weight loss >5% during CRT/BRT (HR 1.130 (95% CI 1.011-1.262), p=0.031). None of the dental status-related parameters showed any significant associative value for TF during CRT/BRT.

Conclusions: Pre-CRT/BRT tooth extractions intended to reduce the risk of ORN, are a risk factor for weight loss during CRT/BRT for OPSCC.

INTRODUCTION

The incidence of oropharyngeal cancer, predominantly squamous cell carcinoma, has increased over the past 30 years from less than 300 new diagnoses in the early 1990s to nearly 700 in 2018 in the Netherlands alone. [1] This is consistent with global figures, in which the increased incidence of Human Papilloma Virus (HPV) related oropharyngeal squamous cell carcinoma (OPSCC) has the largest share in this growth, especially among men in developed countries. [2] A better prognosis for HPV-positive OPSCC, combined with young age at diagnosis and thus a longer life expectancy, has increased awareness of late treatment-related toxicity. [3] Radiotherapy (RT) alone or in combination with chemotherapy (cisplatin) (CRT) or biotherapy (cetuximab) (BRT) is the main therapy for OPSCC with osteoradionecrosis (ORN) as one of the most feared toxicities. Although the risk of ORN has decreased with current advancements in radiotherapy techniques and better oral health regimens, cancer located in the oropharynx remains a risk factor for ORN due to its location proximate to the mandible. [4-7] Comprehensive dental assessment of potential oral sources of infection (poor prognosis teeth) prior to RT is an example of improved oral health regimes. In the Netherlands, oral health recommendations prior to RT are based on a protocol that dates from 1992, which has been revisited in 2018. [8-10] Removal of poor prognosis teeth that are identified as potential oral source of infection is a common recommendation in the prevention of ORN. This is however complex and controversial. Tooth extractions result in a reduced number of functional units (Table 1) and impair the ability to masticate and swallow, contributing to decreased health-related quality of life (QoL). [6, 11-13] Indeed, this deterioration in mastication has been associated with oropharyngeal dysphagia. [14, 15] Furthermore, it has been demonstrated that oropharyngeal dysphagia is significantly related to involuntary weight loss. [16, 17] Cachexia, clinically characterized by unintended weight loss and low muscle mass [18], has a negative effect on treatment-related toxicity and oncological outcome. Head and neck cancer patients with weight loss and/or low muscle mass experienced higher levels of toxicity, more unplanned hospital admissions, and poorer overall survival. [19-21] Therefore, it is of utmost importance to prevent weight loss during oncological treatment and to elucidate contributing risk factors. [21]

Nutritional management targeting malnutrition to prevent or limit weight loss is an essential part of head and neck oncological treatment. Regularly, tube feeding (TF) may be necessary to achieve these goals. [22] A systematic review of longitudinal

studies revealed inconsistent findings on the association between tooth loss and nutritional status in adults. [23] To our knowledge, to date no studies have investigated the effect of incomplete dentition or loss of functional units due to tooth extraction prior to CRT/BRT, on body weight and TF dependency in patients with head and neck cancer.

Therefore, the aim of this study was to evaluate the effect of incomplete dentition, tooth extractions prior to CRT/BRT, and the subsequent loss of functional units on: (1) weight loss during CRT/BRT and (2) the need for TF during CRT/BRT for OPSCC. We hypothesized that OPSCC patients who underwent tooth extractions prior to RT, experienced greater weight loss during CRT/BRT, and were more prone to TF dependency compared to patients whose teeth were not removed.

MATERIALS AND METHODS

Study design and population

Patients with OPSCC, who were treated with primary or postoperative CRT/BRT in the Comprehensive Cancer Center of Maastricht University Medical Center (MUMC+) and Maastro Clinic between January 2013 and December 2016, were included in this retrospective cohort study. Exclusion criteria were single modality treatment with radiotherapy only, previous head and neck radiation, and TF dependency at start of the oncological treatment. Patients were part of a larger MUMC+ sample from a cohort study on alterations in body composition in locally advanced head and neck squamous cell carcinoma (LAHNSCC). [21] Additional data extraction on dental status from the electronic health records was performed by an experienced maxillofacial prosthodontist (DB). This study was approved by the medical ethics committee of the MUMC+ (METC 2020-1589).

All patients received primary CRT or BRT (cisplatin or cetuximab, respectively) or postoperative CRT (cisplatin) with curative intent. RT was administered using intensity-modulated RT (IMRT) for five days per week for six (BRT) or seven (CRT) weeks, in fractions of 2 Gy. Cisplatin was administered intravenously in doses of 100 mg/m^2 every three weeks [24, 25] concurrently with daily fractionated IMRT up to 66 Gy in 33 fractions or 70 Gy in 35 fractions in case of postoperative and primary RT, respectively. Cetuximab was indicated in patients not fit for cisplatin, and consisted of a 400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly, combined with accelerated fractionated IMRT up to 68 Gy in 34 fractions in 38 days. [26]

According to the national standard procedures, the dental status was assessed through oral and radiographic examination (e.g. orthopantomography), at least 14 days before the start of CRT/BRT. [8-10] Teeth with a poor prognosis due to extensive caries, advanced periodontal disease, and non-restorable teeth were considered as potential source of infection for ORN. Radiographic abnormalities like apical radiolucency, (partially) impacted teeth, residual root tips, root resorption, and dental cysts were also considered as potential source of infection. Poor prognosis teeth within the estimated radiation fields were treated, usually by extraction.

During CRT/BRT, instructions were given to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible, and to rinse the mouth with salt-baking soda solution 8 to 10 times a day. [8, 9] Patients received custom-made fluoride trays in combination with a neutral 1% sodium fluoride gel to be used every other day. [8, 9] To relieve the symptoms of mucositis, patients were sprayed with saline 3 times a week by the dental hygienist. [27]

Patients were counselled by a dietician on a weekly basis according to the Dutch malnutrition guideline as part of standard clinical care. [28] TF was indicated if oral intake including oral nutritional supplements did not meet >75% of the calculated nutritional requirements. [29] TF was administered through a nasogastric tube, percutaneous endoscopic gastrostomy or radiologically inserted gastrostomy.

Anthropometric measurements

Weight was measured weekly at the start of RT during the standard visits to the Comprehensive Cancer Center of MUMC+. Height was measured only once before the start of CRT/BRT to calculate the body mass index (BMI). Pretreatment weight loss was a patient-reported outcome measure. Weight loss during the course of CRT/BRT was converted into a binary variable, comparing losses of more than 5% to stable or increased weight, based on the definition of grade 1 weight loss in the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE).

The same CTCAE version was also used by the radiation oncologists to report the severity of oropharyngeal dysphagia at start of RT. At the same time, the World Health Organization Performance Status (WHO PS) was assessed. The Charlson Comorbidity Index (CCI) was determined based on the medical history in the individual electronic health records. [30] The p16 status was used as surrogate marker for HPV-infection. [31]

Dental status was determined at two time points: during the dental assessment at first visit (dental sources of infection and functional dental status) and after tooth extractions prior to the start of CRT/BRT (functional dental status). The dental terminology and classification systems used are listed in Table 1. Whether or not patients underwent tooth extractions, the number of extracted teeth, and additional dental interventions including the removal of exostoses and implant insertion were recorded. The use of TF during CRT/BRT was treated as a binary measure, consisting of TF started during CRT/BRT for any duration versus remaining on a total oral diet.

Table 1 – Terminology clarification.

Edentulous	No functional teeth in place
Functional tooth	A tooth was considered functional if it could make contact with an opposing (prosthetic) tooth. Roots or impacted teeth are considered as nonfunctional.
Functional unit	Functional tooth, bridge pontic or crown (on implants), which could make contact with an opposing (prosthetic) tooth, is considered a functional unit.
Occlusal unit [42]	A measure to represent the chewing surface of the postcanine functional unit. One pair of occluding premolars is equal to one occlusal unit. One pair of occluding molars is considered as two occlusal units. Third molars are excluded.
Eichner Index [43, 44]	A validated measure describing the existing posterior functional units in support zones. It is divided into 3 main classes:
Eichner Index A	Functional units exist in all 4 posterior support zones
Eichner Index B	Functional units are present in one to three posterior support zones or within the anterior area only
Eichner Index C	No functional units left

Statistical analyses

Descriptive statistics were reported as means and standard deviations (SDs) for normally distributed, continuous variables and medians and inter quartile ranges (IQRs) for non-normally distributed data. Comparisons between groups were performed with independent t-tests in case of normal distribution, or the Mann-Whitney U test in case of non-normal distribution. Normal distribution was verified using the Shapiro-Wilk test. Cross-tabulations were made for categorical variables. A Chi^2 test was used for categorical outcomes. When more than 20% of cells had expected frequencies <5, we used Fisher's exact test.

All potential associative variables for weight loss underwent screening through univariable logistic regression. Factors with $p<0.10$ were selected as potentially relevant associative variables and subsequently tested using multivariable logistic regression. Due to limited sample size, the influence of potential associative factors was tested individually, with a maximum of three variables in the multivariable model.

Statistical analyses were regarded as significant if the *p*-value was equal to or lower than 0.05. Data were evaluated using SPSS (IBM version 25 for Windows, Armonk, New York, USA). For the Fisher's exact test with more than 2 by 2 items the R software (R Core Team (2021) R Foundation for Statistical Computing, Vienna, Austria) was used.

RESULTS

Seventy-seven patients with OPSCC met the inclusion criteria and were included in this study. Extractions were performed in 66% of the OPSCC patients. The mean number of extracted teeth was 4.1 ± 5.6 per patient. During CRT/BRT, 40 patients (52%) experienced significant weight loss of more than 5%. Baseline characteristics are presented in Table 2. Patients with significant weight loss during CRT/BRT had a higher BMI at start of treatment compared to patients without significant weight loss. In addition, a higher proportion of patients with significant weight loss had teeth removed to clear them from potential sources of infection.

Table 2 – Baseline characteristics.

	Stable weight or less than 5% loss during CRT/BRT n=37 (48%)	**>5% weight loss during CRT/BRT** n=40 (52%)	***p*-value**
Patient characteristics			
Age (years)			
mean ± SD	58.4 ± 9.5	59.4 ± 6.0	0.971[c]
median (IQR)	60.0 (13)	59.5 (9)	
Male	25 (68%)	29 (73%)	0.637[d]
Female	12 (32%)	11 (28%)	
Smoking history	33 (89%)	35 (88%)	1.000[a]
No history of smoking	4 (11%)	5 (13%)	
Alcohol consumption	19 (51%)	27 (68%)	0.149[d]
No alcohol consumption	18 (49%)	13 (33%)	
BMI at start RT (kg/m^2); mean ± SD	24.5 ± 5.0	26.7 ± 4.2	**0.039[b]**
Percentage weight loss prior to CRT/BRT; mean ± SD	2.4 ± 3.7	1.7 ± 3.2	0.373[b]
Dysphagia (CTCAE grade)			
0 - No symptoms of dysphagia	18 (49%)	15 (38%)	0.077[d]
1 - Symptomatic, regular diet	7 (19%)	17 (43%)	
2 - Symptomatic, altered eating/swallowing	12 (32%)	8 (20%)	
WHO PS 0	9 (24%)	14 (35%)	0.325[a]
WHO PS 1	28 (76%)	25 (63%)	
WHO PS 2	0 (0%)	1 (3%)	
CCI 0	7 (19%)	2 (5%)	0.231[a]
CCI 1	7 (19%)	12 (30%)	
CCI 2	10 (27%)	17 (43%)	
CCI 3	7 (19%)	4 (10%)	
CCI 4	2 (5%)	3 (8%)	
CCI 5	1 (3%)	1 (3%)	
CCI 6	3 (8%)	1 (3%)	
Tumor characteristics			
T1	5 (14%)	7 (18%)	0.287[a]
T2	8 (22%)	12 (30%)	
T3	10 (27%)	4 (10%)	
T4	14 (38%)	17 (43%)	
N0	8 (22%)	6 (15%)	0.886[a]
N1	1 (3%)	1 (3%)	
N2	27 (73%)	32 (80%)	
N3	1 (3%)	1 (3%)	
Stage II	0 (0%)	1 (3%)	0.829
Stage III	3 (8%)	2 (5%)	
Stage IV	34 (92%)	37 (93%)	
p16+	20 (54%)	26 (65%)	0.328[d]
p16-	17 (46%)	14 (35%)	
Dental status			
Edentulous at start RT	13 (35%)	9 (23%)	0.220[d]
Dentate at start RT	24 (65%)	31 (78%)	
Eichner Index A at first assessment	7 (19%)	12 (30%)	0.427[d]
Eichner Index B at first assessment	11 (30%)	8 (20%)	
Eichner Index C at first assessment	19 (51%)	20 (50%)	

	Stable weight or less than 5% loss during CRT/BRT n=37 (48%)	**>5% weight loss during CRT/BRT** n=40 (52%)	***p*-value**
Eichner Index A at start RT	4 (11%)	8 (20%)	0.547[a]
Eichner Index B at start RT	13 (35%)	11 (28%)	
Eichner Index C at start RT	20 (54%)	21 (53%)	
Decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT	4 (11%)	5 (13%)	1.000[a]
No decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT	33 (89%)	35 (88%)	
OU at first assessment; mean ± SD	3.5 ± 4.5	4.0 ± 4.7	0.642[b]
OU at start RT; mean ± SD	2.1 ± 3.6	3.2 ± 4.4	0.249[b]
Loss of OU due to tooth extractions prior to CRT/BRT			
mean ± SD	1.4 ± 2.3	0.8 ± 1.8	0.317[c]
median (IQR)	0.0 (3)	0.0 (1)	
Tooth extractions prior to CRT/BRT	20 (54%)	31 (78%)	**0.030[d]**
No tooth extractions prior to CRT/BRT	17 (46%)	9 (23%)	
Tooth extractions and/or additional interventions	23 (62%)	32 (80%)	0.083[d]
No tooth extractions and/or additional interventions	14 (38%)	8 (20%)	
Number of removed teeth; mean ± SD	3.4 ± 5.0	4.8 ± 6.1	0.289[b]
Treatment characteristics			
Primary CRT/BRT	35 (95%)	38 (95%)	1.000[a]
Postoperative CRT	2 (5%)	2 (5%)	
Cisplatin	27 (73%)	29 (73%)	0.963[d]
Cetuximab	10 (27%)	11 (28%)	
RT dose to contralateral submandibular gland (Gy); mean ± SD	48.1 ± 12.0*	49.7 ± 10.6*	0.529[b]
RT dose to contralateral parotid salivary gland (Gy); mean ± SD	24.2 ± 10.5	22.2 ± 7.1	0.345[b]
RT dose to superior PCM (Gy); mean ± SD	59.3 ± 11.6	59.3 ± 7.5	0.995[b]
RT dose to middle PCM (Gy); mean ± SD	59.8 ± 6.4	60.1 ± 7.1	0.870[b]
RT dose to inferior PCM (Gy); mean ± SD	49.4 ± 10.8	49.5 ± 8.4	0.939[b]
RT dose to oral cavity (Gy); mean ± SD	45.9 ± 11.0	45.2 ± 9.5	0.740[b]
RT dose to cricopharyngeal muscle (Gy); mean ± SD	44.5 ± 7.3	43.3 ± 6.5	0.433[b]
RT dose to cervical esophagus (Gy)			
mean ± SD	41.5 ± 8.3	37.0 ± 11.1	0.129[c]
median (IQR)	42.0 (8.0)	40.1 (17.7)	
TF during CRT/BRT (any duration)	24 (65%)	23 (58%)	0.508[d]
No TF	13 (35%)	17 (43%)	

BMI, body mass index; CCI, Charlson comorbidity index; CRT/BRT, chemoradiotherapy or bioradiotherapy; p16+/-, p16 positive/negative tumor as surrogate marker for Human Papilloma Virus; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TF, tube feeding; TNM-classification, tumor (T), node (N), metastasis (M) classification according to the 7th edition [45]; WHO PS, World Health Organization performance status.

*Bold values denote statistical significance at the p<0.05 level. [a]Fisher's exact test. [b]Independent T-test. [c]Mann-Whitney U test. [d]Chi²-test. *two missing values due to a bilateral neck dissection*

Univariable logistic regression analysis for significant weight loss during CRT/BRT revealed a potential associative value (p-value < 0.10) for the factors BMI, tooth extractions, tooth extractions and/or additional interventions, and RT dose to the cervical esophagus (Table 3a).

In multivariable step backward logistic regression analyses, tooth extractions prior to CRT/BRT and BMI at start of CRT/BRT remained as associative factors for weight loss >5% during CRT/BRT, independent of weight loss prior to CRT/BRT, WHO PS, CCI, dental status at first assessment or at start CRT/BRT, number of occlusal units (OU), and number of removed teeth (Table 3a). When evaluating the individual influence of potential associative factors, the associative value of extractions was reduced to a trend when corrected for alcohol use (p=0.057).

Univariable logistic regression analysis for TF dependency during CRT/BRT revealed a potential associative value (p-value < 0.10) for the following factors: Weight loss prior to CRT/BRT, type of systemic therapy (cisplatin or cetuximab), RT dose to the contralateral submandibular gland, RT dose to the cricopharyngeal muscle, and RT dose to the cervical esophagus. (Table 3b) None of the dental state parameters showed any significant associative value for TF dependency. In multivariable analysis, only a higher RT dose to the contralateral submandibular gland and type of systemic therapy (cisplatin) remained significant associative factors for the risk of TF dependency (Table 3b).

Table 3a - Univariable and multivariable analysis of factors potentially contributing to significant weight loss of >5% during CRT/BRT.

	Univariable analysis				Multivariable analysis*			
	OR	CI 95%		*p*-value	OR	CI 95%		*p*-value
		lower	upper			lower	upper	
Age	1.018	0.960	1.078	0.556				
Sex (male vs. female)	1.265	0.476	3.363	0.637				
Smoking	0.848	0.210	3.434	0.818				
Alcohol	1.968	0.781	4.956	0.151				
BMI	1.113	1.003	1.236	**0.044**	1.130	1.011	1.262	**0.031**
Weight loss prior to CRT/BRT	0.941	0.823	1.075	0.370				
Dysphagia at start RT (CTCAE grade 2 vs. 0 or 1)	0.521	0.185	1.468	0.217				
WHO PS (1 or 2 vs. 0)	0.597	0.221	1.611	0.309				
CCI (≥4 vs. <4)	0.738	0.205	2.659	0.642				
T3 or T4 vs. T0, T1 or T2	0.599	0.239	1.498	0.273				
N2 or N3 vs. N0 or N1	1.821	0.578	5.739	0.306				
p16+ vs. p16-	1.579	0.631	3.948	0.329				
Edentulous vs. dentate	0.536	0.197	1.462	0.223				
Decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT (binary)	1.179	0.291	4.771	0.818				
Tooth extractions (yes vs. no)	2.928	1.094	7.834	**0.032**	3.360	1.185	9.529	**0.023**
Tooth extractions and additional interventions (yes vs. no)	2.435	0.877	6.756	0.087				
Number of removed teeth	1.047	0.961	1.140	0.291				
Loss of OU due to tooth extractions prior to CRT/BRT	0.867	0.687	1.095	0.232				
Cetuximab vs. cisplatin (ref)	1.024	0.375	2.795	0.963				
RT dose to contralateral parotid gland	0.975	0.925	1.028	0.347				
RT dose to contralateral submandibular gland	1.013	0.973	1.056	0.523				
RT dose to superior PCM	1.000	0.954	1.048	0.995				
RT dose to median PCM	1.006	0.941	1.075	0.868				
RT dose to inferior PCM	1.002	0.956	1.050	0.938				
RT dose to oral cavity	0.992	0.950	1.037	0.737				
RT dose to cricopharyngeus muscle	0.974	0.911	1.040	0.428				
RT dose to cervical esophagus	0.952	0.904	1.002	0.060				
TF use	0733	0.292	1.841	0.508				

*BMI, body mass index; CCI, charlson comorbidity index; CRT/BRT, chemoradiotherapy or bioradiotherapy; OU, occlusal units; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TF, tube feeding; WHO PS, World Health Organization performance status. Bold values denote statistical significance at the p<0.05 level. *Step-backward analysis of all variables with p<0.05 in univariable analysis*

Table 3b - Univariable and multivariable analysis of factors potentially contributing to TF dependency.

	Univariable analysis				Multivariable analysis*			
	OR	CI 95%		*p*-value	OR	CI 95%		*p*-value
		lower	upper			lower	upper	
Age	0.980	0.922	1.041	0.509				
Sex (male vs. female)	0.776	0.281	2.141	0.624				
Smoking	0.759	0.175	3.297	0.713				
Alcohol	0.982	0.386	2.501	0.970				
BMI	0.987	0.895	1.089	0.799				
Weight loss prior to CRT/BRT	1.187	1.001	1.407	**0.049**				
Dysphagia at start RT (CTCAE grade 2 vs. 0 or 1)	1.256	0.435	3.627	0.673				
WHO PS (1 or 2 vs. 0)	1.689	0.627	4.547	0.300				
CCI (≥4 vs. <4)	0.732	0.202	2.650	0.634				
T3 or T4 vs. T0, T1 or T2	1.765	0.696	4.476	0.232				
N2 or N3 vs. N0 or N1	1.056	0.333	3.342	0.927				
p16+ vs. p16-	0.487	0.185	1.283	0.145				
Edentulous vs. dentate	0.892	0.325	2.447	0.825				
Decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT (binary)	0.465	0.114	1.894	0.285				
Tooth extractions (yes vs. no)	0.756	0.283	2.019	0.577				
Tooth extractions and additional interventions (yes vs. no)	0.484	0.165	1.425	0.188				
Number of removed teeth	0.995	0.917	1.080	0.909				
Loss of OU due to tooth extractions prior to CRT/BRT	1.125	0.877	1.445	0.354				
Cetuximab vs. cisplatin (ref)	0.355	0.127	0.995	**0.049**	0.226	0.070	0.731	**0.013**
RT dose to contralateral parotid gland	1.018	0.964	1.075	0.524				
RT dose to contralateral submandibular gland	1.048	1.001	1.096	**0.044**	1.067	1.013	1.124	**0.015**
RT dose to superior PCM	1.013	0.966	1.063	0.584				
RT dose to median PCM	1.040	0.970	1.115	0.272				
RT dose to inferior PCM	1.044	0.990	1.102	0.112				
RT dose to oral cavity	1.031	0.983	1.081	0.211				
RT dose to cricopharyngeus muscle	1.088	1.010	1.173	**0.026**				
RT dose to cervical esophagus	1.044	0.995	1.096	0.077				

*BMI, body mass index; CCI, charlson comorbidity index; CRT/BRT, chemoradiotherapy or bioradiotherapy; OU, occlusal units; PCM, pharyngeal constrictor muscles; RT, radiotherapy; WHO PS, World Health Organization performance status. Bold values denote statistical significance at the p<0.05 level. *Step-backward analysis of all variables with p<0.05 in univariable analysis*

DISCUSSION

The results of the current study showed that OPSCC patients who underwent tooth extraction(s) prior to IMRT intended to reduce the risk of ORN, are more likely to experience significant weight loss of more than 5% during CRT/BRT. Interestingly, the number of teeth extracted and the number of functional units lost did not influence the degree of weight loss and the need for TF.

Few researchers studied the effect of dental status on weight loss or nutritional status in head and neck cancer patients. Thereby, uniform methods or widely accepted standardized protocols for dental status assessment are lacking. Despite the use of different study methods and dental status assessment methods, our results are in line with a study published in 2008 suggesting that dental condition, defined by the decayed, missing, and filled teeth index and the masticatory coefficient, are risk factors for weight loss at the outset of management of head and neck cancer. [32] Another study evaluated dental status by using the Eichner Index in a sample of 104 treatment-naïve head and neck cancer patients. [33] These authors reported that a reduced number of functional units was associated with the total nutrition impact symptoms score, but the absence of functional units was not necessarily an absolute impairment to achieve normal dietary intake. In our study, a reduced number of functional units was not associated with weight loss of more than five percent.

Limiting factors in previous studies were amongst others a mixture of tumor sites and limited information on possible associative factors. Also no information was available on tooth loss in the context of pre-treatment tooth extractions or during oncological surgery, and data on weight loss during oncological therapy was underreported as well.

Research in the general population has shown a relationship between the number of natural teeth and weight loss. Having fewer teeth or being edentulous increased the risk of clinically relevant weight loss. [34-37] However, this concerns research among elderly people of at least 65 years of age, in which the dental status was examined and not the effect of tooth extractions as an intervention.

It remains unclear if the negative effect of tooth extractions on body weight is the result of a decrease in functional units or that it is the result of disrupting the existing masticatory system in its motor-sensory functionality and/or willingness

to eat. Previous studies suggested that extractions, masticatory, and swallowing function are interrelated. The number of OU and having functional dentures were positively associated with masticatory performance in a prospective cohort study. [11] A retrospective single center study in oral cancer patients showed that patients lacking OU had an increased risk for swallow impairment. [38]

Therefore, an association between a deterioration of dental status, resulting in reduced masticatory performances, and weight loss seems conceivable.

Tooth extractions or functional units did not predict TF dependency. In a recent study in 450 LAHNSCC patients, nine associative values were added to a prediction model for the need for TF, including amongst others BMI and percentage weight change at baseline. [39] Since we only found type of systemic therapy (cisplatin vs. cetuximab) and RT dose to the submandibular gland as independent TF predictors in the present study population, we have to assume that the study is underpowered and that these preliminary results should be interpreted with caution.

This is the first study addressing the impact of pre-CRT/BRT tooth extractions to reduce the risk of ORN, on weight loss. This weight loss is known to have a negative effect on treatment-related toxicity and oncological outcome. By evaluating the CRT/BRT trajectory, including neat weight reporting, a reliable retrospective assessment was possible. The addition of chemotherapy to RT as radiosensitizer does not only enhance RT efficacy, but may also intensify side effects, including nausea, vomitus, mucositis, and weight loss. [40, 41] As a result, the percentage of patients who become TF-dependent during CRT/BRT could be higher than during RT as a single modality. Therefore, we focused on the vulnerable CRT/BRT group to answer our research question.

Despite the fact that the research was set up on the basis of strictly standardized usual care protocols, we have some limitations to address. The relatively small sample size impeded extensive subgroup stratification and multivariable corrections. The number of patients who were edentulous at baseline was relatively high. Edentulous patients may have had extractions (*e.g.,* root tips or impacted wisdom teeth), but loss of a functional unit or decrease of the Eichner index is not possible. This may explain why extractions emerged as an associative factor for >5% weight loss and the decline in OU and Eichner Index did not reveal an association with weight loss. Although we were able to identify many factors associated with weight loss after tooth extractions, information on socio-economic and education

status, factors associated with health perception, could not be retrieved from the electronic health records, as this information was not reported.

