# Head and neck cancer cachexia

# 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.

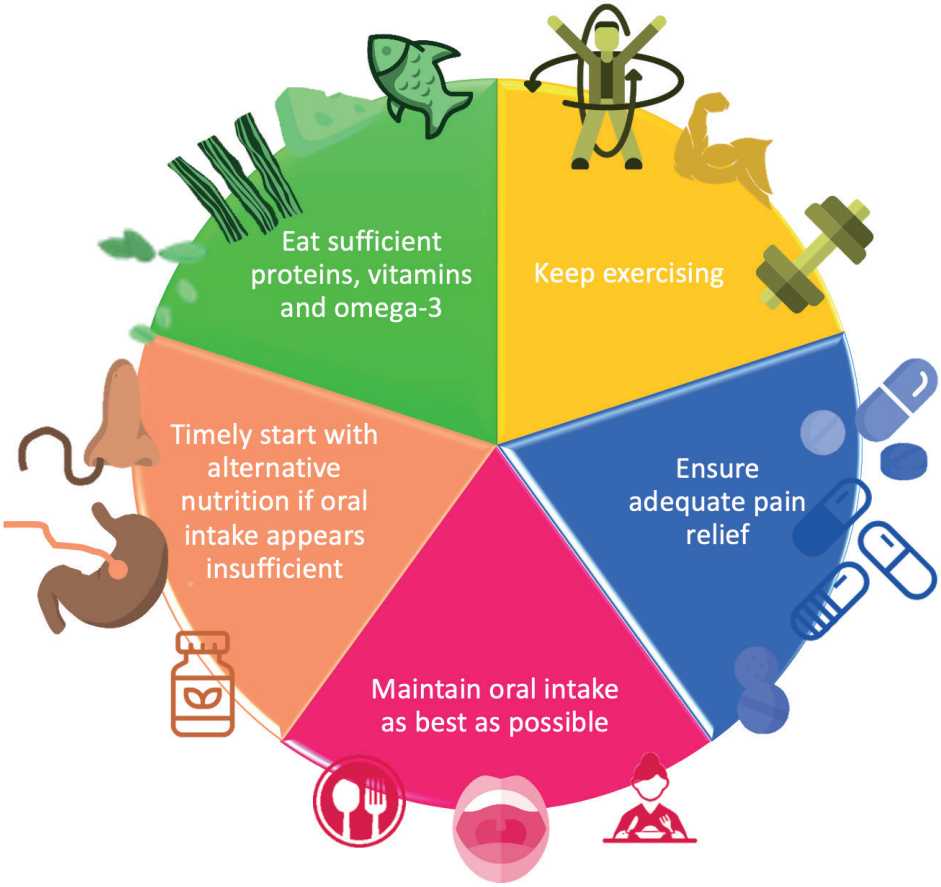


**Figure 1** – the five aspects of minimizing weight loss in head and neck cancer

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.