The patient's financial and intellectual ability to modify their diet after tooth extractions may also have affected their capability to maintain weight, but accessing this privacy-sensitive data remains challenging. Following the procedure of tooth extraction, a reduced oral intake for approximately one or two weeks might lead to weight loss. Due to its retrospective character, we were not able to extract information on weight on the exact day of tooth extractions and on a standardized day after the procedure. However, a uniform moment of baseline measurements was defined, namely right before CRT/BRT initiation. Neither could we evaluate the effect of pain on oral intake since this was not reported in a standardized way and levels of treatment toxicity (mucositis, xerostomia) were not included in this study.

CONCLUSION

Our study suggests that tooth extractions contribute to significant weight loss during treatment. Since body weight maintenance is important for completing planned oncological treatment and for supporting the recovery phase, further weight loss caused by tooth extractions should be minimized or avoided as much as possible. More careful consideration of teeth removal prior to CRT/BRT seems appropriate, but demands close communication with the head and neck cancer team. As RT protocols and thus the doses to the tooth-bearing part of the jaws vary widely, interdisciplinary consultation with the radiation oncologist is highly recommended in order to reduce the risk of ORN due to potential oral sources of infection.

This study prompts further investigation into the adverse effects of tooth extractions and disruption of the masticatory system. That, along with the current improvements in RT techniques, may fuel the discussion to review and deescalate the current tooth extraction protocols aimed at reducing the risk of ORN.

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CHAPTER 7

OROPHARYNGEAL DYSPHAGIA AND CACHEXIA – INTERTWINED IN HEAD AND NECK CANCER

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ABSTRACT

Background: This study aims to investigate the relationship between cancer cachexia and oropharyngeal dysphagia (OD) in head and neck cancer patients prior to chemoradiotherapy or bioradiotherapy (CRT/BRT).

Methods: A prospective cohort study with head and neck cancer patients undergoing CRT/BRT (2018-2021) was conducted. Body composition and skeletal muscle function were evaluated using bioelectrical impedance analysis, handgrip strength, and the short physical performance battery (SPPB). The MD Anderson Dysphagia Inventory (MDADI), Eating Assessment Tool (EAT)-10 questionnaire, and patient characteristics were collected. A standardized videofluoroscopic swallowing study was offered to patients.

Results: Sixty-six patients were included. Twenty-six patients scored EAT-10≥3 and seventeen were cachectic.

ACE-27 score>1, cachexia, abnormal SPPB-derived repeated chair-stand test, lower MDADI scores, and higher overall stage grouping showed potential predictive value ($p \leq 0.10$) for EAT-10≥3. Using multivariable regression analysis, only cachexia remained a significant predictor of EAT-10≥3 (HR 9.000 [95%CI 2.483-32.619], p=0.001).

Conclusion: Cachexia independently predicted the presence of patient-reported OD.

INTRODUCTION

Oropharyngeal dysphagia (OD) is a highly prevalent phenomenon in head and neck cancer patients that affects oral intake leading to a decreased health-related quality of life. [1, 2] Tumor stage, primary tumor site, and side effects of cancer treatment may contribute to the development and maintenance of OD in head and neck cancer patients. Fibrosis and stiffening of the pharyngeal walls and other swallowing structures as a result of chemo or bioradiotherapy (CRT/BRT) may impair the swallowing function. Furthermore, surgical interventions and (C/B)RT may affect the sensory-motor innervation and the anatomy of the swallowing apparatus.

The presence of swallowing impairment at cancer diagnosis naturally advocates an effect of tumor size and location in the development of OD. However, the presence of OD has been described in patients with other non-head and neck tumor sites as well, including lung and gastro-intestinal cancers. [3, 4] This finding supports the hypothesis of other factors contributing to the development of OD in cancer patients. One of these factors is cachexia. Cancer cachexia is defined as a multifactorial syndrome, characterized by an ongoing loss of skeletal muscle mass leading to progressive functional impairment, often accompanied by systemic inflammation. [5] In head and neck cancer, the prevalence of cachexia ranges from 6 to 72%, depending on primary tumor site, cancer stage, and cachexia definition. [6-8] Many studies have shown that cachexia is related to poorer oncological treatment outcomes, including a decreased health-related quality of life, increased dose limiting toxicity, a higher number of surgical complications, and a decreased overall survival. [9-12]

Loss of skeletal muscle mass due to cachexia or sarcopenia affects skeletal muscle function. [13],[14] The question arises whether these syndromes may also lead to a poorer swallowing muscle function. Previous studies found worse swallowing function in sarcopenic elderly compared to non-sarcopenic elderly, in which OD was evaluated using patient-reported outcomes and the water swallowing test. [15-18] However, studies on the relationship between sarcopenia or cachexia and swallowing function in cancer patients using imaging techniques such as videofluoroscopic swallowing study (VFSS) are scarce. [19] VFSS, or modified barium swallow, allows biomechanical evaluation of swallowing safety and efficiency during bolus flow and is often used during or after oncological treatment to support OD rehabilitation. [20] The aim of this study is to investigate the relationship between cancer cachexia and OD in head and neck cancer patients prior to CRT/BRT.

MATERIALS AND METHODS

Study design

Baseline data from a prospective cohort study were analyzed to address the research question. The study took place in Maastricht University Medical Center + (MUMC+) in the Netherlands. The study was approved by the medical ethics committee of the MUMC+ (METC 2018-0540) and was classified according to the non-WMO (Wet Medisch-Wetenschappelijk Onderzoek) obligatory Medical Research Involving Human Subjects Act. [21] Patients signed informed consent upon participation. The study was conducted in accordance with the Declaration of Helsinki.

Patients with head and neck squamous cell carcinoma were enrolled in the study if they were treated with primary or adjuvant CRT/BRT with curative intent between October 2018 and July 2021. Exclusion criteria were a histopathology other than squamous cell carcinoma, re-irradiation of the head and neck, a second primary cancer, a history of stroke and/or a neurodegenerative disorder (e.g., myotonic dystrophy, Parkinson's disease), and a history of total laryngectomy or total glossectomy.

Oncological treatment

Primary or adjuvant CRT consisted of cisplatin (100 mg/m^2 every three weeks or 40mg/m^2 every week) concurrent with radiotherapy. In case of contraindications for cisplatin, patients were treated with carboplatin (AUC 1.5 every week) or BRT. Primary BRT consisted of a loading dose of cetuximab 400mg/m^2, followed by a weekly dose of cetuximab 250mg/m^2 combined with radiotherapy. Radiotherapy was applied in 33 to 35 daily fractions of 2 Gy, by either intensity-modulated radiation therapy (IMRT) as described previously, or proton therapy. [12] Using normal tissue complication probability profiles, optimal treatment plans of both techniques were compared. In case of clinical benefit, patients were offered proton therapy instead of photon therapy. [22, 23]

Assessment of body composition

Standardized measurements of body composition were performed within two weeks before CRT/BRT initiation by bioelectrical impedance analysis. Additionally, body weight and height were measured to calculate the body mass index (BMI),

and handgrip strength (HGS) and the short physical performance battery (SPPB) to assess muscle function.

Bioelectrical impedance analysis (BIA) was performed using the single frequency (50 Hz) Bodystat 1500 (Bodystat Ltd., Douglas, Isle of Man, United Kingdom). The fat-free mass (FFM) was calculated by subtracting fat mass (kg) as provided by BIA from the total body weight (kg). The fat-free mass index (FFMI) was calculated by dividing the FFM by height in meters squared. Cancer cachexia was defined as described in the consensus statement by Fearon et al.: [5] weight loss > 5%, or BMI < 20 and weight loss > 2%, or sarcopenia and weight loss > 2%. Sarcopenia was defined as low muscle strength and muscle quantity, according to the recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP2). [14]

HGS was measured using a Hydraulic Hand Dynamometer SH5001 (SAEHAN corporation, Incheon-City, South Korea). Measurements were performed three times on each side (left and right hand) according to the standard operating procedure provided by the Dutch Nutritional Assessment Platform. [24] The highest value was considered for subsequent analyses. [25] Low HGS was defined as < 27 kg for men and < 16 kg for women, based on the cut-off points of sarcopenia according to the EWGSOP2. [14]

The SPPB provides information on balance, walking speed, and leg strength. [26, 27] The SPPB contains five items, divided in three sub categories: balance (three items including side-by-side stand, semi-tandem stand, and tandem stand, maximum of four points), walking test (one item, maximum four points), and repeated chair-stand test (one item, maximum four points). Measurements were performed according to the standard operating procedure provided by the National Institute on Aging. [28] Due to the limited space in the outpatient clinic rooms, the walking test was performed over three meters, using the cut-off points for this distance. [28] The total SPPB score classifies patients in three risk groups of impaired physical function: severe limitations (score 0-3), high risk (score 4-9), and low risk (score 9-12). The SPPB-derived repeated chair-stand test was considered abnormal when it took the patient longer than fifteen seconds to perform. [14]

Evaluation of swallowing

All patients were evaluated using the investigator-reported Functional Oral Intake Scale (FOIS), [29] and patient-reported OD questionnaires (the M.D. Anderson Dysphagia Inventory (MDADI) [30] and the Eating Assessment Tool (EAT)-10). [31]

The functional oral intake of food and liquid was assessed using the FOIS. The FOIS is an ordinal scale measure that ranges from one to seven: [29] nil per os (NPO; level 1), tube dependency with minimal attempts of food or liquid (level 2), tube dependency with consistent oral intake of food or liquid (level 3), total oral diet of a single consistency (level 4), total oral diet with multiple consistencies requiring special preparation or compensations (level 5), total oral diet with multiple consistencies without special preparation, but with specific food limitation (level 6), and a total oral diet with no restrictions (level 7).

The Dutch version of the MDADI is a patient-reported questionnaire to measure the impact of OD on health-related quality of life. [30, 32] The MDADI consists of different domains: one global assessment question (MDADI-G) for the effect of OD on overall health-related quality of life; the functional scale (MDADI-F) for the impact of OD on daily activities (five questions); the physical scale (MDADI-P) for the physical impact of OD as perceived by the patient (eight questions); and the emotional scale (MDADI-E) for the patients' perceptual response on OD, e.g., self-consciousness, embarrassment, etc. (six questions). The questions are scored on a 5-point scale (1=strongly agree, 2=agree, 3=no opinion, 4=disagree, 5=strongly disagree) and the MDADI total score (MDADI-T) is based on the sum of all domains (20 questions). The minimum score is 20 representing low functioning and the maximum possible score is 100 (high functioning).

The Dutch version of the EAT-10 was used in this study. [33, 34] The Dutch translation consists of a 10-item dysphagia-specific symptom questionnaire with a maximum total score of 40 points. All items are rated by the patient on a 5-point scale in which 0 indicates no problem, and 4 indicates a severe problem. An EAT-10 $\geq$ 3 score is abnormal and indicates a higher self-perception of the presence of OD. [31]

Patients participating in the body composition assessments and questionnaires were invited to additionally visit the interdisciplinary outpatient clinic for OD. In addition to the FOIS, MDADI, and EAT-10, a standardized swallowing protocol was performed within two weeks before CRT/BRT initiation and included a clinical ear, nose, and throat examination with cranial nerve testing, and a standardized VFSS. [35]

During the VFSS examination patients were offered three boluses of thin liquid, three boluses of thick liquid, and three bite-sized crackers. Each thin liquid bolus contained 10 ml barium (40 mL Micropaque® barium sulfate suspension (Guerbet, Villepinte, France) mixed with 60 ml water). Each thick liquid bolus contained 10 ml liquid barium (50 ml applesauce - One 2 fruit mixed with 50 g E-Z-HD® barium sulphate powder (Bracco s.p.a., Milan, Italy)). The bite-sized cracker was a Mini Toast - Delhaize 2 gr coated with barium paste (340 g E-Z-HD® barium sulphate powder with 55 ml water). During the flow test, thin liquid met the descriptive criteria of level 0 'thin' and thick liquid the criteria of level 3 'moderately thick' according to the International Dysphagia Diet Standardisation Initiative. [36] Patients were positioned in the lateral viewing plane with the fluoroscopic visualization field collimated to include the lips, nasal cavity, cervical spinal column, the upper esophageal sphincter, and the proximal esophagus to allow for full visualization of the oral cavity and the pharynx. A radio-opaque coin was attached on the midline of the submental region. Swallowing was evaluated using pulsed fluoroscopy at 30 pulses per second. VFSS images were obtained with the Artis zee Multi-purpose System Siemens AG Medical Solutions Angiography and Interventional X-ray Systems (Siemens, Forchheim, Germany), recorded at 30 frames per second, and stored on the hospital network drive.

During the rating process, the VFSS videos were analyzed at varying speed (normal to frame-by-frame) using Quick Time Media Player (Apple Inc, Cupertina, California, USA). For each swallow visuoperceptual variables were measured by 2 experienced observers in consensus agreement as described in previous studies. [37, 38] Oral transport refers to oral bolus formation and anteroposterior oral bolus transit, clearing swallows are defined as sequential swallows on the same bolus to clear pharyngeal residue, and aspiration was defined as entry of the bolus into the airway below the level of the true vocal folds including bolus at the level of the vocal commissures or true vocal folds secondarily leaking into the trachea (Table A1). [39, 40] Pharyngeal residue was defined as bolus remaining in the pharynx (pharyngeal walls, valleculae, and/or pyriform sinuses) after spontaneous clearing swallows. No distinction was made between right- or left-sided residue. These VFSS variables are presented in the supplementary material (Table A1).

Statistical analysis

The Shapiro-Wilk test was used to assess data for normal distribution. Normally distributed continuous variables were reported in means with standard deviation (SD), non-normally distributed data were reported in medians with interquartile range (IQR). Categorical variables were reported in numbers and proportions.

For the presentation of the skewed FOIS data, the FOIS scores were initially reported using three categories: oral intake with specific food limitation or a total oral diet with no restrictions (FOIS 6-7), oral intake of a single consistency or of multiple consistencies requiring special preparation or compensations (FOIS 4-5), tube feeding dependent with or without varying degrees of oral intake (FOIS 1-3). To improve statistical power in the regression analysis, the FOIS scores were subsequently pooled in two categories, comparing category FOIS 1-5 (thickening of liquids, special food preparation, tube feeding, etc.) to category FOIS 6-7 (few or no restrictions on oral feeding).

Comparisons among groups were performed using Independent samples T-test, Mann-Whitney U test, Pearson's Chi-squared test (χ^2), and Fisher's exact test where appropriate. Results were regarded statistically significant if analysis yielded a *p*-value < 0.05. Univariable logistic regression analysis was performed. Factors yielding a *p*-value < 0.10 were included in the multivariable analysis. All statistical analyses were performed using SPSS (IBM version 25 for Windows, Armonk, New York, USA). For the Fisher's exact test with more than 2 by 2 items, the online calculators http://vassarstats.net/fisher2x4.html and https://www.quantitativeskills.com/sisa/statistics/fiveby2.htm were used.

Table 1 – Comparison of characteristics and measurements between patients with EAT-10 < 3 versus EAT-10 ≥ 3 prior to CRT/BRT.

	No. of patients with EAT-10 < 3 (n=40)	**No. of patients with EAT-10 ≥ 3** (n=26)	***p*-value**
Patient characteristics			
Male	31 (78%)	19 (73%)	0.772[d]
Female	9 (23%)	7 (27%)	
Age in years (median (IQR))	61 (12)	59 (14)	0.664[b]
WHO PS 0	29 (73%)	16 (62%)	**0.017**[d]
WHO PS 1	11 (28%)	5 (19%)	
WHO PS 2	0 (0%)	5 (19%)	
ACE-27 score 0	21 (53%)	7 (27%)	0.132[d]
ACE-27 score 1	10 (25%)	12 (46%)	
ACE-27 score 2	7 (18%)	4 (15%)	
ACE-27 score 3	2 (5%)	3 (12%)	
Smoking			
Current	10 (25%)	12 (46%)	0.213[d]
Former	20 (50%)	10 (39%)	
Never	10 (25%)	4 (15%)	
Alcohol			
None	2 (5%)	3 (12%)	0.810[d]
< 1 unit a day	17 (44%)	10 (39%)	
1-3 unit a day	6 (15%)	3 (12%)	
> 3 unit a day	14 (36%)	10 (39%)	
Missing	*1*	*0*	
Body composition and muscle strength measurements			
Percentage weight change 6 months prior to CRT/BRT (median (IQR))	-0.1 (4.4)	-5.1 (8.1)	**0.001**[b]
Cachexia	4 (10%)	13 (50%)	**< 0.001**[d]
No cachexia	36 (90%)	13 (50%)	
BMI (mean ± SD, kg/m^2)	27.4 ± 5.3	26.3 ± 5.1	0.436[a]
Male	27.7 ± 5.2	26.3 ± 5.2	0.378[a]
Female	26.2 ± 6.0	26.3 ± 5.2	0.990[a]
FFMI (mean ± SD, kg/m^2)	19.4 ± 2.9	18.8 ± 3.2	0.468[a]
Male	20.2 ± 2.5	19.8 ± 3.1	0.622[a]
Female	16.5 ± 2.7	16.1 ± 1.1	0.725[a]
FMI (median (IQR), kg/m^2)	7.5 (2.9)	7.1 (3.2)	0.495[b]
Male	7.1 (3.4)	6.5 (3.0)	0.285[b]
Female	7.6 (5.8)	8.7 (6.5)	0.837[b]
Handgrip strength (mean ± SD, kg)	42.0 ± 9.9	40.3 ± 10.7	0.504[a]
Male	44.9 ± 9.2	45.0 ± 8.3	0.970[a]
Female	32.0 ± 4.1	27.4 ± 3.6	**0.036**[a]
Handgrip strength			
Low (M < 27 kg, F < 16 kg)	0 (0%)	1 (4%)	0.394[d]
Normal	40 (100%)	25 (96%)	
SPPB score > 9	36 (92%)	18 (87%)	0.147[d]
SPPB score 4-9	3 (8%)	4 (11%)	
SPPB score < 4	0 (0%)	1 (2%)	
Missing	*1*	*3*	
SPPB-derived variable			
Normal repeated chair-stand test	38 (97%)	18 (78%)	**0.023**[d]
Abnormal repeated chair-stand test	1 (3%)	5 (22%)	
Missing	*1*	*3*	

	No. of patients with EAT-10 < 3 (n=40)	**No. of patients with EAT-10 ≥ 3** (n=26)	***p*-value**
Swallowing function and patient reported outcomes			
No or few restrictions on oral feeding (FOIS 6-7)	33 (83%)	13 (28%)	**0.008**[d]
Oral intake with special preparation (FOIS 4-5)	7 (18%)	12 (72%)	
Mainly or exclusively tube feeding (FOIS 1-3)	0 (0%)	1 (0%)	
MDADI (median (IQR))			
Total score	100 (10)	67 (25)	**< 0.001**[b]
Global assessment	5 (1)	4 (2)	**< 0.001**[b]
Emotional subscore	30 (3)	22 (10)	**< 0.001**[b]
Functional subscore	25 (0)	18 (6)	**< 0.001**[b]
Physical subscore	40 (5)	25 (8)	**< 0.001**[b]
Tumor characteristics			
Oral Cavity	3 (8%)	3 (12%)	0.755[c]
Oropharynx	26 (65%)	16 (62%)	
Hypopharynx	2 (5%)	2 (8%)	
Larynx	5 (13%)	4 (15%)	
Nasopharynx	3 (8%)	0 (0%)	
Other	1 (3%)	1 (4%)	
T classification			
T0	1 (3%)	2 (8%)	0.253[d]
T1	8 (20%)	1 (4%)	
T2	15 (38%)	8 (31%)	
T3	9 (23%)	8 (31%)	
T4	7 (18%)	7 (27%)	
N classification			
N0	5 (13%)	3 (12%)	0.332[d]
N1	17 (43%)	8 (31%)	
N2	12 (30%)	6 (23%)	
N3	6 (15%)	9 (35%)	
M classification			
M0	40 (100%)	24 (92%)	0.152[d]
M1	0 (0%)	2 (8%)	
Overall stage grouping			
Stage I	13 (33%)	2 (8%)	0.079[d]
Stage II	6 (15%)	3 (12%)	
Stage III	10 (25%)	11 (42%)	
Stage IVabc	11 (28%)	10 (38%)	
HPV + oropharynx	22 (55%)	10 (39%)	0.189[d]
HPV - oropharynx and other tumor sites	18 (45%)	16 (62%)	
Treatment characteristics			
Adjuvant CRT	2 (5%)	4 (15%)	0.403[d]
Primary CRT	31 (78%)	18 (69%)	
Primary BRT	7 (18%)	4 (15%)	

ACE, Adult Comorbidity Evaluation; BMI, Body Mass Index; BRT, Bioradiotherapy; Cachexia as defined by Fearon et al. [5]; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; FFMI, Fat-free Mass Index; FMI, Fat Mass Index; FOIS, Functional Oral Intake Scale; HPV, Human Papilloma Virus; IQR, interquartile range; MDADI, M.D. Anderson Dysphagia Inventory; SPPB, Short Physical Performance Battery; WHO PS, World Health Organization Performance Status.

[a]Independent samples T-test, [b]Mann-Whitney U Test, [c]Pearson's Chi-squared test (χ^2), [d]Fisher's exact test. Missing values were not considered as a separate category in statistical analysis. Bold values denote statistical significance at the p<0.050 level. The values are numbers and percentages (in parentheses) unless indicated differently. Percentages may not add up to 100 due to rounding off.

RESULTS

Cachexia and patient-reported oropharyngeal dysphagia

Between October 2018 and July 2021, 66 patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) were enrolled in this study. Twenty-six (39%) patients had an EAT-10 ≥ 3 and seventeen (26%) patients were considered cachectic prior to CRT/BRT. Differences between patients with EAT-10 ≥ 3 and EAT-10 < 3 are presented in Table 1. Patients with EAT-10 ≥ 3 were significantly more often cachectic compared to patients with EAT-10 < 3. In addition, the number of patients with an abnormal SPPB-derived repeated chair-stand test was significantly higher in the group of patients with EAT-10 ≥ 3 compared to those with EAT-10 < 3. Additionally, patients with EAT-10 ≥ 3 presented with significantly lower MDADI scores and a significantly higher prevalence of oral intake of a single consistency or of multiple consistencies requiring special preparation or compensations (FOIS 4-5). Supplemental Table A2 displays the comparison of characteristics and measurements between cachectic and non-cachectic patients prior to CRT/BRT. Cachectic patients had a significantly higher World Health Organization performance score (WHO PS), a higher ACE-27 score, and a lower performance score on the SPPB compared to non-cachectic patients. The FOIS score and patient-reported outcomes of OD (MDADI and EAT-10) were significantly worse in cachectic patients. Regarding tumor characteristics, cachectic patients had significantly more often laryngeal tumors, a higher tumor and nodal stage, and were less likely to have human papilloma virus (HPV) positive (+) oropharyngeal tumors.

The following variables showed a potential predictive value ($p \leq 0.10$) for EAT-10 ≥ 3 prior to CRT/BRT in univariable regression analysis: ACE-27 score 1, cachexia, abnormal SPPB-derived repeated chair-stand test, lower MDADI scores, and higher overall stage grouping (Table 2). Using multivariable step forward logistic regression analysis only cachexia remained a significant predictor of EAT-10 ≥ 3 (HR 9.000 [95%CI 2.483-32.619], p=0.001), also after correction for age, sex, and HPV-status. The following variables showed a potential predictive value ($p \leq 0.10$) for cachexia prior to CRT/BRT in univariable regression analysis: Age, WHO PS 1 or 2, ACE-27 score 1 and 2, SPPB score > 9, abnormal SPPB-derived repeated chair-stand test, FOIS score 1-5, lower MDADI scores, EAT-10 ≥ 3, tumor site (oral cavity and larynx), higher overall stage grouping, and HPV negative tumors (Supplemental Table A3). Using multivariable step forward logistic regression analysis only WHO PS 1 or 2, FOIS score 1-5, and EAT-10 ≥ 3 remained significant predictors of cachexia also after correction for age, sex, tumor site (except for WHO PS, p=0.076), T classification, overall stage grouping, and HPV status. (Supplemental Table A4).

Videofluoroscopic swallowing study

Twenty out of the 66 patients accepted the invitation to undergo a standardized VFSS. Four of these twenty (20%) patients had an EAT-10 ≥ 3. Patients who underwent a VFSS were significantly younger and had significantly lower EAT-10 scores (< 3) compared to patients who did not undergo a VFSS (Supplemental Table A5). Ten (50%) patients experienced impaired oral transport and ten (50%) patients presented clearing swallows. Pharyngeal residue was considered minimal in six (30%) patients and moderate in five (25%) patients. More than half of the patients (n=13; 65%) swallowed safely without bolus entrance into the airway.

Table 3 displays the comparison of the frequency distribution of patients per category of the different VFSS variables between (1) patients with EAT-10 < 3 versus patients with EAT-10 ≥ 3, (2) patients with cachexia versus patients without cachexia, and (3) patients with FFMI < P10 versus patients with a normal FFMI. VFSS measurements did not significantly differ between patients with EAT-10 < 3 versus EAT-10 ≥ 3, with versus without cachexia, and between patients with normal versus abnormal FFMI. A trend was observed towards more impaired oral transport in patients with EAT-10 ≥ 3 (p=0.051).

Table 2 – Univariable regression analysis for EAT-10 ≥ 3 prior to CRT/BRT.

	HR	**95% CI**		***p*-value**
		Lower	**Upper**	
Patient characteristics				
Male Female (ref)	0.788	0.252	2.466	0.682
Age in years	0.989	0.923	1.059	0.747
WHO PS 0 (ref) WHO PS 1 or 2	1.648	0.576	4.716	0.352
ACE-27 score 0				0.154
ACE-27 score 1	3.600	1.086	11.932	**0.036**
ACE-27 score 2	1.714	0.384	7.659	0.480
ACE-27 score 3	4.500	0.619	32.695	0.137
Smoking Never				0.204
Current	3.000	0.717	12.553	0.132
Former	1.250	0.313	4.998	0.752
Alcohol < 1 unit a day (ref) Daily alcohol consumption *Missing 1*	0.950	0.352	2.563	0.919
Body composition and muscle strength measurements				
Percentage weight change 6 months prior to CRT/BRT	0.865	0.783	0.957	**0.005**
Cachexia	9.000	2.483	32.619	**0.001**
BMI (kg/m^2)	0.961	0.872	1.060	0.430
FFMI (kg/m^2)	0.940	0.796	1.109	0.463
FMI (kg/m^2)	0.947	0.808	1.110	0.501

	HR	95% CI		*p*-value
		Lower	Upper	
Handgrip strength (kg)	0.983	0.936	1.033	0.498
SPPB score > 9 (ref) SPPB score 9 or lower *Missing 4*	3.333	0.715	15.535	0.125
SPPB-derived variable				
Normal repeated chair-stand test (ref) Abnormal repeated chair-stand test *Missing 4*	10.556	1.148	97.098	**0.037**
Swallowing function and patient reported outcomes				
No or few restrictions on oral feeding (FOIS 6-7) (ref) Special food preparation or tube feeding (FOIS 1-5)	4.714	1.537	14.460	**0.007**
MDADI				
Total score	0.857	0.799	0.920	**< 0.001**
Global assessment	0.360	0.205	0.633	**< 0.001**
Emotional subscore	0.731	0.626	0.853	**< 0.001**
Functional subscore	0.583	0.453	0.750	**< 0.001**
Physical subscore	0.644	0.517	0.802	**< 0.001**
Tumor characteristics				
Oropharynx				0.989
Oral Cavity	1.625	0.292	9.050	0.579
Hypopharynx	1.625	0.208	12.705	0.644
Larynx	1.300	0.303	5.569	0.724
Nasopharynx	0.000	0.000	.	0.999
Other	1.625	0.095	27.838	0.738
T classification				
T0				0.349
T1	0.063	0.003	1.496	0.087
T2	0.267	0.021	3.413	0.310
T3	0.444	0.034	5.880	0.538
T4	0.500	0.036	6.862	0.604
N classification				
N0				0.338
N1	0.784	0.149	4.124	0.774
N2	0.833	0.147	4.723	0.837
N3	2.550	0.428	14.607	0.309
M classification				
M0 (ref) M1	.	.	.	0.999
Overall stage grouping				
Stage I - II (ref) Stage III - IV	3.800	1.196	12.073	**0.024**
HPV + oropharynx HPV - oropharynx and other tumor sites (ref)	0.511	0.187	1.399	0.191
Treatment characteristics				
Primary CRT (ref)				0.392
Adjuvant CRT	3.444	0.573	20.713	0.177
Primary BRT	0.984	0.253	3.830	0.982

ACE, Adult Comorbidity Evaluation; BMI, Body Mass Index; BRT, Bioradiotherapy; CI, confidence interval; Cachexia as defined by Fearon et al. [5]; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; EBV, Epstein Barr Virus; FFMI, Fat-free Mass Index; FMI, Fat Mass Index; FOIS, Functional Oral Intake Scale; HGS, Handgrip strength; HPV, Human Papilloma Virus; HR, Hazard Ratio; MDADI, M.D. Anderson Dysphagia Inventory; (ref), reference value; SPPB, Short Physical Performance Battery; WHO PS, World Health Organization Performance Status.

Missing values are not considered a separate category in statistical analysis. Bold values denote statistical significance at the p<0.050 level.

Table 3 – Comparison of characteristics per category of the different VFSS variables prior to CRT/BRT between (1) Patients with EAT-10 < 3 versus patients with EAT-10 ≥ 3, (2) Patients with cachexia versus patients without cachexia, and (3) Patients with FFMI < P10 versus patients with a normal FFMI.

	Total no. of patients	No. of patients with EAT-10 score < 3	No. of patients with EAT-10 score ≥ 3	*p*-value	No. of patients without cachexia	No. of patients with cachexia	*p*-value	No. of patients with normal FFMI	No. of patients with FFMI < P10	*p*-value
Oral transport										
Normal	10	10	0	0.051	10	0	0.237	9	1	0.489
Impaired for 1 consistency	4	2	2		3	1		3	1	
Impaired for 2 or more consistencies	6	4	2		5	1		4	2	
Clearing swallows										
No clearing swallows	10	9	1	0.437	9	1	1.000	9	1	0.437
Efficient clearing swallows	7	5	2		6	1		5	2	
Inefficient clearing swallows	3	2	1		3	0		2	1	
Pharyngeal residue										
No pharyngeal residue	9	8	1	0.777	8	1	1.000	8	1	0.638
Minimal	6	4	2		5	1		5	1	
Moderate	5	4	1		5	0		3	2	
Severe	0	0	0		0	0		0	0	
Penetration-aspiration										
No penetration or aspiration	13	10	3	0.999	11	2	0.999	11	2	0.764
Minimal penetration, no aspiration	3	3	0		3	0		2	1	
Penetration for all consistencies or aspiration for 1 consistency	4	3	1		4	0		3	1	
Aspiration for two or more consistencies	0	0	0		0	0		0	0	

BRT, bioradiotherapy; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; FFMI, Fat-free mass index. Results are given in absolute numbers. All between group statistical analysis are performed with Fisher's exact test.

DISCUSSION

According to our knowledge, this study is the first to examine the relationship between cancer cachexia versus patient-reported OD and videofluoroscopic signs of OD in LAHNSCC patients prior to CRT/BRT. Using this study design, other causes of OD in LAHNSCC such as the effects of CRT/BRT on swallowing were excluded.

Both patient-reported OD and cancer cachexia were frequently co-occurring conditions in LAHNSCC patients prior to CRT/BRT. Nearly forty percent of our population reported clinically relevant symptoms of OD (EAT-10 ≥ 3) and twenty-six percent of the total population was considered cachectic prior to CRT/BRT. This is within the range of previous studies reporting cachexia in 6 to 72% of the patients,[7, 8, 41, 42] and EAT-10 ≥ 3 in 58% prior to oncological treatment. [43] Cancer cachexia was significantly associated with baseline patient-reported signs of OD evaluated with EAT-10, independent of age, sex, comorbidity, and tumor stage.

Only a few studies reported a relationship between OD and body composition or weight loss in oncological populations using different methods, challenging clean comparison with our results. [44-46] For the evaluation of the swallowing function, these studies did not perform any biomechanical measurements using VFSS or fiberoptic endoscopic evaluation of swallowing (FEES) nor dysphagia-specific patient-reported outcome measures, and only two studies evaluated pretreatment OD. [44, 46] Additionally, the presence of OD was evaluated using investigator-reported dietary intake scales (Food Intake Level Scale and FOIS). Previous research has shown that the FOIS or the level of dietary intake is not a reliable indicator for the severity of OD [47] so that the conclusions of the above-cited studies on the relationship between sarcopenia and OD should be interpreted with caution.

Hashida et al. performed postoperative VFSS in combination with preoperative swallowing muscle measurements in computed tomography (CT) scans including the cross sectional area (CSA) of the geniohyoid and masseter muscles in head an neck cancer patients who underwent salvage surgery (surgery after definitive radiotherapy or CRT/BRT). [48] A lower preoperative geniohyoid CSA was significantly associated with higher postoperative scores on the Penetration Aspiration Scale of Rosenbek et al. [39] This finding may suggest that swallowing muscle mass is related to swallowing muscle function although one should take into account possible preoperative radiation effects on the geniohyoid muscle and undiagnosed baseline OD. Furthermore, many cranial nerves and muscles

are involved in hyolaryngeal elevation and airway closure, so penetration and aspiration are not the result of changes in the geniohyoid muscle alone. Therefore, it remains difficult to interpret the relationship between weight loss and/or low muscle mass and the swallowing function. Nevertheless, the study of Hashida et al. is one of the very few explorative studies attempting to measure swallowing muscle mass and further development and validation of these measurements is relevant to understand the mechanism(s) and relationship between OD and swallowing muscle wasting in cancer.

The prevalence of signs of OD in our sample of LAHNSCC patients who underwent a VFSS was high (n=10/20; 50%) and one third of the patients (n=7/20; 35%) had an unsafe swallowing function with entrance of the bolus into the airway. In the present study the videofluoroscopic signs of OD were less prevalent compared to previous studies reporting on baseline signs of OD such as pharyngeal residue in approximately 80% of the patients prior to CRT. [49, 50] However, these studies included higher numbers of laryngeal and pharyngeal cancers and more advanced tumor stages compared to the present study.

The swallowing function of newly diagnosed head and neck cancer patients can be affected in multiple ways. First, the tumor itself may cause obstruction and invasion of the swallowing apparatus, complicating deglutition. Furthermore, cancer-related pain in the affected and surrounding structures may cause odynophagia. In addition to local effects of the tumor, there may also be systemic effects of cancer that contribute to swallowing impairment. The catabolic processes of cancer cachexia promote skeletal muscle wasting, which most likely also affects the muscles involved in swallowing. For example, impaired oral bolus transport can be the result of decreased tongue strength. A recent meta-analysis supports this example by showing an association between reduced tongue strength and sarcopenia. [51] In the present study population, tongue strength was not evaluated. However, patients with EAT-10 $\geq$ 3 had significantly more often an abnormal SPPB-derived repeated chair-stand test, showing a relation between reduced leg performance and patient-reported OD. Furthermore, two of the twenty patients who underwent a VFSS were cachectic and both patients had an impaired oral bolus transport.

Another important mechanism of swallowing impairment in newly diagnosed head and neck cancer patients finds its origin in a decreased or impaired sensory

feedback function. A disruption of sensory feedback processes can contribute to OD as shown in patients with cerebrovascular accidents. [52, 53] Also for head and neck cancer patients it is most likely that a decreased oral intake, as a result of reduced appetite or OD, results in a loss of stimuli such as different tastes, temperatures, and food textures, which may contribute to a disrupted sensory feedback and subsequently impaired motor execution for deglutition by the brain. [54] Whereas cancer cachexia does not affect the neuromuscular junction (muscle control, efferent), alterations in taste perception may arise from an inflammatory state and taste is, as mentioned above, part of an important sensory feedback mechanism for swallowing (afferent) potentially leading to disturbances in the swallowing motor execution. [55-57] The underlying pathophysiology still requires further investigation to fully understand the interactions between sensory stimuli such as taste and swallowing function.

Studies on the underlying mechanisms of the relationship between OD and skeletal muscle wasting in head and neck cancer are underway, but at present high-quality scientific evidence to confirm the more than likely causal relationship between both phenomena is lacking.

Despite the lack of high-quality head and neck cancer-specific literature on this topic, the Japanese position paper on sarcopenia and OD is an interesting source of information from which to draw parallels with the current study. [58] The Japanese position paper on sarcopenia and OD was endorsed by four professional organizations in 2019 and the authors proposed a consensus on the diagnosis of sarcopenic dysphagia. Sarcopenic dysphagia was defined as “dysphagia caused by sarcopenia of the whole-body and swallowing-related muscles.” [58] The proposed diagnostic criteria are applicable to patients aged 65 and above. However, the current LAHNSCC study population includes patients with a younger chronological age, but most likely higher biological age due to their life style and comorbidities. [59] Thus, even though the authors of the position paper have successfully made way for discussing and studying the concept of sarcopenic dysphagia, the pathophysiology is still underexplored and requires further understanding to implement the diagnosis of sarcopenic dysphagia in clinical (oncological) practice.

Because of the high prevalence of OD and cachexia in head and neck cancer and the coincident character of these conditions prior to CRT/BRT, clinical practice demands an accessible screening for OD and cachexia in the oncological care

trajectory. Pretreatment signs of OD have been shown to predict the presence of post-CRT OD. [43] Likewise, presence of cachexia in the pretreatment phase can lead to poorer oncological treatment outcomes, so early identification of both OD and cachexia is considered essential. Elucidating the mechanism(s) of the relationship and the mutual influence of cancer cachexia and OD, may enable the development of targeted interventions for both phenomena to limit further physical deterioration. The clinical utility of this study is based on the high prevalence of cachexia that supports the importance of early baseline and follow-up screening of cachexia, referral to a dietitian, and early initiation of nutritional interventions as an integral part of usual care for head and neck cancer patients.

Limitations

This study has some limitations. Not all LAHNSCC patients were willing to undergo a VFSS. Given the burden of diagnostic tests that newly diagnosed LAHNSCC patients often undergo, it is understandable that patients did not want to have a VFSS in addition to all the other investigations. Patients who underwent a VFSS reported lower EAT-10 scores compared to those who were not evaluated with VFSS. Due to the limited sample size of patients with a VFSS, we can only draw preliminary conclusions regarding biomechanical measurements of swallowing function.

Skeletal muscle mass index measured using CT scans is often considered the gold standard for the diagnosis of decreased skeletal muscle mass. However, in the present sample of LAHNSCC patients, abdominal CT scans including the level of the third lumbar vertebrae were not carried out as this examination is not part of standard care for head and neck cancer patients in the Netherlands. Instead, BIA was used in the present study as this is an easily accessible measurement tool that allows a reliable estimation of body composition in head and neck cancer patients. Implementation of BIA as integral part of a physical performance evaluation protocol in clinical practice as in the current study, to identify head and neck cancer patients at risk for poor survival is recommended. [60]

CONCLUSION

Cancer cachexia and OD prior to CRT/BRT are both highly prevalent conditions in the LAHNSCC population. Additional research is needed to unravel the underlying

mechanisms and direction of the causal relationship between cancer cachexia and OD as both phenomena seem inextricably linked. We conclude that baseline multidimensional screening for OD with the FOIS, MDADI, and EAT-10 and screening for decreased muscle mass and weight loss with BMI, HGS, SPPB, and BIA are feasible and useful for newly diagnosed LAHNSCC patients. These screening measurements can immediately lead to further steps on an individual patient-related basis such as referral for further OD diagnostics using among others VFSS and further cachexia diagnostics followed by integrated therapeutic interventions in order to prepare the patient as best as possible for the CRT/BRT.

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APPENDIX

Table A1 – Description of the videofluoroscopic swallowing study variables.

Oral transport (oral bolus formation and anteroposterior oral transit)	Bolus formation and transit from the oral cavity to the pharynx. Normal oral transport. Impaired oral transport for one consistency. Impaired oral transport for two or more consistencies.
Clearing swallows to clear pharyngeal residue	Sequential swallows on the same bolus. No clearing swallows (one swallow). Efficient clearing swallows. Clearing swallows were considered efficient when there was no pharyngeal residue left after the final clearing swallow. Inefficient clearing swallows leaving pharyngeal residue.
Pharyngeal residue (efficiency)	Bolus retention in the entire pharynx after the swallow. No clinically relevant pharyngeal residue (0-10%). Minimal pharyngeal residue (10–49% for one or more consistencies). Moderate pharyngeal residue (50–90% for one or more consistencies). Severe pharyngeal residue (>90% for one or more consistencies).
Penetration-aspiration (safety)	Bolus entrance into the airway. Bolus in the laryngeal vestibule above or on the level of the true vocal folds (penetration) or bolus below the true vocal folds (aspiration). No penetration or aspiration. Minimal penetration, no aspiration. Penetration for all consistencies or aspiration for one consistency. Aspiration for two or more consistencies.

Table A2 – Comparison of characteristics and measurements between cachectic and non-cachectic patients prior to CRT/BRT.

	No. of patients without cachexia (n=49)	**No. of patients with cachexia** (n=17)	***p*-value**
Patient characteristics			
Male Female	36 (73%) 13 (27%)	14 (82%) 3 (18%)	0.533[d]
Age in years (median (IQR))	58 (13)	64 (13)	0.091[b]
WHO PS 0 WHO PS 1 WHO PS 2	39 (80%) 8 (16%) 2 (4%)	6 (35%) 8 (47%) 3 (18%)	**0.002** [d]
ACE-27 score 0 ACE-27 score 1 ACE-27 score 2 ACE-27 score 3	26 (53%) 14 (29%) 6 (12%) 3 (6%)	2 (12%) 8 (47%) 5 (29%) 2 (12%)	**0.012**[d]
Smoking			
Current Former Never	14 (29%) 22 (45%) 13 (27%)	8 (47%) 8 (47%) 1 (6%)	0.123[d]

	No. of patients without cachexia (n=49)	**No. of patients with cachexia** (n=17)	***p*-value**
Alcohol			
None	5 (10%)	0 (0%)	0.634[d]
< 1 unit a day	20 (42%)	7 (41%)	
1-3 unit a day	6 (13%)	3 (18%)	
> 3 unit a day	17 (35%)	7 (41%)	
Missing	*1*	*0*	
Body composition and muscle strength measurements			
Percentage weight change 6 months prior to CRT/BRT (median (IQR))	-0.2 (4.4)	-9.3 (8.0)	**< 0.001**[b]
BMI (mean ± SD, kg/m^2)	27.3 ± 5.4	26.0 ± 4.7	0.365[a]
Male	27.4 ± 5.3	26.5 ± 5.0	0.570[a]
Female	26.9 ± 5.9	23.4 ± 1.6	0.337[a]
FFMI (mean ± SD, kg/m^2)	19.2 ± 3.0	19.0 ± 3.2	0.814[a]
Male	20.2 ± 2.6	19.7 ± 3.1	0.547[a]
Female	16.4 ± 2.3	15.8 ± 0.1	0.651[a]
FMI (median (IQR), kg/m^2)	7.5 (3.3)	7.2 (3.2)	0.441[b]
Male	6.9 (3.2)	7.1 (3.6)	1.000[b]
Female	8.7 (6.8)	7.5 (n.a.)	0.201[b]
Handgrip strength (mean ± SD, kg)	41.6 ± 10.3	40.5 ± 10.2	0.694[a]
Male	45.7 ± 8.6	43.0 ± 9.2	0.333[a]
Female	30.3 ± 4.6	28.7 ± 4.2	0.582[a]
Handgrip strength			
Low (M < 27, F < 16)	0 (0%)	1 (6%)	0.258[d]
Normal	49 (100%)	16 (94%)	
SPPB score > 9	45 (94%)	9 (64%)	**0.008**[d]
SPPB score 4-9	3 (6%)	4 (29%)	
SPPB score < 4	0 (0%)	1 (7%)	
Missing	*1*	*3*	
SPPB-derived variable			
Normal repeated chair-stand test	46 (96%)	10 (71%)	**0.020**[d]
Abnormal repeated chair-stand test	2 (4%)	4 (29%)	
Missing	*1*	*3*	
Swallowing function and patient-reported outcomes			
No or few restrictions on oral feeding (FOIS 6-7)	41 (84%)	5 (29%)	**< 0.001**[d]
Oral intake with special preparation (FOIS 4-5)	7 (14%)	12 (71%)	
Mainly or exclusively tube feeding (FOIS 1-3)	1 (2%)	0 (0%)	
MDADI (median (IQR))			
Total score	97 (20)	70 (22)	**< 0.001**[b]
Global assessment	5 (1)	3 (3)	**< 0.001**[b]
Emotional subscore	29 (6)	21 (10)	**< 0.001**[b]
Functional subscore	25 (4)	18 (8)	**< 0.001**[b]
Physical subscore	39 (9)	25 (8)	**< 0.001**[b]
EAT-10 score < 3	36 (73%)	4 (24%)	**< 0.001**[d]
EAT-10 score ≥ 3	13 (27%)	13 (76%)	

	No. of patients without cachexia (n=49)	**No. of patients with cachexia** (n=17)	***p*-value**
Tumor characteristics			
Oral Cavity	2 (4%)	4 (24%)	**0.007**[c]
Oropharynx	34 (69%)	8 (47%)	
Hypopharynx	4 (8%)	0 (0%)	
Larynx	4 (8%)	5 (29%)	
Nasopharynx	3 (6%)	0 (0%)	
Other	2 (4%)	0 (0%)	
T classification			
T0	1 (2%)	2 (12%)	**0.030**[d]
T1	8 (16%)	1 (6%)	
T2	21 (43%)	2 (12%)	
T3	10 (20%)	7 (41%)	
T4	9 (18%)	5 (29%)	
N classification			
N0	4 (8%)	4 (24%)	**0.024**[d]
N1	21 (43%)	4 (24%)	
N2	16 (33%)	2 (12%)	
N3	8 (16%)	7 (41%)	
M classification			
M0	48 (98%)	16 (94%)	0.452[d]
M1	1 (2%)	1 (6%)	
Overall stage grouping			
Stage I	15 (31%)	0 (0%)	**0.012**[d]
Stage II	8 (16%)	1 (6%)	
Stage III	13 (27%)	8 (44%)	
Stage IVabc	13 (27%)	8 (50%)	
HPV + oropharynx	28 (57%)	4 (23%)	**0.024**[d]
HPV - oropharynx and other tumor sites	21 (43%)	13 (77%)	
Treatment characteristics			
Adjuvant CRT	3 (6%)	3 (18%)	0.135[d]
Primary CRT	39 (80%)	10 (59%)	
Primary BRT	7 (14%)	4 (24%)	

ACE, Adult Comorbidity Evaluation; BMI, Body Mass Index; BRT, Bioradiotherapy; Cachexia as defined by Fearon et al. [5]; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; FFMI, Fat-free Mass Index; FMI, Fat Mass Index; FOIS, Functional Oral Intake Scale; HPV, Human Papilloma Virus; IQR, interquartile range; MDADI, M.D. Anderson Dysphagia Inventory; SPPB, Short Physical Performance Battery; WHO PS, World Health Organization Performance Status.

[a]Independent samples T test, [b]Mann-Whitney U Test, [c]Pearson's chi-squared test (χ^2), [d]Fisher's exact test. Missing values are not considered a separate category in statistical analysis. Bold values denote statistical significance at the p<0.050 level. The values are numbers and percentages (in parentheses) unless indicated differently. Percentages may not add up to 100 due to rounding off.

Table A3 – Univariable regression analysis for cachexia prior to CRT/BRT.

	HR	95% CI		*p*-value
		Lower	Upper	
Patient characteristics				
Male Female (ref)	1.685	0.416	6.827	0.465
Age in years	1.080	0.991	1.176	0.079
WHO PS 0 (ref) WHO PS 1 or 2	7.150	2.125	24.057	**0.001**
ACE-27 score 0				0.063
ACE-27 score 1	7.429	1.384	39.866	**0.019**
ACE-27 score 2	10.833	1.679	69.917	**0.012**
ACE-27 score 3	8.667	0.873	86.062	0.065
Smoking				
Never				0.200
Current	7.429	0.814	67.831	0.076
Former	4.727	0.530	42.197	0.164
Alcohol				
Less than 1 unit per day (ref) Daily alcohol consumption *Missing 1*	1.553	0.507	4.757	0.441
Body composition and muscle strength measurements				
Percentage weight change 6 months prior to therapy	0.259	0.100	0.670	**0.005**
BMI (kg/m^2)	0.949	0.848	1.062	0.361
FFMI (kg/m^2)	0.978	0.814	1.174	0.810
FMI (kg/m^2)	0.873	0.710	1.072	0.194
Handgrip strength (kg)	0.989	0.936	1.045	0.689
SPPB score > 9 (ref) SPPB score 9 or lower *Missing 4*	8.333	1.682	41.288	**0.009**
SPPB-derived variable				
Normal repeated chair-stand test (ref) Abnormal repeated chair-stand test *Missing 4*	9.200	1.476	57.349	**0.017**
Swallowing function and patient reported outcomes				
No or few restrictions on oral feeding (FOIS 6-7) (ref) Special food preparation or tube feeding (FOIS 1-5)	12.300	3.388	44.652	**< 0.001**
MDADI				
Total score	0.930	0.894	0.967	**< 0.001**
Global assessment	0.401	0.246	0.654	**< 0.001**
Emotional subscore	0.821	0.729	0.923	**0.001**
Functional subscore	0.784	0.680	0.905	**0.001**
Physical subscore	0.846	0.774	0.925	**< 0.001**
EAT-10 score <3 (ref) EAT-10 score ≥3	9.000	2.483	32.619	**0.001**

	HR	95% CI		*p*-value
		Lower	Upper	
Tumor characteristics				
Oropharynx				0.156
Oral Cavity	8.500	1.318	54.817	**0.024**
Hypopharynx	0.000	0.000	.	0.999
Larynx	5.312	1.158	24.381	**0.032**
Nasopharynx	0.000	0.000	.	0.999
Other	0.000	0.000	.	0.999
T classification				
T0				0.082
T1	0.063	0.003	1.496	0.087
T2	0.048	0.003	0.787	**0.033**
T3	0.350	0.026	4.654	0.426
T4	0.278	0.020	3.884	0.341
N classification				
N0				0.042
N1	0.190	0.033	1.097	0.063
N2	0.125	0.017	0.943	0.044
N3	0.875	0.157	4.874	0.879
M classification				
M0 (ref) M1	3.000	0.177	50.784	0.447
Stage I - II (ref) Stage III - IV	14.154	1.739	115.207	**0.013**
HPV + oropharynx HPV- oropharynx and other tumor sites (ref)	0.231	0.066	0.810	**0.022**
Treatment characteristics				
Primary CRT (ref)				0.220
Adjuvant CRT	3.900	0.681	22.322	0.126
Primary BRT	2.229	0.543	9.140	0.266

ACE, Adult Comorbidity Evaluation; BMI, Body Mass Index; BRT, Bioradiotherapy; CI, confidence interval; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; F, female; FFMI, Fat-free Mass Index; FMI, Fat Mass Index; FOIS, Functional Oral Intake Scale; HPV, Human Papilloma Virus; HR, Hazard Ratio; M, male; MDADI, M.D. Anderson Dysphagia Inventory; (ref), reference value; SPPB, Short Physical Performance Battery; WHO PS, World Health Organization Performance Status. Missing values are not considered a separate category in statistical analysis. Bold values denote statistical significance at the p<0.050 level.

Table A4 – Multivariable regression analysis for cachexia prior to CRT/BRT.

	HR	95% CI		*p*-value
		Lower	Upper	
WHO PS 0 (ref) WHO PS 1 or 2	20.135	2.334	173.737	**0.006**
Normal diet (FOIS 6-7) (ref) Modified diet (FOIS 1-4)	19.865	2.704	145.949	**0.003**
EAT-10 score < 3 (ref) EAT-10 score ≥ 3	18.975	2.229	161.530	**0.007**

CI, confidence interval; EAT-10, Eating Assessment Tool; FOIS, Functional Oral Intake Scale; HR, Hazard Ratio; (ref), reference value; WHO PS, World Health Organization Performance Status. Bold values denote statistical significance at the p<0.050 level.

Table A5 – Comparison of characteristics and measurements between patients without VFSS and with VFSS.

	No VFSS n=47	**VFSS** n=20	***p*-value**
Patient characteristics			
Male Female	36 (77%) 11 (23%)	15 (75%) 5 (25%)	0.889[c]
Age in years (median (IQR))	62 (13)	53 (22)	**0.005**[b]
ACE-27 score 0 ACE-27 score 1 ACE-27 score 2 ACE-27 score 3	16 (34%) 19 (40%) 8 (17%) 4 (9%)	13 (65%) 3 (15%) 3 (15%) 1 (5%)	0.096[d]
Smoking			
Current Former Never	13 (28%) 24 (51%) 10 (21%)	10 (50%) 6 (30%) 4 (20%)	0.713[d]
Alcohol			
None < 1 beverages a day 1-3 beverages a day > 3 beverages a day *Missing*	4 (9%) 19 (41%) 7 (15%) 16 (35%) *1*	1 (5%) 9 (45%) 2 (10%) 8 (40%) *0*	0.952[d]
Body composition and muscle strength			
Percentage weight change 6 months prior to CRT/ BRT (median (IQR))	-1.1 (6.1)	-0.2 (2.6)	0.203[b]
Cachexia No cachexia	15 (32%) 32 (68%)	2 (10%) 18 (90%)	0.072[d]
BMI (mean ± SD, kg/m^2) Male Female	27.2 ± 4.7 27.7 ± 4.6 25.5 ± 5.0	26.8 ± 6.6 26.4 ± 6.7 27.9 ± 6.8	0.787[a] 0.437[a] 0.438[a]
FFMI (mean ± SD, kg/m^2) Male Female	19.3 ± 3.1 20.3 ± 2.6	19.1 ± 3.1 19.7 ± 3.1	0.828[a] 0.459[a] 0.199[a]
FMI (median (IQR), kg/m^2) Male Female	7.6 (3.1) 7.3 (2.9) 8.7 (4.4)	7.1 (9.3) 6.3 (3.1) 7.5 (7.8)	0.188[b] 0.063[b] 0.865[b]
Handgrip strength (mean ± SD, kg) Male Female	40.5 ± 9.6 43.9 ± 8.0 29.5 ± 4.9	43.6 ± 11.3 47.7 ± 9.8 31.2 ± 3.3	0.254[a] 0.148[a] 0.485[a]
Short Physical Performance Battery > 9 4-9 < 4 *Missing*	 37 (86%) 5 (12%) 1 (2%) *4*	 18 (90%) 2 (10%) 0 (0%) *0*	 1.000[d]
SPPB-derived variable Normal repeated chair stand test Repeated chair stand test > 15 s *Missing*	 38 (88%) 5 (12%) *4*	 19 (95%) 1 (5%) *0*	 0.655[d]
Swallowing function and patient reported outcomes			
No or few restrictions on oral feeding (FOIS 6-7) Oral intake with special preparation (FOIS 4-5) Mainly or exclusively tube feeding (FOIS 1-3)	30 (64%) 16 (34%) 1 (2%)	16 (80%) 4 (20%) 0 (0%)	0.482[d]

	No VFSS n=47	**VFSS** n=20	***p*-value**
MDADI (median, (IQR))			
Total score	90 (29)	97 (19)	0.184[b]
Global assessment	4 (1)	5 (1)	0.347[b]
Emotional subscore	27 (7)	29 (6)	0.113[b]
Functional subscore	25 (7)	25 (4)	0.246[b]
Physical subscore	33 (13)	37 (8)	0.307[b]
EAT-10 score < 3	24 (51%)	16 (80%)	**0.032**[d]
EAT-10 score ≥ 3	23 (49%)	4 (20%)	
Tumor characteristics			
Oral Cavity	5 (11%)	1 (5%)	0.051
Oropharynx	31 (66%)	11 (55%)	
Hypopharynx	0 (0%)	4 (20%)	
Larynx	8 (17%)	2 (10%)	
Nasopharynx	2 (4%)	1 (5%)	
Other	1 (2%)	1 (5%)	
T classification			
T0	2 (4%)	1 (5%)	0.808[d]
T1	7 (15%)	2 (10%)	
T2	14 (30%)	9 (45%)	
T3	13 (28%)	5 (25%)	
T4	11 (23%)	3 (15%)	
N classification			
N0	6 (13%)	2 (10%)	0.699[d]
N1	16 (34%)	9 (45%)	
N2	12 (26%)	6 (30%)	
N3	13 (28%)	3 (15%)	
M classification			
M0	47 (100%)	18 (90%)	0.086[d]
M1	0 (0%)	2 (10%)	
Overall stage grouping			
Stage I	9 (19%)	6 (30%)	0.480[d]
Stage II	7 (15%)	2 (10%)	
Stage III	17 (36%)	4 (20%)	
Stage IVabc	14 (30%)	8 (40%)	
HPV + oropharynx	23 (49%)	9 (45%)	0.768[c]
HPV - oropharynx and other tumor sites	24 (51%)	11 (55%)	
Treatment characteristics			
Adjuvant CRT	6 (13%)	1 (5%)	0.757[d]
Primary CRT	33 (70%)	16 (80%)	
Primary BRT	8 (17%)	3 (15%)	

ACE, Adult Comorbidity Evaluation; BMI, Body Mass Index; BRT, Bioradiotherapy; Cachexia as defined by Fearon et al. [5]; CRT, chemoradiotherapy; EAT-10, Eating Assessment Tool; FFMI, Fat-free Mass Index; FMI, Fat Mass Index; FOIS, Functional Oral Intake Scale; HPV, Human Papilloma Virus; IQR, interquartile range; MDADI, M.D. Anderson Dysphagia Inventory; SPPB, Short Physical Performance Battery.

[a]Independent samples T-test, [b]Mann-Whitney U Test, [c]Pearson's chi-squared test (χ^2), [d]Fisher's exact test. Missing values were not considered as a separate category in statistical analysis. Bold values denote statistical significance at the p<0.050 level. The values are numbers and ≥ercentages (in parentheses) unless indicated differently. Percentages may not add up to 100 due to rounding off.

CHAPTER 8

PREDICTION MODEL FOR TUBE FEEDING DEPENDENCY DURING CHEMORADIOTHERAPY FOR AT LEAST FOUR WEEKS IN HEAD AND NECK CANCER PATIENTS: A TOOL FOR PROPHYLACTIC GASTROSTOMY DECISION MAKING

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ABSTRACT

Background and aims: Chemoradiotherapy and bioradiotherapy (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often comes with high toxicity rates, interfering with oral intake and leading to temporary tube feeding (TF) dependency. High-quality scientific evidence for indicators of prophylactic gastrostomy insertion is not available. The aim of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks.

Methods: Four-hundred-fifty LAHNSCC patients receiving CRT/BRT with curative intent between 2013 and 2016 were included in the study. Primary outcome was TF-dependency for four weeks or longer. Patient, tumor, and treatment characteristics were extracted from the medical records and their effects on the use of TF were analyzed using univariable and multivariable analysis. The prediction model was internally validated using bootstrapping techniques.

Results: Sixty-five percent (294/450 patients) required TF for four weeks or longer. Variables included in the model were: body mass index and adjusted diet at start of CRT/BRT, percentage weight change at baseline, World Health Organization performance status, tumor subsite, TNM-classification, CRT/BRT, mean radiation dose on the contralateral submandibular and parotid gland. The corrected Area Under the Curve after internal validation was 72.3%, indicating good discriminative properties of the prediction model.

Conclusions: We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.

INTRODUCTION

The current treatment with curative intent for patients ≤70 years with stage III and IV Locally Advanced Head and Neck Squamous Cell Carcinoma (LAHNSCC) consists of primary or adjuvant radiotherapy (RT) with concurrent radiosensitizing systemic therapy (cisplatin, carboplatin or cetuximab). [1-4] Side effects of this chemo or bioradiotherapy (CRT/BRT) protocol include, among others, mucositis, [5] xerostomia, sensory changes/taste distortion, pain, dysphagia, and nausea and vomitus. [6, 7] These side effects may contribute to reduced oral intake and consequently weight loss during and after CRT/BRT, [5-8] resulting in worse functional and oncological outcomes. [9-12] Maintaining body weight leads to improved therapy tolerance, reduced risk of complications and therapy delay, increased response rate, [13] and higher survival rate. [14] When oral intake is insufficient to meet protein and energy requirements, tube feeding (TF) is required. [15, 16] TF can be administered by means of a nasogastric tube (NGT) or a percutaneous radiologic or endoscopic gastrostomy (PRG or PEG). Current guidelines recommend gastrostomy insertion, not NGT, when TF is expected to be required for at least four weeks. [13, 17, 18]

Currently, there is a lack of consentient directives, leading to various policies for tube insertion in CRT/BRT patients in different institutions. Prophylactic gastrostomy insertion has been the subject of debate, because prophylactic TF in all patients might lead to increased long-term dysphagia, considering the “use it or lose it” principle with respect to swallowing structures. [19-21] Moreover, gastrostomy insertion is not a risk-free procedure with complication rates of about 3.3-19% [22, 23] and between 9-47% of the prophylactic gastrostomies are never used. [24, 25] Therefore, gastrostomies should not be placed prophylactically in every individual, but only upon indication as stated in the Dutch Head and Neck Cancer Society (DHNCS) guidelines. [26] However, this indication has not been described properly due to a lack of scientific evidence.

Previous studies [24, 27] identified predictive factors for prophylactic gastrostomy placement and TF during CRT/BRT but failed to develop a strong prediction model. More recently, a prediction model for identifying CRT/BRT patients at risk for long-term (>90 days) tube dependency was presented. [28] By using a model only focusing on long-term TF-dependency, a large proportion of patients requiring TF due to acute toxicities remains unidentified: 68-81% of the patients require TF during CRT/BRT [6, 24, 28] compared to 20-45% at three months after treatment. [20, 24, 29]

The purpose of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks. [26]

PATIENTS AND METHODS

Subjects and study design

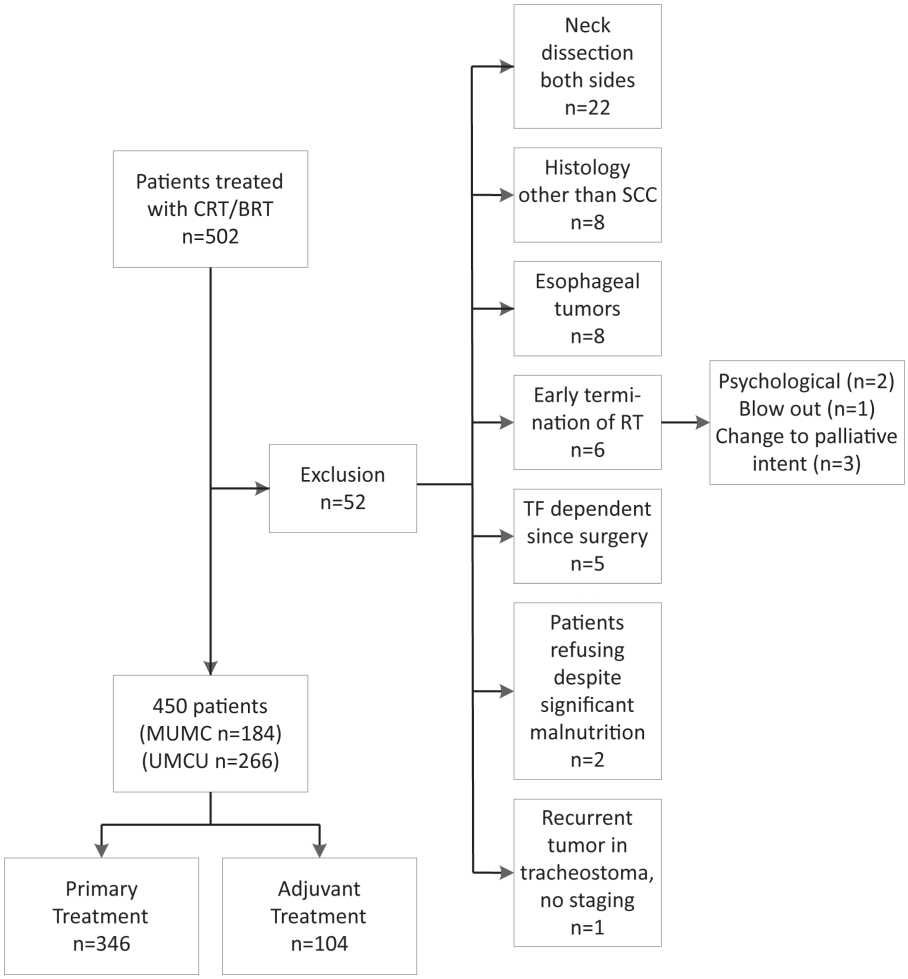
This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. Data were collected in patients with LAHNSCC starting CRT/BRT in Maastricht University Medical Center (MUMC+) and the University Medical Center Utrecht (UMCU) between January 1st 2013 and December 31st 2016. Patients received primary or adjuvant RT combined with either cisplatin, carboplatin or cetuximab with curative intent. Exclusion criteria were histology other than squamous cell carcinoma, esophageal tumors, bilateral resection of the submandibular glands because RT dose to submandibular glands cannot be calculated here, early termination of RT, TF-dependency since surgery, patients refusing TF despite significant malnutrition, and age under 18 years. Part of the UMCU cohort has been described previously. [24] Figure 1 shows the inclusion flowchart.

Oncological treatment

Cisplatin was administered intravenously on days 1, 22, and 43, in doses of 100 mg/m^2 [3, 30] to patients without significant cardiovascular or renal disease, neuropathy or hearing impairment. In case of significant side effects during cisplatin treatment, radiosensitizing systemic therapy was either completely ceased or replaced by carboplatin (dose: area under curve (AUC) 5) for the remaining cycles. Cetuximab was indicated in patients having a contraindication for cisplatin. For cetuximab, a loading dose of 400 mg/m^2 was administered intravenously one week before RT initiation, followed by 250 mg/m2 weekly during RT. [2]

RT was administered using intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) and applied five times per week for seven weeks, in 35 daily fractions of 2 Gy to a total dose of 70 Gy. Patients on cetuximab received 30 daily fractions of 2.3 Gy to a total dose of 69 Gy or accelerated fractionated RT twice daily in the final week of IMRT with a total dose of 68 Gy in 34 fractions. Patients undergoing adjuvant CRT received a total dose of 66 Gy in 33 fractions concurrent with cisplatin.

Figure 1 - Flowchart of inclusion



Primary endpoint and tube feeding policy

The primary endpoint of this study was the use of TF for at least four weeks during CRT/BRT or within 30 days after CRT/BRT completion. The four-week cut off point was based on the Dutch national dietary guidelines, recommending gastrostomy insertion as being superior to NGT when TF is required for a period of four weeks or longer. [31, 32]

According to the Dutch guideline on malnutrition, [32] patients were initially recommended to use oral nutritional supplements or TF in addition to oral

intake when 50-75% of the calculated nutritional requirements were met. When oral intake was less than 50% of the calculated nutritional needs, without rapid improvement of oral intake, full TF was indicated, supplemented with any feasible and safe oral intake. [33] Patients were advised to remain on oral intake as much as possible in order to maintain swallowing function.

Potential predictors

Potential predictors were preselected based on clinical reasoning and evidence of previous research. We preselected patient's age, [34-38] gender, [29, 37] tobacco, [39] and alcohol use, body mass index (BMI), [40, 41] weight loss, [42, 43] and texture modified diet at baseline (as indicator for dysphagia), [29, 37, 42] in which baseline is considered right before treatment initiation, World Health Organization performance status (WHO PS), [44-46] tumor subsite, [35, 37, 41, 47, 48] tumor stage, [35-37, 40, 42, 43, 47-51] nodal stage, [24, 36, 37, 39, 41] (TNM-classification [52]) human papilloma virus (HPV) in situ hybridization (ISH) or p16 expression (surrogate biomarker of HPV infection) of the tumor, [34] primary or adjuvant setting, [41, 44, 47] type of radiosensitizing systemic therapy (platinum-based chemotherapy or immunotherapy), [35, 39, 42-44, 47] bilateral neck irradiation, [24, 49, 53] mean RT dose on the contralateral submandibular [44] and parotid gland. [43, 44]

Sample size

The inclusion of at least ten events per variable is widely accepted as the sample size rule of thumb for multivariable logistic regression analyses. [54] The least frequent outcome, receiving TF less than four weeks (n=156), was defined as an event. Thus, a maximum of fifteen predictors was considered appropriate for developing a model for the cohort in the present study.

Data collection

Patient data were extracted from electronic medical records. Texture modified diet or the use of tube feeding was used as an indicator for dysphagia. Texture modification includes ground, minced or liquid. This information was collected from questionnaires (e.g. functional oral intake scale) if available or patient reported modifications such as eating bread without crust or mashing food.

Missing data

Only for the variables mean contralateral submandibular and parotid gland dose, missing data were imputed through stochastic regression imputation, based on the following covariates: BMI and weight change at baseline, tumor subsite, tumor stage, nodal stage, p16 expression/ HPV ISH in oropharyngeal tumors, primary or adjuvant setting, CRT/BRT, neck irradiation and mean RT dose to the contralateral submandibular and parotid gland. In case of a midline tumor, the contralateral side was considered the side receiving the lowest mean RT dose.

Statistical analysis

Descriptive statistics were reported as mean and standard deviation or absolute numbers and percentages. Baseline differences between those who received TF for at least four weeks and those who did not were tested using the independent samples t-test and the Chi–squared test. A *p*-value <0.050 was considered statistically significant.

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p<0.300$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. We used stepwise backward elimination to omit all predictors from the model that did not contribute substantially, using a *p*-value for selection of 0.100. The resulting prediction model was subsequently internally validated using bootstrapping techniques. The bootstrap validation yields a shrinkage factor between 0 and 1. The regression coefficients were multiplied by this shrinkage factor to penalize the coefficients which counteracts effects of overfitting. Additionally, the bootstrap validation provides estimates of model performance corrected for optimism (i.e., it gives estimates of model performance in future patients compared to the patients used to develop the model). [55, 56]

Model performance was quantified as the model's ability to discriminate between those who will and those who will not develop the need for TF for at least four weeks using the area under the receiver operating characteristic curve and measures of calibration. Calibration is the agreement between predicted probabilities and observed probabilities and was tested using the Hosmer and Lemeshow goodness-of-fit test. [57] A significant *p*-value would denote significant deviation from good model calibration. In addition, we visually inspected a calibration plot. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM, Armonk, NY) and R version 3.5.1 (R Core Team, Vienna, Austria). [58]

RESULTS

Patient sample

Data of both MUMC+ and UMCU yielded 502 patients from which 450 patients met the inclusion criteria. Patient, tumor, and treatment-related characteristics are shown in Table 1. Mean RT dose on contralateral submandibular and parotid gland was missing in 34% (n=151) and 1% (n=6) respectively. These were statistically imputed as described earlier. In 72% of our total population (n=322) a gastrostomy was placed and six percent (n=26) received a NGT. In total 69% (n=311) of all patients used TF during or within 30 days after completion of treatment with a median duration of 107 days (Interquartile range (IQR) 129). Sixty-five percent (n=294) of the patients used TF for four weeks or longer. The median duration of TF use did not significantly differ between subsites oral cavity or oropharynx or hypopharynx on the one hand versus other or remaining subsites on the other hand: 111 (IQR 143) versus 97 (IQR 96) days respectively (p=0.086).

Table 1 – Frequency distribution of patient, tumor, and treatment characteristics of the studied population.

Variables	**Total oral diet or tube feeding <4 weeks** n=156 (35%)	**Tube feeding >4 weeks** n=294 (65%)	***p*-value**
Patient characteristics			
Mean age	59.7 ± 7.2	58.7 ± 8.0	0.223[1]
Male Female	101 (65) 55 (35)	193 (66) 101 (35)	0.848[2]
Tobacco use No tobacco use	138 (89) 18 (12)	256 (87) 38 (13)	0.671[2]
Alcohol consumption ≥1 per day Alcohol consumption <1 per day	91 (58) 65 (42)	166 (57) 128 (44)	0.703[2]
BMI at baseline (kg/m^2)	25.4 ± 4.9	23.8 ± 4.6	**0.001**[1]
Weight change at baseline (%)	-2.7 ± 6.0	-5.0 ± 7.4	**0.001**[1]
No modified diet at baseline Texture modified diet* at baseline	114 (73) 42 (27)	175 (60) 119 (41)	**0.004**[2]
WHO PS 0 WHO PS 1 WHO PS 2 WHO PS 3	51 (32) 98 (63) 6 (4) 1 (1)	58 (20) 206 (70) 28 (10) 2 (1)	**0.007**[2]
Tumor characteristics			
Tumor subsite			
Oral cavity	40 (26)	54 (18)	0.151[2]
Nasopharynx/sinus	6 (4)	25 (8)	
Oropharynx	58 (37)	125 (43)	
Hypopharynx	24 (15)	37 (13)	
Larynx	20 (12)	34 (1)	
Unknown primary	5 (3)	5 (2)	
Synchronous tumors	1 (1)	8 (3)	
Neck recurrence	2 (2)	7 (2)	

Variables	Total oral diet or tube feeding <4 weeks n=156 (35%)	Tube feeding >4 weeks n=294 (65%)	*p*-value
Tumor classification (TNM)			
Tx	3 (2)	1 (0)	**0.033**[2]
T0	4 (3)	11 (4)	
T1	20 (13)	23 (8)	
T2	39 (20)	50 (17)	
T3	31 (20)	77 (26)	
T4	59 (38)	132 (45)	
Nodal classification (TNM)			
N0	40 (26)	48 (16)	**0.025**[2]
N1	23 (15)	30 (10)	
N2	87 (56)	205 (70)	
N3	6 (4)	11 (4)	
Tumor stage			
Stage II	7 (5)	6 (2)	**0.030**[2]
Stage III	26 (17)	29 (10)	
Stage IV	123 (79)	259 (88)	
p16 expression			
p16+ oropharynx	30 (19)	49 (17)	0.496[2]
Others	126 (81)	245 (83)	
Treatment characteristics			
Primary treatment	112 (72)	230 (78)	0.128[2]
Adjuvant	44 (28)	64 (22)	
Radiosensitizing systemic therapy			
Platinum (carbo-/cis-)	111 (71)	230 (78)	0.095[2]
Cetuximab	45 (29)	64 (22)	
Unilateral neck irradiation	24 (15)	21 (7)	
Bilateral neck irradiation	116 (74)	259 (88)	**0.001**
No neck irradiation	16 (10)	14 (5)	
RT dose to contralateral submandibular gland (Gy)	34.7 ± 17.2	42.3 ± 14.4	**<0.001**[1]
RT dose to contralateral parotid salivary gland (Gy)	15.8 ± 8.8	20.4 ± 8.4	**<0.001**[1]
Tube type			
PEG	26 (17)	159 (54)	**<0.001[2]**
PRG	20 (13)	114 (39)	
PEJ	0 (0)	2 (1)	
Surgical gastrostomy	0 (0)	1 (0)	
NGT	8 (5)	18 (6)	
No feeding tube	102 (65)	0 (0)	

*Abbreviations: BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray; PRG, percutaneous radiologic gastrostomy; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; NGT, nasogastric tube. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.[1]Independent samples t-test. [2]Pearson's chi-square test.*

Univariable regression analysis output (Table 2) yielded a *p*-value <0.300 for the following factors: age, BMI, weight change, texture modified, WHO PS, tumor subsite, tumor stage, nodal stage, primary or adjuvant setting, radiosensitizing systemic therapy, neck irradiation and mean RT dose to the contralateral submandibular

and parotid gland. In multivariable regression analysis (Table 3), age and adjuvant setting did not yield a *p*-value <0.100 and were therefore eliminated from the final model. Tumor stage was not statistically significant in multivariable analysis but was considered clinically relevant and proven in previous studies [37, 41, 47, 50] and was therefore nevertheless included in the model. Figure 2 shows the receiver operating characteristic (ROC) curve of the crude prediction model. The AUC was 74.8% (95% CI = 70.1-79.6%), which indicates good discriminative ability.

Table 2 – Results of univariable logistic regression analysis of potential predictors presented in odds ratios and *p*-values.

	OR	CI 95%		p value
		lower	upper	
Age (years)	0.984	0.959	1.010	0.224
Female (ref) Male	0.961	0.640	1.444	0.848
No tobacco use (ref) Tobacco use	0.879	0.483	1.598	0.672
Alcohol consumption <1 per day (ref) Alcohol consumption ≥1 per day	0.926	0.625	1.372	0.703
BMI at baseline (kg/m^2)	0.932	0.894	0.971	**0.001**
Weight change at baseline (%)	0.951	0.921	0.982	**0.002**
No modified diet at baseline (ref) Texture modified diet* at baseline	1.846	1.208	2.819	**0.005**
WHO PS 0 (ref) WHO PS >0	1.976	1.272	3.072	**0.002**
p16 expression Others (ref) p16+ oropharynx	0.840	0.508	1.389	0.497
Tumor subsite Others (ref) Oral cavity, oropharynx, and hypopharynx	0.772	0.487	1.222	0.270
Tumor classification (TNM) T0, T1, Tx (ref) T2, T3, T4	1.549	0.898	2.670	0.115
Nodal classification (TNM) N0, N1 (ref) N2, N3	1.876	1.243	2.831	**0.003**
Treatment setting Primary Adjuvant	0.725	0.462	1.139	0.163
Radiosensitizing systemic therapy Platinum (carbo-/cis-) (ref) Cetuximab	0.686	0.441	1.069	0.096
No or unilateral neck irradiation (ref) Bilateral neck irradiation	2.552	1.542	4.223	**<0.001**
RT dose to contralateral submandibular glands (Gy)	1.032	1.019	1.046	**<0.001**
RT dose to contralateral parotid salivary glands (Gy)	1.072	1.044	1.102	**<0.001**

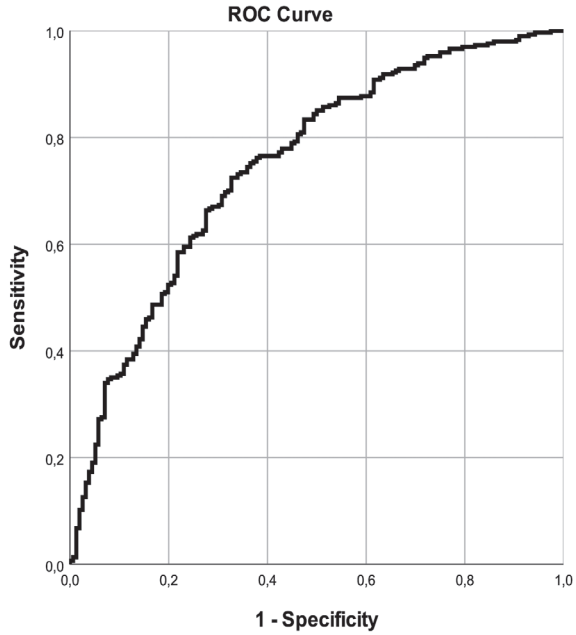
*Abbreviations: BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.*

Table 3 – Results of multivariable logistic regression analysis presented in odds ratios and *p*-values. The shrunk regression coefficients represent the regression coefficients after internal validation yielded a shrinkage factor of 0.87.

	Crude OR (CI-95%)	***p*-value**	**Crude regression coefficient**	**Shrunk regression coefficients**
Model intercept			-0.661	-0.506
BMI at baseline (kg/m^2)	0.953 (0.910-0.999)	**0.045**	-0.048	-0.042
Weight change at baseline (%)	0.966 (0.931-1.002)	0.066	-0.035	-0.030
No modified diet at baseline(reference) Texture modified diet* at baseline	1.682 (1.034-2.737)	**0.036**	0.520	0.452
WHO PS 0 (reference) WHO PS >0	2.012 (1.235-3.279)	**0.005**	0.699	0.608
Tumor subsite Others (reference) Oral cavity, oropharynx, and hypopharynx	0.556 (0.329-0.940)	**0.028**	-0.586	-0.510
Tumor classification (TNM) T0, T1, Tx (reference) T2, T3, T4	1.430 (0.766-2.670)	0.262	0.358	0.311
Nodal classification (TNM) N0, N1 (reference) N2, N3	1.906 (1.186-3.062)	**0.008**	0.645	0.561
Radiosensitizing systemic therapy Platinum (carbo-/cis-) (reference) Cetuximab	0.471 (0.283-0.783)	**0.004**	0.753	-0.655
Mean RT dose to contralateral submandibular gland (Gy)	1.017 (1.001-1.034)	**0.037**	0.017	0.015
Mean RT dose to contralateral parotid gland (Gy)	1.050 (1.017-1.084)	**0.003**	0.049	0.042

*Abbreviations: BMI, body mass index; CI, confidence interval; Gy, Gray; OR, Odds ratio; RT, radiotherapy; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; WHO PS, World Health Organization Performance status. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.*

Figure 2 - Receiver operating characteristic curve of the prediction model before internal validation (AUC 74,8%; 95% CI 70.1-79.6%), indicating the good discriminative performance of the model.



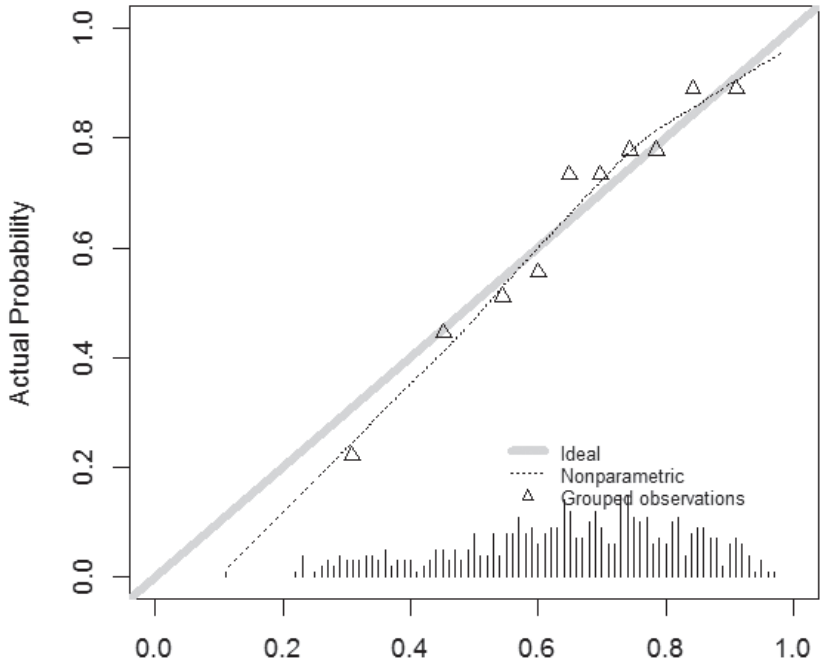
Internal validation

Internal validation of the model yielded a shrinkage factor of 0.87. The last column of Table 3 shows the shrunken regression coefficients and the model intercept.

Furthermore, internal validation gave a degree of optimism of 2.5%, leading to an AUC corrected for optimism of 72.3%. The calibration plot (Figure 3) shows a good agreement between predicted probability of TF for at least four weeks and the observed use of TF. The Hosmer and Lemeshow goodness-of-fit test presented a *p*-value of 0.844.

F

Figure 3 - Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.



Formula of the model

The individual probability for TF for at least four weeks can be calculated as:

LP(TF ≥ 4 weeks) = 1/(1 + e^{-LP}), in which LP is the linear sum of all predictor values multiplied by the regression coefficients, or:

-0.506 -0.042 (BMI) -0.030 (pretreatment weight change) +0.452 (modified diet or TF [*yes = 1*]) +0.608 (WHO PS [*WHO>0 = 1*]) -0.510 (tumor location [*oral cavity, oropharynx and hypopharynx = 1*]) +0.311 (T classification [*T2, T3, or T4 = 1*]) +0.561 (N classification [*N2 or N3 = 1*]) -0.655 (systemic therapy [*Cetuximab = 1*]) +0.015 (mean RT dose to contralateral submandibular gland [*Gy*]) +0.042 (mean RT dose to contralateral parotid salivary gland [*Gy*]).

For example, a patient with a cT3N2bM0 oropharyngeal tumor will receive locoregional RT including bilateral neck irradiation concurrent with cisplatin. She has a BMI of 19.5 kg/m^2, 8% weight loss at baseline, only eats mashed meals, her WHO PS is 0, and the mean RT dose to the contralateral submandibular and parotid gland will be 36 Gy and 29 Gy respectively.

LP = -0.506 - 0.042 × **19.5** - 0.030 × **-8** + 0.452 × **1** + 0.608 × **0** - 0.510 × **1** + 0.311 × **1** + 0.561 × **1** - 0.655 × **0** + 0.015 × **36** + 0.042 × **29** = 1.487

P(TF ≥ 4 weeks) = 1 / (1+e$^{-1.487}$) = 0.82. This patient has a probability of 82% that she will require TF for a period of four weeks or longer.

Sensitivity and specificity

When choosing 90% as cut off value, the model yields a sensitivity of 9%, specificity of 98%, positive predictive value of 90%, and negative predictive value of 64%. In case of 80% as cut off value, the model yields a sensitivity of 31%, specificity of 93%, positive predictive value of 85%, and negative predictive value of 56%.

DISCUSSION

The purpose of this study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks in LAHNSCC patients treated with CRT/BRT. To our knowledge, this is the first study using TF for four weeks or longer as an outcome measure in a large retrospective cohort (n=450) of LAHNSCC patients receiving CRT/BRT. If the model predicts a high chance of TF for four weeks or longer, prophylactic gastrostomy insertion is advised and preferred over reactive tube insertion, whereby reactive is defined as tube insertion “as required”. After internal validation, the model has good accuracy (AUC 72.3%) in discriminating LAHNSCC patients planned for CRT/BRT who will versus will not need TF for at least four weeks and thus would benefit from prophylactic gastrostomy insertion. Our final model includes the following predictors: BMI, weight loss, texture modified diet, WHO PS, tumor subsite, tumor stage, nodal stage, type of radiosensitizing systemic therapy and RT dose to the contralateral submandibular and parotid gland. Previous smaller studies showed largely similar predictors but failed to construct a solid prediction model: BMI <25 [40, 41], >10% baseline weight loss, [42] tumor-related symptoms at diagnosis (e.g. pain and dysphagia), [29, 40, 42, 45, 47, 59, 60] WHO PS, [44, 46] tumor located in

oropharynx, [27, 41, 44, 49] tumor stages T3-T4, [36, 40, 42, 47-49] nodal stage, [24, 36, 39, 41] clinical TNM-stage IV, [39, 49, 61] bilateral neck irradiation, [24, 49] age>60, [61] pack years, [39] and surgery prior to CRT/BRT. [41, 46] We used texture modified diet as a surrogate marker for dysphagia. Previous studies showed that a higher mean RT dose to the submandibular and parotid glands was associated with dry mouth and sticky saliva, respectively, due to reduced salivary output and a change in salivary composition. [62, 63] Remaining salivary production will therefore highly correlate with the RT dose on the spared contralateral salivary glands. [64] To our knowledge, this is the first study including RT dose to the contralateral salivary glands as a possible predictor for TF need combined with other patient and tumor characteristics. Strikingly and unlike other studies, a tumor located in the oral cavity, oropharynx or hypopharynx did not increase the risk of TF for at least four weeks as compared to the remaining tumor subsites in the present patient sample. [35, 37, 41, 47, 48] This result might be explained by the chosen cut off point of TF for at least four weeks. The median duration of TF use did not significantly differ between the two subgroups (111 versus 97 days, p=0.086), but the IQR of TF use was larger in the oral cavity, oropharynx, hypopharynx subgroup (143 vs 96 days) and more outliers towards longer TF duration were seen in these subsite groups. However, long-term TF-dependency was not our primary endpoint and total TF duration could be studied in more detail in future studies.

Limitations of our study include its retrospective design, although we do not think this greatly affected our outcomes; the small amount of randomly missing data could be compensated using statistical imputation. Our cohort was derived from two different university medical centers, both working according to the Dutch Head and Neck Cancer Society guideline, minimizing the possibility of a local therapist effect on group performance or on treatment outcomes. Thereby, this heterogeneity also enables generalization of applicability of the prediction model. Potentially, TF was started earlier in case of early prophylactic insertion, because there were no additional barriers to initiate TF and a better patient compliance was expected compared to reactive feeding tube placement. [65] However, to our experience patients also frequently report barriers initiating TF when the tube was already inserted and ready to use.

Because of a lack of high quality randomized studies, it remains unclear whether prophylactic gastrostomy insertion is superior to reactive insertion. Considering the effect of gastrostomy insertion and TF on weight loss, dehydration, treatment

interruptions or change in treatment schedule, [24, 66] and post treatment health-related quality of life, [67, 68] prophylactic gastrostomy insertion might be preferred above reactive placement in well selected cases.

Available literature is inconsistent about whether prophylactic gastrostomy insertion increases the risk of long-term dysphagia. [65, 67, 69-74] The risk of long-term dysphagia can be reduced using a proactive policy of feeding tube removal, guidance by a speech and language pathologist, and swallowing exercise. [75]

The aim of the present prediction model was to support clinicians in obtaining best clinical practice protocols to prevent delayed reactive gastrostomy insertions. Based on the outcome of the prediction model, upfront prediction of TF-dependency can be performed which immediately enables the decision-making on prophylactic tube insertion in patients at risk for TF for four weeks or longer. We are currently working on the external validation of our model, through collaborations with other Dutch head and neck cancer centers. External validation is required to develop and widespread implement this model as a generalizable decision aid for prophylactic feeding tube insertion with consistent cut off values. By combining our data we will preferably develop one tool for the identification of LAHNSCC patients treated with CRT/BRT who need prophylactic gastrostomy placement.

CONCLUSION

We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.

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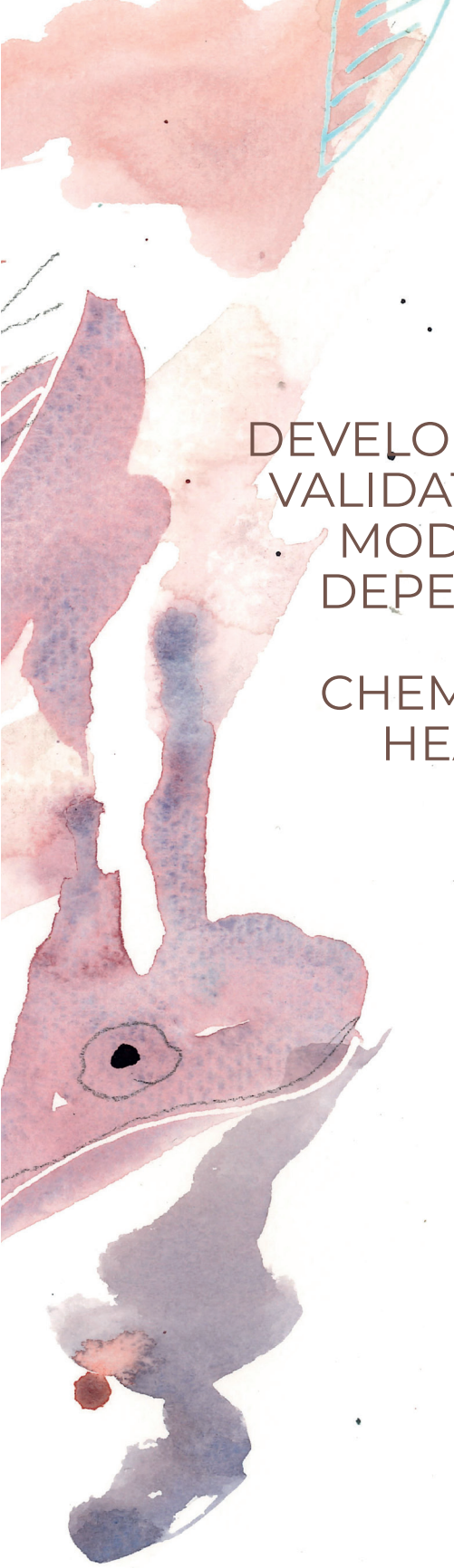

CHAPTER 9

DEVELOPMENT AND EXTERNAL VALIDATION OF A PREDICTION MODEL FOR TUBE FEEDING DEPENDENCY FOR AT LEAST FOUR WEEKS DURING CHEMORADIOTHERAPY FOR HEAD AND NECK CANCER

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ABSTRACT

Background & aims: Patients who receive chemoradiotherapy or bioradiotherapy (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often experience high toxicity rates interfering with oral intake, causing tube feeding (TF) dependency. International guidelines recommend gastrostomy insertion when the expected use of TF exceeds 4 weeks. We aimed to develop and externally validate a prediction model to identify patients who need TF ≥4 weeks and would benefit from prophylactic gastrostomy insertion.

Methods: A retrospective multicenter cohort study was performed in four tertiary head and neck cancer centers in the Netherlands. The prediction model was developed using data from University Medical Center Utrecht and the Netherlands Cancer Institute and externally validated using data from Maastricht University Medical Center and Radboud University Medical Center. The primary endpoint was TF dependency ≥4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. Potential predictors were extracted from electronic health records and radiotherapy dose-volume parameters were calculated.

Results: The developmental and validation cohort included 409 and 334 patients respectively. Multivariable analysis showed predictive value for pretreatment weight change, texture modified diet at baseline, ECOG performance status, tumor site, N classification, mean radiation dose to the contralateral parotid gland and oral cavity. The area under the receiver operating characteristics curve for this model was 0.73 and after external validation 0.62. Positive and negative predictive value for a risk of 90% or higher for TF dependency ≥4 weeks were 81.8% and 42.3% respectively.

Conclusions: We developed and externally validated a prediction model to estimate TF-dependency ≥4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

INTRODUCTION

Side effects of concurrent chemoradiotherapy or bioradiotherapy (CRT/BRT) often impair oral intake in patients with locally advanced (stage III/IV) head and neck squamous cell carcinoma (LAHNSCC), which may contribute to involuntary weight loss. [1] Weight loss has a detrimental effect on the risk of side effects, therapy tolerance, response rate, and survival. [2-6] In order to maintain sufficient nutritional intake, tube feeding (TF) has to be initiated in 37-74% of LAHNSCC patients undergoing CRT/BRT. [7-9] TF can be administered using a nasogastric tube (NGT) or a percutaneous gastrostomy, either placed radiologically (PRG) or endoscopically (PEG). The advantages of a gastrostomy compared to a NGT are increased physical mobility, less cosmetic disadvantage, and better quality of life. Patients fed via NGT experience more dislodgement and weight loss compared to patients with a gastrostomy tube. [10]

Previously, prophylactic gastrostomy insertion (before onset of side effects impairing oral intake) in all LAHNSCC patients undergoing CRT/BRT, used to be common in the majority of the clinical settings. [11-13] However, gastrostomy insertion is not a risk-free procedure; tube-related and infectious complications occur in 6-16%. [14] Therefore, new guidelines recommend that a prophylactic gastrostomy should only be inserted upon indication in LAHNSCC patients treated with CRT/BRT. [15] It is generally agreed that when the expected use of TF exceeds four weeks, gastrostomy insertion should be considered. [16-20] Ideally, patients at risk of TF ≥4 weeks are identified prior to treatment, so they can be provided with a gastrostomy before the onset of side effects potentially complicating insertion, e.g. mucositis (painful insertion), neutropenia (infection risk), and ongoing weight loss (higher complication risk). [21]

Until recently it remained challenging to predict for which patient prophylactic gastrostomy insertion would be appropriate. In a previously published study, we developed and internally validated a prediction model for calculating a patients' individual probability of TF dependency ≥4weeks. [22] New normal tissue complication probability (NTCP) models shed light on the potential additional value of RT doses on the pharyngeal constrictor muscles (PCM) and oral cavity (OC) in predicting swallowing outcomes. [23-25] Therefore, we considered it worth investigating whether these RT parameters could increase the performance of the new model. The present study describes the development and external validation

of a prediction model to identify patients at risk for TF dependency ≥4 weeks who would benefit from prophylactic gastrostomy insertion.

METHODS

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. We reported this study in accordance with Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines. [26]

Source of data

The electronic health records of patients treated in four Dutch cancer centers were retrospectively reviewed to compile the development and validation dataset. For every center, data was collected by different independent researchers, in consultation with the executive researchers about the methods of data extraction and any uncertainties about the way of reporting.

Populations

The developmental dataset consisted of LAHNSCC patients treated between 2013 and 2016 in University Medical Center Utrecht (UMCU) and patients treated between 2014 and 2017 in Netherlands Cancer Institute (NCI). The external validation of the model was performed on data from patients treated between 2013 and 2016 in Maastricht University Medical Center + (MUMC+) and Radboud University Medical Center (RUMC).

LAHNSCC patients were included when they were treated with primary or adjuvant concurrent CRT or BRT. Patients were excluded from the study in case of histology other than squamous cell carcinoma, esophageal tumor location, bilateral neck dissection with removal of submandibular glands (RT dose calculation on contralateral gland not possible), refusing TF despite the physician's strong recommendation, premature discontinuation of RT, switch to palliative treatment, or death during oncological treatment.

Oncological treatment was previously described in detail. [22, 27, 28] In brief, patients treated with CRT received cisplatin (100mg/m^2 three weekly or 40mg/m^2 weekly) or carboplatin (1.5 AUC weekly) combined with RT. BRT treatment consisted of a

loading dose of cetuximab (400 mg/m^2), followed by a weekly dose of cetuximab (250 mg/m^2) combined with RT. RT was given in 33 to 35 daily fractions of 2 Gy (CRT) or 30 to 34 fractions of 2 Gy (BRT). All patients were counseled by a dietitian.

Outcome

The primary endpoint of this study was the use of TF ≥4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. TF was initiated when oral nutritional intake was insufficient in meeting nutritional requirements according to the Dutch guideline on malnutrition [29] as described earlier. [22]

Predictors

The potential predictors of TF dependency we based on the literature and included: age, [30] gender, [31, 32] tobacco use, [33] alcohol use, Body Mass Index (BMI) at baseline, [34, 35] pretreatment weight change, [36] texture modified diet at baseline (e.g. ground, minced or liquid), [31] Eastern Cooperative Oncology Group performance status (ECOG PS), [37] tumor site, [31, 35] T classification, [31, 38] N classification [31, 35] (AJCC 7th edition TNM staging system [39]), disease stage, p16 status [40] (immunohistochemically as a surrogate marker for human papillomavirus (HPV), treatment setting (primary or adjuvant), [35] type of systemic therapy (platinum based or cetuximab), [33] and neck irradiation (non or unilateral versus bilateral). [38] The dosimetric parameters extracted from electronic health records were: mean RT dose (in Gy) to the contralateral submandibular and parotid gland, swallowing muscles (PCM), and oral cavity (OC). The contours for the PCM and the OC were not available in all cases in the radiation treatment planning system and were delineated for the purpose of this study. All organs at risk were contoured according to Brouwer et al. [41] and added to the database.

Sample size

As a rule of thumb, at least ten events should be included for each candidate predictor to minimize the risk of overfitting. [42] The least frequent outcome is defined as an event. In our study, receiving TF <4 weeks was the least frequent outcome and was therefore defined as an event. For the external validation set, at least 100 events and 100 non-events are recommended. [43]

Missing data

Missing data were imputed using stochastic regression imputation with full conditional specification, while considering the following covariates: age, gender, tobacco use, alcohol use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, systemic therapy, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, mean RT dose to the OC, and TF ≥4 weeks. Values to be imputed were drawn using predictive mean matching.

Statistical analysis methods

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p<0.30$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. Stepwise backward elimination was used to omit all predictors from the model that did not contribute substantially, using a p-value for selection of 0.10. Model performance was quantified as the model's ability to correctly discriminate between those who will and those who will not develop TF dependency ≥4 weeks using the area under the receiver operating characteristic curve (AUC).

For external validation, we applied the model to our validation dataset. For evaluating the performance, the AUC was computed. The Hosmer and Lemeshow goodness-of-fit test was used to assess the agreement between predicted and observed probabilities. A significant p-value would denote significant deviation from a good model. [44]

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, NY). [45]

RESULTS

Patient sample

The development cohort consisted of 409 patients. The validation cohort included 334 patients. Characteristics of both datasets are displayed in Table 1. Of note is the difference between the cancer centers with regard to the tube insertion protocol: In both UMCU and MUMC+ gastrostomies were placed prophylactically in the

majority of patients, NCI placed reactive gastrostomies and the RUMC prefers insertion of a NGT, instead of a gastrostomy tube. Details on tube insertion and TF use per cancer center are shown in supplemental Table A1.

In the development cohort, 261 out of 409 patients (64%) required TF ≥4 weeks, whereas in the validation cohort, 176 out of 334 (53%) required TF ≥4 weeks, *p*=0.003.

In the development cohort, 36% (n=148) remained on a total oral diet or used TF <4 weeks. The risk of overfitting is minimized if no more than fourteen predictors are included in the model. Regarding the 36% without TF or TF <4 weeks, we aimed to compile an external validation set of at least 278 subjects (100/36 × 100%). With 158 patients (47%) receiving TF <4 weeks and 176 patients (53%) receiving TF ≥4 weeks, our validation dataset meets the criteria of at least 100 events and 100 non-events.

Table 1 - Frequency distribution of patient, tumor, and treatment characteristics of the developmental and validation cohort.

	Development cohort UMCU and NCI n=409 [a] (%)	**Validation cohort MUMC+ and RUMC** n=334 [a] (%)	***p*-value**
Patient characteristics			
Age (mean ± SD)	60.2 ± 8.1	58.5 ± 8.1	**0.003**
Male	274 (67.0)	222 (66.5)	0.880
Female	135 (33.0)	112 (33.5)	
History of tobacco use	220 (53.8)	292 (87.4)	0.383
No history of tobacco use	39 (9.5)	42 (12.6)	
Missing	150 (36.7)	0 (0.0)	
Alcohol consumption ≥ 1 per day	145 (35.5)	196 (58.7)	0.510
Alcohol consumption < 1 per day	114 (27.9)	138 (41.3)	
Missing	150 (36.7)	0 (0.0)	
BMI at baseline (kg/m^2) (mean ± SD)	24.4 ± 4.6	24.9 ± 4.9	0.120
Weight change baseline (%) (mean ± SD)	-4.4 ± 7.0	-2.9 ± 5.5	**0.003**
No modified diet at baseline	246 (60.1)	230 (68.9)	**0.014**
Texture modified diet* at baseline	163 (39.9)	104 (31.1)	
ECOG PS 0	142 (34.7)	85 (25.4)	**<0.001**
ECOG PS 1	180 (44.0)	224 (67.1)	
ECOG PS 2	32 (7.8)	24 (7.2)	
ECOG PS 3	2 (0.5)	1 (0.3)	
Missing	53 (13.0)	0 (0.0)	
Tumor characteristics			
Oral cavity	85 (20.8)	41 (12.3)	**<0.001**
Nasopharynx/sinus	35 (8.6)	29 (8.7)	
Oropharynx	174 (42.5)	156 (46.7)	
Hypopharynx	56 (13.7)	49 (14.7)	
Larynx	29 (7.1)	54 (16.2)	
Unknown primary	13 (3.2)	5 (1.5)	
Synchronous tumors	9 (2.2)	0 (0.0)	
Neck recurrence	9 (2.0)	0 (0.0)	

	Development cohort UMCU and NCI n=409 [a] (%)	**Validation cohort MUMC+ and RUMC** n=334 [a] (%)	***p*-value**
Tumor classification (TNM)			
T0	20 (4.9)	8 (2.4)	0.233
T1	32 (7.8)	38 (11.4)	
T2	78 (19.1)	64 (19.2)	
T3	101 (24.7)	83 (24.9)	
T4	178 (43.5)	141 (42.2)	
Nodal classification (TNM)			
N0	69 (16.9)	77 (23.1)	0.106
N1	53 (13.0)	35 (10.5)	
N2	269 (65.8)	213 (63.8)	
N3	18 (4.4)	9 (2.7)	
Disease stage			
Stage I	0 (0.0)	1 (0.3)	
Stage II	12 (2.9)	6 (1.8)	
Stage III	47 (11.5)	49 (14.7)	
Stage IV	350 (85.6)	278 (83.2)	
p16 expression in oropharynx only			
p16+	74 (42.5)	87 (55.8)	**0.017**
p16-	92 (52.9)	74 (47.4)	
Missing	8 (4.6)	5 (3.2)	
Treatment characteristics			
Primary treatment	324 (79.2)	291 (87.1.)	**0.005**
Adjuvant	85 (20.8)	43 (12.9)	
Systemic therapy			
Platinum-based	313 (76.5)	264 (79.0)	0.413
Cetuximab	96 (23.5)	70 (21.0)	
Unilateral neck irradiation	47 (11.5)	22 (6.6)	
Bilateral neck irradiation	333 (81.4)	308 (92.2)	**0.040**
No neck irradiation	29 (7.1)	4 (1.2)	
Mean RT dose to contralateral submandibular gland (Gy) (mean ± SD)	44.4 ± 17.4	46.6 ± 15.4	0.060
Missing	4 (1.0)	0 (0.0)	
Mean RT dose to contralateral parotid salivary gland (Gy) (mean ± SD)	20.6 ± 9.9	21.3 ± 10.7	0.279
Missing	5 (1.2)	0 (0.0)	
Mean RT dose to PCM (Gy) (mean ± SD)	52.6 ± 15.0	53.1 ± 11.4	0.480
Missing	7 (1.8)	0 (0.0)	
Mean RT dose to OC (Gy) (mean ± SD)	42.6 ± 16.1	39.1 ± 16.3	**0.010**
Missing	6 (1.5)	0 (0.0)	
Tube type			
Gastrostomy	256 (62.6)	132 (39.5)	**<0.001**
Nasogastric tube	38 (9.3)	86 (25.7)	
No feeding tube	115 (28.1)	116 (34.7)	
Missing	0 (0.0)	0 (0.0)	
Tube feeding use	274 (67.0)	200 (59.9)	**0.040**
No tube feeding use	135 (33.0)	134 (40.1)	
Tube feeding use ≥ 4 weeks	261 (63.8)	176 (52.7)	**0.003**
No tube feeding use ≥ 4 weeks	148 (36.2)	158 (47.3)	

*Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; PCM, pharyngeal constrictor muscle; RT, radiotherapy; TNM-classification, tumor, node, metastasis classification according to the 7th edition. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake. [1]Independent samples t-test. [2]Pearson's chi-square test. [a]Original data (not imputed) presented as mean (SD) for continuous variables or absolute n (%) for categorical variables.*

Model development

Univariable regression analysis revealed $p<0.30$ for the following variables in the development cohort: tobacco use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, and mean RT dose to the OC (Table 2).

Table 2 – Results of univariable logistic regression analysis of potential predictors for tube feeding for at least four weeks.

	OR	**CI-95%**		***p*-value**
		lower	**upper**	
Age (years)	0.988	0.963	1.013	0.341
Male gender	0.947	0.617	1.452	0.801
Tobacco use	1.523	0.751	3.091	0.244
Alcohol consumption one or more per day	0.944	0.554	1.610	0.834
BMI at baseline (kg/m^2)	0.950	0.909	0.993	**0.023**
Baseline weight change (%)	0.943	0.911	0.976	**0.001**
Texture modified diet* at baseline	1.981	1.291	3.040	**0.002**
ECOG PS ≥ 1	2.124	1.400	3.223	**<0.001**
Oral cavity, oropharynx, and hypopharynx	0.689	0.419	1.133	0.143
T classification ≥ T2 (TNM)	1.472	0.817	2.652	0.198
N classification ≥ N2 (TNM)	1.984	1.285	3.062	**0.002**
Disease Stage IV	2.205	1.263	3.849	0.005
p16 + oropharynx	0.699	0.424	1.151	0.159
Primary treatment setting	0.765	0.469	1.247	0.283
Cetuximab	0.985	0.612	1.584	0.949
Bilateral neck irradiation	2.315	1.397	3.837	**0.001**
RT dose to contralateral submandibular glands (Gy)	1.022	1.010	1.034	**<0.001**
RT dose to contralateral parotid glands (Gy)	1.046	1.022	1.070	**<0.001**
RT dose to PCM (Gy)	1.027	1.013	1.041	**<0.001**
RT dose to OC (Gy)	1.028	1.015	1.041	**<0.001**

*Abbreviations: BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; OR, Odds ratio; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TNM-classification, tumor, node, metastasis classification according to the 7th edition [37]. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.*

Model specification

In the multivariable regression analysis tobacco use, BMI at baseline, T classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and PCM did not yield a *p*-value <0.10 and were therefore eliminated from the model. Pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, mean RT dose to the contralateral parotid gland and OC were significant predictors of risk of TF use ≥4 weeks. Table 3 shows the regression coefficients for all predictors included in the final multivariable regression model.

The individual probability for TF ≥4 weeks can be calculated as: P(TF ≥4 weeks) = $1/(1 + e^{-LP})$, in which LP is the linear sum of all predictor values multiplied by the regression coefficients, as shown in Figure 1.

The formula is accessible via the online supplemental material (scan QR code) and invites the reader to use the prediction model in clinical practice, as suggested in Figure 1.

Table 3 – Regression coefficients in the model for predicting tube feeding use for at least four weeks.

	Regression coefficients	S.E.	*p*-value	OR (95%CI)
Model intercept	-1.419		**0.001**	
Pretreatment weight change (%)	-0.038	0.020	0.054	0.963 (0.926-1.001)
Texture modified diet* at baseline No modified diet (reference)	0.448	0.247	0.070	1.565 (0.965-2.538)
ECOG PS 0 (reference) ECOG PS >0	0.674	0.232	**0.004**	1.963 (1.246-3.092)
Tumor site Others (reference) Oral cavity, oropharynx, and hypopharynx	-0.793	0.286	**0.006**	0.452 (0.258-0.792)
N classification (TNM) N0, N1 (reference) N2, N3	0.646	0.246	**0.009**	1.908 (1.179-3.088)
Mean RT dose to contralateral parotid gland (Gy)	0.027	0.008	**0.038**	1.027 (1.001-1.054)
Mean RT dose to the OC (Gy)	0.022	0.013	**0.004**	1.022 (1.007-1.037)

*Abbreviations: BMI, body mass index; CI, confidence interval; Gy, Gray; OC, oral cavity; OR, Odds ratio; RT, radiotherapy; S.E. standard error; TNM-classification, tumor, node, metastasis classification according to the 7th edition [37]; ECOG PS, Eastern Cooperative Oncology Group performance status. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.*

Formula

$P(TF \geq 4 \text{ weeks}) = 1/(1 + e^{-LP})$

LP = -1.419 - 0.038 * pretreatment weight change + 0.448 * texture modified diet at baseline + 0.674 * ECOG PS – 0.793 * tumor site + 0.646 * N classification + 0.027 contralateral parotid gland dose + 0.022 oral cavity dose

Variable explanation

Pretreatment weight change: "-5" is 5% weight loss
Texture modified diet at baseline: yes =1, no = 0
ECOG PS: ECOG PS ≥ 1 = 1, ECOG PS 0 = 0
Tumor site: oral cavity, oropharynx or hypopharynx = 1, others = 0
N classification: N2-3 = 1, N0-1 = 0
Parotid gland dose: mean dose in Gy
Oral cavity dose: mean dose in Gy

Example calculation

A patient with a cT4aN3bM0 hypopharynx tumor will receive locoregional CRT. She had 8% weight loss at baseline, only used mashed meals, had an ECOG PS score of 1, and will receive a mean RT dose to the contralateral parotid gland and oral cavity of 29 Gy and 36 Gy respectively:

LP = -1.419 - 0.038 * -8 + 0.448 * 1 + 0.674 * 1 – 0.793 * 1 + 0.646 * 1 + 0.027 * 29 + 0.022 * 36 = 1.435

$P(TF \geq 4 \text{ weeks}) = 1 / (1+e^{-1.435}) = 0.81$.
This patient has a probability of 81% that she will require TF for a period of four weeks or longer.

Flow chart for use in clinical practice

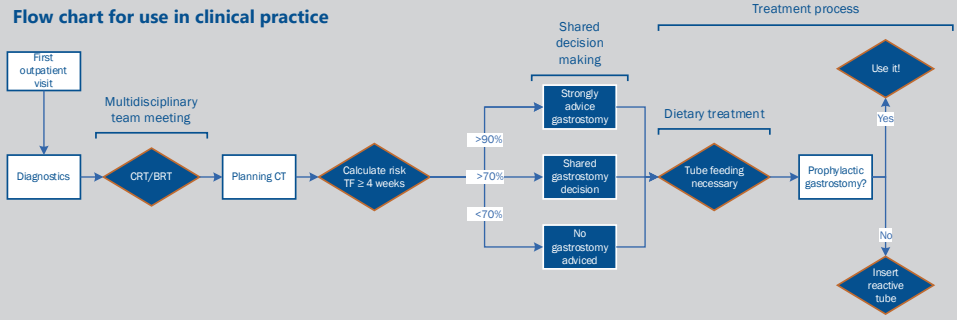


Figure 1 - Example calculation and flow chart for the use of the model in clinical practice.

Model performance

Figure 2a-d and 3 show the performance of the prediction model. The receiver operating characteristic (ROC) curve of the model yielded an AUC of 72.8% before external validation. The Hosmer-Lemeshow test statistics showed a *p*-value of 0.46, indicating a good model calibration. External validation in the combined MUMC+ and RUMC sample showed an AUC of 62.4%. External validation in the MUMC+ sample only showed a considerably higher AUC of 70.8%, whereas external validation in the RUMC sample only showed an AUC of 55.3%. The calibration plot shows a good agreement between predicted probability and the observed use of TF ≥4 weeks.

Sensitivity and specificity

The positive and negative predictive value for a risk of 90% or more of TF dependency ≥4 weeks were 81.8% and 42.3%, respectively. Specifications of sensitivity and specificity at different cut-off values are shown in supplemental Table A2.

Figure 2 – Receiver operating characteristic curve of the prediction model before external validation (A); after external validation in MUMC+ and RUMC combined (B); after external validation in MUMC+ only (C); and after external validation in RUMC only (D).

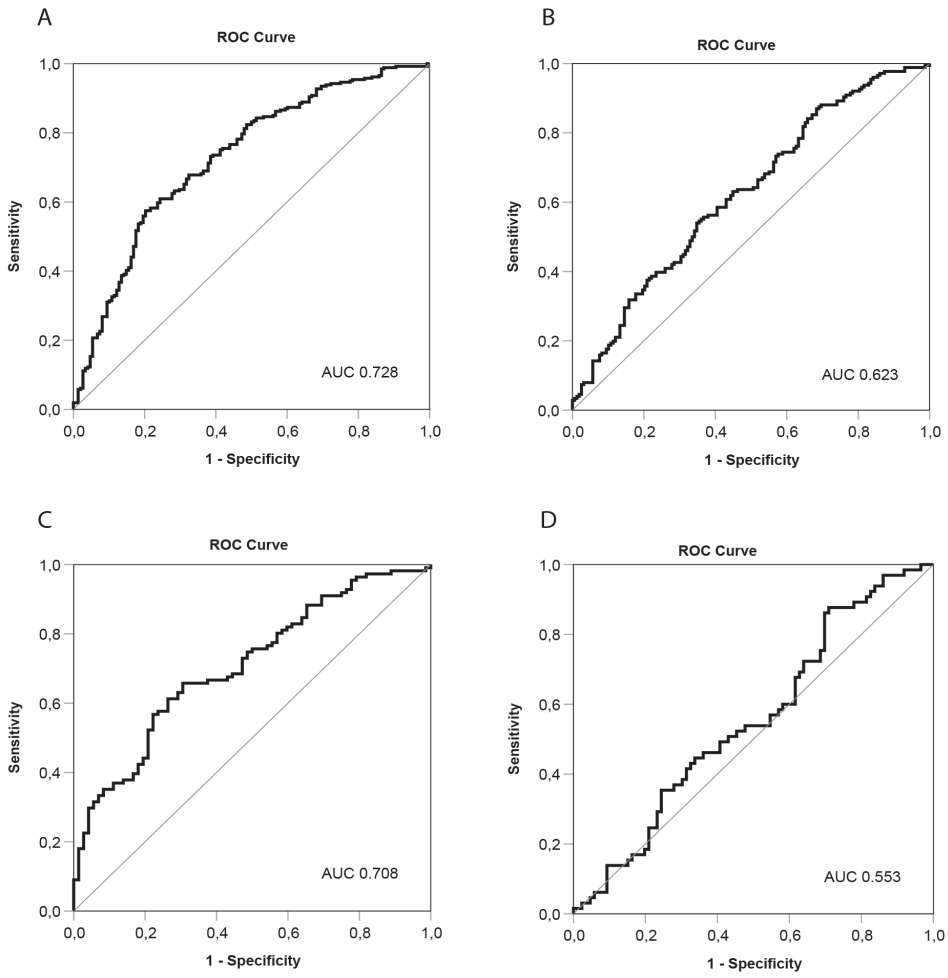
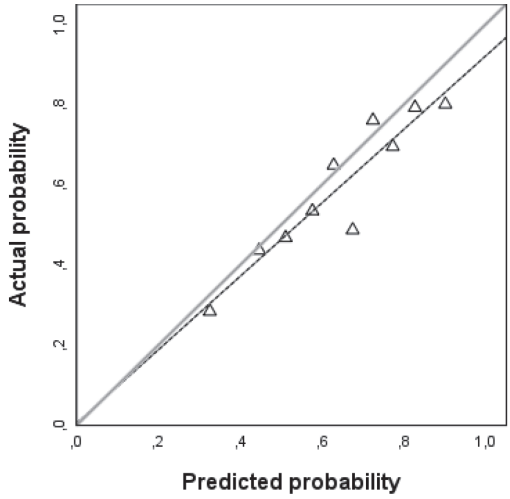


Figure 3 - Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.



DISCUSSION

In the current study we developed and externally validated a prediction model to identify LAHNSCC patients who are expected to use TF ≥4weeks and thus would benefit from prophylactic gastrostomy insertion. According to our knowledge, this is the first external validation study in a large multicenter retrospective cohort (n=409 and n=334). The model includes the following predictors: pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, and mean RT dose to the contralateral parotid gland and OC.

Remarkably, RT dose to the PCM was not a significant predictor of TF dependency in the model. Previous studies described a significant relationship between increasing RT dose to the PCM and the rising incidence and duration of TF dependency and long-term dysphagia. [24, 25, 46] An explanation for these different outcomes might be that we used total RT dose to all PCM, while other studies often used RT dose per PCM subtype; superior, middle, and inferior PCM, with dose to the superior PCM being highly predictive for dysphagia. [25] Although dose to the PCM is not a predictor in our multivariable model, it does not mean that minimizing dose to the PCM in radiotherapy planning is not useful. Indeed our univariable results indicate that dose to the PCM is associated with the risk of TF ≥4 weeks. The association

between OC dose and TF dependency may be explained by the fact that the OC has an important function in salivation, taste, chewing, and bolus transport. In a recent study by Van de Bosch et al. on the dosimetric effects of organs at risk, the oral cavity was involved in several toxicity-related effects including dysphagia. [47]

Previous studies have also shown that dosimetric variables were statistically dependent, particularly dose to the PCM and OC, the latter being a predictor in our model. Inclusion of such a dependent variable might make the other variable non-significant following correction in the statistical model. [46]

In addition, dysphagia, toxicity-related nausea and severe taste alterations (dysgeusia) causing food aversion can also negatively affect oral intake leading to TF requirement. Up to now, it remains difficult to predict which patients will experience dysgeusia during CRT/BRT.

In contrast to our previously published model, BMI at baseline, disease stage, type of systemic therapy and mean dose to the contralateral submandibular gland were not included into this new model as they did not yield a $p<0.10$ in the multivariable analysis. We included RT dose to the contralateral salivary glands as potential predictors as the remaining saliva production will correlate with the dose on the spared gland. [48] Although one study previously reported mean RT dose to the contralateral submandibular gland to have a predictive value for TF at six months, [49] this was not a significant predictor in our model. This could be explained by the different endpoints of both studies: TF initiation during CRT/BRT versus TF dependency at six months. Mean dose to the parotid gland was a significant predictor in accordance with our previously published model. [22]

It should also be noted that potential predictors not included in our final model could still have predictive value. However, the current combination of predictors presented the strongest prediction model.

Performance of the model

The model has good accuracy (AUC on internal validation 0.73 and after external validation 0.62 and 0.71 depending on the composition of the validation cohort), but there was a remarkable difference between the two cancer centers participating in the external validation process. While the AUC did not differ much in the MUMC+ validation cohort, a marked decrease of AUC was seen in the pooled cohort of MUMC+

and RUMC together. Despite adherence to national guidelines on when to initiate TF, individual and institutional preferences in feeding tube insertion policy might have affected the external validity outcome. RUMC had fewer patients receiving TF ≥4 weeks compared to the three other centers (43% versus 70%, 61% and 54% for RUMC and UMCU, MUMC+ and NCI respectively). This difference might be explained by the variations in patient characteristics. Also the effect of the cisplatin administration protocol, weekly in RUMC versus three weekly in all other cancer centers, cannot be ruled out as additional explanation for the differences in TF prevalence. High level evidence for best treatment regimen in primary setting in terms of toxicity and survival is lacking. [50],[51] Another remarkable difference that should be highlighted is the significantly lower number of gastrostomy insertions in the validation cohort versus the developmental cohort (39.5% and 62.6%). This is the result of a different policy in the RUMC regarding prophylactic gastrostomy insertion where reactive NGT insertion is preferred with only 5% of the RUMC patient sample receiving a gastrostomy.

To our clinical experience, prophylactic gastrostomy insertion could lower the threshold for TF initiation. Studies have shown that reactive NGT insertion is associated with a shorter duration of TF use. [10, 52, 53] This was also reflected in our study population, as the median TF duration in RUMC (reactive NGT) was 23 days versus 85 and 82 days in UMCU and MUMC+ respectively (prophylactic gastrostomy). It has been argued that (prophylactic) gastrostomies might be related to long term swallowing dysfunction based on the 'use-it-or-lose-it' paradigm of dysphagia rehabilitation, but the literature remains controversial on this side effect. [54-57] The present study did not evaluate long-term swallowing function after CRT/BRT with or without gastrostomy insertion. Differences in feeding tube policy between the cancer centers, as shown by our nationwide survey, [58] could be considered a limitation of the current study. However, we decided to accept this heterogeneity in patient populations to validate our model, since this reflects real world inter-center heterogeneity. An explanation for the diverse policies is the existence of regional differences in hospital logistics, but also differences in the sociocultural background of patients and health professionals and the lack of high-quality evidence in the literature regarding the indication for prophylactic gastrostomy insertion. These findings emphasize the challenge of standardizing gastrostomy insertion management nationwide. This study was not designed to investigate the best approach for TF initiation and feeding tube insertion. Differences in the effect of reactive versus prophylactic feeding tube insertions on oncological therapy outcome, weight loss and quality of life cannot be evaluated here.

Generalizability of the model (external validity)

We suggest that in case the model estimates a probability >90% for TF dependency, a prophylactic gastrostomy insertion should be recommended. In case of a probability >70%, a prophylactic gastrostomy insertion should be discussed with the patient. For patients' comfort and to reduce the risk of side effects, we recommend prophylactic gastrostomy insertion in high-risk patients before or within the first two weeks of oncological treatment when mucositis and neutropenia have not developed yet. [59, 60] This data-driven model indicates that in case of a probability >90%, approximately 18.2% of the patients with a prophylactic gastrostomy insertion will not develop TF dependency ≥4 weeks. However, that does not mean that these 18.2% patients do not benefit from a gastrostomy. They may still need TF but for a period <4 weeks or they may use their gastrostomy for supplemental fluid administration to prevent nephrotoxicity. In 57.7% of the patients with a probability <90%, a reactive feeding tube insertion will be necessary.

CONCLUSION

We developed and externally validated a prediction model to estimate TF-dependency ≥4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

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APPENDIX

Table A1 – Frequency distributions per center.

	UMCU n=259 (%)	**NCI** n=150 (%)	**MUMC+** n=183 (%)	**RUMC** n=151 (%)	***p*-value**
Age (mean ± SD)	59.2 ± 7.8	62.0 ± 8.1	58.9 ± 7.7	58.0 ± 8.5	**<0.001**
Male	167 (64)	107 (71)	121 (66)	101 (67)	0.561
Female	92 (36)	43 (29)	62 (34)	50 (33)	
History of tobacco use	220 (85)		166 (91)	125 (83)	0.107
No history of tobacco use	39 (15)	150 (100)	17 (9)	25 (17)	
Missing	0 (0)		0 (0)	0 (0)	
Alcohol consumption ≥ 1 per day	145 (56)		109 (60)	87 (58)	0.755
Alcohol consumption < 1 per day	114 (44)	150 (100)	74 (40)	64 (42)	
Missing	0 (0)		0 (0)	0 (0)	
BMI at baseline (kg/m^2) (mean ± SD)	24.1 ± 4.6	24.9 ± 4.7	24.8 ± 5.1	25.0 ± 4.6	0.133
Weight change baseline (%) (mean ± SD)	-5.1 ± 7.6	-3.1 ± 5.5	-2.8 ± 5.8	-3.2 ± 5.0	**<0.001**
No modified diet at baseline	155 (60)	91 (61)	131 (72)	99 (66)	0.060
Texture modified diet* at baseline	104 (40)	59 (39)	52 (28)	52 (34)	
ECOG PS 0	70 (27)	80 (53)	38 (21)	47 (31)	**<0.001**
ECOG PS 1	159 (61)	32 (21)	138 (75)	86 (57)	
ECOG PS 2	28 (11)	10 (7)	6 (3)	18 (12)	
ECOG PS 3	2 (1)	28 (19)	1 (1)	0 (0)	
Oral cavity	69 (27)	16 (11)	21 (11)	20 (13)	**<0.001**
Nasopharynx/sinus	19 (24)	16 (11)	11 (6)	18 (12)	
Oropharynx	96 (37)	78 (52)	85 (46)	71 (47)	
Hypopharynx	35 (14)	21 (14)	26 (14)	23 (15)	
Larynx	18 (7)	11 (7)	35 (19)	19 (13)	
Unknown primary	5 (2)	8 (5)	5 (3)	0 (0)	
Synchronous tumors	9 (3)	0 (0)	0 (0)	0 (0)	
Neck recurrence	8 (3)	0 (0)	0 (0)	0 (0)	
T classification (TNM)					
T0	12 (5)	8 (5)	5 (3)	3 (2)	0.834
T1	21 (8)	11 (7)	20 (11)	18 (12)	
T2	50 (19)	28 (19)	38 (21)	26 (17)	
T3	61 (24)	40 (27)	46 (25)	37 (25)	
T4	115 (44)	63 (42)	74 (40)	67 (44)	
N classification (TNM)					
N0	51 (20)	18 (12)	37 (20)	40 (26)	0.065
N1	36 (14)	17 (11)	15 (8)	20 (13)	
N2	161 (62)	108 (72)	125 (68)	88 (58)	
N3	11 (4)	7 (5)	6 (3)	3 (2)	
Disease stage					
Stage I	0 (0)	0 (0)	0 (0)	1 (1)	0.216
Stage II	10 (4)	2 (1)	3 (2)	3 (2)	
Stage III	31 (12)	16 (11)	22 (12)	27 (18)	
Stage IV	218 (84)	132 (88)	158 (86)	120 (79)	
p16 expression in oropharynx					
p16+	35 (36)	44 (56)	46 (54)	44 (62)	**<0.001**
p16-	61 (64)	34 (44)	39 (46)	27 (38)	

	UMCU n=259 (%)	**NCI** n=150 (%)	**MUMC+** n=183 (%)	**RUMC** n=151 (%)	***p*-value**
Primary treatment	184 (71)	140 (93)	160 (87)	131 (87)	**<0.001**
Adjuvant	75 (29)	10 (7)	23 (13)	20 (13)	
Systemic therapy					
Platinum-based	204 (79)	109 (73)	130 (71)	134 (89)	**0.001**
Cetuximab	55 (21)	41 (27)	53 (29)	17 (11)	
Neck irradiation					
Unilateral	31 (12)	16 (11)	11 (6)	11 (7)	**<0.001**
Bilateral	199 (77)	134 (89)	171 (93)	137 (91)	
No neck RT	29 (11)	0 (0)	1 (1)	3 (2)	
Mean RT dose to contralateral submandibular gland (Gy) (mean ± SD)	18.0 ± 7.5	24.7 ± 12.1	21.2 ± 11.5	21.5 ± 9.6	**<0.001**
Mean RT dose to contralateral parotid salivary gland (Gy) (mean ± SD)	18.0 ± 7.5	24.7 ± 12.1	21.2 ± 11.5	21.5 ± 9.6	**<0.001**
Mean RT dose to PCM (Gy) (mean ± SD)	51.5 ± 16.6	54.5 ± 11.9	52.1 ± 10.5	54.3 ± 12.3	0.075
Mean RT dose to OC (Gy) (mean ± SD)	45.0 ± 16.4	38.3 ± 14.8	36.7 ± 17.0	42.0 ± 14.9	**<0.001**
Tube type					
Gastrostomy	193 (75)	64 (43)	124 (687)	8 (5)	**<0.001**
Nasogastric tube	15 (6)	23 (15)	10 (5)	76 (50)	
No feeding tube	51 (20)	63 (42)	49 (27)	67 (44)	
Tube feeding use					
Yes	189 (73)	86 (57)	118 (64)	82 (54)	**<0.001**
No	70 (27)	64 (43)	65 (36)	69 (46)	
Tube feeding use ≥ 4 weeks					
Yes	180 (69)	81 (54)	111 (61)	65 (43)	**<0.001**
No	79 (31)	69 (46)	72 (39)	86 (57)	
Median TF duration in days (IQR)	85 (176)	49 (144)	82 (137)	23 (51)	0.549

*Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; PCM, pharyngeal constrictor muscle; RT, radiotherapy; TF, tube feeding; TNM-classification, tumor, node, metastasis classification according to the 7th edition. Bold values denote statistical significance at the p<0.05 level. *Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.*

Table A2 – Sensitivity, specificity and predictive values of the prediction model at different cut-off values for the chance on tube feeding for at least four weeks.

Cut-off value %	**Prevalence of TF ≥4 weeks** (n, % of total population n=743)	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
95%	5 (0.1%)	1.4	100.0	100	41.5
90%	27 (3.6%)	6.2	98.0	81.8	42.3
85%	64 (8.6%)	14.6	94.8	80.0	43.7
80%	116 (15.6%)	26.5	90.5	80.0	46.3
75%	165 (22.2%)	37.8	83.0	76.0	48.3
70%	224 (30.1%)	51.3	77.1	76.2	52.6

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

CHAPTER 10

GENERAL DISCUSSION

NEDERLANDSE SAMENVATTING

IMPACT

DANKWOORD

LIST OF PUBLICATIONS

CURRICULUM VITAE

GENERAL DISCUSSION

Cancer cachexia is a prevalent phenomenon that is characterized by involuntary weight loss having a major impact on patient outcomes. A substantial number of head and neck cancer patients suffer from cachexia, with percentages ranging up to 72%, depending on tumor stage, tumor location, and cancer treatment. [1, 2] It is hypothesized that reversing the catabolic condition of cachexia may potentiate the effect of cancer treatments, and thus increase response rates and survival of cancer patients. Unraveling the composition of weight loss and factors associated with weight loss contribute to further understanding of the pathophysiology of this multifactorial syndrome of cachexia and makes way for suitable cachexia biomarkers and therapeutic targets. In this thesis, we explored several determinants of involuntary weight loss in patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) and we evaluated the prognostic value of weight loss and its composition in both curative and palliative cancer treatment settings, using a multidimensional approach.

Prognostic value of involuntary weight loss and changes in body composition in LAHNSCC patients

Involuntary weight loss should be regarded as a manifestation (symptom) of an underlying disturbance in the immune system, appetite regulation, swallowing apparatus, and/or internal metabolic processes. These imbalances may lead to both fat and skeletal muscle mass loss, which both show different mechanisms of tissue loss. [3, 4] Body composition could thus serve as a surrogate biomarker for these altered internal processes and is a highly relevant patient characteristic.

The prognostic value of involuntary weight loss and low skeletal muscle mass is increasingly recognized within the field of oncological research. This thesis showed that patients with LAHNSCC and a low fat free mass index (FFMI) at start of chemoradiotherapy (CRT) had a higher risk of dose-limiting toxicity, and showed shorter overall survival compared to patients with a normal baseline FFMI (**chapter 3**). Other studies in HNSCC patients supported and endorsed the findings that patients with weight loss and/or low skeletal muscle mass have a greater likelihood of adverse treatment outcomes of both surgery and (C)RT. [5-7] Independent prognostic value of weight loss was also observed in patients with recurrent/metastatic HNSCC treated with palliative immune checkpoint inhibitors

(ICI) (**chapter 5**). In contrast to the predictive value of skeletal muscle mass loss of patients treated with chemotherapy, the predictive value of weight loss of patients starting ICI treatment appeared to be mainly attributed to fat mass loss. Further research is required to unravel the underlying metabolic processes and to elucidate potential differences in target mechanisms for both anti-cancer therapies.

Factors influencing involuntary weight loss in LAHNSCC patients

This thesis provides insight in the multifactorial phenomenon of cancer cachexia in HNSCC patients and shows that HNSCC-related cachexia might be one of the most complex cachexia syndromes compared to other squamous cell carcinomas with similar etiology and treatment (e.g., lung cancer). The complexity is caused by the multiple ways in which oral intake is reduced, enhancing the catabolic process of cachexia again leading to loss of skeletal and thus swallowing muscle mass.

Reduced oral intake and treatment-related factors causing weight loss

This dissertation revealed HNSCC-specific factors influencing weight loss, including pre-radiotherapy (RT) tooth extractions for the prevention of osteoradionecrosis (**chapter 6**) and pre-CRT/bioradiotherapy (BRT) oropharyngeal dysphagia (OD) (**chapter 7**). It appeared that weight loss was not correlated with the number of teeth extracted, but that a disruption of the masticatory function in itself was related to significant weight loss. Novel RT techniques including proton therapy [8, 9] and magnetic resonance linear accelerator (MR-linac) [10] enable further dose reduction to healthy structures. Future studies have yet to prove whether improved RT techniques can lead to a reduction in the number of required tooth extractions. In terms of swallowing function, more accurate RT techniques could reduce doses to the salivary glands and swallowing structures. This may reduce the prevalence of severe and long-term OD. [11-14] Nevertheless, optimizing RT techniques will not prevent OD in (LA)HNSCC, because OD is a multi-causal and complex symptom. [15]

OD in newly diagnosed (LA)HNSCC patients can be the result of a direct effect of tumor location, including obstruction and/or invasion of swallowing structures. [15] Additionally, OD might be caused indirectly through catabolic activity associated with cancer cachexia. [16] The associated loss of skeletal muscle mass will most likely result in loss of swallowing muscle mass and function causing OD.

Furthermore, treatment of LAHNSCC with CRT or BRT may cause weight loss through multi-causally impaired oral intake on the one hand, and direct catabolic effects of chemotherapy on skeletal muscle tissue on the other. [17, 18] RT-related toxicity (e.g., mucositis, xerostomia, pain) usually affects the oral intake of nutrients. This RT-related toxicity has a greater share in weight loss than the the gastro-intestinal radiosensitizer-related toxicity (e.g., nausea, vomitus). [19] Not only RT dose, but also low skeletal muscle mass has been associated with severe mucositis during CRT, [20] that in turn can contribute to the vicious circle of weight loss through impairment of oral intake. (Figure 1).

Weight loss during treatment can be limited using oral nutritional supplements (ONS) and/or tube feeding. Our study (**chapter 3**) showed that tube feeding reduced fat mass loss in locally advanced HNSCC patients treated with CRT/BRT, but the exact effects of tube feeding on skeletal muscle mass maintenance and the catabolic processes associated with cachexia, require further investigation.

Proactive gastrostomy insertion could lower the threshold to start tube feeding and improve patient adherence, [21] hypothetically limiting weight loss. Recent studies showed that prophylactic gastrostomy insertion before CRT resulted in shorter and less frequent hospital admissions than reactive gastrostomy insertion, enhancing cancer treatment tolerance. [22, 23] Nevertheless, future prospective studies should reveal whether a proactive approach positively influences treatment outcomes in the broadest sense of the word (e.g., survival, toxicity, maintenance of swallowing function, health-related quality of life, medical costs, rehabilitation, etc.). [24] In addition, it remains unclear to what extent tube feeding and/or ONS support weight maintenance during immunotherapy and to what extent they affect treatment outcome.

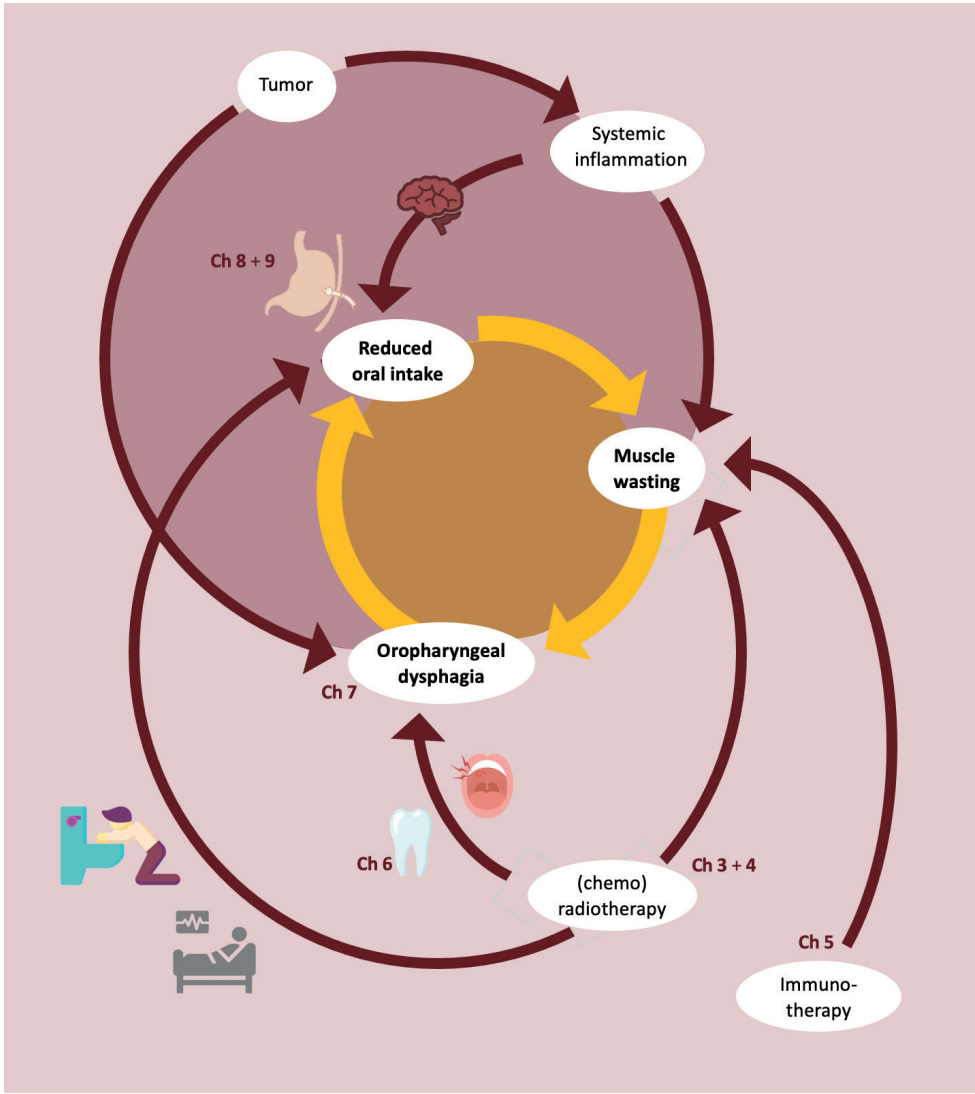

Figure 1 – The vicious circle of weight loss and impaired oral intake in head and neck cancer

An additional question that still needs to be tackled is to what extent impaired oral intake in HNSCC is a result of the tumor and its treatment or a systemic effect on appetite regulation. [3, 25, 26] In **chapter 4**, we showed that the amount of weight loss in locally advanced HNSCC patients during CRT is significantly higher than in non-small cell lung carcinoma (NSCLC) patients undergoing a comparable treatment regimen, especially in terms of fat mass loss. This advocates a larger share

of oral intake-related problems in HNSCC patients. Anorexia as a consequence of hypothalamic-pituitary-adrenal-axis (HPA-axis) alterations may be similar in both cancer types, [27-29] but impaired oral intake (i.e., OD, masticatory impairment, etc.) in HNSCC patients leads to weight loss through "fasting". Changes in appetite and taste perception caused by both tumor metabolites and treatment could potentially reflect in different activation patterns of the (food) reward center and gustatory cortex of the brain. [30] Through an ongoing functional magnetic resonance (fMRI) study, we aim to elucidate these potential changes in brain activation.

Host-related and tumor-related biological factors affecting muscle tissue

It is suggested that there are two main intertwined sources of systemic inflammation: (1) the tumor and its microenvironment, (2) characteristics of host metabolism and immune system, including the intestinal immune system.

The tumor microenvironment (TME) refers to the direct surroundings of the tumor, including vessels, immune cells, signaling molecules, and the extracellular matrix, which all interact. The TME plays an important role in tumor development and its response to treatment through the expression of (pre)inflammatory factors. Nuclear factor kappa B (NF-κB) is a key regulator in inflammatory responses through its induction of pro-inflammatory genes such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and its regulation of both innate and adaptive immune cells. [31] Abnormal activation of for example IL-1β has been related to tumor progression and metastasis. [32] Furthermore, multiple studies have shown the contribution of NF-κB in the regulation of muscle atrophy. [33] Since skeletal muscle loss is predictive of poor cancer treatment outcome as is the presence of inflammation, it would be very interesting to evaluate whether NF-κB activation is induced by circulating factors in the blood of head and neck cancer patients. The identification of these potential factors could lead to the development of biomarkers and target genes or future therapies.

Using C2C12 myoblasts transfected with a NF-κB reporter, we examined differences in NF-κB activation between patients by transferring patient serum onto the cell systems. This can be considered an in vitro evaluation of catabolism. Additionally, using another set of C2C12 myoblasts with recombination-dependent luciferase activity, we studied the effect of patient serum on myonuclear accretion, a process essential for skeletal muscle growth, repair and regeneration. Data evaluation of the performed translational experiments is still in progress.

Dealing with involuntary weight loss and changes in body composition in HNSCC patients in current clinical practice

For decades, involuntary weight loss is considered a “red flag” when patients first present with symptoms at a general practitioner or medical specialist, pointing towards the risk of a malignancy. [34, 35] Strikingly, once patients are diagnosed with cancer, this involuntary weight loss is no longer incorporated in the clinical reasoning including the development of treatment plans.

Cachexia screening should be included in standardized oncological care to improve patient characterization and to design and optimize individual treatment strategies, including anti-cancer treatment, muscle maintenance, and nutritional interventions. It is hypothesized that the catabolic hyperactivity and associated weight loss will resolve in case of successful cancer treatment. However, we have shown that patients with weight loss presented worse survival rates and treatment effectiveness. As shown in **chapter 5**, we observed a subgroup of recurrent and/or metastatic HNSCC patients who were able to reverse the weight loss process as soon as treatment started, and they outperformed patients with a continuum of weight loss during ICI treatment in terms of overall survival. Therefore, it is important to elucidate the intricate interdependence between involuntary weight loss, cancer biology, and treatment response. Strikingly, in the curative setting, weight loss during CRT was not predictive for cancer treatment outcome, as shown in **chapter 4**. This finding was recently confirmed by another study. [36]

Thus, cancer cachexia at diagnosis should be considered a risk factor for treatment-related side effects and poor prognosis (**chapter 3**), but not as an exclusion criterion for treatment. Therefore, we should aim to create a protocol to assess the “cachexia risk profile” embedded in the oncological diagnostic trajectory, using a combination of easily accessible measurements providing maximum information. For head and neck cancer diagnostics, this risk profile should at least contain information on body composition (both fat and fat free mass), muscle strength, and swallowing function.

Extensive assessment is time-consuming and burdensome for patients, who already experience high levels of distress due to the oncological diagnostic trajectory and treatment planning. Additionally, a low patient adherence can be expected in the head and neck cancer population due to multiple psychosocial aspects. [37, 38] To minimize the risk of excessive burden for the patients, screening

with minimal invasive methods, integrated in the standard of care, is preferred over extensive assessment (e.g., videofluoroscopic swallowing study for swallowing function and whole-body MRI for body composition) in every individual.

Evaluation of body composition

Despite a stable weight, a cancer patient's body composition may change over time. [39] Changes in body composition (both fat and fat free mass) influence treatment response and outcome (overall survival) independently of change in body weight. [39] This highlights the relevance of body composition evaluation.

Different techniques for body composition assessment are being used and each has its own pros and cons. Non-invasive techniques include waist-to-hip ratio and skinfold measurements, but these measurements provide limited information on muscle mass quality and distribution because they mainly focus on body fat. [40, 41] Another non-invasive technique includes bioelectrical impedance analysis (BIA). Controversial results have been reported on the correlation between the measurement of whole-body fat free mass using BIA and cross sectional area of skeletal muscle on computed tomography (CT) scans. [42-44] Despite the fact that CT-scans are often regarded as golden standard, the use of BIA has shown to be of prognostic value in multiple cancer types using both FFMI and phase angle, a proxy for the functionality of the cell membrane. [45-50] (**chapter 2**) This low cost, accessible tool can be operated without extensive training, which enables easy implementation. It is particularly interesting for identifying abnormal body composition in normal to overweight patients, as underweight patients are often already considered at risk. However, one should be aware of the influence of hydration status and fasting conditions on measured BIA values in patients. [51]

Dual energy X-ray absorptiometry (DEXA) is a rapid imaging method and allows for lean mass, fat mass, and bone mineral content measurements. This relatively cheap method can only estimate skeletal muscle mass of the limbs and fatty infiltration of the muscles cannot be observed. Additionally, hydration status of the patient and different brands of the device may introduce variability. [51, 52]

Whereas BIA and DEXA do not allow for individual tissue compartment evaluation and assessment of separate muscle groups, CT scans or magnetic resonance imaging (MRI) do provide detailed information on body composition. In clinical practice, whole-body MRI or CT is not routinely included in standard care of

HNSCC patients, so alternative methods have been investigated. Despite many attempts of evaluating different anatomical levels, [53-58] image analysis at the level of the third lumbar vertebrae remains the most accurate reference site to assess whole-body muscle mass. [59] Diagnostic CT scans that reach to the L3 level could be used for body composition evaluation, but delineation of different tissue compartments is still time-consuming and requires training. Current advances in automatic segmentation could enable fast delineation, contributing to manageable implementation of body composition in future clinical practice. [60-62] The measurement of visceral adipose tissue based on single-slide assessments can cause inter and intrapatient differences because of the organ positioning that is affected by breathing. Three-dimensional segmentation of thoracic and abdominal scans would be the ultimate method because it enables higher levels of measurement accuracy of visceral adipose tissue as well. [63, 64] The automation of this manually time-consuming process still requires further optimization.

Evaluation of skeletal muscle performance

In **chapter 3, 4, and 7**, handgrip strength (HGS) was evaluated using a handheld dynamometer. Strikingly, only a very small percentage of the studied HNSCC population presented with low HGS according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, despite a considerable number of patients being cachectic according to the consensus definition by Fearon et al. [65] Therefore, the use of the current cut-off values for low HGS are probably not sensitive enough for identifying patients at risk in the relatively young (<70 years) HNSCC population starting CRT. The low HGS cut-off values were primarily intended for the diagnosis of sarcopenia in the elderly. [66] Hence, higher cut-off values could be more suitable and of better prognostic value in the oncological population. [67-69]

The short physical performance battery (SPPB) is another accessible tool to evaluate physical performance and lower extremity function. [70] We showed that SPPB was feasible and that abnormal SPPB scores were associated with cachexia in HNSCC patients starting CRT/BRT (**chapter 7**). In principle, the SPPB was developed to evaluate frailty in the elderly and was presented as prognostic tool in older patients with and without cancer. [70-72]

Thus, HGS and SPPB have shown their value in predicting frailty in the elderly population, but their potential value in the younger oncological population has

barely been investigated. [73] Before introducing more intensive methods of measuring muscle strength to characterize patients, further investigation is required to identify the best combination of measurements (including i.e., HGS and SPPB as preliminary and currently insufficiently researched measuring tool in aged <70 years) and to establish optimal cut-off points in several stages of oncological disease.

Evaluation of swallowing function

Because cachexia and OD are interrelated (**chapter 7**), the lack of a standardized swallowing screening and assessment in cachectic patients should be considered as a missed opportunity. Proactive screening for OD is important to break the vicious circle of weight loss and muscle wasting in HNSCC patients. Early detection of swallowing problems may prevent further weight loss by starting adequate nutritional support and raising awareness on safe and efficient swallowing through among others swallowing exercises during and after finalizing cancer treatment. [74] Additionally, studies in older adults showed that adequate nutritional intake of ≥30kcal/kg/day increased tongue strength and improved swallowing function. [75, 76] It is unknown whether these effects are also evident in HNSCC patients.

The presented definition of sarcopenic OD in the elderly population includes both loss of swallowing muscle volume and strength as characteristics. [77] Future studies should show whether swallowing muscle volume can be linked to swallowing function and skeletal muscle mass wasting in a younger population with chronic diseases. In the exploratory phase of this thesis, swallowing muscle measurements on available CT and MRI scans proved to be very difficult due to differences in head positioning, edema, and anatomical alterations due to tumor invasion. Therefore, evaluating swallowing muscle volume in patients with different cancer types, such as non small cell lung carcinoma (NSCLC), would be more accurate and reproducible. This swallowing muscle volume measurement should be standardized and preferably combined with a standardized swallowing assessment such as a videofluoroscopic swallowing study (VFSS). Differences in metabolic changes between skeletal muscle tissue and swallowing muscle tissue can be evaluated using residual tissue from (partial) glossectomies or total laryngectomies.

No systematic reviews have been performed to evaluate the psychometrically best screening tool for OD in HNSCC patients. [15] Based on studies in nursing

homes and patients with neurological diseases, the water-swallowing test seems the most appropriate OD screening tool. [78-80] Besides the use of patient-reported outcome measures, this water-swallowing test could have added value when implemented in the oncological trajectory. If the water-swallowing test is deviant, patients can be referred for further diagnostic assessment using a VFSS or fiberoptic endoscopic evaluation of swallowing (FEES), during which the effect of different swallowing interventions, including diet modification, compensatory strategies, and airway protective swallow maneuvers, can be assessed. [15, 81] Patient-tailored OD treatment can be advised based on these results.

Future perspectives for targeting cachexia in head and neck cancer patients

Led by the additional patient characterization prior to and during cancer treatment, future research should focus on developing supportive therapy to optimize the patient's condition around the anti-cancer treatment trajectory. Supportive therapy must include a combination of nutrition, exercise, and anti-inflammatory elements, either pharmaceuticals or nutritional supplements.

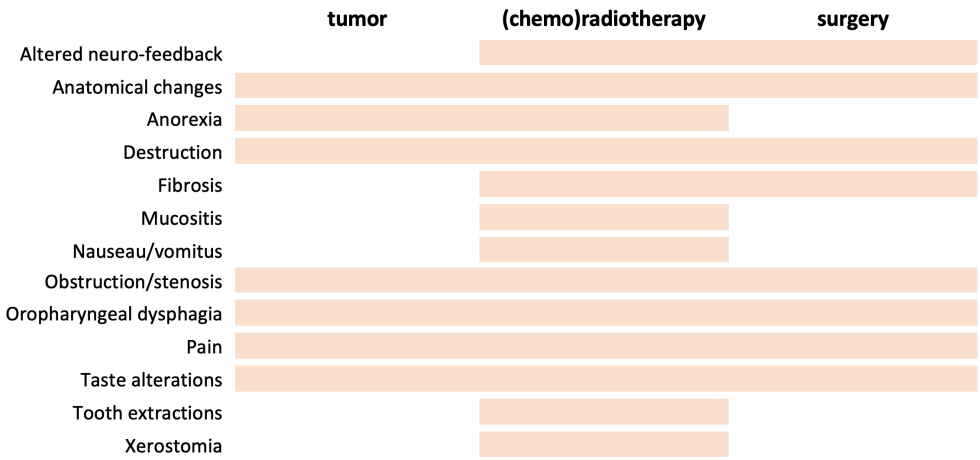

Figure 2 – nutrition impact factors in head and neck cancer

Nutritional support

Patients with HNSCC are prone to malnutrition due to systemic catabolic processes caused by the disease and the cancer treatment, and due to multiple factors affecting oral intake, also referred to as nutritional impact symptoms (**Figure 2**). Therefore, nutritional interventions should be considered as the modality of supportive therapy with the greatest potential of improvement.

Taste alterations, xerostomia, and thick mucus not only lead to an altered eating experience during treatment, but also continue to hinder patients long after treatment completion. [82-84] In addition to the fact that nutrition should have anti-catabolic properties, nutrition in cancer patients should also be pleasant and safe to consume. In patients with LAHNSCC, several aspects of nutrition need to be addressed when it comes to optimizing physical condition through nutrition:

First, voluntary nutritional intake starts with appetite and the enjoyment of food. During CRT/BRT, adequate (prophylactic) pharmacological management of nausea and vomitus is required, including proper patient instructions to improve patient adherence. Taste alterations as a result of RT, CRT/BRT, and/or sacrifice of cranial nerves during surgery have a large share in the loss of appetite. Personalized nutrition is needed, taking into account the individual nutritional requirements, swallowing function, taste perception, personal preferences, and allergies. Based on clinical experience, ONS are often experienced as “very filling”, “too sweet”, and “sticky”, and the palatability of certain ONS can change over time. [85, 86] In cancer patients in general, refrigerated and frozen products enhance palatability, and liquid ONS improve compliance compared to solid ONS. [87, 88] In clinical practice, sweet supplementary foods seem to be predominantly prescribed, while individual patients may prefer savory ONS. Future studies should gain more insight into the different taste disturbances to improve the tolerance of ONS and provide personalized advice.

The second important aspect of nutritional supplementation in head and neck cancer is to maintain and stimulate swallowing function as much as possible, considering the “use it or lose it” principle. [89] Before introducing modified diet consistencies in patients with aspiration and/or pharyngeal residue, the effect of compensatory swallowing strategies should be examined. [15] In case of persistent unsafe swallowing, texture-modified diets and the thickening of liquids may be useful. Several studies showed that sensory stimulation through menthol or

capsaicin could improve the swallowing reflex in the elderly. [90, 91] Hypothetically, a bland-taste, monotrophic diet would stimulate the swallowing apparatus too little due to a reduced variation in sensory, visual, and tactile stimuli. Therefore, in the development of nutritional supplements, manufacturers should consider the organoleptic properties of food to maintain adequate sensory feedback and appetite. However, HNSCC patients experience oropharyngeal side effects of cancer treatment (i.e., mucositis) making the oral mucosa very thin and vulnerable. Spicy, hot, acidic, or very sweet food are considered irritants that may worsen complaints of mucositis. Evidence on supplements reducing mucositis and taste alterations is limited, [92, 93] which demands for more evidence to optimize ONS in patients with HNSCC.

If oral intake is considered unsafe, impossible, or insufficient, tube feeding should be initiated. The debated downside of tube feeding without any oral intake is that the swallowing apparatus comes to a near standstill, potentially inducing long-term swallowing dysfunction ('use it or lose it'). However, studies evaluating long-term swallowing function after tube feeding via a gastrostomy report contradictory results. [94-97] It is increasingly being realized that maintaining an optimal nutritional status and skeletal muscle mass may contribute to maintenance of swallowing muscle mass and function, although the exact mechanisms are not fully understood. [15, 75] The upside of full tube feeding dependency is that hypothetically it could allow for an optimal diet composition in terms of nutrients and supplements, independent of the patient's preferences and capacity.

As a logical consequence, nutritional support should focus on optimization of nutrient composition specifically aimed at cachexia and immunological aspects of cancer metabolism. Several experimental attempts have been made to target cachexia with nutritional supplements, with omega-3 polyunsaturated fatty acid (PUFA) as probably the most frequently evaluated supplement, although still premature with a high variance in results. [98-100] Whereas short-term (4 weeks) use of PUFA enriched nutritional supplements did not show any positive effects on inflammatory markers and weight loss in HNSCC patients, [101, 102] longer attempts (9 weeks - 3 months) of nutritional support with additional whey protein and/or PUFA did show improved body composition and reduced chemotherapy toxicity in multiple advanced stage cancer patients. [103-105] Studies on the relationship between the use of PUFA and overall survival are scarce without any studies on HNSCC. [105, 106] Additionally, a low level of evidence was found for the

effect of ONS on functional status and adverse effects of cancer treatment. [107] It is suggested that ONS may even lead to adverse events such as nausea, vomiting, and a feeling of fullness. [107]

The majority of HNSCC patients treated with CRT/BRT is advised to use ONS at some point during cancer treatment due to side effects that affect oral intake and body weight. In the Netherlands, these standardized ONS already contain i.e., PUFA's. [108] It would be of added value to investigate to what extent nutritional deficiencies are present in newly diagnosed HNSCC patients. The combination of reduced oral intake due to OD and appetite loss, and a life style often including an unhealthy diet makes them prone to nutritional deficiencies including vitamins (e.g., Vitamin D [109]) and anti-oxidants. Vitamin D supplementation in HNSCC patients has been shown to improve the function of immune cells and pro-inflammatory cytokines. [109-112] Early identification of deficiencies is preferred so that early personalized nutritional interventions prior to cancer treatment, potentially contributing to enhanced treatment tolerance and success rates, can be initiated. There is still much knowledge to be gained in terms of timing and composition of ONS.

With respect to all of the above, challenges lie in maintaining the balance between optimizing nutritional status by means of tube feeding and keeping the swallowing apparatus active by preserving the oral intake. In addition, one should be aware of (possible) interactions of nutrients with the efficacy of chemotherapy, immunotherapy, and RT. [113, 114] Careful consideration and experimentation is advised.

Physical exercise

Exercise to improve physical condition

Disease and intense cancer-treatment schedules with side effects often lead to fatigue, which contributes to high levels of sedentary behavior in many HNSCC patients recovering from cancer treatment. [115] Sedentary behavior retains muscle atrophy and may even lead to further skeletal muscle deterioration, which in turn contributes to a decreased health-related quality of life and survival. As resistance exercise contributes to muscle gain in the general population, muscle training in cancer patients could theoretically combat muscle loss in cachexia. Immunomodulatory effects of physical exercise should not be underestimated. Both endurance and resistance exercise have shown to reduce TNF-α production

and induce interleukin secretion (IL-6, IL-7, IL-10) by muscle cells, which in turn stimulate CD8+ cells, natural killer cells, and mobilization of B-cells. [116]

Over the last years, "prehabilitation programs" have gained interest. Prehabilitation is meant to enhance patients' physical and mental condition to optimally prepare them for cancer treatment, and potentially further activate the immune system.

Guidelines of the Dutch Federation of Oncological Societies (Stichting Oncologische Samenwerking - SONCOS) state that head and neck cancer patients should start cancer treatment within 30 days after the first visit to minimize disease progression due to treatment delay. [117] This short time-window challenges research on adequate prehabilitation. It is unclear whether extending those 30 days for optimization of the physical condition can contribute to improved cancer treatment outcomes. One should weight the potentially aggressive tumor growth against the gain that can be achieved through prehabilitation. Several studies have evaluated the feasibility of heterogeneous exercise programs in small samples of HNSCC patients. [118-124] Exercise programs included both resistance and walking programs, and varied in time and frequency (six up to fourteen weeks, two times per week versus five times per week, and training with and without supervision.) Positive effects were observed for physical performance, [118, 119] fatigue, [119, 122, 124] quality of life, [121, 122] and mental health. [118, 119] Strikingly, reports on the effects of exercise on body composition and muscle strength were inconsistent, with no observed changes in body composition in one [121] and improved muscle strength and lean body mass in two other studies. [119, 122]

In non-oncological settings such as cardiac surgery and hip replacement surgery, physical therapy prior to surgery reduced the postoperative complication rate and hospital admission days. [125, 126] In 26 patients undergoing chemotherapy and surgery for esophagogastric cancer, a 15-week program of multimodal prehabilitation, comprising supervised and home-based exercises and psychological coaching, showed improved neoadjuvant treatment completion and improved health-related quality of life. [127] Nevertheless, meta-analyses of exercise programs in various cancer types reported low levels of evidence and divergent results when focusing on cancer treatment outcome and complication rates. [128, 129]

Although previous trials stated that exercise programs in HNSCC are feasible, the willingness to participate of approximately 30% was relatively low, and some studies

were terminated early because of slow recruition. [123] So, only a selected group of HNSCC patients seems willing and fit for exercise participation. [119] Multiple barriers and facilitators to physical activity in HNSCC patients exist, with cancer treatment-related side effects including fatigue as most frequently observed barrier. [130] Considering the low participation rates, future attempts to develop physical training programs demand for individualized exercise and support plans to optimize participation rate and adherence through easy-accessible and feasible training programs. The required key-information includes the patient's motivation, needs, and wishes. The use of neuromuscular electrical stimulation (NMES) would be a worthwhile exploration in physical training programs. [131] In case of physical deterioration, NMES could be an alternative exercise modality. It has been shown to improve muscle strength, functional capacity, and health-related quality of life. [132, 133] Additionally, NMES has been linked to anti-inflammatory activity through the release of myokines and other cytokines such as TNF-α. [132] Large prospective randomized studies are warranted to properly investigate the best multimodal training setup and the effects on prehabilitation tolerance, response, and survival.

Exercise to improve swallowing function

Over the last years, several studies have evaluated the effect of prehabilitation of swallowing in HNSCC patients starting (C)RT. [134-137] The current evidence for prehabilitation is limited due to i.e., heterogeneity in performed intervention programs, and again, poor adherence to exercises. [138] The long-term effects of swallowing prehabilitation remain unclear. [139] Because of the low level of evidence for swallowing prehabilitation, limited patient adherence, and the additional burden for patients, the primary focus during the pretreatment phase should be on optimizing the overall physical condition (physical exercise and nutrition). In addition, full-body exercises have been related to better OD outcomes in stroke patients, and another study suggests that full-body resistance training may be simultaneously beneficial for overall physical performance and for swallowing function in the elderly. [140, 141] In case of OD in sarcopenic or cachectic patients, isolated muscle exercises focusing on swallowing muscles only will most likely not improve swallowing function in patients with a sedentary lifestyle. This could advocate a more general approach considering full-body muscle exercises instead of swallowing muscle training only or a combination of both.

Pharmaceutical antagonists for cachexia

TNF-α, IL-6, and IL-1α are well-known factors related to muscle wasting in cancer cachexia through activation of catabolic pathways. [142] High levels of circulating inflammatory cytokines in cancer patients have been associated with weight loss, low body mass index, low protein levels and worse treatment outcomes. [143, 144] Targeting these cytokines and involved pathways could potentially attenuate the development of cachexia.

Drugs targeting these inflammatory pathways that are already available for non-cachexia indications (e.g., rheumatoid arthritis) could provide insight in potential advantages. Meta-analyses on the impact of TNF-α inhibitors and IL-6 signaling pathway inhibitors on body weight found an overall increase in body weight. [145, 146] Unfortunately, the limited number of studies in cancer patients presented less promising results. Studies on anti-TNF-α interventions showed conflicting results, varying from no differences in weight [147-149] to less weight loss compared to placebo. [150]

Preliminary in vivo experiments using tocilizumab (anti-IL-6) and cisplatin in squamous cell carcinoma bearing mice showed potential synergistic effects. [151] In vitro experiments using tocilizumab also showed a growth suppression of cisplatin-resistant HNSCC cells. [152] These studies suggest that the use of anti-IL-6 in HNSCC is worth further exploration.

It is important to realize that the pathophysiology in cancer cachexia is not lead by one single cytokine expression. Strategies to tackle cachexia require a multimodal approach, focusing on all the above-mentioned aspects.

To conclude, cancer cachexia and low skeletal muscle mass have a detrimental effect on the patients' health-related quality of life, cancer treatment efficacy, and overall survival. The phenomenon of cachexia is gaining increased recognition in clinical practice, but is not optimally embedded in the standard care pathway yet. This thesis highlighted determinants of weight loss in HNSCC patients, providing insight in future targets for nutritional intervention, physical therapy, and cancer treatment adaption. Future studies into the underlying (immunological) mechanisms of this paraneoplastic syndrome should further elucidate anti-cachexia targets.

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NEDERLANDSE SAMENVATTING

Ongewenst gewichtsverlies is een veelvoorkomend verschijnsel bij kankerpatiënten, zo ook bij patiënten met hoofd-halskanker. Wanneer er sprake is van >5% gewichtsverlies, of >2% gewichtsverlies in combinatie met een lage BMI of in combinatie met een lage spiermassa en spierfunctie spreekt men van cachexie. Juist bij hoofd-halskanker is de oorzaak van dit gewichtsverlies zeer complex, waardoor het tegengaan ervan ook een uitdaging wordt. De complexiteit komt voort uit de multipele factoren die de voedingsinname beïnvloeden, zowel veroorzaakt door de tumor als door de behandeling. Dit proefschrift was gericht op de prognostische waarde van ongewenst gewichtsverlies en veranderingen in lichaamssamenstelling (deel 1). Tevens werden er verscheidene factoren uitgesplitst die positief en negatief van invloed zijn op voedingsinname en gewichtsverlies (deel 2).

Hoofdstuk 3 beschreef de resultaten van een retrospectieve studie in hoofd-halskankerpatiënten die behandeld zijn met radiotherapie in combinatie met systemisch therapie (chemotherapie cisplatinum of biotherapie cetuximab). De vetvrije massa van patiënten werd bepaald met behulp van een bioelektrische impedantie analyse (BIA). Drieëntwintig procent van de patiënten die chemoradiatie kregen had een lage vetvrije massa index (VVMI, vetvrije massa / lengte^2) voorafgaand aan de behandeling. In de patiënten die behandeld werden met bioradiatie bedroeg dit percentage 46%.

Patiënten met een lage VVMI vóór start van behandeling, hadden tíjdens de behandeling grotere kans op ongeplande ziekenhuisopnames. Daarnaast werd gezien dat in de chemoradiatiegroep een significant hoger aantal patiënten te maken kreeg met dosis-beperkende toxiciteit wanneer zij een lage VVMI hadden. Daarbovenop bleek dat patiënten met een lage VVMI een significant kortere overlevingsduur hadden in vergelijking met patiënten met een normale VVMI. Na twee jaar was respectievelijk 57.3% ten opzichte van 83.5% nog in leven. Na vijf jaar was dit verschil nog groter namelijk 35.7% ten opzichte van 74.5%.

Tijdens de behandeling van zes tot zeven weken verloren patiënten gemiddeld 3.7 ± 3.5 kg lichaamsgewicht en nam ook hun handknijpkracht (spierfunctie) af met 3.1 ± 6.0 kg. Vierenzestig procent van de patiënten werd tijdelijk afhankelijk van sondevoeding tijdens de behandeling. Dit had een gunstig effect op het gewichtsverlies, maar kon het niet volledig ondervangen.

De resultaten van deze studie lieten zien dat een lage vetvrijemassa, waar ook spiermassa onder valt, een voorspeller is voor slechtere therapietolerantie en kortere overleving. Het is daarom van belang om deze uiting van ziekte tijdig te herkennen en mee te nemen in de overwegingen voor (ondersteunende) behandelingen.

Door de ingrijpende bijwerkingen die hoofd-halskankerpatiënten ervaren tijdens hun behandeling, is het binnenkrijgen van voldoende voedingsstoffen vaak een grote uitdaging. Onder andere mucositis en xerostomie zorgen voor pijn en slikproblemen, waardoor de orale voedingsinname in het geding komt. Logischerwijs zou dit bijdragen aan het gewichtsverlies tijdens de behandeling. Om de verschillende determinanten van het gewichtsverlies tijdens de behandeling op te helderen, werd in **hoofdstuk 4** de vergelijking gemaakt tussen patiënten met een squameus niet-kleincellig longcarcinoom (sNSCLC) en humaan papilloma virus negatieve (HPV-) hoofd-halskankerpatiënten. Beide groepen delen dezelfde risicofactoren zoals roken en ondergaan vergelijkbare behandelingen (radiotherapie in combinatie met systeemtherapie). Daarentegen ervaren sNSCLC-patiënten minder orale bijwerkingen van de therapie. Deze retrospectieve studie liet zien dat het percentuele gewichtsverlies tijdens chemoradiatie tussen beide kankerpatiënten niet verschilde maar dat de samenstelling van dit gewichtsverlies wel significant uiteenliep: HPV- hoofd-halskankerpatiënten verloren meer vetmassa (-8.7 ± 9.0%) ten opzichte van de sNSCLC-patiënten (-1.4 ± 14.5%). Daarnaast zagen we een trend naar een groter verlies van vetvrijemassa in sNSCLC ten opzichte van hoofd-halskankerpatiënten. Het verlies van vetmassa tijdens de behandeling bleek daarbij een voorspeller voor kortere overleving in sNSCLC-patiënten, maar niet in hoofd-halskankerpatiënten. Mogelijkerwijs zijn deze verschillen te verklaren door factoren die de orale voedingsinname beïnvloeden, maar ook het verschil in comorbiditeiten en tumorload kan een rol spelen.

Waar de negatieve effecten van ongewenst gewichtsverlies tijdens de behandeling van chemotherapie uitgebreider onderzocht zijn, is dat in de voor hoofd-halskanker recent beschikbaar gekomen immunotherapie minder bestudeerd. Deze vorm van therapie is slechts succesvol in een zeer klein gedeelte van de patiënten die de behandeling starten. Naast de expressie van programmed death-ligand 1 in de tumor en de omliggende cellen, de zogenaamde combined positive score (PD-L1 CPS), zijn er nog geen klinisch beschikbare prognostische markers voorhanden. Daarom hebben we in samenwerking met het Universitair Ziekenhuis Leuven, België, de prognostische waarde van gewichtsverlies bestudeerd in

hoofd-halskankerpatiënten met teruggekeerde of gemetastaseerde ziekte die behandeld werden met immuun-checkpoint remmers. Door middel van CT-scan analyses werd de lichaamssamenstelling geëvalueerd in **hoofdstuk 5** en werd ook het gewichtsbeloop bestudeerd. We zagen dat patiënten die bij aanvang van therapie cachectisch waren en gewicht bleven verliezen tijdens de eerste zes weken van behandeling de slechtste prognose hadden. Dit was onafhankelijk van de PD-L1 CPS. Een opvallende bevinding was dat het gewichtsverlies in een gedeelte van de cachectische patiënten tijdens de behandeling juist stabiliseerde. Deze patiëntengroep had een vergelijkbare overleving met de patiënten die niet cachectisch waren voorafgaand aan de behandeling. Het evalueren van gewicht blijkt dus ook hier een ondersteunende factor te kunnen zijn in het voorspellen van behandeluitkomst. Immunotherapie heeft op een nog onduidelijke wijze effect op het proces van gewichtsafname. Ophelderen van deze mechanismen kan potentieel bijdragen aan targets om behandeluitkomsten te verbeteren.

Het tweede gedeelte van het proefschrift richt zich op factoren die van invloed zijn op de voedingsinname van hoofd-halskankerpatiënten. Naast dat de radiotherapie zelf bijwerkingen geeft die de orale voedingsinname kunnen beperken, zijn ook de voorbereidingen op de radiotherapie van invloed. Patiënten ondergaan een focusonderzoek waarin de status van het gebit beoordeeld wordt. Slechte tanden of tandresten die in het bestralingsgebied liggen vormen namelijk een risico voor de ontwikkeling van osteoradionecrose in een later stadium. Daarom wordt het gebit gedeeltelijk of soms geheel gesaneerd voorafgaand aan de radiotherapie. We verwachtten dat dit effect zou hebben op het kauwapparaat, de voedingsinname en daarmee zou leiden tot meer gewichtsverlies. In **hoofdstuk 6** hebben we deze hypothese getoetst in 77 patiënten met een tumor in de mond-keelholte. Gemiddeld werden er 4.1 ± 5.6 tandextracties uitgevoerd bij deze patiëntengroep. De resultaten laten zien dat er een associatie bestaat tussen tandextracties en >5% gewichtsverlies tijdens chemoradiatie. Het aantal extracties had echter geen invloed op de hoeveelheid gewichtsverlies.

Deze studie geeft aanleiding tot nader onderzoek naar de nadelige effecten van tandextracties en verstoring van het kauwsysteem. Samen met de huidige verbeteringen in radiotherapietechnieken kan dit de discussie aanwakkeren om de huidige tandextractieprotocollen te herzien, rekening houdend met de risico's op osteoradionecrose.

Naast het kauwsysteem is ook het slikapparaat een belangrijk orgaan dat aangedaan is bij hoofd-halskankerpatiënten. Er wordt vaak gedacht dat slikproblemen voortkomen uit de grootte en locatie van de tumor. Echter is er ook sprake van slikproblemen in patiënten met andere oncologische ziektebeelden, zoals bijvoorbeeld longkanker. Mogelijk dragen andere factoren dus bij aan de ontwikkeling van slikproblemen. Aangezien cachexie een multifactorieel syndroom is dat verlies van skeletspiermassa veroorzaakt, en dat slikfunctie ook aangedreven wordt door spieren, was het interessant om te onderzoeken of slikfunctie en skeletspierfunctie en –massa met elkaar geassocieerd waren. In **hoofdstuk 7** beschrijven we de resultaten van een prospectieve studie die deze hypothese onderzocht. In de 66 patiënten die startten met radiotherapie in combinatie met chemotherapie of biotherapie waren er 17 cachectisch en rapporteerden 26 patiënten significante slikproblemen (score ≥ 3) op de EAT-10 screeningslijst voor orofaryngeale dysfagie. Cachexie was een onafhankelijke voorspeller voor een EAT-10 ≥ 3. De hoge prevalentie van zowel cachexie als patiënt-gerapporteerde slikproblemen, geven aanleiding voor screening op deze problematiek voorafgaand aan de behandeling, zodat er tijdig op ingespeeld kan worden en verslechtering zoveel mogelijk kan worden vooromen.

Vanwege de slikproblemen en bijwerkingen van de (chemo)radiotherapie wordt zo'n twee derde van de patiënten tijdelijk afhankelijk van sondevoeding. In samenwerking met Maastro Clinic, het UMC Utrecht, het Antoni van Leeuwenhoek en het Radboud UMC presenteren we in **Hoofdstuk 8 en 9** een predictiemodel waarmee de sondevoedingsafhankelijk tijdens chemoradiatie voorspeld kan worden. Wanneer een patiënt meer dan vier weken sondevoeding nodig heeft kan een gastrostomie overwogen worden in plaats van een neusmaagsonde. Idealiter is deze gastrostomie reeds in situ voordat de radiotherapie start, om vertraging en complicaties tijdens de therapie te voorkomen. Door de ontwikkeling en validatie van het predictiemodel in hoofdstuk 8 en 9 kan er nu vroegtijdig een risico-inschatting worden gemaakt, en in overleg met de patiënt indien nodig alvast een gastrostomie geplaatst worden.

IMPACT

Scientific research is an important requirement to develop knowledge, on the basis of which protocols, policies, and working methods can be optimized in clinical practice. This chapter describes the impact of this thesis and its relevance to science, clinical practice, and society.

Research goals and conclusions of this thesis.

The overall aim of this thesis was to assess how weight loss and body composition influence cancer treatment outcome in locally advanced head and neck cancer patients, and to evaluate determinants of involuntary weight loss. The results of the studies presented in this thesis are relevant to patients, healthcare professionals, and society and a large part of these results can be implemented immediately in daily practice.

In **chapter 3, 4, and 5** we showed that cancer patients experiencing involuntary weight loss and/or low skeletal muscle mass have a greater risk of developing dose-limiting toxicity of chemo- or bioradiotherapy (CRT/BRT) compared to patients without weight loss. In addition, weight loss and/or low muscle mass was a risk factor for shorter overall survival in both curative and palliative treatment settings.

Patient, disease, and cancer treatment-related factors affecting oral intake and body weight included tooth extractions prior to and during CRT (**chapter 6**), oropharyngeal dysphagia (OD) (**chapter 7**), a tumor located in the oral cavity, oropharynx or hypopharynx, a higher nodal stage, and radiotherapy dose to a.o. the parotid gland and oral cavity (**chapter 8 and 9**). In chapter 8 and 9 we present a prediction model to identify patients at risk for tube feeding dependency for at least four weeks, which can be used to guide personalized decision-making on prophylactic gastrostomy insertion.

Relevance for clinical practice and future research

Adequate patient stratification may contribute to optimization of patient-tailored treatment plans, minimizing the risks of cancer treatment dropout, and to a better estimation of the prognosis. In this thesis, we report high clinical relevance of three important aspects related to cancer cachexia in HNSCC: (1) body composition assessment, (2) screening for OD, and (3) predicting tube feeding dependency.

Body composition and muscle function in the outpatient clinic

This thesis has raised awareness of the adverse consequences of involuntary weight loss in oncological care. By being aware of the potential shorter survival and increased risk of dose-limiting toxicity due to involuntary weight loss, the treating physician can make informed decisions in the best interest of the patients. Therefore, it is essential to properly characterize the patient and to objectify weight changes. The minimum requirement to achieve this is a scale (and its use) in every single outpatient clinic room, regardless of the medical discipline involved.

Additional investigations to obtain valuable information on the patients' physical condition are not necessarily time-consuming or expensive. In **chapter 3 and 4** we demonstrated that the use of easy-accessible instruments such as bioelectrical impedance analysis (BIA) or a handheld dynamometer to measure handgrip strength (HGS), provides useful information for patient characterization and prognosis estimation. Partly due to the results presented in this thesis, an extensive multidimensional screening program has been introduced in the rapid diagnostic trajectory for head and neck cancer in Maastricht University Medical Center+ (MUMC+). In addition to screening of the psychosocial and cognitive condition and swallowing function using validated questionnaires, the patient's physical condition is screened by using HGS and the short physical performance battery (SPPB). These screening tools are important in the context of awareness among healthcare professionals, patients, and their families. They can be the inducement of an in-depth discussion and subsequent diagnostic workup for additional supportive treatment such as nutritional interventions, OD (p)rehabilitation, psychosocial care, etc. Maintaining adequate skeletal muscle mass may contribute to faster recovery and earlier reintegration into society, improving both social and financial aspects.

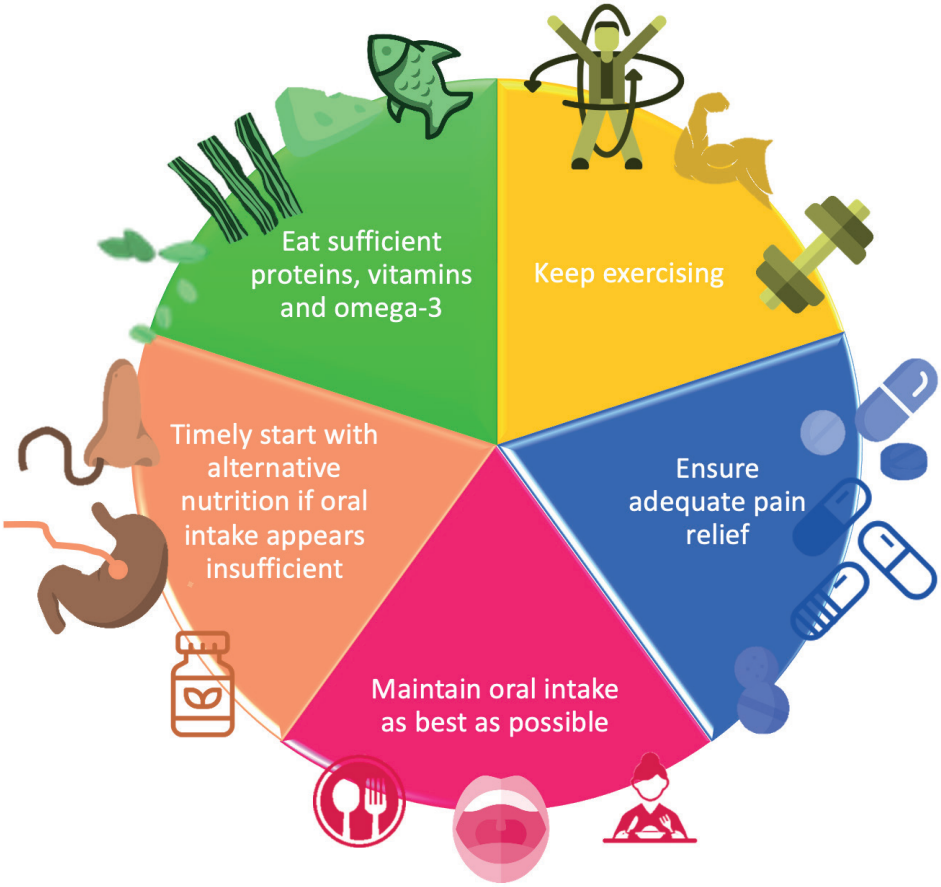

Figure 1 – the five aspects of minimizing weight loss in head and neck cancer

Adequate provision of information to the patient about the importance of muscle maintenance is required to improve adherence to advised physical and nutrition interventions. The results from this thesis contribute to an additional transfer of information on the importance of weight maintenance to the patient, to improve awareness amongst cancer populations and could be the basis for hospital-wide information maps (example figure 1). However, it remains challenging to optimally prepare and support every individual in the diagnostic and treatment process. As shown in **chapter 7**, less than one third of the invited patients were open to an additional evaluation of swallowing function in the interdisciplinary outpatient clinic for OD. Nevertheless, the vast majority of patients was willing to participate in the accessible study measurements that were integrated in their regular

appointment schedule, including HGS, SPPB, and BIA. Thus, study participation appears to be highly dependent on the additional effort and time burden. Our research shows that integration of accessible measurements of body composition, muscle strength and subjective perception of swallowing in standard care is key, and may provide useful and valuable information for individual patients and for the entire population of HNSCC patients. Researchers should keep the importance of integration in mind while setting up new study protocols.

Cachexia and oropharyngeal dysphagia

In **chapter 7** we showed that cachexia and OD are interrelated. This information is relevant for a.o. dieticians, speech and language therapists, and oncologists, as their treatment efficacy may be dependent on both swallowing function and physical condition of patients. More specifically, a dietitian must pay attention to the presence of swallowing problems, and a speech and language therapist should evaluate muscle mass loss to exclude or confirm interference with muscle function, including the muscles involved in swallowing. Chapter 7 serves as a hypothesis-generating article that facilitates new studies on swallowing optimization.

Oral intake and tube feeding dependency

The results of this thesis shed light on several determinants of oral intake impairment in HNSCC. In the present care pathway, loss of taste and appetite are scarcely taken into account. Elucidating the contribution of changes in taste perception to weight loss raises awareness among clinicians and other caregivers. This offers new leads for medical nutrition and other approaches to improve appetite. With this in mind, we are currently working on functional magnetic resonance imaging (fMRI) of the brain to assess differences in food-reward and taste perception-related brain activity between LAHNSCC patients in the recovery phase after CRT and healthy controls. By gaining insight into taste perception and experience, patients might be able to maintain their oral intake on a sufficient level through personalized taste advice and adapted oral nutritional supplements.

When oral intake during CRT becomes insufficient, tube feeding becomes necessary. Current clinical practice repeatedly shows that it is difficult to predict which patients will require tube feeding during their CRT trajectory. This is mainly due to the diversity of symptoms such as OD, nausea, vomitus, and taste loss.

The developed prediction model (**chapter 8 and 9**) for tube-feeding dependency of at least four weeks may contribute to an improvement of proactive tube feeding initiation and may thus limit weight loss and treatment interruptions due to a deterioration of the patient's physical condition.

At the end of 2021, a grant was awarded to Maastricht UMC+ and UMC Utrecht by the Michel Keijzer Fonds to implement the prediction model in clinical practice. In consultation with a.o. patients, dieticians, speech-language therapists, medical oncologists and radiotherapist-oncologists, this grant will be used to develop decision tools that will support both patient and caregiver in the choice for timing (prophylactic versus reactive) and type (gastrostomy or nasogastric tube) of feeding tube insertion. The use of decision tools contributes to *shared decision making* and provides insight into individual choices and considerations, generating patient-tailored treatment plans.

Translational research

To reveal underlying mechanisms contributing to muscle wasting, we have attempted to evaluate whether catabolic activity can be measured in patient serum using innovative cell systems. The laboriousness of these experiments have highlighted that these type of studies can be very interesting for exploratory purposes but will be challenging to implement in clinical practice. These cell systems are not suitable for use in clinical practice because they are subject to changes and heterogeneity of cell growth. The data analysis is still ongoing. Identification of catabolic factors could contribute to the development of alternative methods such as liquid biopsies to provide more accessible and reproducible biomarkers in the future.

Adequate patient characterization may contribute to better patient selection and more effective use of chemotherapy and immunotherapy. This in turn may limit the administration of unsuccessful treatments and associated costs. This mainly applies to the use of immunotherapy, which is currently beneficial in only a small selection of HNSCC patients starting ICI treatment. The results presented in **chapter 5** have led to currently ongoing research into the relation between systemic inflammation, body composition, and the tumor microenvironment. We hope to elucidate immunological factors predicting treatment response.

Dissemination of knowledge

The results of our studies were shared with other researches through publications in international peer-reviewed open access journals. Additionally, we presented our data at several national and international scientific meetings, such as the Conference on Cachexia, Sarcopenia and Muscle Wasting, the joint International Congress on Innovative Approaches in Head and Neck Oncology, the American Society of Clinical Oncology annual meeting, and at scientific meetings of the Dutch Working Group of Head and Neck Tumors (NWHHT). Part of the performed research has been discussed in an interview with MEDtalks Nederland.

For the planned future development of the decision tool for feeding tube insertion, we will host focus groups during which both patients and physicians will share their experience and knowledge on the different policies. The Dutch head and neck patient association is involved as well, which enables direct knowledge sharing with the patient population.

DANKWOORD

Het zit erop! Mijn eerste stappen in de onderzoekswereld zijn eindelijk gebundeld in een proefschrift. Het huidige resultaat was er niet geweest zonder de vele mensen met wie ik heb mogen werken, leren en groeien. Ik wil dan ook graag iedereen die hier een rol in heeft gespeeld bedanken.

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CURRICULUM VITAE

Anna Catharina Hendrika Willemsen, given name Rianne, was born in Arnhem, The Netherlands, on December 29th 1993 and grew up in Huissen. In 2011 she graduated from the Overbetuwe College in Bemmel and additionally obtained her international baccalaureate in English. In the same year, she started her bachelor in Medicine, which she obtained in 2015. She started her master in Medicine afterwards which included an internship in Hospital Universiti Sains Malaysia. In April 2017, Rianne begun her clinical and scientific participation in Maastricht University Medical Center+, where she became acquainted with the head and neck cancer population. From there she developed an extensive interest in this population and scientific research. On December 31st 2017, she graduated as medical doctor. In 2018 Rianne was awarded the Nutrim Graduate Programme with her own research proposal “From Head to Toe – Personalised Medicine in Head and Neck Cancer Cachexia”. This allowed her to fulfill a PhD-trajectory within two Maastricht University research schools; NUTRIM, School of Nutrition and Translational Research in Metabolism and GROW, School for Oncology and Reproduction. During her PhD trajectory, Rianne presented her research at several national and international conferences and was nominated for the Pelerin Wetenschapsprijs in 2021. She also obtained grants from Nutricia Research Foundation, Espen Research Fellowship, and the Michel Keijzer Fonds. In April 2022, she started working as a resident Internal Medicine in Diakonessenhuis, Utrecht.